osteoporosis of senile type; the age and sex of the other patients suggest that these may be important underlying factors.

The onset of sudden pain in rheumatoid arthritis may lead one to suspect such a fracture, although initially the radiograph may be normal, as the fractures often seem to develop slowly. Some features of these fractures are discussed.

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STAPHYLOCOCCAL SEPTICAEMIA WITH PYOARTHROSIS IN RHEUMATOID ARTHRITIS

REPORT OF THREE FATAL CASES

BY

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Although occasional instances of staphylococcal septicaemia occurring in patients with rheumatoid arthritis had been described earlier, Kellgren *et al.* (1958) were the first to emphasize the importance of this complication. They described 12 cases of rheumatoid arthritis in which severe bacterial infection of connective-tissue structures occurred. In nine cases this was predominantly a suppurative arthritis—often polyarticular and resembling an exacerbation of the established rheumatoid arthritis. The infecting organisms were coliform in two cases and staphylococci in 10. The latter were resistant to penicillin in all but two cases. Despite this detailed study staphylococcal septicaemia with pyoarthrosis still lacks sufficiently wide recognition as a dangerous complication of rheumatoid arthritis, and the current editions of standard textbooks do not refer to it (Hollander, 1960; Copeman, 1955). For this reason it seemed appropriate to present the clinical and pathological features of three cases of rheumatoid arthritis in which fatal staphylococcal infection with pyoarthrosis occurred.

Case 1

A man aged 68 had suffered from rheumatoid arthritis (sheep-cell agglutination test (S.C.A.T.) 8 to 128) for 20 years with chronic ulcers on the legs and feet. Past therapy included sodium aurothiomalate and prednisolone 10 mg. daily, the latter from February, 1959.

He was admitted to Stoke Mandeville Hospital on February 29, 1960, with a productive cough and breathlessness for several weeks. He was in poor general health with remittent fever (up to 40° C.), a haemoglobin of 3 g./100 ml., marked rheumatoid changes, particularly in the elbows, hands, wrists, knees, and ankles, and unhealed ulcers on the left leg. Severe anaemia with an undiagnosed fever in a patient with rheumatoid arthritis was diagnosed.

Treatment was initially with transfusions and penicillin, and later with tetracyclines, streptomycin, and erythromycin in turn. Prednisolone was omitted on admission but was restarted on March 10, and then steroids were continued, at times in increased dosage, until death.

On March 19 he suddenly developed a parotid abscess with a temperature of 40° C. The leucocyte count was 27,000, with neutrophilia, and culture of sputum grew *Staphylococcus aureus* sensitive to chloramphenicol and resistant to penicillin, streptomycin, tetracyclines, "evramycin," and oleandomycin. Chloramphenicol was started with a reduction in fever and general improvement.

On April 24 he became disorientated and pyrexial, with moist sounds in the lung bases. Culture of sputum continued to grow *Staph. aureus*. Chloramphenicol was continued, and evramycin and tetracyclines were also given. Initially his general condition improved but later it deteriorated. The knees became more swollen, and fluctuant swellings appeared over the sacrum and on the dorsum of the left hand on May 6. He died on May 12, 73 days after admission to hospital.

Post-mortem Findings.—The body was that of a tall lean elderly man. There were many small areas of partially necrotic skin over the sacrum and buttocks with one small area of ulceration. Internally there were two large chronic basal empyemata filled with thick pus. The lungs showed only severe oedema and congestion. The heart showed left ventricular hypertrophy but no other gross or microscopical changes. The liver showed severe centrilobular congestion and necrosis. The spleen was a little enlarged with a pale soft cut surface showing a large area of old infarction. Histology revealed areas of recent infarction and numerous pyaemic abscesses containing large clumps of Gram-positive cocci. The kidneys were slightly reduced in size with granular scarred external surfaces. The renal parenchyma was pale with blurring of the cortico-medullary margins and irregular loss of the cortical tissue. Histology showed mild chronic pyelonephritis and a few pyaemic abscesses in the medulla. In the skeletal system the disk space between the second and third lumbar vertebrae was completely destroyed, being replaced by a cavity containing thick pus communicating with a large irregular paravertebral abscess under the left psoas muscle. On being opened both knee-joints showed severe rheumatoid arthritis, the left joint cavity containing purulent fluid. Histology revealed an acute purulent exudate superimposed upon the changes of subacute rheumatoid arthritis. Cultures taken at necropsy from the left empyema, left knee-joint, paravertebral abscess, and sacral ulcer all grew profuse *Staph. aureus* showing the same antibiotic sensitivities as the organism grown from the sputum.

Comment.—This was a case of multiple deep-seated chronic staphylococcal abscesses with pathological evidence of terminal staphylococcal septicaemia and pyoarthrosis. The source of infection was either sacral ulcer or the sputum. Steroid treatment probably prevented a more acute clinical reaction, and the diagnosis was not suspected until six days before death. Only the knee-joints were opened at necropsy as the occurrence of multiple pyoarthroses with staphylococcal infections was not appreciated at this time.

Case 2

A woman aged 62 had suffered from rheumatoid arthritis (S.C.A.T. 2,048 to 4,096) for 20 years, involving both hands, both wrists, both elbows, the metatarsophalangeal joints of the left foot, both knees, and the left hip. She had multiple flexor tendon nodules in both hands and was in poor general health with anaemia. Previous treatment included a course of sodium aurothiomalate, phenylbutazone, various forms of physiotherapy, splintage, and intra-articular hydrocortisone (last injection one year before death).

She held her own until May, 1961, when she developed severe pain in the left hip over the course of a week, with difficulty in sleeping. The other joints were also more painful. The movements of the left hip were restricted and an x-ray film was taken of this joint to exclude fracture.

She was admitted to Stoke Mandeville Hospital on June 2, in a semiconscious state with delirium, gross dehydration, pyrexia of 39° C., icteric conjunctiva and skin, a pulse of 120 a minute, and blood-pressure of 150/90 mm. Hg. She had a large pressure sore over the sacrum 3 in. (7.5 cm.) in diameter with a slough in its base. Her haemoglobin was 16.1 g./100 ml., blood urea 295 mg./100 ml., and leucocyte count 13,500 with neutrophilia. She passed no urine on the day of admission, and on catheterization only 100 ml. was obtained. Cultures of blood and urine grew *Staph. aureus* sensitive to penicillin, streptomycin, tetracyclines, chloramphenicol, and neomycin. An ante-mortem diagnosis of oliguric renal failure and septicaemia was made and she was treated with tetracycline and fluids. She died the next day, June 3.

Post-mortem Findings.—The body was that of a thin old woman with a large pressure sore over the sacrum 3 in. (7.5 cm.) in diameter. Internally the thoracic organs showed no remarkable macroscopic changes. Microscopy of the lungs, however, revealed occasional small pyaemic abscesses containing large clumps of Gram-positive cocci. The spleen was normal macroscopically, but microscopy revealed small areas of necrosis composed of disintegrating polymorphs with no surrounding inflammatory response. The kidneys were normal in size, the capsules stripped with difficulty, leaving a granular surface with multiple small subcortical cysts. There were a few small calculi in the calices and the cortico-medullary demarcation was blurred. Histology showed moderate focal chronic pyelonephritis with numerous small congenital and acquired cysts. The tubules showed a severe degree of cloudy swelling but there was no evidence of tubular necrosis or pyaemia. Both knee-joints, the left hip-joint, the right tarsal joints, and the left sternoclavicular joint were opened and all contained large amounts of thin anchovy-coloured pus. Culture of pus from the knee- and hip-joints grew profuse *Staph. aureus* with the same antibiotic sensitivities as the organism grown from the blood and urine. Histology showed the changes of subacute rheumatoid arthritis with a recent superficial purulent exudate composed of necrotic pus cells and Gram-positive cocci.

Comment.—This patient, not on steroid therapy, was admitted in *extremis*. Although the diagnosis of staphylococcal septicaemia was made during life, it was too late for any effective treatment. One month before death she had had acute pain in the left hip. In retrospect this was probably a pyoarthrosis (at necropsy

the left hip contained pus). Although she was in poor general health at that time there was nothing more to suggest septicaemia. This case, though one of clinically manifest septicaemia, gave no clear indications of pyoarthrosis during life. Failure to examine the joints at necropsy would have left the existence of pyoarthroses undiagnosed. The striking post-mortem findings were multiple acute staphylococcal pyoarthroses with only very slight histological evidence of pyaemia. This case illustrates the susceptibility of rheumatoid joints to become infected in staphylococcal septicaemia.

Case 3

A man aged 59 had suffered from severe rheumatoid arthritis (S.C.A.T. 512 to 8,192) for 10 years, which involved the hands, wrists, elbows, shoulders, knees, ankles, and feet. He also had subcutaneous nodules and was in poor general health. He was treated with sodium aurothiomalate, phenylbutazone, splints, intra-articular steroids, manipulation of the left foot, and operations on the feet. Prednisolone 5 mg. daily was started in May, 1960, and this was increased to 7.5 mg. daily in December.

He was admitted to hospital on March 3, 1961, with a large ulcer on the left medial malleolus 3½ in. (9 cm.) in diameter with unhealthy margins, sloughing floor, adherent base, pigmentation, and atrophy of the surrounding skin, and dilated varicose veins. He was in poor general health, with considerable rheumatoid activity and circular patches of necrotic skin about 3/16 in. (5 mm.) in diameter over the elbows. His prednisolone was continued together with phenylbutazone 300 mg. daily, rest, and physiotherapy. After treatment the ulcer became clean but showed no signs of healing.

On March 29 a skin biopsy was taken from the point of the left elbow, including a nodule and an area of necrosis. Histology showed an ulcerated subcutaneous active rheumatoid nodule. The biopsy wound broke down and secondary suture was done twice without success. During April to June he had multiple operations for grafting the leg ulcer and stripping and ligation of varicose veins. The operation wounds failed to heal. On June 19 steroids were omitted in the hope of assisting wound-healing, but his general condition deteriorated and the wounds did not improve, so steroids were restarted on July 7.

On July 31 he developed an unexplained deterioration in his general condition with slight pyrexia. On August 2 he was obviously ill with a remittent fever. This was thought to be due to adrenal insufficiency precipitated by an infection, possibly septicaemia. Culture of blood and joint fluid from the right knee grew *Staph. aureus* sensitive to methicillin, erythromycin, and chloramphenicol; and resistant to penicillin, streptomycin, and tetracyclines. He was treated with intravenous prednisolone, fluids, methicillin, and erythromycin. On August 3 he developed oliguria with a daily output of 120 ml., a blood urea of 128 mg./100 ml., and deterioration of his general condition with a falling blood-pressure. He died on August 6, 156 days after admission to hospital.

Post-mortem Findings.—The body was that of a normally built middle-aged man with skin ulceration over both olecranon, two unhealed surgical incisions in both groins, and an almost healed chronic ulcer on the left ankle. Internally the pleural cavities were obliterated by fibrous adhesions and there was a large recent purulent fibrinous exudate at the right base. Both lower lobes of the lungs were completely consolidated and histology confirmed confluent bronchopneumonia, but there was no pyaemic abscess formation. The pericardial cavity was obliterated by recent fibrous adhesions. The heart was moderately enlarged, and the only gross abnormality was an acute ulcerative endocarditis of the mitral valve. Histological investigation showed destruction of the valve cusps with adherent masses of fibrin containing large clumps of Gram-positive cocci. The liver was enlarged and microscopy

showed small areas of subcortical infarction with focal pyaemic necrosis of liver cells. In the spleen there were numerous areas of pyaemic infarction. The kidneys were enlarged, and showed numerous large pink wedge-shaped cortical infarcts. These were shown histologically to be due to pyaemic thrombosis of large renal arteries. In addition pyaemic abscesses were scattered throughout the viable renal tissue. The brain was congested and oedematous, and histology revealed small pyaemic foci in the medulla and cerebral cortex. Both knee-joints, the left elbow, and the right wrist-joint contained large amounts of thin anchovy-coloured pus. The tendon sheaths of the right wrist were also swollen and were filled with similar pus. Histologically the synovium from the right knee-joint showed the changes of subacute rheumatoid arthritis with a superficial exudate composed of fibrin, necrotic polymorphs, and Gram-positive cocci. The tendon sheaths were filled with a similar exudate.

Comment.—This case was the classic setting for staphylococcal septicaemia—severe rheumatoid arthritis, a chronically infected leg ulcer, steroid treatment, and recent operations. Yet the only clinical indications of septicaemia were sudden general deterioration and a remittent fever. Post-mortem examination revealed acute staphylococcal infections of the heart valves, kidney, liver, spleen, brain, tendon sheaths, and joints.

Discussion

Incidence.—In the Oxford Regional Rheumatic Diseases Research Centre at the Stoke Mandeville Hospital from 1953 to 1960, 649 cases of classical or definite rheumatoid arthritis (American Rheumatism Association, 1959) have been seen and closely supervised. During that time from this large group of patients with rheumatoid arthritis there have been two cases of staphylococcal septicaemia with pyoarthrosis—Cases 2 and 3 above—and three cases of monarticular pyoarthrosis—two occurring after intra-articular injections of steroids and one after arthrotomy. Case 1 was seen and treated in one of the medical units at the same hospital.

Predisposing Factors.—Smith and Vickers (1960) and Powell (1961) emphasize the importance of factors that lower host resistance in the production of staphylococcal septicaemia, mentioning in particular surgery and steroid therapy. It is surprising that staphylococcal septicaemia does not occur more often in rheumatoid arthritis, as this chronic debilitating disease would seem to lower host resistance. In all our cases those joints that were infected showed signs of previous rheumatoid activity, and all three patients had long-standing rheumatoid arthritis involving multiple joints. Two of them, including the one who had undergone surgery, had had steroids. In the third, neither steroids nor surgery could be implicated, and this suggested to us that rheumatoid arthritis *per se* is sufficient to lower host resistance. All authors are agreed that the skin is the commonest source of the staphylococcal infection. In our three cases there is good presumptive evidence that long-standing trophic ulcers or ulcerated subcutaneous nodules were the source of infection. Cases of rheumatoid arthritis commonly develop skin ulcers which may be due to ulcerating nodules, decubitus ulceration, or arteritic lesions. These ulcers heal with difficulty, are prone to infection with staphylococci, and hence are a ready source of this organism. Lowenstein (1931) emphasizes the grave consequences of a staphylococcal focus that cannot be removed or sterilized.

Diagnostic Features.—Kellgren *et al.* (1958) pointed out the diagnostic difficulty in these cases and stated that this infection should be suspected when there is a "sudden deterioration or an unexplained remittent fever, especially if a history of rigors can be elicited." If in addition to these points steroid therapy has been given or there is a focus of staphylococcal infection, then the clinician should be even more aware of this complication. Aspiration of the inflamed joint with culture of the fluid is essential and repeated blood cultures are often necessary for diagnosis. In all our cases the general health of the patient deteriorated for about a week before increased joint inflammation was detected, and by this time septicaemia was firmly established and pus widely distributed.

Pathological Features.—These three cases illustrate not only the protean nature of generalized staphylococcal infections, but also that pus may be found where least expected. They serve to remind pathologists not accustomed to performing post-mortem examinations on cases of rheumatoid arthritis that it is always necessary to open the joints—more than one if possible. The remarkable experience of anchovy-coloured pus exuding from many joints was a most memorable feature in two of these cases. Pus in the joints was not found in five subsequent cases of septicaemia in non-rheumatoid patients. This further strengthens our impression that rheumatoid joints are especially susceptible to infection by staphylococci. Powell (1961) noted that staphylococcal septicaemia may cause renal failure due to cortical necrosis. Although our three patients died in uraemia none showed this lesion. It is worth noting that there was no evidence of either amyloidosis or arteritis in any of these cases.

Summary

The clinical and pathological features of three cases of staphylococcal septicaemia with pyoarthrosis in rheumatoid arthritis are presented.

The diagnostic problems of this often fatal complication are reviewed. Although more likely to occur in the presence of skin staphylococcal sepsis, steroid treatment, and surgery, it may develop in any long-standing case of rheumatoid arthritis. The most frequent warning symptoms are sudden deterioration in general health, acute exacerbation of joint pain, or a remittent fever with rigors.

At necropsy the staphylococcal infection may almost be confined to the joints, and the true nature of the diagnosis overlooked unless these are routinely explored.

Only increased awareness of this often fatal complication of rheumatoid arthritis will lead to the early diagnosis essential for its successful treatment.

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