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NON-CLOSTRIDIAL GAS INFECTIONS IN DIABETES MELLITUS

BY

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The abnormal susceptibility of diabetics to infection is well known. It may result in a rapidly spreading pyogenic infection starting from a trivial local lesion, sometimes caused by organisms which usually are non-invasive and comparatively non-virulent. Occasionally such an infection may be accompanied by marked production of gas in the tissues, and the condition may simulate clostridial gas-gangrene.

The occurrence of "gas infections" in diabetes was first recorded by Chiari in 1893; he described the formation of gas due to the colon bacillus in the gangrenous tissues of the leg of a diabetic. He believed that the diabetic state favoured the production of gas in the soft tissues. Hirschmann and Linderthal (1899) reported a further case of a diabetic clinically thought to have gas-gangrene, but on culture *Escherichia coli*, *Streptococcus pyogenes*, and an unidentifiable rod were the only organisms obtained; only the coliform bacillus produced gas when grown in culture media. Warren (1938) described the cases of two diabetics with a clinical

diagnosis of gas-gangrene from whom the only organisms obtained on repeated aerobic and anaerobic culture were *E. coli* and staphylococci. Gillies (1941) described four diabetics with infections due to the colon bacillus, alone or in association with other organisms. One of these cases had an infection of the urinary tract with perirenal gas; the other three had gas in the subcutaneous tissues of the lower extremity.

Spring and Kahn (1951) reported one case of their own, and two further cases from the records of the Bronx Hospital from 1932 to 1950, of non-clostridial gas infections in diabetics. The organisms obtained on culture in two of these cases was *E. coli*, but in the third case smear showed Gram-positive cocci, Gram-negative bacilli, and Gram-positive bacilli, with no growth on culture. Altmeier and Culbertson (1948) listed five cases of "non-clostridial crepitant cellulitis" from the literature and recorded 12 further cases, at least two of which were diabetics. The organisms most commonly present included: *aerobic*—non-haemolytic streptococci and *E. coli*; and *anaerobic*—*Bacterium melanogenicum* and anaerobic streptococci.

This paper describes the cases of four elderly patients who developed rapidly spreading non-clostridial "gas infections" of the leg. All four were diabetics of long standing with peripheral neuropathy and vascular disease. The infections in Cases 1 and 2 were at first thought to be examples of clostridial gas-gangrene.

These cases are of interest for three reasons. First, owing to the absence of much pain the diagnosis was not suspected until the infection was far advanced. Second, in one of the cases deterioration continued despite treatment with antibiotics to which the organisms were subsequently shown to be sensitive. Finally, early diagnosis from clostridial gas-infection was difficult and led to uncertainty regarding the best method of treatment.

Case 1

A retired typist aged 60, whose diabetes had been discovered in 1952, had been controlled on soluble insulin by her own doctor. She had previously been admitted to another hospital in November, 1958, with multiple abscesses of both thighs, one of which required surgical drainage. Culture of swabs from these abscesses yielded a coagulase-positive *Staphylococcus aureus*, which was reported as resistant to several antibiotics. Treatment with a course of tetracycline was carried out with good response, and eventually she was discharged home, having been re-established on insulin zinc suspension. She was noted at this time to have evidence of neuropathy and vascular disease.

On February 22, 1959, she was admitted as an emergency case with a deep discharging abscess of the right buttock that had been present for some weeks. There was associated oedema of the upper right thigh, which was 2½ in. (6.3 cm.) greater in circumference than the left. There was no tenderness of the thigh. A type 80 *Staph. aureus*, resistant to penicillin, streptomycin, and tetracycline, was cultured from the abscess, and treatment with chloramphenicol and erythromycin 0.5 g. statim then 0.25 g. eight-hourly of each, was begun.

Her condition deteriorated and on February 26 she complained of pain in the right leg. Examination revealed evidence of gas in the subcutaneous tissues with marked crepitation extending down the leg to the posterior aspect of the right ankle. Clostridial infection was diagnosed. In view of this she was given 5 mega units of crystalline penicillin and taken to the theatre. At operation multiple incisions confirmed the presence of large quantities of watery pus and gas, mainly in the subcutaneous tissues but also beneath the deep fascia and in between the muscle bundles.

The muscles appeared viable and contracted, and bled on biopsy. Aerobic and anaerobic cultures of three separate specimens of pus and two specimens of muscle revealed only *Str. faecalis* and bacteroides. The latter, which was present in very large numbers, was later identified as *Bacteroides varius* (Bergey, 1948). Both organisms were sensitive to chloramphenicol and erythromycin and resistant to penicillin and streptomycin. Section of muscle from the thigh showed healthy fibres with large numbers of Gram-negative bacilli and a few Gram-positive cocci lying between the bundles.

The patient's condition continued to deteriorate, and on March 5 cultures of pus from the wounds yielded klebsiellae, *Bacteroides varius*, and yeasts. On March 10, in view of spreading gangrene of the leg, a high above-knee amputation was carried out. The stump became grossly infected with *Bacteroides varius*, *Pseudomonas pyocyanea*, klebsiellae, and a few colonies of a clostridium. Because of the presence of the last-mentioned organism, 40,000 units of anti-gas-gangrene serum was given intravenously and crystalline penicillin 2 mega units six-hourly was started—both unnecessary measures because the clostridium was later proved to be *Clostridium sporogenes*, a non-pathogen. The patient died on March 19. Post-mortem examination revealed evidence of septicaemia and acute bacterial endocarditis caused by *Ps. pyocyanea*.

Case 2

A housewife aged 60 had been a known diabetic for 16 years. For the past four years she had been noted as showing evidence of peripheral neuropathy, retinopathy, and a chronic septic lesion on the left fifth toe for which surgery had been advised and refused.

On admission to hospital on March 9, 1959, there was a foul-smelling, necrotic, discharging area on the sole of the right foot, with a smaller lesion on the left foot. She showed clinical evidence of widespread vascular disease and some renal damage as reflected by a blood non-protein nitrogen of 50 mg./100 ml. She was stabilized on insulin with reasonably good control of her diabetes as judged by urine sugar analysis. The foot lesions were treated with bed rest and local toilet.

Swabs taken on admission from the ulcers of both feet yielded *E. coli* and a non-haemolytic aerobic streptococcus which was sensitive to penicillin. She was given an eight-day course of crystalline penicillin, 500,000 units b.d. intramuscularly.

Her condition deteriorated. Her legs and feet were examined daily, and on March 25 the right calf was found to be swollen, with well-marked crepitation spreading up the right calf from the gangrenous patch on the foot. A diagnosis of "gas-gangrene" was made. She was given 1 mega unit of crystalline penicillin and taken to the theatre that afternoon, where an above-knee amputation was carried out. However, she collapsed and died at the end of the operation.

At the time of operation material for culture was obtained from the ulcerated area on the foot and by direct swab and muscle biopsy through a clean incision made in the calf some 12–13 in. (30.5 to 33 cm.) from the original lesion. From all these materials the only organisms obtained on culture were micrococci and *E. coli*. The latter were present in very large numbers in the calf.

Post-mortem examination showed the cause of death to be *E. coli* septicaemia and septic infarction of the spleen with perisplenic abscess.

Case 3

A railway portress aged 50, a known diabetic for nine years, was poorly controlled on insulin. She was admitted to hospital on May 11, 1959, in coma as an emergency case. Two years previously she had been found to have evidence of diabetic retinopathy, peripheral neuropathy, and vascular

disease. Three months before this admission she had developed a right hemiplegia after a cerebrovascular accident.

On admission she was stuporous, with a raised respiratory rate, a temperature of 99.5° F. (37.6° C.), and signs of pneumonia and pleurisy. There was an ulcer on the posterior aspect of the right ankle. The diabetes was fairly well controlled with a six-hourly regime of insulin and glucose, and the infection was treated with intramuscular injection of crystalline penicillin 1 mega unit, followed by 0.5 mega unit six-hourly. Despite this she continued to run a temperature of 101–102° F. (38.3–38.9° C.), her condition deteriorated, and she died four days after admission. At necropsy one and a quarter hours after death an abscess was found which extended from the ankle to the middle of the right thigh. It contained foul-smelling watery pus and gas. Crepitus was detected in the thigh, but it is not certain that this was present before death.

Aerobic and anaerobic cultures of specimens of pus obtained from the subcutaneous tissues at three different sites in the leg and thigh, and of biopsies of muscle from the thigh and of the original ulcer, yielded a profuse growth of *E. coli* with a moderate growth of an anaerobic streptococcus sensitive to penicillin.

Additional findings at necropsy were old myocardial and cerebral infarction with recent bronchopneumonia.

Case 4

A retired European-Indian railway worker aged 63 had been a diabetic for 16 years. He had not taken insulin, despite advice, until his attendance at a clinic in this hospital a year prior to death. On examination at this time he was noted to have neuropathy, vascular disease, retinopathy, and albuminuria; there was a small ulcer on his right toe and his electrocardiogram showed a right bundle-branch block. During his follow-up attendances the ulcer gradually increased in size and a further lesion developed on his left heel despite good control of his diabetes on insulin as judged by urine sugar analysis. In view of these ulcers he was admitted to hospital for conservative treatment on May 20, 1959, but there was little improvement, and he was discharged home on August 1.

On September 1 he was readmitted as an emergency case. He was drowsy, with uncontrolled diabetes, a raised blood non-protein nitrogen, and some congestive cardiac failure. The diabetes was brought under control with insulin and his condition slightly improved.

Routine examination of the leg on September 10 showed crepitation in the left calf, spreading upwards from the lesion on the left heel. Lateral x-ray films demonstrated gas in the soft tissues around the heel and in the lower part of the leg. A swab taken from the heel lesion at the time grew a heavy growth of *E. coli* sensitive to streptomycin, chloramphenicol, and tetracycline. He was started on crystalline penicillin, 1 mega unit b.d., and chloramphenicol, 250 mg. six-hourly, and taken to the theatre, where mid-thigh amputation was carried out. Culture of calf muscle, taken some 8 in. (20 cm.) from the heel lesion, produced a good growth of *E. coli*. After amputation his condition somewhat improved for the next 10 days. However, it then deteriorated again, and he developed severe ischaemic pain in the legs, thrombosis of the radial artery, and a heavy proteus urinary infection. He developed a terminal bronchopneumonia and died on October 3.

Discussion

The true incidence of non-clostridial "gas infection" is difficult to assess. Small quantities of gas are not infrequently found in intra-abdominal abscesses caused by intestinal organisms such as coliform bacilli, streptococci, and bacteroides. The occurrence of a virulent rapidly spreading infection in a limb, accompanied by the production of large quantities of gas due to non-

clostridial infection, would appear to be most unusual, and, except in diabetes mellitus, is outside our experience.

The combination of vascular disease and neuropathy with severe diabetes evidently can so lower the patient's resistance to infection that organisms which normally possess little virulence can very rapidly invade the limb, starting from a small local lesion such as an ulcer on the foot. It is possible that the increased glucose in the tissue may enhance the gas-production by organisms such as *E. coli*. The rapid multiplication of the bacteria may result in the production of gas in sufficient quantity to be clinically apparent. The ability of this bacillus to produce gas in culture media containing carbohydrate is well known, and a parallel exists in the pneumaturia of diabetes, which has been reviewed by Foord *et al.* (1956), who have suggested a similar mechanism. The accumulation of gas in the affected limb may also be enhanced by the impairment of circulation delaying absorption.

Spreading infection in the limb of a diabetic, whether gas be present or not, requires prompt treatment, and early recognition of the condition is essential. The diabetic neuropathy and possibly the toxæmia appear to minimize the pain usually experienced in acute infections of the limb and also the awareness of other new symptoms; the limb must be repeatedly and carefully examined.

In Case 1, oedema of the thigh without tenderness was the first sign of spread. The spread of crepitus in infection commonly leads to the diagnosis of a clostridial infection. The clinical picture in these cases, however, is more in keeping with that described by MacLennan (1943) of the similar anaerobic streptococcal cellulitis and myositis seen in the Middle East Campaign. The tempo of the infection is slower than that of clostridial infection. Pain is not so marked, toxæmia is slower in onset, and the temperature and pulse are not as elevated. The diagnosis is confirmed at operation. The gas appears maximal in the fascial layers, and the muscle on biopsy is contractile, and, apart from some oedema, is normal in colour. Immediate search for organisms in pus and muscle should be made. Treatment with antibiotics was disappointing in the one case (Case 1) where the organisms were shown to be sensitive by *in vitro* methods to the antibiotics used. Choice of antibiotics may be complicated by uncertainty of the causative organism, as various bacteria may be cultured from the local lesion. In view of this it may be justifiable to give large doses of more than one antibiotic. Early diagnosis and surgery would appear to be essential for success. In Case 4 it was felt that some measure of success had been achieved, as the ultimate cause of death was unrelated to the initial infection.

Summary

Four fatal cases of non-clostridial gas-infections in diabetics are described and the literature is briefly reviewed.

The organisms cultured from these cases were: Case 1, *Str. faecalis* and *Bacteroides varius*; Case 2, micrococci and *E. coli*; Case 3, *E. coli* and anaerobic streptococci; Case 4, *E. coli*.

The effect of diabetes on the production of large quantities of gas and the enhanced invasiveness of organisms which usually are not markedly gas-forming or invasive is discussed.

The insidious onset of pain is noted and the differential diagnosis from clostridial gas-gangrene is discussed. Emphasis is put on the slower tempo and the findings at operation.

Successful treatment is based on early diagnosis.

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ARGENTAFFINOMA OF THE LUNG WITH CARCINOID SYNDROME

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Malignant carcinoid of the small intestine producing a peculiar complex of symptoms known as the carcinoid syndrome is now well recognized, but a similar condition arising in the lung is rare enough to warrant this report, since only six similar cases have so far been published.

The first description of carcinoid tumours was by Lubarsch (1888), followed by Oberndorfer (1907). In 1914 attention was drawn to the possibility that the chromaffin cells of these tumours could constitute an endocrine reservoir, and Cassidy (1930) reported the case of a young man with an abdominal tumour and hepatic metastases, with flushing of the face and a systolic murmur due to pulmonary stenosis. However, twenty years elapsed before a relationship was established between carcinoid tumours and a certain endocrine symptom-complex. In 1952 enteramine, or serotonin, the specific hormone of enterochromaffin cells, had been identified as 5-hydroxytryptamine, and in the next year serotonin was found in carcinoid tumours. In 1955 the degradation product of serotonin, 5-hydroxy-indole acetic acid, was found in the urine of patients with carcinoid tumours, since when the syndrome of the functioning carcinoid has become widely recognized.

The primary lesion is usually in the gastro-intestinal tract, in which event there are invariably hepatic metastases in those cases presenting the carcinoid syndrome. In a series of 50 cases of ileal carcinoid reviewed by Thorson (1958), 10 had an associated carcinoid syndrome and all of these had hepatic metastases.