Peripheral Gangrene in Infancy and Childhood

ANNE LLOYD,* M.B., B.S., M.R.C.P., D.C.H.; MARGARET KEMBALL,† M.B., B.S., M.R.C.P.
GRAHAM FRASER,‡ M.B., CH.B., F.R.C.S., F.R.C.S.ED.

Brit. med. J., 1967, **1**, 468–470

A 5-month-old infant with symmetrical gangrene of the extremities was recently admitted to the Hospital for Sick Children. This condition is now rare in the paediatric age group, and only three other children with similar features have been seen at this hospital in the past 15 years. Peripheral vascular obstruction due to primary arterial disease would appear to be a significant cause of limb gangrene in childhood, as illustrated by the following case reports.

Case 1

This infant, a male, was born on 1 January 1965 after a normal pregnancy and delivery. His parents and elder brother were healthy. He was well until the age of 5 months, when he developed a transient morbilliform rash on the limbs, followed by a febrile illness which was associated with extreme pallor and coldness of all four extremities. Within two days the right hand and forearm had become gangrenous, with a sloughing ulcer on the flexor aspect of the wrist.

He was first seen at this hospital on the third day of his illness, when he looked pale and ill, and had a faint, blotchy rash over the upper abdomen and chest. In addition to the gangrene of the right arm the other limbs were cold, with colour changes varying from pallor to cyanosis. Both axillary and femoral pulses were present, but no distal pulses were palpable. The blood pressure was unobtainable except in the right leg, where it was 130/95 mm. Hg. Physical examination was otherwise normal.

Laboratory Investigations.—Hb 7.8 g./100 ml. (54%); W.B.C. 54,000/ cu. mm. (polymorphonuclear cells 80%); E.S.R. 59 mm./ hour. Serum gammaglobulins: gamma G 640 mg./100 ml., gamma M 175% of standard normal serum, gamma A 31% of standard normal serum. Sheep-cell agglutination: titre of 1 in 8. Blood cultures: no growth obtained from three specimens. E.C.G.: left ventricular hypertrophy. Chest *x*-ray examination: heart size normal, lungs clear. C.S.F.: protein 15 mg./100 ml., sugar 72 mg., culture sterile. Urine: normal microscopy and culture. Urine chromatography: lactose 200 mg./100 ml., sucrose 200 mg./100 ml.; raised excretion of tyrosine, phenylalanine, glutamine, threonine, serine, alanine. Other investigations, which included lupus erythematosus preparations, Wassermann reactions, cold agglutinins, macroglobulins, and heavy-metal estimations, were all negative.

Treatment

Initially he received a transfusion of 210 ml. of whole blood, and treatment was started with prednisone 40 mg./day. Antibiotic cover was provided with cloxacillin 500 mg. and ampicillin 250 mg. daily. In order to improve the peripheral circulation he was given 240 ml. of rheomacrodex intravenously, but in spite of this the changes in the left foot progressed to gangrene. An effort to halt this process by means of hyperbaric oxygen was then made.[1] During the next five days he received a total of 40 hours' compression at two and a half atmospheres, this being given for periods of two hours at a time. During treatment in the oxygen chamber striking colour changes occurred in the limbs, the cyanosis being replaced by a bright pink colour. Such improvement, however, was variable and not maintained between treatment periods.

One week after admission his condition deteriorated sharply with the appearance of tachycardia, central cyanosis, and abdominal distension. The distension was an entirely new development, and did not appear to coincide with the changes of atmospheric pressure to which he had been subjected.

Plain *x*-ray films in the erect position showed a large pneumoperitoneum, and accordingly an emergency operation was undertaken with a provisional diagnosis of gangrenous intestinal perforation.

Laparotomy was carried out by one of us (G. F.) on 4 June. On opening the peritoneum there was a puff of gas under pressure. The proximal loop of jejunum had become gangrenous and there were three perforations in it. The total length of gangrenous bowel was some 8 in. (20 cm.), beginning 1½ in. (3.8 cm.) distal to the duodenal-jejunal flexure. The affected portion was resected and a two-layer anastomosis performed.

Postoperatively the patient progressed well for seven days, then he again became acutely ill with abdominal distension and signs of peritonitis. Reoperation was undertaken.

At laparotomy (G. F.) on 11 June the skin stitches were removed. There was no evidence of healing whatsoever in the transverse abdominal wound. The wound parted at the touch of a finger, and several loops of bowel were found to be adherent to the back of the wound. The bowel proximal to this was dilated and part of the original anastomosis had given way. There was no sign of healing at the site of the anastomosis. A swab was taken from the peritoneum, and the bowel was decompressed from below. The edges of the anastomosis were then freshened, and a new anastomosis was performed.

It was decided that no attempt should be made at this stage to deal surgically with the peripheral gangrene, but to wait until the lines of demarcation between viable and gangrenous tissue became more definite. In view of the delayed healing of the abdominal wall the high dose of prednisone administered was gradually reduced. The reopened laparotomy wound healed cleanly without further incident. Four weeks after the onset of the illness

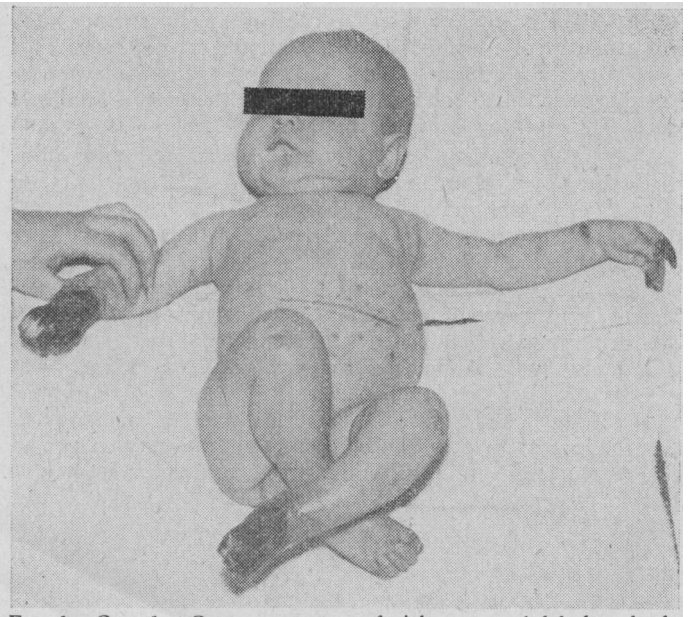

FIG. 1.—Case 1. Gangrenous areas of right arm and left leg clearly demarcated.

* Medical Registrar, Hospital for Sick Children, Great Ormond Street, London W.C.1. Now Honorary Lecturer, Makerere Medical School, Kampala, Uganda.
† House physician, Hospital for Sick Children, Great Ormond Street, London W.C.1.
‡ Resident Assistant Surgeon, Hospital for Sick Children, Great Ormond Street, London W.C.1.

[1] The hyperbaric oxygen chamber was kindly supplied by Oxygenaire.

the immunosuppressive agent azathioprine (Imuran), 5 mg./kg. daily, was started, as it seemed possible that autoimmune mechanisms might be responsible for the gangrene. After one week the dose was halved to 2.5 mg./kg. daily. Two weeks later the patient's general condition had improved, and the ischaemic changes in the limbs were no longer progressing. When the gangrenous areas of the right arm and left leg were clearly demarcated (Fig. 1) amputations were performed as two-stage procedures. At the initial operation the gangrenous part was removed and debridement of the wound was undertaken. In the second stage the apex of the stump was fashioned to fit a prosthesis and the wound edges were sutured. No attempt was made to amputate through the "classical" amputation sites, maximum remaining length being the primary consideration. Both stumps healed by first intention (Fig. 2).

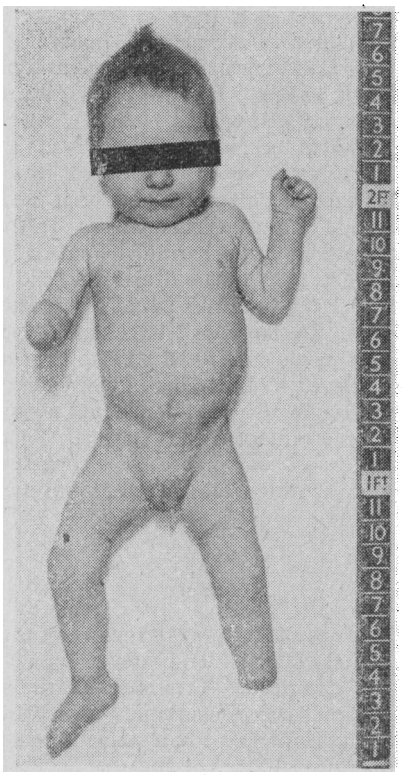

FIG. 2.—Case 1. Both stumps healed.

At the time of writing the patient's condition was satisfactory, and the right arm and left leg had been fitted with prostheses. Pulsations were palpable in the peripheral arteries, and the skin circulation was adequate. He had developed normally both physically and mentally. Repeated electrocardiographs had shown persistence of the left ventricular hypertrophy, but a systolic murmur that had been noted one month after admission had now disappeared. There had been no evidence of involvement of any other system. At the time of admission urine chromatography showed a generalized amino-aciduria and a raised excretion of lactose and sucrose. These findings were unexplained, but may have been due to absorption of toxic substances from the gangrenous areas. Five weeks after admission urinary chromatogram was normal.

He was maintained on azathioprine 2.5 mg./kg. daily for six months, and then, after reduction of the dose over a period of four weeks, the drug was stopped. The total dose he received was 2,930 mg. Because azathioprine decreases resistance to infection, he was kept isolated from other children in the ward and remained free of intercurrent illness. Frequent blood counts were performed to detect the development of agranulocytosis or anaemia, but no cytotoxic effects of the drug were noted. There has been no deterioration in his condition since discontinuing the drug.

Biopsies of skin, muscle, and intestine were taken at both laparotomies and amputations. Histology of the intestine showed oedema, congestion, and infarction, with inflammatory cell infiltration and a fibrinous peritonitis. The amputation specimens showed necrotic muscle and connective tissue, occlusions of vessels by thrombosis, and polymorphonuclear infiltration. None of the many specimens examined histologically showed the pathognomonic lesions of arteritis. Nevertheless, the clinical features of the illness suggest a collagen disease involving major arteries—for example, polyarteritis nodosa.

Case 2

This female infant was born in 1959 after a normal pregnancy and delivery. Her family history was normal. Her illness started at the age of 4 days, and progressed with transient remissions until her death from complications after cervical sympathectomy at 14 months of age. She had Raynaud's phenomenon of hands and feet, nose tip, and ear lobes. Blistering and secondary infection occurred, and were followed by gangrene and sloughing of the fingers and toes. Peripheral pulses, including the digital arteries of the gangrenous fingers, were palpable. She appeared to have an increased susceptibility to infections, with severe pustular skin lesions and a staphylococcal septicaemia. Impaired healing ability was suggested by wound breakdown after lumbar sympathectomy. Treatment included antibiotics, vasodilator drugs, and lumbar and cervical sympathectomy. A two-week course of prednisone 50 mg. daily was given.

A renal biopsy was performed after an episode of haematuria, proteinuria, and transient hypertension. The biopsy specimen showed changes reported as "focal glomerulonephritis," and the renal and muscle arterioles showed medial hypertrophy suggestive of hypertension, but there was no evidence of primary arteritis. Permission for necropsy was not obtained.

Case 3

This male infant, the third child of first cousins, was born in 1951 after a normal pregnancy and delivery. His eldest brother had died at the age of 15 months, after an obscure illness, with anaemia, eosinophilia, and eczema. The patient became ill at the age of 2 months, and despite transient remissions deteriorated until his sudden death from heart failure at the age of 3 years. During his illness he developed gangrene of both feet, requiring amputation. He had skin involvement with periorbital and limb oedema, episodes of widespread eczema, and indurated plaques with necrotic centres on the trunk and limbs. Severe, persistent steatorrhoea was found to be due to pancreatic deficiency. Transient episodes of anaemia, neutropenia, and thrombocytopenia resulted in rectal bleeding, epistaxes, microscopical haematuria, and spontaneous bruising. A staphylococcal empyema responded to antibiotics, but later, in the absence of detectable infection, he developed fever controlled only by steroids. Pancreatin, blood transfusion, antibiotics, and a 10-week course of cortisone 100 mg. daily were given.

Examination of postmortem specimens showed that the left coronary artery was occluded, and there were histological changes characteristic of polyarteritis nodosa. The posterior tibial, dorsalis pedis, and gastrocnemius muscle arteries were similarly affected. There was eosinophilic infiltration of a purpuric skin nodule.

Case 4

This patient was born in 1942. Her illness began at the age of 5 years and ended nine months later with a spontaneous and lasting remission. During her illness she had cyanosis progressing to gangrene and sloughing of the tip of the nose and fingers. She had facial oedema, a macular rash on the face and limbs, and indurated necrotic skin nodules. There was arthritis with effusion in the knees. Fever, anaemia, tachycardia, and transient heart failure also occured. Her E.S.R. varied between 60 and 75 mm./hour, and she had a polymorphonuclear leucocytosis without eosinophilia. Antibiotics were the only treatment given. Biopsy of a skin nodule showed necrosis of the skin surface. The vessels were involved by gross endothelial proliferation and showed changes characteristic of polyarteritis nodosa.

Discussion

Since the advent of chemotherapy for infections, and parenteral fluid administration in dehydration, peripheral gangrene has become rare in infancy. In congenital heart

disease both embolism and polycythaemia may contribute to gangrene due to vascular occlusion. Cryoglobulins and circulating toxins such as ergot may also, on rare occasions, cause peripheral gangrene.

Gross (1945) collected 41 cases of neonatal peripheral gangrene from the literature and added six of his own. All but two of these patients were under 5 weeks old. Though in some of the babies predisposing factors were present, which included sepsis, trauma, and congenital heart disease, in many the cause of the arterial occlusion remained obscure. Aird (1957) described four cases of gangrene starting a few days after birth. No histology was available, but on the basis of the clinical features he suggested the term "arteritis neonatorum." All four patients survived, but one of them developed progressive arterial insufficiency at puberty. A similar latent interval occurred in a 36-year-old woman reported by Messent (1954). As a neonate she had gangrene requiring amputation of four toes. She was well until late childhood, when she developed Raynaud's phenomenon, and as a young adult she showed evidence of occlusive arterial disease. Of surgical importance is the fact that infants with peripheral gangrene may develop similar lesions of the viscera requiring urgent operation (Case 1).

Cases of fulminating anaphylactoid purpura leading to gangrene were described by Turin *et al.* (1959), Crawford and Riddler (1959), Dodge *et al.* (1963). All these children had a feverish infection of the upper respiratory tract preceding their illness, which was therefore thought to be an expression of bacterial hypersensitivity. The same mechanism may also have accounted for the occurrence of gangrene after scarlet fever in 17 patients discussed by Hoyne and Smollar (1941).

In adults, gangrene has been described in many of the separate syndromes grouped together as collagen diseases, but it is rare in these conditions in children. There are no reported cases of gangrene in Still's disease, though this complication occurs in adult rheumatoid arthritis (Bywaters, 1957). In disseminated lupus erythematosus gangrene of the extremities has been reported in adults by Dubois and Arterberry (1962) and Schoch (1962). The youngest patient, reported by Keat and Shore (1958), was a 14-year-old girl who developed Raynaud's phenomenon with gangrene of the legs, and who died soon after amputation.

Barnard and Burbury (1934) were the first to report gangrene due to polyarteritis nodosa. Their patient, an 8-year-old girl, had multiple visceral lesions as well as involvement of the fingers and toes. Visceral involvement does not always occur in polyarteritis nodosa. Neale (1949) described the case of an 8-year-old boy who died with gangrene confined to the skin, subcutaneous tissues, and muscles. He mentioned two similar patients reported by Veran (1945) and Galan (1945), both of whom eventually recovered. In a recent review of 20 patients with polyarteritis nodosa in infancy Roberts and Fetterman (1963) found two with gangrene of the extremities. None of the 20 infants survived. Even at necropsy it was often difficult to make the diagnosis, as the characteristic lesions were sparse and sometimes limited to the coronary arteries. However, the clinical features formed a fairly constant syndrome which included fever, rashes, rhinitis, proteinuria, and hypertension. Cardiomegaly was present both electrocardiographically and radiologically. The four cases we have reported showed many of these features, and though there is only histological proof in two it seems likely that the gangrene was due to polyarteritis nodosa in all four.

Various forms of treatment for gangrene have been employed recently. Hyperbaric oxygen was used by Saltzman (1965) in a 19-month-old child with extensive purpura gangrenosa who was given eight five-hour treatments at two atmospheres pressure. Immediate improvement in the colour of the limbs occurred during treatments, and the patient eventually recovered with the loss of only a small area of skin. Stansell (1965) has studied the histopathological effects of hyperbaric oxygen in arteriosclerotic patients with gangrene. During this study it became evident that the pathologist was able to decide from the amputation specimens alone whether or not the patient had received preoperative hyperbaric oxygen. When treatment had been given, the line of demarcation was more clear-cut, and there was increased vascular proliferation with reduced inflammatory infiltration at the margin of the gangrenous zone. Stansell suggests that during periods of treatment enough oxygen reaches the marginal tissues to prevent hypoxic capillary damage and thus reduces the extent of the gangrene to a minimum. Objective assessment was difficult in our patient (Case 1), but in the acute stage of his illness hyperbaric oxygen treatment may have been of benefit.

On the assumption that polyarteritis nodosa represents an abnormal hypersensitivity response, treatment with immunosuppressive drugs is logical. Corticosteroids, by reducing the damaging effects of antigen-antibody contact on cell surfaces, have been the most successful agents used till recently. Chemical immunosuppressive drugs derived from mercaptopurine (including azathioprine) have now been used with some success in systemic lupus erythematosus (Dameshek and Schwartz, 1960), autoimmune haemolytic anaemia (Schwartz and Dameshek, 1962), a rheumatoid arthritis, and scleroderma (Eisen *et al.*, 1962). We have not found a report of its use in polyarteritis nodosa. In our Case 1 large doses of steroids were ineffective and may have contributed both to the intestinal perforation and the delayed healing which followed surgical repair. Definite improvement in his condition began about two weeks after treatment with azathioprine was started. Though no firm conclusion can be drawn, our observations suggest that azathioprine has arrested the progress of the disease in our patient.

Summary

As a result of therapeutic advances gangrene of the extremities has become rare in childhood. The cases of four children with this condition are described. Treatment of the most recent patient included hyperbaric oxygen and azathioprine (Imuran). The presumptive diagnosis in all four patients was polyarteritis nodosa. The literature is reviewed and the diagnosis and treatment are discussed.

We are grateful to the members of the medical staff at the Hospital for Sick Children for permission to examine the records of patients under their care, and especially to Professor O. H. Wolff for his helpful advice and encouragement in the preparation of this paper.

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