ACUTE HAEMATogenous OSTEOmyELITIS AND SEPTIC ARTHRITIS—A SINGLE DISEASE

AN HYPOTHESIS BASED UPON THE PRESENCE OF TRANSPHYSEAL BLOOD VESSELS

MARK ALDERSON, DAVID SPEERS, KERRY EMSLIE, SYDNEY NADE

From the University of Western Australia

The acute childhood diseases haematogenous staphylococcal osteomyelitis and septic arthritis were studied concurrently using avian models which closely resemble the human diseases. Ultrastructural studies during the initial stages of bone and joint infection showed that adherence of bacteria to cartilage, bacterial proliferation, cartilage destruction and subsequent bacterial spread along the vascular channels within cartilage were common to both disease processes. Histological studies revealed that transphyseal blood vessels were present in the growing chickens and were a likely explanation for the frequency of the concurrence of acute osteomyelitis and adjacent joint infection following intravenous injection of bacteria. Transphyseal vessels provide a direct connection between the growth plate (physis) and epiphyseal cartilage supplying a route for bacteria to spread from an osteomyelitic focus in the metaphysis to the epiphysis and subsequently to the joint lumen.

Acute haematogenous osteomyelitis and acute septic arthritis occur most commonly in infants and children. The most frequent causative organism is *Staphylococcus aureus*. Our laboratory has developed reproducible experimental models of acute osteomyelitis and acute septic arthritis in growing chickens. These animal models resemble the human diseases in several respects, and they are induced with no initial interference or trauma to the bone or joint.

Our studies of the natural history of the two diseases have indicated that the strain of *S. aureus* used to produce experimental infection may exhibit a specific tropism for cartilage, either growth plate or articular cartilage (Emslie and Nade 1983; Alderson and Nade 1985; Speers and Nade 1985). Once there has been a primary focus of bacteria localised at either of these two sites, the subsequent spread through cartilage appears to occur by a similar mechanism.

It is well known that acute osteomyelitis often occurs concurrently with adjacent joint sepsis in children (Green and Shannon 1936; Gillespie 1973). This co-existence of bone and joint infections can have serious complications and may be associated with long-term morbidity (Weissberg, Smith and Smith 1974). If the hip

joint is involved, necrosis of the femoral head is a common sequel, leading to major dysfunction.

It is a common belief among clinicians that necrosis of the femoral head following an infected hip is an aseptic process, due to "compression" of the blood vessels supplying the femoral capital epiphysis, rather than a spread of infection through the bone (Kemp and Lloyd-Roberts 1974). However, due to the lack of autopsy material the evidence is primarily conjectural.

Acute osteomyelitis results from bacteria initially localising in the growth-plate region of long bones with subsequent development of an abscess in metaphyseal bone (Emslie and Nade 1983). However, in many cases bacteria can also be cultured from the adjacent joint (Emslie 1983). A means of direct passage across the growth plate through the epiphysis requires exposition.

There is considerable controversy about the existence of transphyseal blood vessels (channels extending across the growth plate to connect the metaphyseal and epiphyseal circulatory systems) in humans. Several authors have claimed that the growth plate is an effective barrier between the metaphysis and the epiphysis (Starr 1922; Siffert 1957; Kahn and Pritzker 1973). In contrast, Trueta (1959) and Ogden (1974) maintained that these vessels do exist, but only during certain periods of skeletal growth. These might allow spread of bacteria from an osteomyelitic focus across the growth plate into the epiphysis, and subsequently into the joint.

Howlett, Dickson and Sheridan (1984) carefully examined the blood supply of the avian growth plate and denied the existence of transphyseal vessels. We have evidence to the contrary (Emslie, Fenner and Nade 1984;

M. Alderson, BSc, Research Officer
D. Speers, BSc, Research Officer
K. Emslie, PhD, MSc, BSc, Research Fellow
S. M. L. Nade, MD, MRCP, FRCS, FRACS, Professor of Orthopaedic Surgery
University Department of Surgery (Orthopaedic Surgery), Queen Elizabeth II Medical Centre, Nedlands 6009, Western Australia.

© 1986 British Editorial Society of Bone and Joint Surgery
0301 620X/86 2027 \$2.00

Alderson *et al.* 1986) and we also suggest that the age of the animal is a critical factor in their appearance.

It was the aim of this study to use our experimental models of acute osteomyelitis and septic arthritis to determine the mechanisms for the initiation of infection, and to examine the possibility that bacteria may spread along transphyseal vessels to cause concurrent osteomyelitis and septic arthritis.

MATERIALS AND METHODS

Bacterial inoculum. The organism used was a strain of *S. aureus* originally isolated from a spontaneous case of chicken tenosynovitis. The strain was passaged through the hock joint (Alderson and Nade 1985) or the growth plate of the proximal tibia as previously described (Emslie and Nade 1983). Prior to infection the bacteria were grown in brain-heart infusion broth with shaking for 6 hours at 37 °C, then centrifuged (1400 *g*) for 10 minutes and resuspended in 10 ml of 0.85% (wt/vol) saline.

Experimental model. For the production of combined osteomyelitis and septic arthritis male broiler chickens aged 29 days were injected intravenously with 0.1 ml of a suspension containing 10⁹ colony forming units (CFU) *S. aureus* per millilitre. For production of septic arthritis alone chickens of the same age were injected with 0.1 ml of a suspension containing 10⁵ CFU *S. aureus* per millilitre into the hock joint.

Light microscopy. The histological technique for the study of the natural history of both diseases has been previously described (Emslie and Nade 1983; Alderson and Nade 1985). Briefly, bone and cartilage samples were removed 1 to 8 days after infection, fixed in buffered formal saline and decalcified in 2.3 M-formic acid. After

embedding the tissue in paraffin, sections were cut at 6 µm and stained with haematoxylin and eosin.

Electron microscopy. The preparation of antiserum for stabilisation of the bacterial capsular glycocalyx, and staining and processing techniques for electron microscopy have been previously described (Speers and Nade 1985). Briefly, after removal of cartilage specimens from infected tibiae and treatment for 1 hour with specific antiserum raised in rabbits, the specimens were fixed in 2.5% glutaraldehyde in cacodylate buffer containing 0.15% ruthenium red. The samples were then washed in cacodylate buffer containing 0.05% ruthenium red, post-fixed in 1% osmium tetroxide containing 0.05% ruthenium red and dehydrated in ascending concentrations of ethanol and finally propylene oxide. Tissues were embedded in araldite, ultrathin sections were cut, post-stained with uranyl acetate and lead citrate, and examined using a Philips 201 transmission electron microscope.

RESULTS

Combined osteomyelitis/septic arthritis and septic arthritis alone were produced by intravenous and intra-articular injection of an avian strain of *S. aureus* respectively. Bacterial lesions were detected in the joints and long bones of the legs of the chicken but not in any of the major organs. The osteo/chondro tropism of the organism was therefore confirmed.

Following *intravenous injection* of staphylococci, histological examination of the tibiae and femora revealed small foci of bacteria in the metaphyseal vessels of the growth-plate cartilage of these bones within 24 hours (Fig. 1). It was not possible to culture bacteria from the adjacent joint fluid at this time. *Intra-articular injection* of staphylococci resulted in visible aggregations

Fig. 1

Fig. 2

Figure 1—Light micrograph of chicken proximal tibia 24 hours after intravenous bacterial injection, the long axis of the tibia running from left to right. A metaphyseal tunnel within the growth plate (GP) is totally occluded with bacteria (L). A second focus of infection is present in an adjacent vessel (arrow). E, epiphyseal cartilage; M, metaphysis (haematoxylin and eosin, × 35). Figure 2—Light micrograph of the surface of the articular cartilage 24 hours after intra-articular injection of bacteria. Clusters of staphylococci have adhered to the cartilage surface and have occluded blood vessels within the cartilage (haematoxylin and eosin, × 120).

Fig. 3

Fig. 4

Figure 3—Electron micrograph of the growing tip of a metaphyseal vessel 12 hours after intravenous bacterial injection. Circulating bacteria (arrow) in the lumen (*L*) of the vessel are in free contact with the cartilage matrix (*M*) due to the absence of an endothelial lining. *D.* degenerate hypertrophic chondrocyte. Bar represents 2 μ m. Figure 4—Electron micrograph of the articular surface of the distal femur 12 hours after intra-articular injection of bacteria. The bacteria are depositing on the articular surface. Much bacterial glycocalyx can be seen (arrows). *J.* joint space. Bar represents 2 μ m.

Fig. 5

Fig. 6

Figure 5—Electron micrograph of a metaphyseal vessel 24 hours after bacterial injection. The bacterium has an extensive network of surrounding glycocalyx (arrows) anchoring it to the cartilage surface. Bar represents 1 μ m. Figure 6—Electron micrograph of articular cartilage 12 hours after intra-articular injection of bacteria. The bacterium is bound to the collagen fibres of the cartilage by its glycocalyx (arrows). Bar represents 1 μ m.

Fig. 7

Fig. 8

Figure 7—Electron micrograph of the articular surface of the distal femur 24 hours after intra-articular bacterial injection. A dense layer of bacteria has formed along the articular surface. Superficial articular cells (*A*) are dead and the collagen fibres near the surface are disrupted. Bar represents 2 μ m. Figure 8—Electron micrograph of articular cartilage 24 hours after intra-articular bacterial injection; the articular surface is to the left. Bacteria can be seen penetrating through the fragmented collagen fibres of the disturbed cartilage matrix. Deeper layers of collagen fibres to the right are not disrupted. Bar represents 2 μ m.

of bacteria on the surface of the articular cartilage after 6 to 12 hours. Within 24 hours the bacteria had occluded blood vessels within the depths of articular cartilage (Fig. 2).

Ultrastructural studies of the early osteomyelitic lesions following intravenous injection confirmed that bacteria initially congregated in metaphyseal vessels. At the tips of the metaphyseal vessels the bacteria were found to make free contact with the cartilage surface because of the absence of a protective endothelial lining (Fig. 3). Similarly, when bacteria were injected directly into the joint lumen (intra-articular injection) to produce septic arthritis, the bacteria were seen to be closely associated with the surface of the cartilage within 12 hours as small discrete foci of infection (Fig. 4).

In each case the bacteria adjacent to the cartilage were physically attached. The attachment of bacteria during osteomyelitic infection appeared to be a function of the bacterial glycocalyx. When the glycocalyx was appropriately stabilised and stained it was found to act as an anchor binding the bacterium to the cartilage surface (Fig. 5). Similar treatment of specimens from septic arthritic infections showed that the bacteria were also bound to the larger collagen fibres of the articular cartilage by the bacterial glycocalyx (Fig. 6).

The bacteria attached to the articular surface proliferated rapidly, establishing thick layers of bacteria at many separate sites on the cartilage surface within 24 hours (Fig. 7). The presence of these bacteria disturbed the adjacent cartilage with the collagen fibres becoming fragmented and in disarray. At several sites bacteria from the main focus of infection were seen to penetrate through this disturbed articular matrix into the deeper epiphyseal cartilage (Fig. 8).

Bacteria deposited in *metaphyseal* vessels were able to proliferate and totally occlude the vessel. Similarly, bacteria depositing in *epiphyseal* blood vessels either by direct penetration through the articular surface or by a vascular route could also completely occlude the channel. When subjected to electron microscopy these lesions, although at different sites, appeared identical with a mass of bacteria embedded in an extensive matrix of glycocalyx (Fig. 9).

The entire process from the initial injection of bacteria into the blood stream or joint lumen to occlusion of the vascular channels in the metaphysis and epiphysis occurred in less than 24 hours. Destruction of metaphyseal bone and the secondary ossification centre of the epiphysis occurred in the following days if antibiotic treatment was not instigated.

Uninfected chickens displayed three types of blood vessels in the region of the growth plate. Metaphyseal vessels occurred most frequently with epiphyseal vessels being less common. Vessels passing through the entire thickness of the growth plate (transphyseal vessels) were seen occasionally (Fig. 10). In chickens with combined osteomyelitis/septic arthritis these transphyseal vessels

Fig. 9

Electron micrograph of an occluded metaphyseal tunnel 24 hours after bacterial injection. Bacteria are present in large numbers within a matrix of glycocalyx. Note the absence of any vascular structure in the metaphyseal tunnel. Bar represents 2 μ m.

Fig. 10

Light micrograph of the secondary epiphyseal ossification centre (O), epiphyseal cartilage (E) and growth-plate cartilage (GP) from an uninfected chicken. A transphyseal blood vessel (arrow) is seen to pass from the epiphysis through the entire thickness of the growth plate (H & E, $\times 35$).

were often occluded with polymorphonuclear cells (Fig. 11).

Four days after intravenous bacterial injection staphylococci could be isolated from the joint fluid in large numbers. At this stage the growth plate had moved away from a primary osteomyelitic focus due to normal bone elongation. Histological analysis confirmed that bacterial lesions were present in both the metaphysis and epiphysis (Figs 12, 13). Bacteria were also found adhering to the surface of the articular cartilage in small foci. Large areas of the growth plate and epiphysis showed

Fig. 11

Fig. 12

Fig. 13

Light micrographs of epiphyseal cartilage (E), growth-plate cartilage (GP) and metaphysis (M) 4 days after intravenous injection of bacteria. Figure 11—A transphyseal blood vessel (arrow) is occluded with polymorphonuclear cells and the surrounding cartilage shows loss of uptake of stain (H & E, × 90). Figure 12—Blood vessels in all three regions are occluded with bacteria (arrows) (H & E, × 35). Figure 13—Large clusters of staphylococci are seen in the epiphyseal cartilage and growth-plate cartilage extending into the metaphysis. Areas of necrotic debris and polymorphonuclear leucocytes have replaced the growth-plate cartilage surrounding the bacterial lesions (H & E, × 25).

signs of acute inflammation and loss of uptake of alcian blue stain.

Intra-articular injection of *S. aureus* infrequently resulted in a combined osteomyelitis/septic arthritis infection although the spread from the primary lesions in the articular cartilage through the growth plate to the metaphysis was delayed. By 14 days after intra-articular injection bacterial destruction of the articular cartilage had spread to involve the secondary epiphyseal ossification centre and, also occasionally, to the growth plate. Inflammatory cells were seen in epiphyseal and transphyseal vessels and sometimes deep into the metaphysis.

DISCUSSION

Acute haematogenous staphylococcal osteomyelitis can be a serious, crippling and potentially fatal disease. When it occurs concurrently with adjacent joint sepsis the problems of treatment are complicated and the risk of chronic disability and disordered growth is increased. Acute osteomyelitis of children occurs most frequently in the femur and tibia (Nade 1983a), and acute septic arthritis usually affects the hip and knee joints (Nade 1983b). Concurrence of the two diseases is most common in the proximal femur and adjacent hip joint. This can result in sequestration of the femoral head, fibrous or bony ankylosis or hip dislocation (Nade 1983b).

Such a numerical association of the two conditions should have a pathogenetic basis. From the evidence provided by our studies we would suggest that two little-explored clues are the key to this association. Firstly, there is an anatomical passage which allows the organisms to spread from their initial site of infection to a secondary site and, secondly, that the host-pathogen interaction for the two diseases is similar.

The histopathology of the interaction between the

chicken and the *S. aureus* strain has been previously studied during acute haematogenous osteomyelitis (Emslie and Nade 1983) and during acute septic arthritis (Alderson and Nade 1985). Subsequent ultrastructural studies of acute osteomyelitis have clearly demonstrated the importance of bacterial adherence in the infective process (Speers and Nade 1985), as was previously shown for chronic osteomyelitis in a rabbit model (Mayberry-Carson *et al.* 1984).

Similarities between osteomyelitis and septic arthritis

Ultrastructural studies during septic arthritis have shown many similarities to the disease process of acute osteomyelitis. An important step in osteomyelitic infection is the contact and subsequent attachment of circulating bacteria to the growth-plate cartilage (Speers and Nade 1985). Following intra-articular injection of staphylococci, the bacteria are soon found in contact with the articular cartilage surface, forming bonds which anchor them to this surface. Within hours of the first bacterium binding to the surface, thick layers of adherent bacteria are found distributed at many sites along the cartilage surface.

An important structure probably involved in this adherence is the glycocalyx of the staphylococci which forms a capsule of polysaccharide fibres around the bacterium (Caputy and Costerton 1982). This glycocalyx binds the bacteria to the growth-plate cartilage during osteomyelitic infection. However, due to the small size (10 to 20 nm diameter) of the collagen microfibrils of this cartilage (Howlett 1979) it was not possible to resolve the actual site of attachment of the bacteria. The collagen fibres of articular cartilage are much larger (125 nm diameter) and the bacterial glycocalyx binding to these fibrils can be seen easily.

The spread of infection following the initial adherence of staphylococci to growth-plate cartilage and articular cartilage is also very similar in both osteomyelitis and septic arthritis. Bacteria that had adhered to the surface of the articular cartilage directly invaded the cartilage matrix. Serial histological sections indicated that these bacteria had entered the *epiphyseal* vascular network and subsequently spread, establishing new foci of bacteria in the deeper zones of the cartilage.

Within hours these bacteria had proliferated to occlude the vascular channel with necrosis of the adjacent cartilage. The appearance of such a lesion in the *epiphysis* was identical to that of a lesion in the growth plate (physis) during osteomyelitic infection. In both cases masses of bacteria were lodged in the channel by a network of glycocalyx which together formed a plug resisting the infiltration of inflammatory cells which could be found at the periphery of the lesion and in adjacent blood vessels (Emslie and Nade 1983).

The initial steps of attachment to cartilage, followed by proliferation, cartilage degradation and bacterial spread are common to both septic arthritis and osteomyelitis in these acute models. Bacterial adherence is probably achieved in each case by the bacterial glycocalyx. Once blood vessels are involved, the spread of infection in both diseases is through the vessel lumen, presumably representing the path of least resistance. Secondary foci of bacteria establish along these vessels resulting in widespread cartilage degradation and eventually bone destruction in the secondary ossification centre (epiphysis) or metaphysis.

Are staphylococcal osteomyelitis and septic arthritis a single disease entity?

The presence of transphyseal blood vessels in the long bones of 29-day-old chickens is analogous to the situation in infants and children described by Trueta (1959) and Ogden (1974). These authors claimed that such vessels allow for the passage of bacteria from a primary metaphyseal focus across the growth plate to the epiphysis. We have shown a similar mechanism allowing spread of infection from the bone to the adjacent joint (or vice versa) in young chickens.

Ogden (1979) described six important findings from his study on neonatal sepsis, osteomyelitis and septic arthritis, which we have found to be common features of chicken haematogenous osteomyelitis/septic arthritis. Firstly he mentioned multiple bone involvement, which also occurred in intravenously injected chickens. Secondly, he found *secondary* sepsis in joints adjacent to osteomyelitic foci. Similarly we found that joints were not septic until three or four days after injection whereas primary foci of staphylococci could be detected in metaphyseal blood vessels within 24 hours.

One of our interesting findings was that regions of normal growth-plate cartilage and epiphyseal cartilage were seen in bones that also displayed marked destruc-

tion of cartilage. Ogden also found highly variable destruction of the growth plate in human osteomyelitis/septic arthritis. In both human neonatal and chicken osteomyelitis/septic arthritis, there is extensive destruction of epiphyseal cartilage and loss of uptake of metachromatic stains by glycosaminoglycans in the cartilage matrix.

Finally, Ogden found variable occlusion of cartilage blood vessels and an important role for transphyseal vessels in allowing the spread of infection across the growth plate. These two features of neonatal osteomyelitis/septic arthritis are also characteristic of the disease in young chickens.

The pathogenesis of avian osteomyelitis and septic arthritis: an hypothesis

The pathogenesis of haematogenous osteomyelitis/septic arthritis in chickens can be postulated as follows. Circulating staphylococci specifically bind, apparently via the glycocalyx of their capsule, to the growth-plate cartilage matrix of the long bones exposed during the growth and formation of normal metaphyseal blood vessels. These established bacteria proliferate until there is occlusion of the metaphyseal vessel which is recognised as the primary osteomyelitic focus within 24 hours of injection. Secondary foci of bacteria form in adjacent metaphyseal vessels and there is also passage of bacteria across the growth plate by two mechanisms: the infection may spread directly to the epiphysis via transphyseal vessels, or there may be direct destruction and lysis of growth-plate cartilage by bacteria and/or polymorphonuclear leucocytes at the sites of least resistance. Once the bacteria are established in the epiphysis, spread towards the joint occurs via direct bacterial destruction of the cartilage matrix and passage of bacteria in epiphyseal vascular channels. Bacteria enter the joint lumen by direct erosion of superficial articular cartilage. The staphylococci in the joint lumen then proliferate, adhere to, and destroy the surface of the articular cartilage in a manner similar to the destruction following intra-articular bacterial injection.

Alternatively, osteomyelitis secondary to septic arthritis may occur if bacteria initially lodge in the joint lumen after intra-articular injection. Free staphylococci in the joint lumen primarily adhere to the surface of the articular cartilage, once again by their glycocalyx. These bacteria then directly degrade the articular cartilage matrix and invade the vascular network of the epiphyseal cartilage. Following invasion and destruction of the secondary epiphyseal ossification centre, spread across the growth plate may occur via transphyseal vessels or direct chondrolysis. Secondary foci of bacteria and inflammatory cells may then become established as metaphyseal abscesses.

We do not dispute that septic arthritis may, and probably does, occur without *clinical* evidence of osteomyelitis, when the joint capsule has not been breached

from without. Whether the entry of organisms from the bloodstream into the joint is via a leak in synovial capillaries, or by the mechanism suggested above, has not yet been resolved.

We believe that there is sound experimental evidence for our proposal that acute osteomyelitis/septic arthritis in chickens is a good representation of the combined disease in infants and children and that osteomyelitis and septic arthritis are manifestations of the same disease. The pathogenesis is similar, the site of initiation of infection, and local anatomical and cellular defence mechanisms determining the clinical presentation. The infectious processes which originate from small foci of bacteria lead to gross destruction of the metaphysis, growth plate and epiphysis by mechanisms which are identical in young chickens and human infants.

The salaries of Dr Emslie and Mr Alderson were provided by TVW Telethon Foundation, whose support for the project over five years is greatly appreciated. Mr Speers was supported by a Special Research Grant from the Commonwealth Tertiary Education Commission of Australia to The University of Western Australia and allocated by the University Research Committee. The Australian Orthopaedic Association Research Fund and the Orthopaedic Research and Education Foundation of Western Australia also contributed funds which were used in this project. The manuscript was typed by Mrs B. Blewett.

REFERENCES

- Alderson M, Emslie KR, Speers DJ, Nade SML. Transphyseal blood vessels exist in avian species. *J Anat* 1986; in press.
- Alderson M, Nade SML. The natural history of acute septic arthritis in an avian model. Unpublished observations, 1985.
- Caputy GG, Costerton JW. Morphological examination of the glyco-calices of *Staphylococcus aureus* strains Wiley and Smith. *Infect Immun* 1982; **36**: 759-67.
- Emslie KR. *Studies of experimental acute haematogenous osteomyelitis*. PhD thesis, The University of Western Australia, 1983.
- Emslie KR, Fenner LM, Nade SML. Acute haematogenous osteomyelitis. II. The effect of a metaphyseal abscess on the surrounding blood supply. *J Pathol* 1984; **142**: 129-34.
- Emslie KR, Nade SML. Acute hematogenous staphylococcal osteomyelitis: a description of the natural history in an avian model. *Am J Pathol* 1983; **110**: 333-45.
- Gillespie R. Septic arthritis of childhood. *Clin Orthop* 1973; **96**: 152-9.
- Green WT, Shannon JG. Osteomyelitis of infants: disease different from osteomyelitis of older children. *Arch Surg* 1936; **32**: 462-93.
- Howlett CR. The fine structure of the proximal growth plate of the avian tibia. *J Anat* 1979; **128**: 377-99.
- Howlett CR, Dickson M, Sheridan AK. The fine structure of the proximal growth plate of the avian tibia: vascular supply. *J Anat* 1984; **139**: 115-32.
- Kahn DS, Pritzker KPH. The pathophysiology of bone infection. *Clin Orthop* 1973; **96**: 12-9.
- Kemp HBS, Lloyd-Roberts GC. Avascular necrosis of the capital epiphysis following osteomyelitis of the proximal femoral metaphysis. *J Bone Joint Surg [Br]* 1974; **56-B**: 688-97.
- Mayberry-Carson KJ, Tober-Meyer B, Smith JK, Lambe DW Jr, Costerton JW. Bacterial adherence and glycocalyx formation in osteomyelitis experimentally induced with *Staphylococcus aureus*. *Infect Immun* 1984; **43**: 825-33.
- Nade SML. Acute haematogenous osteomyelitis in infancy and childhood. *J Bone Joint Surg [Br]* 1983a; **65-B**: 109-19.
- Nade SML. Acute septic arthritis in infancy and childhood. *J Bone Joint Surg [Br]* 1983b; **65-B**: 234-41.
- Ogden JA. Changing patterns of proximal femoral vascularity. *J Bone Joint Surg [Am]* 1974; **56-A**: 941-50.
- Ogden JA. Pediatric osteomyelitis and septic arthritis: the pathology of neonatal disease. *Yale J Biol Med* 1979; **52**: 423-48.
- Siffert RS. The effect of juxta-epiphyseal pyogenic infection on epiphyseal growth. *Clin Orthop* 1957; **10**: 131-9.
- Speers DJ, Nade SML. Ultrastructural studies of adherence of *Staphylococcus aureus* in experimental acute hematogenous osteomyelitis. *Infect Immun* 1985; **49**: 443-6.
- Starr CL. Acute hematogenous osteomyelitis. *Arch Surg* 1922; **4**: 567-87.
- Trueta J. The three types of acute haematogenous osteomyelitis: a clinical and vascular study. *J Bone Joint Surg [Br]* 1959; **41-B**: 671-80.
- Weissberg ED, Smith AL, Smith DH. Clinical features of neonatal osteomyelitis. *Pediatrics* 1974; **53**: 505-10.