ACUTE HAEMATOGENOUS OSTEITIS IN CHILDHOOD.

by

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PREFACE.

The problems of acute haematogenous osteitis have exercised the minds of medical men throughout the ages.   Recently however, there has been a remarkable change in the picture presented by the disease itself.   In the last two decades the mortality has fallen from over 30 per cent to less than 2 per cent.   Metastic lesions are now almost unknown and stay in hospital has been reduced from many months to a few weeks.   Pale emaciated children with discharging sinuses are no longer seen in our out-patient departments. Wriggling maggots no longer compete for popularity with acriflavine, vaseline gauze and "Bipp".   In the wards, the screams of children undergoing daily dressings gave way to the stench of pus-soaked plasters until the introduction of penicillin, since when the only grievance of the young victim of osteitis is the regular appearance of the syringe.

My interest in pyogenic osteitis was first aroused during my period of residence in the "septic" wards in the Western Infirmary in 1932.   I saw many cases of acute and subacute osteitis and I recall one outstanding example of the morbidity of this disease.   Three male patients suffering from chronic osteitis lay in adjoining beds.   Their combined ages amounted to 90 years and of these 62 had been spent in hospital.   A later appointment in the Royal Hospital for Sick Children during 1933 led to further experience of this death-dealing and disabling disease.   In spite of all forms of surgical intervention - from simple immobilisation through drilling, guttering and diaphysectomy to primary amputation, a third of the children died from septicaemia and pyaemia.   There is little wonder that I came to regard osteitis as the most depressing disease of childhood which the surgeon

was /

was called upon to treat.

During the war years I had few opportunities of studying the problems of childhood and had little personal experience of the improvements which followed the introduction of effective chemotherapy. On my return to civil life in 1945 I was given the opportunity of taking charge of all cases of osteitis in one unit of the Royal Hospital for Sick Children. The results of treatment with penicillin were to me little short of miraculous. Detailed investigation of all cases led to interesting discoveries and showed up many gaps in our knowledge (Dennison 1948). Several problems have now been solved; others are still being investigated.

The term OSTEITIS is preferred to OSTEOMYELITIS as the bone marrow plays only a small part in bone suppuration (Nowicki 1931, Romanis and Mitchiner 1932, White 1937, and Dennison 1948). Throughout the thesis, the older terms periostitis, osteitis and osteomyelitis as denoting separate diseases are abandoned and the inflammations of bone tissue are alluded to as OSTEITIS - a term which covers all the essential structures of a bone.

This thesis is concerned with the aetiology, treatment and investigation of 212 cases of acute haematogenous osteitis admitted to one of the surgical units of the Royal Hospital for Sick Children, Glasgow, during the years 1936 to 1949. The patients were drawn from Glasgow and the West of Scotland, and except for the war years 1940 to 1945 they were treated, or their treatment was supervised, by me. They are dealt with in three groups –

I.   75 cases treated before the introduction of effective chemotherapy (1936-40).

II.   55 cases treated with chemotherapy (1941-45).

III. 82 cases treated with penicillin (1945-49).
(Penicillin /

(Penicillin became available in the hospital during 1945 and during this year 8 cases were treated with chemotherapy and 12 with penicillin).

In bone inflammation "there is no hard and fast line between what is acute and what is subacute or even chronic". Lloyd (1932) made this statement and continued "... at one end of the scale is the author who includes such smouldering fires as osteomyelitis of the jaw and at the other is he who almost comes to believe that no case is acute unless the patient dies!" It is therefore essential that we should define our conception of acute osteitis. In opening a discussion on this subject at a meeting of the Scottish Surgical Paediatric Club in Aberdeen in May 1949 I put forward the following definition -

"Acute osteitis is a sudden illness associated with severe toxaemia and definite evidence of inflammation of bone, the duration of the illness being days rather than weeks".

Higgins et al (1947) claimed that "the abortive action of penicillin is so great that a diagnosis (of osteitis) made on purely clinical grounds may never be confirmed in any other way". White and Dennison (1947) pointed out that the diagnosis of osteitis requires conclusive evidence of inflammation of bone. A positive blood culture, or even a growth of pathogenic staphylococci from the marrow, prove only the presence of septicaemia. Pus obtained by aspiration may be from a soft tissue abscess without underlying bone disease. In the complete absence of clinical or radiographic evidence of bone disease the diagnosis of osteitis cannot be confirmed.

All cases in the present series conform to the definition of osteitis given above and in every case there was evidence of inflammation of bone.

Two /

Two groups of cases which by their nature or age incidence differ from the disease which we are considering have been excluded from the present series. These are Streptococcal Osteitis of Infancy (Dennison 1948) and Osteitis of the New Born (Thomson and Lewis 1950).

The thesis is divided into four parts. In Part I the history of osteitis is reviewed and the accepted anatomy and pathology are considered. In Part II the disease as seen in a large children's hospital is described in three groups. Part III is devoted to present day treatment and the common complications are described. In Part IV the disease is discussed on the basis of the facts already presented. The work is briefly summarised and various appendices have been added to lighten the burden of the reader.

CONTENTS

ACUTE HAEMATOGENOUS OSTEITIS IN CHILDHOOD

PART I

HISTORICAL SURVEY

SURGICAL ANATOMY AND PATHOLOGY

HISTORICAL SURVEY

"We stand upon the intellectual shoulders of

the medical giants of bygone days and, because

of the help they afford us, we are able to see

a little more clearly than they were able to do".

Claude Bernard (1813-78).

Pyogenic infection of bone is as old as man.   We do not know all
the diseases to which the flesh of palaeolithic man was heir, but his
surviving bones tell us that a common disease was inflammation of the bones
involving a joint and producing deformity.

The first written record of knowledge of bone disease comes to us
in the Smith Surgical Papyrus written about 1600 B.C. (Breasted 1930).   The
Egyptians could not eliminate magic from their medicine and the ibis-headed
Thos, the hawk-headed Horus, the lion-headed Sekhmet, and other such gods,
overwhelmed the laws of science.   The papyrus tells us that bone caries and
suppuration were treated by poultices of ground snakes, frogs and puppies and
by decoctions of various herbs.   Evidence of osteitis has been found in some
of the earliest Egyptian mummies.

In ancient China, inflammation was treated by the application of
small pieces of slow-burning wood over the painful area, while the Hindus had
an old dogma - "The fire cures diseases which cannot be cured by the knife and
drugs".   The Hindus were skilled surgeons and they immobilised inflamed and
broken limbs by light wooden splints.

In /

In the fifth century B.C. HIPPOCRATES expelled the gods from medicine and turned Greek medicine into a science. He wrote wisely of compound fractures and advocated rest and immobilisation. But his writings are marred by one baneful rule - "Diseases which are not cured by medicines are cured by iron; those not cured by iron are cured by fire; those not cured by fire are incurable". Although Hippocrates rationalised medicine by stepping over the hurtful traditions of former ages, he fell with the cautery in his hand (and according to Maister Peter Lowe, with a volvulus in his abdomen). In his name the actual cautery was employed until the advent of Ambroise Paré.

The classic period of Greek science passed away in the third century B.C., but for a time Greek medicine continued to flourish in Alexandria. When Rome came to rule the world Greek medicine left the ebbing Nile and came to dwell beside the flowing Tiber. The Greek physicians however found it more difficult than the Greek gods to establish themselves in Rome. Although medicine was practiced almost exclusively by Greeks one of best accounts of it comes from the pen of a Roman. CELUS was probably a contemporary of Virgil, Livy, and Horace and he is remembered by the medical student for his classical description of inflammation. ANTYLLUS, the father of vascular surgery, described the removal of necrotic bone and diaphysectomy. GALEN, a native of Pergamum, famous for its shrine to Aesculapius and for its medical school, came to Rome in 162 A.D. He described bone infection following compound fracture but unfortunately through his support the appalling fallacy that suppuration was essential to healing was perpetuated through the centuries. He insisted that the right kind of pus was "laudable".

In /

In the long centuries of medievalism which followed the downfall of Rome, surgery was debased almost to extinction. The followers of Mohammed overran three continents and for centuries Europe acknowledged the medical supremacy of Islam. The Canon of AVICENNA became the epitome of Graeco-Arabian medicine but ALBUCASIS lamented that "the operative Art has disappeared from among us almost without leaving any trace behind" (Leclerc 1876). Even in the great medical schools of Salerno and Montpellier, surgery received scant attention. THEODORIC of Cervia in the thirteenth century at last denounced Galen's doctrine of "laudable pus" and advocated the dry treatment of wounds. Two other brilliant exceptions in this period of surgical decadence are HENRI de MANDEVILLE and GUY de CHAULIAC, both of whom left us an outstanding surgical treatise (Pilcher 1895). De Mandeville is almost as famous for his epigrams as for his surgery. Unfortunately he died of tuberculosis before completing the section of his book dealing with fractures and affections of bone. His plea for surgical cleanliness was hundreds of years in advance of his time. He advised irrigation of wounds with boiled or pure spring water and stated that - "Many more surgeons know how to cause suppuration than how to heal a wound. Wash the wound scrupulously from all foreign matter; use no probes, no tents; apply no oily or irritant matters; avoid the formation of pus, which is not a stage of healing but a complication".

The exact date when the Middle Ages merged into the Renaissance is much disputed. The border years are marked by the discovery of printing and of the New World and as far as science is concerned, with the publication in 1543 of the epoch making works of Copernicus and Vesalius. Most of the surgery /

surgery in these centuries was performed by army surgeons who were generally men of little ability and less culture.   Until the sixteenth century the physician was supreme in both medicine and surgery and he decided when operation should be required.   The physician called in the barber surgeon who was only a craftsman with a superficial knowledge of anatomy but with considerable dexterity with a knife.   AMBROISE PARÉ (1510-1590) - Barber-Surgeon to the King of France and PETER LOWE - "Scottishman", (1550-1620), were outstanding exceptions.   Paré treated traumatic osteitis with poultices and gave instructions about removing dead bone fragments.   He was probably the first to denounce the cautery.   Maister Peter Lowe, the founder of the Faculty of Physicians and Surgeons of Glasgow, discussing "corruption of boane" in "A Discourse of the Whole Art of Chyrurgie" (1612) showed knowledge of the blood supply of bone - "By the defluxion of the humor in the proper substance of the boane... the which consumeth the periost, rotteth the boane ... and consumeth the bloud which is the proper nouriture thereof".   In dealing with sequestra, he says - "if any piece of boane bee separated, thou must by fitte medicaments, helpe the separation and not draw it by force, for that causeth great accidentes as the fistules, fevers, sincope (and) convulsion, as saith AUICEN".   He gives full instruction in the use of the cautery (cauters actuall and potentiall) but points out that some surgeons only use it "in great extremities ... like the corrupt and rotten boanes, they (the cautery) being the enemies to all rottenesse and corruption and helpeth the separation of the boanes".

In a law suit for a medical fee in Massachusetts in 1660 (Radbill 1946) there is an interesting description of a case of chronic osteitis diagnosed as the King's Evil.

Not /

Not until the eighteenth century was there any attempt to differentiate tuberculous, syphilitic and pyogenic infection of bone and the following description is taken from what is probably one of the first text books on operative surgery written in English. It is from the pen of SAMUEL SHARP (1739) of Guy's Hospital. "These caries that happen from the Matter of Abscesses lying too long upon a bone are most likely to recover. Those of the Pox very often do well because that Distemper fixes ordinarily upon the middle and outside of the densest Bones, which admit of exfoliation; but those produced by the evil, where the whole extremities or spongy parts of the Bone are affected, are exceedingly dangerous". He cautioned against attempts to remove sequestra before they have separated and condemned the cautery in these words - "However if it be only uncertain that whether the actual cautery is beneficial or no, the cruelty that attends the use of it should entirely banish it out of Practice". ALEXANDER MONRO (primus) (1740) also differentiated bone infection following trauma from that resulting "from constitutional indisposition, such as syphilis, scrofula or a deficiency of nutrition". He drew a complete clinical picture of osteitis and remarked on the grave prognosis when the disease affects the vertebral column. Unlike Sharp, Monro advocated the use of the cautery. SPARROW (1740) described diaphysectomy for osteitis of the tibia by sawing the bone in two in its middle and extracting the two parts. PERCIVAL POTT emphasised the importance of post-operative care and like his contemporary Sharp, he strongly denounced the cautery. In 1751, JOHN HUNTER became "surgeon's pupil" with Pott and the lessons he learned from Pott in St. Bartholomew's Hospital, Hunter later confirmed on the battlefields of Europe. Hunter was the first man to describe the mechanism of sequestrum formation (1786) and showed his appreciation /

appreciation of the importance of the periosteal blood supply in the following sentence - "As soon as ever it is known that suppuration has taken place, it should be opened, to prevent as much as possible the separation of periosteum".   He also preached the gospel of immobilisation and rest in the treatment of inflammation.

In 1803 HEY described a case of osteitis of the tibia and his treatment was little different from that carried out in the early part of the twentieth century.   In early America the unorganised and even ignorant state of the medical profession is seen in the lack of thought-provoking communication during the colonial era.   But in 1818, DORSEY wrote at length on necrosis of bone and he preferred amputation to the "painful, difficult and hazardous operation (of sequestrectomy) which is often performed by British Surgeons".   Ten years later, the classical paper of NATHAN SMITH (1827) was published.   He knew that there was increased tension within the bone in the early stages of osteitis and that it was necessary to incise the periosteum and drill the bone to avoid interference with the blood supply.   He noted that the disease is "almost exclusively confined to young subjects".
SAMUEL D. GROSS (1830) divided the etiology of necrosis (osteitis) into local causes (blows, wounds, fractures and burns) and general causes (constitutional diseases and the effects of prolonged and debilitating febrile illness).   In Europe, amputation was the principal method of treating compound fractures and Napoleon's military surgeon BARON LARREY (1832[a]) had more than his share of this type of surgery.   In his Syrian campaign Larrey (1832[b]) described involvement of wounds by maggots and he was of the opinion that they had no harmful effects.

Both acute and chronic osteitis were fully described by LISTON (1837) in his "Elements of Surgery".   In the acute case, he advised bleeding the patient /

patient and administration of purgatives and nauseating doses of antimony, plus free incision. He summarised treatment thus - "Prevent necrosis, if possible - open abscesses whenever they appear; encourage the patient to move the neighbouring joints; support the strength; remove sequestra when loose - but do not interfere until they have ascertained to be so; give the limb support and rest".

The name of BENJAMIN BRODIE is perpetuated in surgical literature by two conditions which bear his name - Brodie's Tumour of the Breast and Brodie's Chronic Abscess of Bone (1845). Brodie described the symptomatology of his first case of this type of osteitis but it was only after amputation of the limb that he discovered an abscess at the lower end of the tibia. Thereafter he treated similar cases by evacuating the pus by trephine or by chiselling the bone.

In 1852 MATHIJSEN introduced plaster of Paris bandages and paved the way for the Winnet Orr treatment of osteomyelitis, seventy-five years later. Mathijsen's invention did not become popular until publicised by SAYRE in 1877. JOHN HILTON (1863) relied on leather and iron splints to show that "Rest is a most important therapeutic agent in the cure of accidents and surgical diseases". In Lecture 18 of his surgical classic on "Rest and Pain" he described the clinical and local post-mortem findings in a patient with "osteitis" of the lower tibia, "followed by death - I believe from pyaemia - twelve days after the accident".

We thus see that bone necrosis was recognised and written about very early but its cause was not understood until PASTEUR'S work about 1860 and the demonstration of bacteria in the abscesses. He observed that the same organism /

organism caused both boils and osteitis and designated the latter as bone carbuncle (Phemister 1924). JOSEPH LISTER applied Pasteur's discovery to surgery and by swabbing out wounds and compound fractures with lint saturated with carbolic acid prevented the growth of organisms - the hitherto invisible "disease demons" of primitive Medicine Man. Modern surgery dates from that morning in 1865 when Lister and his house surgeon HECTOR CAMERON entered the wards of Glasgow Royal Infirmary bearing hopefully their first specimen of crude carbolic acid. During the following year Cameron treated fifteen cases of compound fracture so successfully that the hitherto dreaded traumatic osteitis no longer ended inevitably in loss of life or limb. The common infecting organism, the Staphylococcus aureus was first described by OGSTON in 1882 (Bergey 1934) and in 1894 LEXER described and demonstrated the pathogenicity of micro-organisms in acute osteitis.

Following the valuable contributions of LANNELONGUE (1879) French authors referred to osteitis as "la maladie de O. Lannelongue" (Cromby 1938). Like Hilton and THOMAS (1886), he helped to establish rest as a prime requisite.

In 1895, WILHELM KONRAD von ROENTGEN gave mankind the X-ray as a Christmas gift and a further step was taken in the understanding of bone changes in osteitis.

Surgical intervention became more drastic and KETTLING (1885) advocated sterilisation of the bone cavity by complete removal of the marrow by scraping and swabbing with carbolic acid and strong solutions of bichloride of mercury. NICHOLS (1904) however, demonstrated that the bone marrow and endosteum were as important as the periosteum in the regeneration of bone. He showed that thorough scraping and the application of strong antiseptics delayed /

delayed healing.   VON MOSETIG-MOORHOF (1903) filled bone cavities with plugs

of wax composed of iodoform, spermacete and oil of sesame and twenty years

later ASHURST (1924) was still using this wax.   MOORE (1905) packed the

cavities with gutta percha, while BECK (1909) favoured a bismuth paste.   A

great surgical pioneer, SIR WILLIAM MACEWEN extended the frontiers of every

branch of operative surgery.   In 1912 he described in detail the mechanism

of involucrum formation and he pointed out that thrombosis of the nutrient

artery led to death of the bone shaft.   His classical experiments on dogs did

much to establish orthopaedic surgery on a scientific basis.

Following experience in World War I, the CARREL-DAKIN method of

irrigation was widely practised (Keen 1917), while other surgeons followed the

practice of RUTHERFORD MORRISON (1916) and packed the bone cavities with Bipp.

Like Paré in the sixteenth century and Larrey two hundred years later, the army

surgeons of the twentieth century found that wounds infested with maggots were

often in excellent condition.   BAER (1931) used maggots in the treatment of

chronic osteitis in civilian practice but this form of therapy never became

popular in England.

The first authoritative teaching based on a large series of cases

came from STARR of Toronto in 1922, while in 1927 WINNET ORR, following lessons

learned on the battlefields of Europe, insisted on adequate drainage, an

antiseptic dressing and immobilisation in a well-fitting plaster of Paris case.

ALBEE (1933), who described methods of dealing with bone cavities

throughout the centuries as varying from "boiling oil, incinerated toads, ashes

and natural balsams and even sprayed perfume and soft music", claimed improved

results following injection of a specific bacteriophage into the cavity and of

necessity /

necessity ceased to use antiseptics.

In 1935 DOMAGK showed that an amide of sulphonic acid (Prontosil rubrum) prevented the development of streptococcal septicaemia in mice but the chemotherapy of staphylococcal infections by the early sulphonamides was disappointing.   In spite of MITCHELL'S (1938) success with Uleron (a dimethyl sulphonilamide), it was not until the introduction of sulphathiazole that improved results in staphylococcal osteitis were reported by HOYT and his colleagues (1941).

The contamination in 1928 of a plate of staphylococci by spores of a species of Penicillium was the beginning of the study of penicillin (FLEMING 1929) and in 1943 Sir Howard and Lady FLOREY prophesied that "one might anticipate the time when osteomyelitis, treated early and intensively with penicillin would not require surgical intervention".   This prophecy has now been fulfilled.   Penicillin has not only revolutionised the treatment of osteitis but has altered its clinical pattern.

It is certainly no small advantage on our side to live at the present day and to have received from our ancestors the arts already brought to such a degree of perfection.   (Galen 130-200 A.D.)

SURGICAL ANATOMY AND PATHOLOGY.

Before discussing the effects of infection in bone it is essential
to have a clear conception of the structure of bone and the effect of the
peculiarities of this structure on the processes of inflammation and repair.
Every bone consists of an outer shell of compact bone and an inner filling of
cancellous bone.   Compact bone consists mainly of a series of concentric
plates of bone tightly packed around Haversian canals and penetrated by fine
channels radiating from these.   The vessels and nerves are thus lying in
canals with rigid bony walls.   When inflammation occurs with consequent
engorgement and effusion the vessels are obliterated by pressure within the
canals and the blood supply to varying areas of the bone is cut off with
consequent death of these areas.   The pressure on the nerves causes acute
pain.   As the vessels are adherent to the bony walls of the canals, they
cannot collapse so that infected clot can be carried into the circulation,
thus explaining the frequency of pyaemia in untreated bone infection.

Cancellous bone is arranged in a series of trabeculae within the
shell of compact bone.   The trabeculae vary in arrangement and density,
determined by lines of stress and strain (D'Arcy Thomson 1941).   The
interstices between the trabeculae are packed with bone marrow.   In the
marrow run vessels and nerves which are prolonged in the Haversian canals.
As in the compact bone, inflammatory processes may lead to extensive necrosis.

The bone is surrounded by the fibrous but vascular sheath of
periosteum which is firmly attached at the epiphyseal plates.   The periosteum
adheres to the surface of the bones but not to the cartilage covering the
articular /

articular surfaces.   In young bones it is thick and very vascular and a network of vessels penetrate the cortex.   In later life the periosteum is thinner and less vascular.

The problems encountered in investigating the detailed blood supply of a long bone are discussed in another section (Part IV), but for the present the accepted anatomy of the blood supply (Lexer et al 1904, Hobo 1921, Gray 1926, Johnson 1927) will be described.

A long bone is supplied by blood from three sources —
1.   The nutrient artery, which enters the bone at approximately the mid-shaft and sends branches towards each end of the bone.
2.   Metaphyseal vessels enter through numerous foramina in the juxta-epiphyseal region.
3.   Periosteal vessels pass through minute orifices in the cortex and run in the Haversian canals.

The branch of the nutrient artery becomes smaller and splits into branches as it approaches the metaphysis.   Just short of the epiphysis, the branches loop back and end in large venous capillaries which run back towards the medulla.   The blood stream is therefore slowed down in this region.   All three sets of vessels come into communication at the metaphysis which is thus an extremely vascular region.

The distribution is shown diagrammatically in Figure 1.

BACTERIOLOGY   By far the most common infecting organism in acute haematogenous osteitis is the Staphylococcus pyogenes.   Following the classical description of the disease by Fraser (1926) it became the custom to detail /

Figure 1.

BLOOD SUPPLY OF BONE

Epiphysis

Metaphyseal Vessels

Cortex

Periosteum

Periosteal Vessels

Nutrient Artery
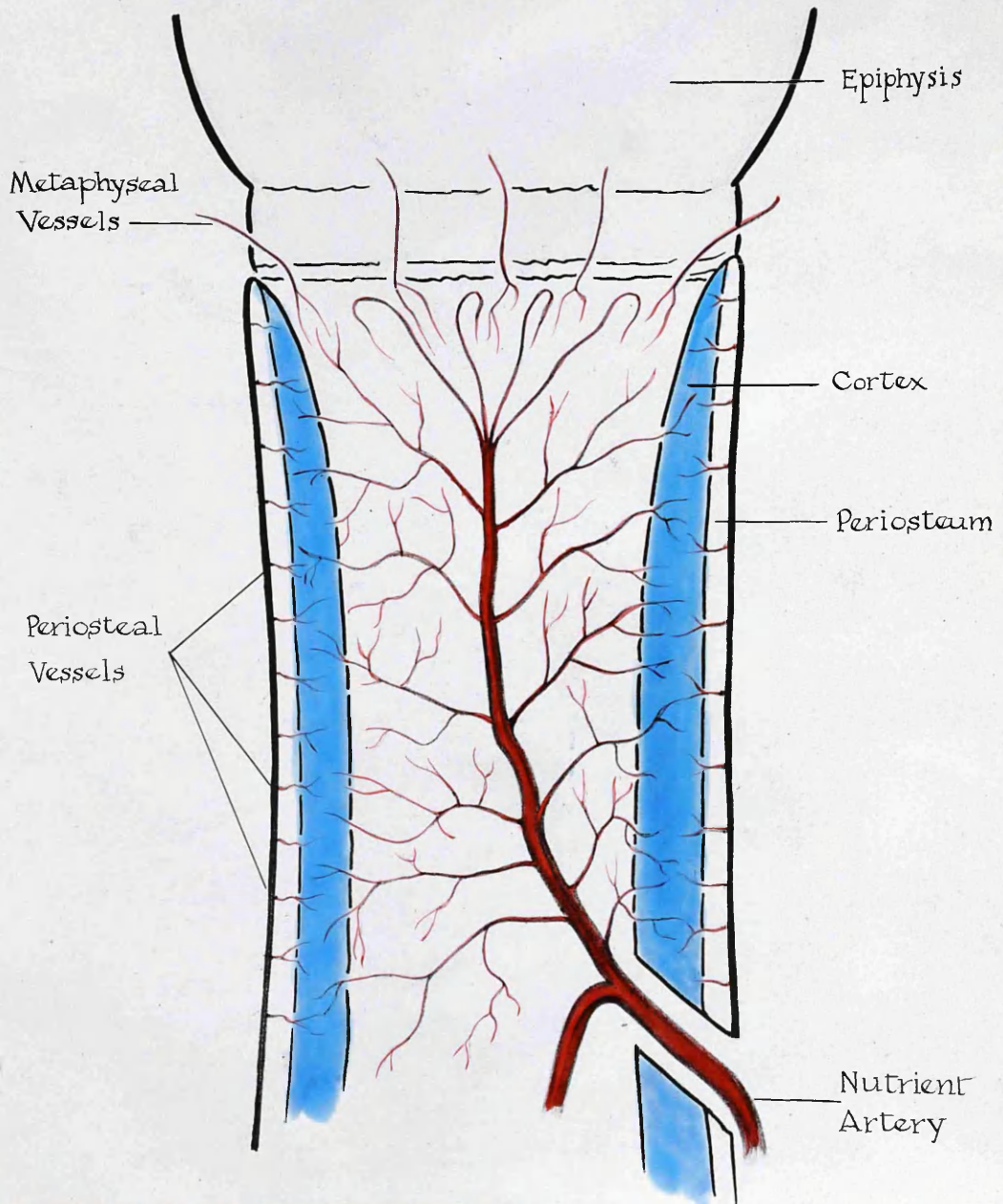
detail the causal organism in each series.   In Table I the bacteriology

from a few of the better known papers is contrasted with the present series.

TABLE I

	Fraser (1926)	Platt (1928)	Ogilvie (1928)	Pyrah & Pain (1933)	Butler (1940)	Hudson (1946)	Altemeier & Wadsworth (1948)	Author's Cases
Staph aureus	122	33	42	66	342	30	42	202
Staph albus	6	1	1	-	22	-	-	-
Streptococcus	12	4	-	3	45	7	7	7
Strep.& Staph.	-	-	-	2	-	-	-	-
Pneumococcus	58	-	-	-	1	-	1	3
B. Typhosus	2	-	1	-	-	-	-	-
Staph.aureus & B. proteus	-	-	1	-	-	-	-	-
Short-chained diplococci	-	-	-	1	-	-	-	-
Gram. + cocci	-	-	-	-	-	-	1	-
B. coli	-	-	-	1	-	-	-	-
Anaerobes	-	-	-	-	2	-	-	-
Not known	-	3	6	189	87	-	20	-
Total	200	41	51	262	500	37	71	212

Staphylococcal /

Staphylococcal Infections

In culture, the Staphylococcus pyogenes displays a greater or less power of pigment production, the colonies varying in colour from golden brown to white, the more highly pathogenic strains being usually well pigmented. In this series any Staphylococcus albus grown, particularly from a blood culture, has been considered as a contaminant. Apart from the exotoxins (α-toxin, β-toxin and leucocidin), staphylococci produce _coagulase_. Coagulase causes the clotting of plasma and this phenomenon was first described by LOEB (1903) and more fully investigated by MUCH (1908). GENGOU (1933) suggested that coagulation of plasma is only the first effect of coagulase. Its main function is fibrinolytic for which action preliminary fibrin formation or coagulation is necessary. The majority of pathogenic staphylococci coagulate rabbit plasma but many specimens of human plasma are resistant to coagulase. The difference is explained by the presence of anticoagulase in many human bloods, the result of frequent infections of man by staphylococci. In vitro, anticoagulase may prevent the coagulation of plasma, but in a staphylococcal lesion it probably only delays coagulation and later serves the purpose of holding up liquification until a defence barrier of polymorphonuclear leucocytes has collected around the site of invasion.

Streptococcal Infections

The streptococcal infections in the present series were virulent and the patients were seriously ill. Generally, streptococcal osteitis is more common in infancy and differs in so many respects from the staphylococcal osteitis of older children that it is considered as a subacute infection (Dennison 1948) and as such has been excluded from the present series.

Pneumococcal /

Figure 2

Raising of the Periosteum cuts off the Blood Supply to Outer Cortex.
Increased intramedullary pressure occludes branches of Nutrient
Artery and thrombosis may lead to the death of large areas of
the Metaphysis and Shaft.
New Subperiosteal bone is laid down in the ossifiable medium under
the periosteum.

Nutrient Artery

Periosteal Vessels

Periosteum raised by pus, cutting off blood supply.

Pressure on Nutrient Artery

Increased intramedullary pressure
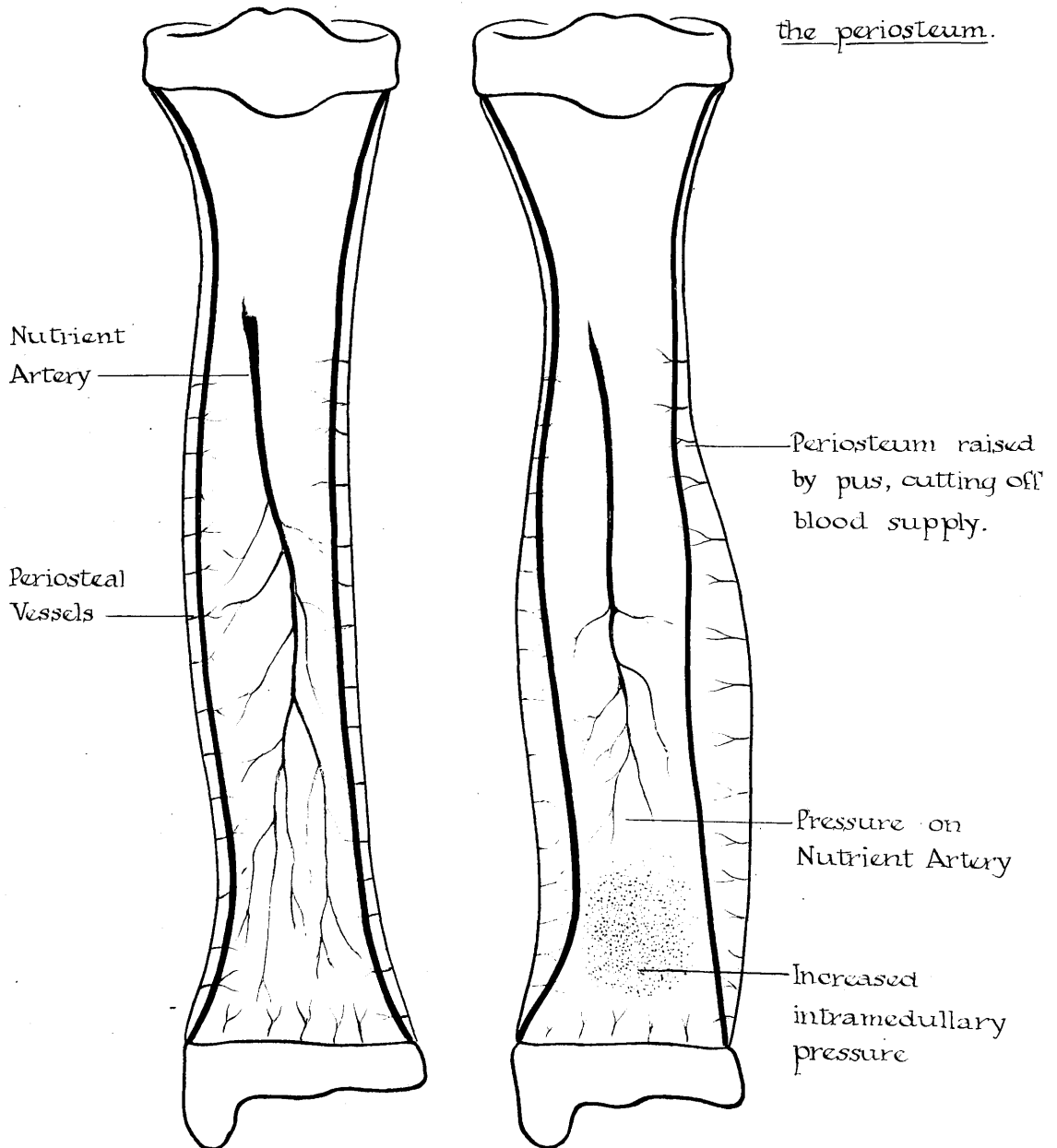
Pneumococcal Infections

Acute pneumococcal osteitis is rare but when it occurs it is clinically indistinguishable from staphylococcal osteitis.

PATHOLOGY   In most cases, the disease appears to start as a septicaemia. The septicaemic phase may be of short duration or it may be prolonged for several days.   The circulating organisms then settle in a favourable situation, usually the vascular metaphysis of a long bone and there lead to an acute suppurative inflammation.   Around this bone focus there is an outpouring of leucocytes and a tiny abscess (Starr 1922) forms surrounded by a zone of intense hyperaemia.   The infection extends close to the epiphyseal line to the cortex and periosteum and the periosteum is raised from the bone, first by oedema then by pus.   The small periosteal arteries are obliterated and the blood supply to the cortex is impaired (Figure 2).   Superficial portions of the bone undergo necrosis and may later form sequestra.   Since the periosteum is closely attached to the circumference at the epiphyseal cartilage, the infection does not spread into the joint at an early stage except in certain regions such as the hip, where the metaphysis is intra-articular.   As the result of increased tension the pus spreads backward through the Haversian canals at different levels and invades the medulla (Figure 3) giving the "spotty" character to the shaft infection which is clearly seen radiographically.   Direct spread into the medulla occurs late. The nutrient artery may be occluded by oedema or by actual thrombosis with death of large areas of the bone (Figure 2).

If untreated, the medulla is converted into oily pus owing to the destruction of the fatty tissue and the surface of the bone is bathed in pus. The /

Figure 3.
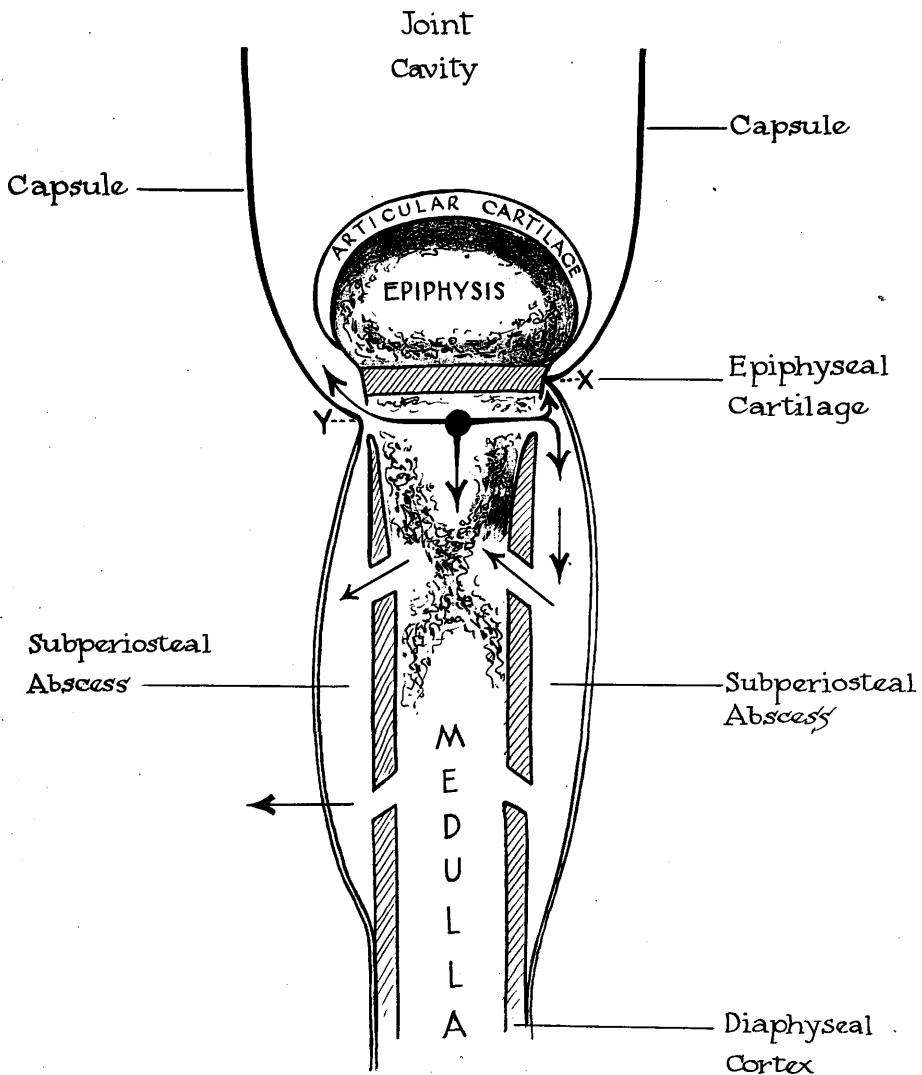
X.——— Represents point of firm attachment of Capsule and Periosteum when Metaphysis is extra-capsular.

Y.——— Is point of fixation when Metaphysis is intra capsular.

Infection may spread from focus in Metaphysis as indicated by arrows.

Diagramatic illustration of the spread of infection from the metaphyseal focus in acute haematogenous osteitis. (After Starr).

The bone loses its healthy shining appearance and becomes a dull opaque white.   Necrosis of bone is usually greatest in the region of the metaphysis where thrombosis and tension destroy the living framework of the bone. Extensive necrosis is now only seen in museum specimens.   The dead portion of bone is at first continuous with the living but demarcation is not long delayed and small portions of dead bone may be absorbed.   Around the dead mass vascular granulation tissue develops and before the dead mass is set free as a sequestrum it shows an eroded, worm-eaten appearance.   New bone forms both on the surface and in the depths of the old, as the calcium released by the hyperaemia is deposited in the primitive mesenchyme formed by the granulation tissue (GREIG 1931).   When the periosteum has been widely separated an extensive new case of subperiosteal bone - an involucrum - may develop.   This involucrum is at first light and porous but as the blood supply diminishes it eventually becomes sclerosed.   Its surface is rough and irregular and it is usually perforated by cloacae marking the position of sinuses through which purulent discharge escapes to the surface.   Figure 4 is a composite drawing made from two specimens in the Museum of the Royal Hospital for Sick Children (IB2 and IB3).

At any stage, septic thrombi may give rise to emboli and pyaemia. The blood culture is positive and the septicaemia may be so overwhelming that death may occur before any extensive changes take place in the metaphysis. The adjacent joint may become filled with a sterile serous effusion or the process may rupture into the joint to cause a purulent arthritis.

The relevant bacteriology, autopsy findings and pathological complications of the present series will be discussed in the clinical sections.

21

underlineFigure 4

Diagramatic representation of Chronic Osteitis with Septic Arthritis. Periosteum has been partially removed to show smooth Sequestrum covered by new bone (Involucrum) perforated by Cloacae.

Involucrum with Cloacae

Smooth white Sequestrum.

Oedematous raised Periosteum.

Cartilage flaked off & irregularly destroyed
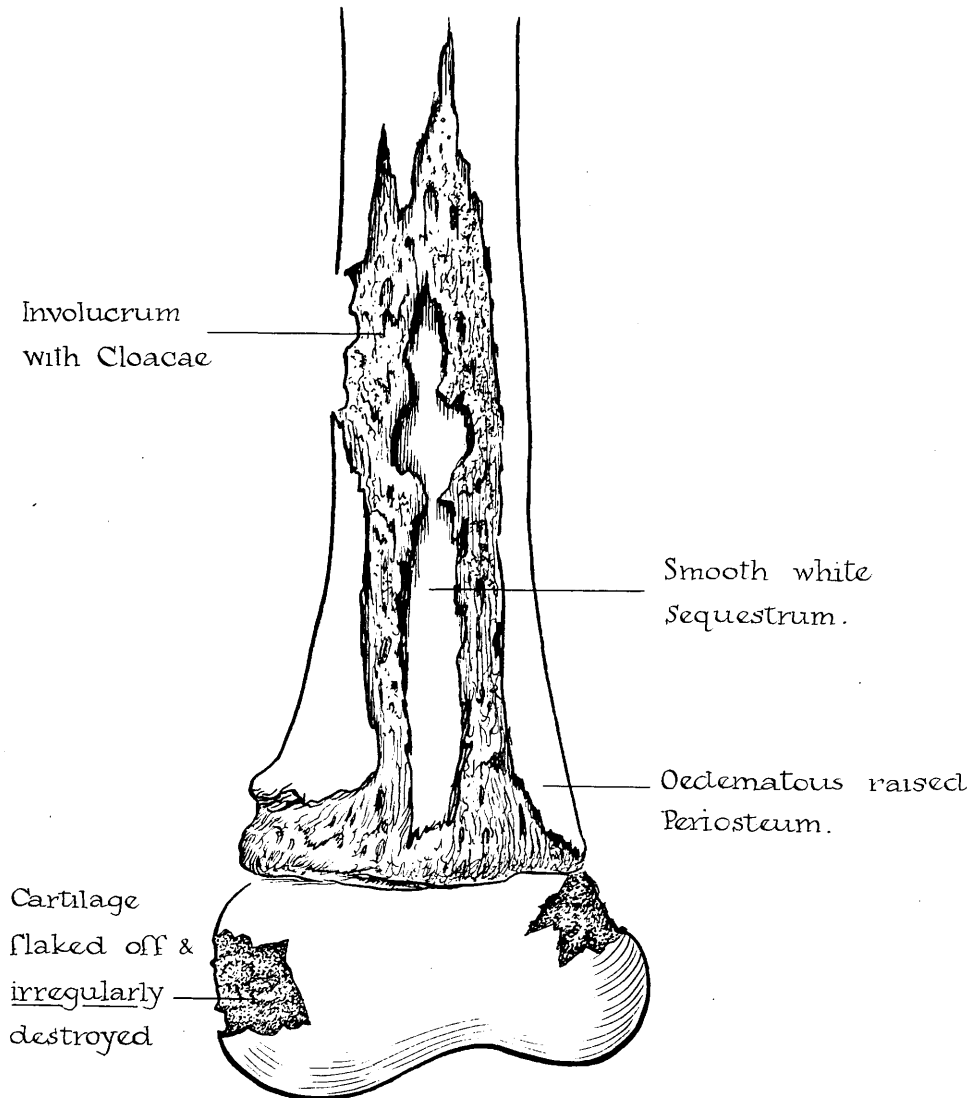
C.F. Peripheral erosion of T.B. and Rheumatoid

PART II

OBSERVATIONS ON THE TREATMENT OF ACUTE HAEMATOGENOUS OSTEITIS

The disease as seen in the

Royal Hospital for Sick Children, Glasgow.

GROUP I.   1936 - 1940   (Pre-chemotherapy)

GROUP II.   1941 - 1945   (Sulphonamide era)

GROUP III.   1945 - 1949   (Penicillin era)

<u>PART II</u>

<u>INTRODUCTION</u>

The treatment of osteitis falls naturally into three periods – (1) the period before the introduction of chemotherapy; (2) the period of effective chemotherapy; and (3) the penicillin "era". The present survey offers a unique opportunity of assessing the various therapeutic agents in three comparable groups of patients treated in one unit of the Royal Hospital for Sick Children, Glasgow, between 1936 and 1949.

<u>Group I</u>   1936 – 1940; the five year period immediately before the introduction of effective chemotherapy. The mortality was 36 per cent.

<u>Group II</u>   1941 – 1945; Sulphathiazole group. During this period the mortality fell to 12.7 per cent.

<u>Group III</u>   1945 – 1949; Penicillin group. In this group there has been only one death – a mortality of 1.2 per cent. (Penicillin became available in the hospital during 1945; eight cases were treated with sulphathiazole; they are included in Group II, and twelve patients were treated with penicillin and they are included in Group III).

The mortality in all three groups is shown in Figure 5.

<u>Figure 5</u> /

Figure 5

Relative mortality in Groups I, II and III

MORTALITY
1936–1949

GROUP I (1936 - 1940)
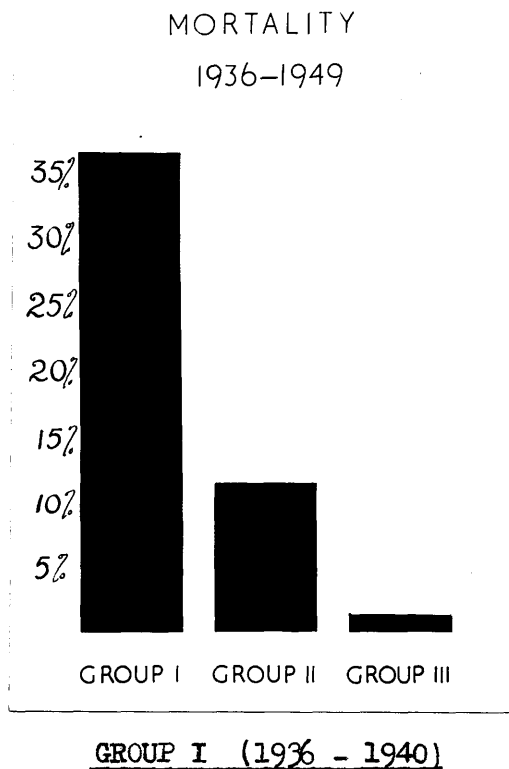
During the five year period 1936-1940 inclusive, 130 patients were admitted to the unit with a diagnosis of osteitis.   Of these, 75 were of the acute septicaemic type and conformed to the definition given in the preface.

Incidence   There were 43 males and 32 females and their ages varied from nine months to twelve years.   The disease was uncommon under the age of two years (Figure 6)

Figure 6

Age incidence in acute haematogenous osteitis 1936 - 1940
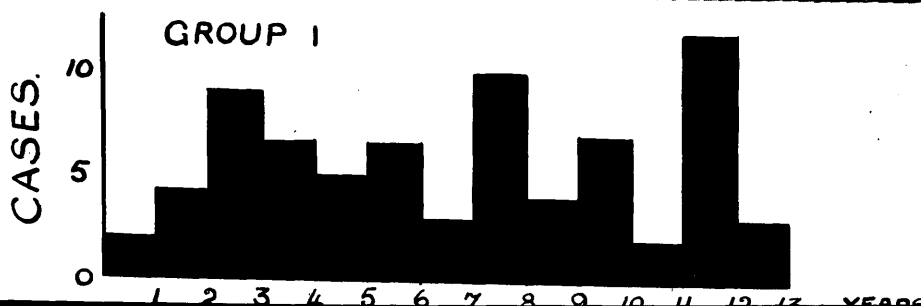
<u>Onset</u>   It is impossible to be accurate about the exact time of onset of
the disease.   The duration of the disease before admission to hospital is
taken from the time of onset of local pain in the affected limb.   This varied
from one to ten days in this group and 41 patients were admitted within four
days of onset.   Duration of disease before admission to hospital is shown on
Figure 7.

<div align="center"><u>Figure 7</u></div>

DURATION OF PAIN BEFORE ADMISSION 1936-1940

60 OF 75 CASES.
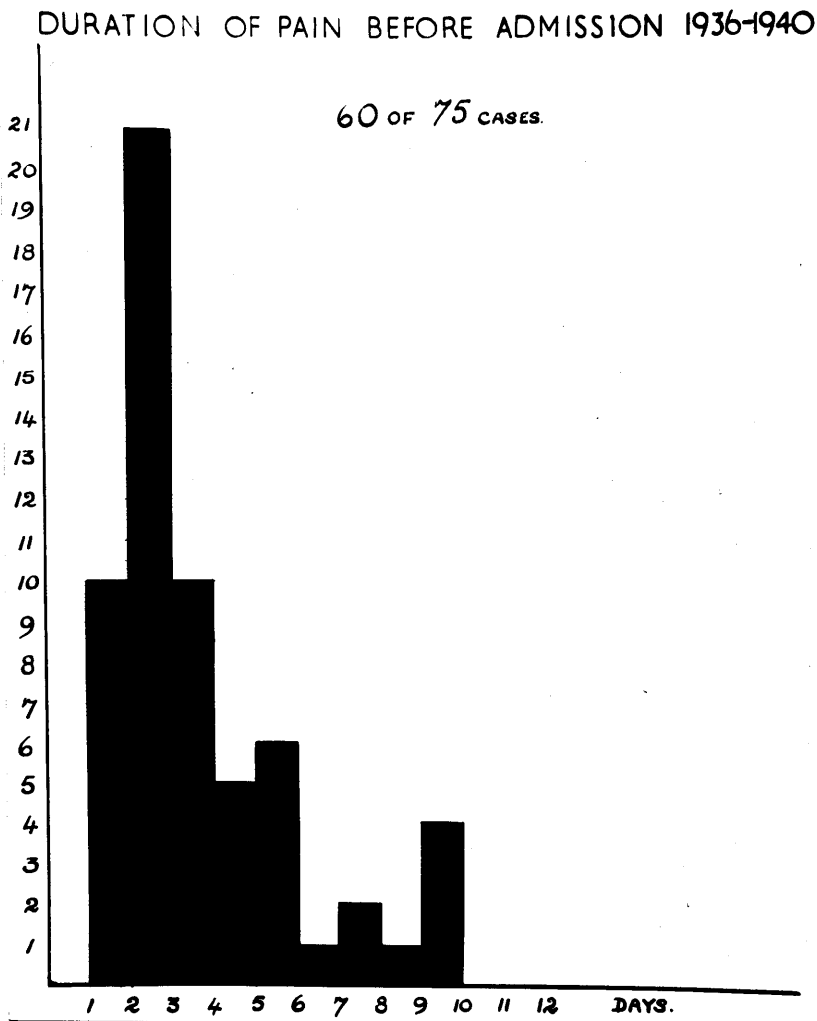
<u>Trauma and Septic Focus</u>   There was a history of trauma in 41 cases (53%)
and evidence of a septic focus was found in 27 (36%).

<u>Bacteriology</u> /

<u>Bacteriology</u>   Blood culture was positive in 38 patients (50%) before treatment began and was rarely positive after the ninth day in those that survived.   Colony counts are considered by some to give an indication of the severity of the infection.   Butler (1940 and 1946) found that patients with a high colony count (over 500) usually died; those with a colony count of over 30 had a 40 per cent mortality; cases with a colony count of less than 20 showed a 20 per cent mortality.   Colony counts in the blood culture were performed in only two patients in this group.   One with a colony count of only 15 died; the other had a colony count of 150 and she lived.   It is possible that a rising colony count is more important than the actual count per c.c.   The infecting organism (grown from the blood or pus) was a staphylococcus aureus in 71 cases (95%); 3 infections were streptococcal and one was due to a pneumococcus.   27 patients died - a mortality of 36 per cent. Staphylococcal infection was responsible for 26 of the fatalities, the remaining one being due to the pneumococcus (Table II).

TABLE II

Bacteriological findings in Group I

Infection	Number	Deaths	Mortality
Staphylococcal	71	26	36%
Streptococcal	3	-	-
Pneumococcal	1	1	100%
Total	75	27	36%

<u>Bones affected</u>   The most common sites were the femur and tibia as in most reports.   The frequency and relative death rate of each site is shown in Figure 8.

<u>Figure 8</u> /

Figure 8

SITE AND MORTALITY.
1936 — 1940

☐ NUMBERS

■ DEATHS.

Bar chart with y-axis labelled 25, 20, 15, 10, 5. X-axis labels: TIBIA. FEMUR. HUMERUS. RADIUS. ULNA. PELVIS. FIBULA. MANDIBLE. RIBS. TARSUS. META-TARSUS. MAXILLA.
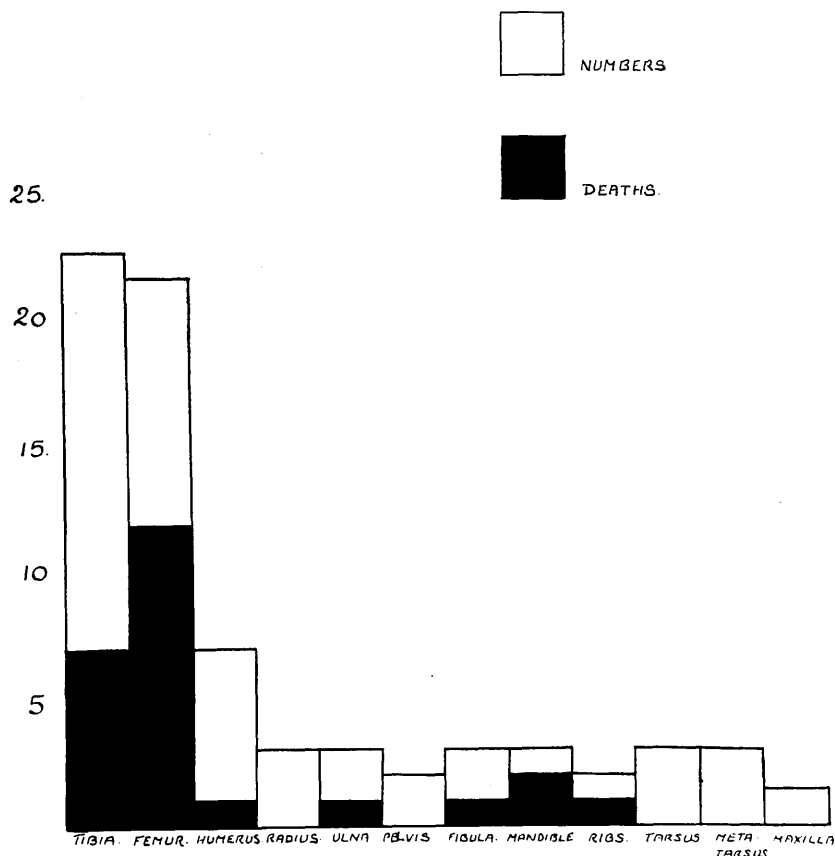
Clinical Course   All cases in this group were obviously ill on admission with a flushed face, bright eyes and dry furred tongue.   Attempts at examination were usually resented and the child screamed when any attempt was made to touch or move the affected limb.   Only too frequently the toxaemia was so severe that the child was comatose on admission and localisation was exceedingly difficult.   But even in less severe infections generalised pain and tenderness rendered accurate diagnosis difficult.   The temperature was usually high (103 - 105°F) but in severe cases a subnormal temperature was sometimes /

sometimes recorded. A typical temperature chart in a fatal case is shown in Figure 9. In the more successful cases the temperature usually remained elevated for several weeks.

Figure 9.

Typical temperature chart in a fatal case of osteitis

Name { RONALD
H —

Age 6 3/12 YRS.

Ward

DATE OF ADMISSION
10.3.39

Disease ACUTE
OSTEITIS
FEMUR

Result
DIED 15.3.39

TEMPERATURE

PULSE

P.M. ACUTE OSTEITIS
FEMUR. PYAEMIA.
MULTIPLE ABSCESSES
LUNGS & KIDNEYS
SUPPURATIVE
PERICARDITIS.
BILATERAL
EMPYEMA.

RESPIRATION
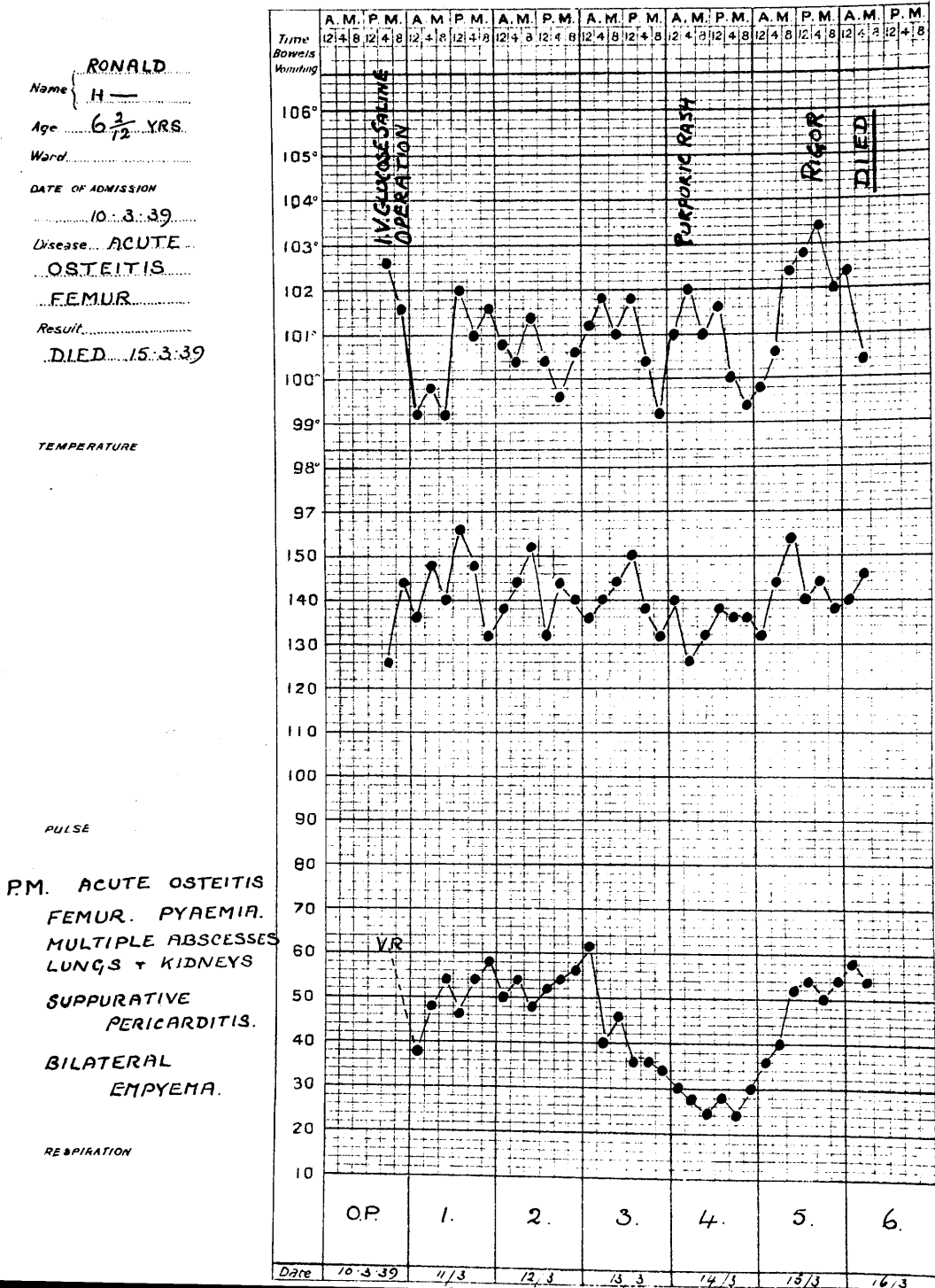
In the more superficially placed bones, local swelling usually appeared early and was followed by a red discolouration and effusion into an adjacent joint.   These classical local signs were late in lesions of the pelvis, ribs and upper femur.   Leucocytosis was present in all but the most fulminating cases.   Rigors usually indicated pyaemic abscess formation although the presence of such lesions could usually only be confirmed at autopsy.   Apart from soft tissue oedema radiographic changes were rarely seen before the tenth or twelfth day of the illness and radiology had little to offer in the early diagnosis of acute osteitis.

Duration of stay in hospital of non-fatal cases.   There were many factors affecting the duration of stay in hospital.   Quite apart from the general and local condition of the patient, home conditions often affected the decision to detain the patient in hospital for a prolonged period.   The figures are shown in graphic form in Figure 10 but the many and varied factors concerned vitiate any conclusions.

<u>Figure 10</u>

Duration of stay in hospital in 40 non-fatal cases.
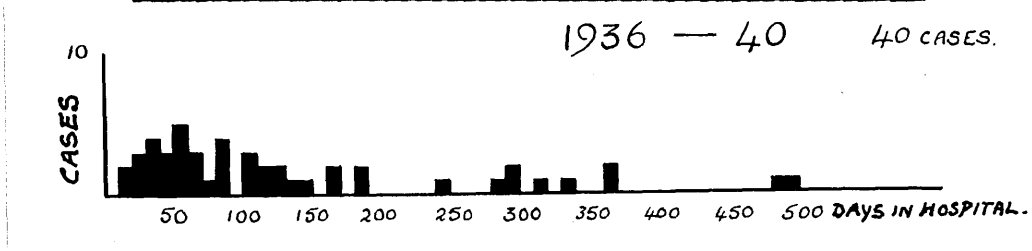
Radiography   Many of the X-ray films taken of cases during this period have been destroyed and many more were X-rayed through plaster of Paris with consequent blurring of bone detail.

For ten or twelve days there were no bony changes (Brailsford 1945) and /

and then a layer of new subperiosteal bone could be seen.   Within a few days, areas of rarefaction in the metaphysis appeared but the changes were soon obscured by dense involucrum formation.   Almost invariably the changes appeared throughout the shaft and after four weeks the dense dying shaft could be seen through the more porous involucrum.   (Figure 11).   Over a period of months sequestra of varying size could be seen to separate, while the involucrum became even more dense, obscuring the details of bony change.

Figure 11

Case E.A. 1937.   Extensive osteitis of left humerus with gross involucrum formation and pathological fracture.

Mortality   As stated above, 27 of the 75 patients died and almost half of the deaths (13) occurred within five days of admission.   In Table III the mortality is compared with other groups treated during this pre-chemotherapy period.

TABLE III

Results of treatment of acute osteitis before the
introduction of chemotherapy.

Author		Cases	Deaths	Mortality Rate (per cent)
Ogilvie (1928)		51	11	21.6
Lloyd (1932)		40	13	32.5
Williams (1932)		91	18	19.8
Pyrah & Pain (1933)		262	71	27.1
White (1937)		200	33	16.5
Butler (1940)	1919-1921	100	31	31
	1922-1924	100	28	28
	1925-1927	100	19	19
	1928-1931	100	23	23
	1932-1937	100	26	26
Wilkinson (1948)		674	140	20.7
Mason Brown (1936-1940)		48	12	25
Present Series (1936-1940)		75	27	36

Autopsy Findings   Of 27 fatal cases, 19 were submitted to autopsy and all showed pyaemic lesions.   Such lesions were usually widespread, suppurative pericarditis, abscesses in the lungs and kidneys being particularly common (Table IV)./

(Table IV).

TABLE IV

Results of Autopsy in 19 cases.

Total number of autopsies	19
Pericarditis	10
Empyema	4
Abscesses in lungs	16
Abscesses in kidneys	15
Arthritis	5
Metastatic osteitis	0
Subcutaneous and intramuscular abscesses	2
Abscesses heart wall	2
Endocarditis	3
Abscesses liver	1
Meningitis	1
Supp. otitis media	1

In all cases there was a large septic spleen from which abundant Staphylococcus aureus was grown. 14 cases (50%) died within the first week and in none of these were there gross changes in the metaphysis either at operation or at autopsy. 19 patients (66%) died within the first fourteen days.

Complications

Arthritis   Of the 48 cases which recovered, 2 presented definite evidence of pyogenic arthritis, without evidence of osteitis in the adjacent metaphysis; 10 cases presented evidence of pyogenic arthritis by direct extension with involvement /

involvement of twelve joints.   Two joints were drained by repeated aspirations with return of complete range of movement.   Of 8 cases treated by open drainage 4 subsequently became ankylosed, 1 developed a full range of movement and 3 regained about 50 per cent. of normal function.   Butler (1940) reported 118 cases of arthritis occurring in a series of 500 cases of acute osteitis.   His results are shown in Table V.

TABLE V

Results of treatment of 118 cases of pyogenic arthritis (Butler 1940)

Treatment	Total	Good	Limited	Ankylosis	Amputation	Died	Untraced
Aspiration	56	8	7	12	8	14	10
Drainage	48	3	3	9	9	18	7
Nil done	14	0	0	7	0	4	3

Limb Lengthening   Gross lengthening was noted in the case records in seven instances and 5 patients in this group with limb lengthening were seen again in 1949.   In none was there any measurable difference in length at this last visit. Unfortunately accurate measurements were not taken in Group I cases and there was no radiographic comparison of the sound and diseased bones.

Pathological Fracture   Unfortunately the case records do not give details of pathological fractures and many of the X-rays of this period have been destroyed.   I still have the impression that pathological fracture was common and union so certain that the incident was scarcely worth recording on the case notes.   Butler (1940) on the other hand, reports only six pathological fractures in a series of 500 cases treated in the London Hospital between 1919 and 1937.

Contemporary /

Contemporary Methods of Treatment

Treatment during this period was essentially surgical. The use of maggots (Baer 1931) and maggot extract had been abandoned by 1936. The results of administration of intramuscular anti-scarletinal serum (Romanis and Michiner 1932) and intravenous mercurochrome (Mercer 1932) were disappointing. Sulphanilamide (Prontosil) raised hopes for a short period but even in massive doses this drug had no effect in staphylococcal infection. Uleron (a dimethyl sulphanilamide) proved useful in the hands of Mitchell (1938) but there was no evidence of any beneficial effect in the cases in this series. Fluid was given freely by all routes and intravenous glucose-saline (6% glucose in normal saline) was administered to all acutely ill patients. Exsanguination and replacement transfusion (Robertson 1927) was not used in any case in this group.

The methods of surgical intervention were based essentially on the teaching of Starr (1922) as modified by Winnet Orr (1927). A long incision was made over the affected metaphysis, down to and through periosteum. If much pus was evacuated nothing further was done to the bone and the wound was lightly packed with vaseline gauze and immobilised in a bivalved plaster of Paris cast. If no gross pus formation was found under the periosteum the periosteum was elevated to ensure that the incision was in the correct place. If no pus was encountered, holes were drilled obliquely from the cortex towards the epiphysis about $\frac{1}{4}$" apart - at least into the centre of the shaft. Although pus was not always obtained, culture from the oedematous marrow or blood oozing from the drill holes always revealed the infecting organism. Within 24-48 hours pus was usually draining freely. In this group the plaster was always bivalved to allow access to the wound until the tissues gained the upper /

upper hand in the fight (White 1935). All dressings were done in theatre with full aseptic precautions.

The results of this method of treatment were satisfactory and the major objection was the intolerable odour of the pus. During the summer these patients were nursed on the large verandahs at the end of each ward, but the usual indication for a change of plaster was the odour which affected not only the patient but other patients and the nursing staff. Obvious indications for change of dressing were rise in temperature and increase in local pain.

More radical surgery was carried out in some instances and gutters of varying extent were made in the affected bone in 14 cases. It is doubtful if the more radical intervention gave more satisfactory drainage (Appendix V). Periosteum strips readily from unhealthy bone and the bone shows neither its usual gloss nor red stippling. The problem of what to do when pus was found beneath extensively stripped periosteum was fully discussed in the section of Surgery at the Royal Society of Medicine in 1931 (Williams et al 1932).

Primary diaphysectomy (Mitchell 1928) was not performed in any case in this group. White (1935) pointed out that no surgeon who has had to wrestle with the case in which the shaft has failed to grow will lightly embark on primary diaphysectomy. The resulting disability is grave and apart from disease of the fibula White's statement was only too true. An exception to this was the almost unique case reported by Rankin (1927) and Blacklock and Rankin (1935). Diaphysectomy was performed on the tibia on two occasions but owing to a further recurrence of infection in the tibia the limb was finally amputated. All three tibiae from the one limb are preserved in the Museum of the /

the Royal Hospital for Sick Children, Glasgow (specimen Nos. 1B 3a, 1B 3b, and 1B 3c).

End Results

In assessing the results of treatment during this period, four factors must be considered (Williams 1932) -

1. The immediate mortality;

2. The saving of the limb;

3. The extent of necrosis of the bone;

4. The persistance of suppuration in after years.

The mortality has already been discussed.   In no case in the group was amputation performed.   Although it is not difficult to produce mortality figures, it is almost impossible to assess statistically the morbidity which followed osteitis before the introduction of effective chemotherapy and antibiotics.   Even to-day, surgeons all over the world are called upon to deal with cases treated in this way; adherent scars which break down and ulcerate, and discharging sinuses due to underlying cavities and sequestra following osteitis which first occurred during the period under discussion are still seen.

Only 16 of the 48 surviving cases were traced.   Of these 2 still had discharging sinuses with ankylosis of the hip joints.   In the others, the wounds were soundly healed although all the scars were depressed and many were adherent.   4 had had further operations since discharge from hospital but at the time of examination the wounds were soundly healed and radiography revealed no evidence of active bone disease.   The number unfortunately is too small to enable one to draw any conclusions and the larger series of Butler (1940) is shown in Table VI.

TABLE VI /

TABLE VI

Follow-up of 223 of 500 cases (Butler 1940)

	No.	Percentage
At work	195	87
Dead	11	4
Good result	110	49
Recurrent operation	87	39
Recurrent discharge	45	20
Recurrent pain	45	20
Deformity	73	32
Other bone operations	44	19

GROUP II   1941 - 1945

During the second period (1941-1945) sulphathiazole was given to all patients suffering from acute haematogenous osteitis.

Incidence   55 such cases were admitted to the unit.   Of these, 31 were males and 24 females.   The ages varied from one to twelve years and the incidence in each age group is shown in Figure 12.

Figure 12

Age incidence in acute osteitis 1941 - 1945
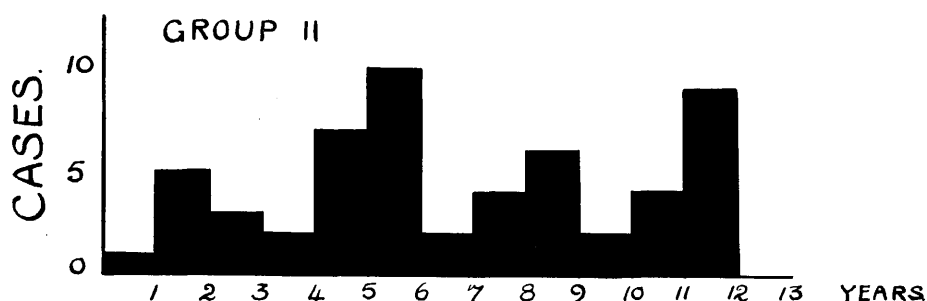
Onset   The duration of local pain before admission to hospital varied from one to nine days and as in Group I most patients were admitted within four days of onset of pain, Figure 13.

Figure 13 /

Figure 13

DURATION OF PAIN BEFORE ADMISSION 1941-1945

49 OF *55* CASES.
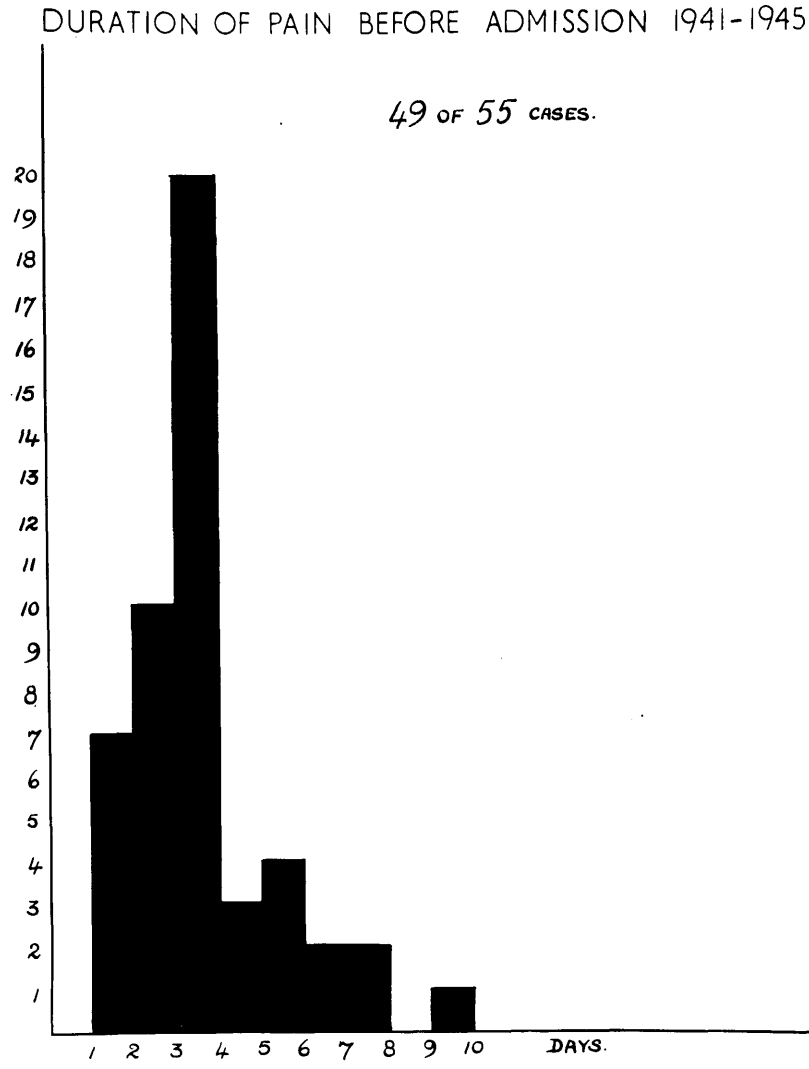
Trauma and Septic Focus   There was a history of trauma in 21 cases (38%) and a septic focus was found in 22 (40%).

Bacteriology   Owing to shortage of medical staff, blood was not taken for culture in every case during the war years.   A positive culture was reported in 22 (40%) of the 55 cases.   The infecting organism was a Staphylococcus aureus in 52 cases, a streptococcus in 2 and one infection was pneumococcal. There was a fatal outcome in 7 cases giving a mortality of 12.7 per cent (Table VII).

TABLE VII /

TABLE VII

Incidence of staphylococcal, streptococcal and pneumococcal infections in Group II.

Infection	Number	Deaths	Mortality Rate (per cent)
Staphylococcus	52	6	11.5
Streptococcus	2	1	50
Pneumococcus	1	-	-
Total	55	7	12.7

Bones affected   The most common sites were the tibia and femur and the sites and deaths from each are shown in graphic form in Figure 14.

Figure 14

SITE AND MORTALITY
1941 — 1945

NUMBER

DEATHS.
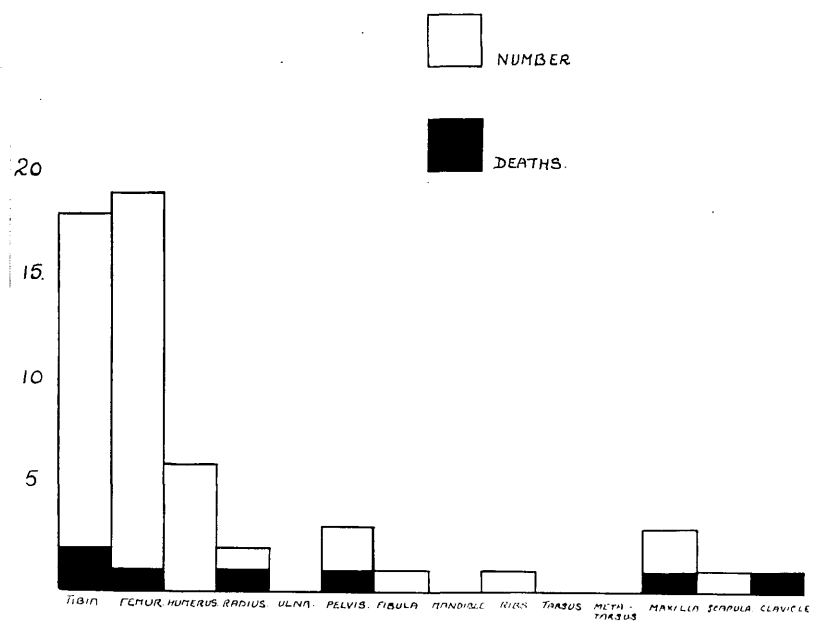
Clinical /

Clinical Course   From a study of the case notes and temperature charts I could detect no spectacular change in the course of the disease when treated with sulphathiazole.   The duration of fever was shorter and metastases were fewer but healing was no more rapid.   From a study of the X-ray films the degree of bone destruction appeared to be less but on the whole the changes were very similar to those seen in the previous group.   McKeown (1943) reported minimal bone changes in a large percentage of his cases but I could not confirm this.   I discussed the problem with McKeown in the Middle East during 1945 and he was enthusiastic about the improvement following the administration of sulphathiazole.

Duration of stay in hospital.   The duration of stay in hospital varied from twenty days to just under two years.   The details are shown in Figure 15.

Figure 15

Duration of stay in hospital in 48 non-fatal cases
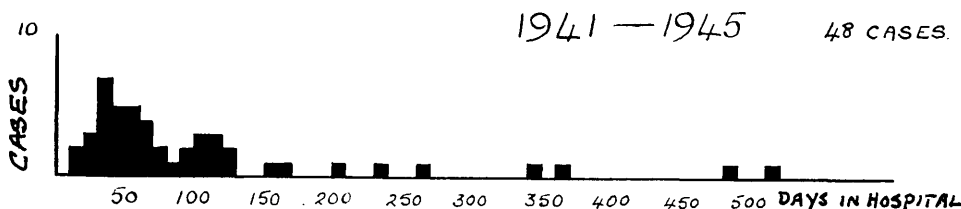
As in Group I, the duration of in-patient treatment does not necessarily indicate prolonged illness.   Stay in the convalescent branch of the hospital is included in in-patient treatment.

Radiographic Changes   McKeown (1943) reported minimal bone changes in a large percentage of his cases, but in this series of acute cases the radiographic changes were on the whole very similar to those in the earlier group.

Figures /

Figure 16

Case M.M. **Osteitis of ulna.** **Day of admission –**
no evidence of bone change; soft tissue oedema

Figure 17

Case M.M. (continued) Osteitis of ulna

(a) <u>raised periosteum</u>; <u>decalcification lower end ulna</u>.
(b) <u>patchy decalcification</u>; <u>subperiosteal bone formation</u>
    <u>throughout shaft</u>.
(c) <u>gross new bone formation</u>.

Figure 18

Case M.M. (continued) Osteitis of ulna.

      (a) old shaft faintly visible through sclerotic new bone
      (b) shaft remoulding and marrow cavity re-appearing.

Figure 19

Case M.M. (continued)   Osteitis of ulna.   X-ray film of both
forearms showing increase in girth of right ulna
and increase in length of right ulna AND radius,
two years after onset of osteitis.

Figures 16 to 19 are selected from the series of films of acute staphylococcal osteitis of the ulna in a child of two years. The lesion healed without sequestrum formation and the radiographs show the changes from soft tissue oedema on the day of admission to increase in length and girth two years later.

Mortality   In this group of 55 cases, 7 patients died (12.7%) and 4 of the deaths (57%) occurred within fourteen days of admission. The mortality in this group is compared with the mortality in the few available reported series of cases treated with sulphathiazole (Table VIII).

<div align="center">TABLE VIII</div>

<div align="center">Mortality in acute osteitis treated with sulphathiazole.</div>

Author	Cases	Deaths	Mortality Rate (per cent)
McKeown (1943)	26	–	–
Hoyt (1944)	27	–	–
Baker et al (1944)	56	1	1.8
Mason Brown (1941-1945)	52	5	9.6
Present Series (Group II)	55	7	12.7

Autopsy Findings   Of 7 fatal cases 6 were submitted to autopsy. All exhibited pyaemic lesions. As in the 1936-1940 group these were most commonly abscesses of lungs and kidneys and purulent pericarditis (Table IX).

<div align="center">TABLE IX /</div>

TABLE IX

Results of Autopsy in 6 cases.

Total number of autopsies	6
Abscesses in lungs	5
Abscesses in kidneys	4
Purulent pericarditis	4
Abscesses in heart	3 *
Endocarditis	1
Arthritis	2
Empyema	4
Subcutaneous and intramuscular abscesses	2

* 1 caused rupture of heart with sudden death on the fourteenth day.

Complications   From the information in the case records it appeared that the complications in this group differ in no respect from those discussed in Group I.

Figure 20 shows typical radiographic changes of sclerosis and increase in length and girth of the affected femur in case A.L. treated with sulphathiazole.   The accompanying photographs show not only the limb lengthening and resulting pelvic tilt but also the depressed and adherent scar which so often followed surgical treatment before the introduction of penicillin.

Contemporary Methods of Treatment   In this group surgical intervention was carried out on similar lines to the methods adopted in Group I.   Drilling of the metaphysis and plaster of Paris immobilisation was combined with fluid administration and sulphathiazole.   The dose of sulphathiazole was based on the minimum effective blood concentration of 2.5 mgms. per cent (McKeown 1943) and was approximately 1 gm. per 20 lbs. body weight per diem.   Sulphathiazole was /

Figure 20   Case A.L.   Osteitis of left tibia.   Photographs show gross lengthening of left leg with pelvic tilt, corrected by 3 cms. block under foot on sound side.   The unsightly depressed and adherent scar is also shown.   X-ray of both tibiae on one film shows sclerosis and increase in girth of left tibia and increase in length of both tibia and fibula.

was given for a week; if considered necessary a second course was given three weeks later. On fifteen occasions the affected bone was guttered (Appendix V).

Hoyt et al (1941) presented a series of cases treated with sulphathiazole without operation on the local lesion and Hoyt (1944) reported 27 cases treated in the same way without a death. McKeown (1943) reviewed 26 cases treated with sulphathiazole combined with various types of surgical intervention from simple incision of the periosteum to drilling and guttering. There were no deaths. Baker et al (1944) reported two series - one treated by open drainage and the second by the closed method - sulphathiazole or sulphadiazine being given to both. Staphylococcal antitoxin was administered to the septicaemic cases. Their results are shown in Table X.

TABLE X

Result of Routine Therapy plus Sulphathiazole or Sulphadiazine or both.

Additional Treatment	No. of cases	Survived	Died	When last seen Healed	When last seen Draining
Surgical Drainage	30	30	0	9	21
Aspiration	26	25	1	21	4
Totals	56	55	1	30	25

All these reports quoted were a mixed series of children and adults.

End Results   Once again, the follow-up was disappointing. Only 19 of the 48 surviving patients were traced; 9 were well with no disability and no radiographic evidence of active bone disease. Of the remaining 11 cases, 5 had been readmitted for removal of sequestra. 4 of these showed gross overgrowth of the affected limb, and lengthening was obvious in other 3 patients. Adherent scars were present in 4 of the 11 cases. Two joints (hip and ankle) were /

were ankylosed and one hip joint was subluxated.   There was one sinus associated with an intrapelvic abscess.   One patient had a flexion deformity of the knee following damage to the posterior aspect of the lower femoral epiphysis. (Figure 21).

During this period the profession had impressive lessons on the dangers of dehydration and changes in the blood chemistry with the result that whether emphasised or not in case reports, patients undoubtedly received more careful attention to maintenance of normal fluid and electrolytic balance. Such acknowledged therapeutic advances must be taken into consideration in evaluating the results of chemotherapy.

Figure 21

Case B.M. Osteitis left femur.   Flexion deformity
following damage to lower epiphysis.

GROUP III   1945 - 1949

Between 1945 and 1949, 82 cases of acute haematogenous osteitis were admitted and were treated with penicillin.

Incidence   There were 48 males and 34 females, and the ages varied from one month to twelve years six months.   The age incidence is shown in graphic form in Figure 22.

Figure 22

Age Incidence in Acute Haematogenous Osteitis 1945 - 1949
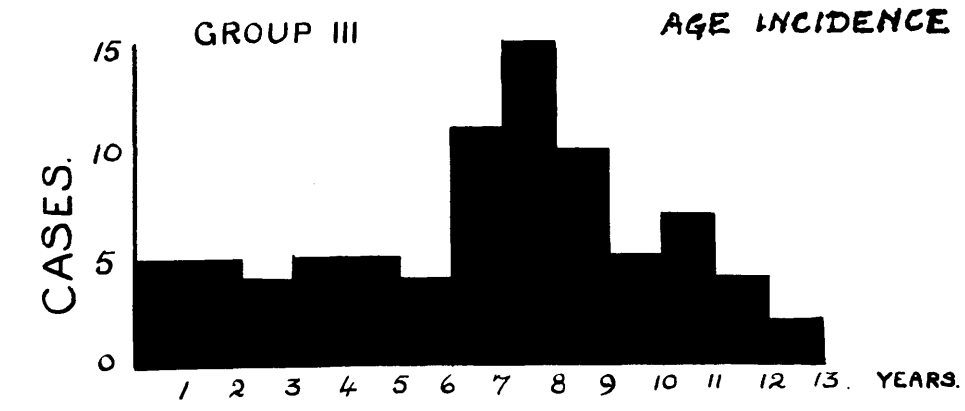
Onset   The duration of local pain before admission to hospital varied from one day to twelve days.   In 5 cases the history of onset was vague, but the duration in 77 cases is shown in graphic form in Figure 23.

Figure 23 /

Figure 23.

DURATION OF PAIN BEFORE ADMISSION 1945 1949

77 OF 82 CASES.
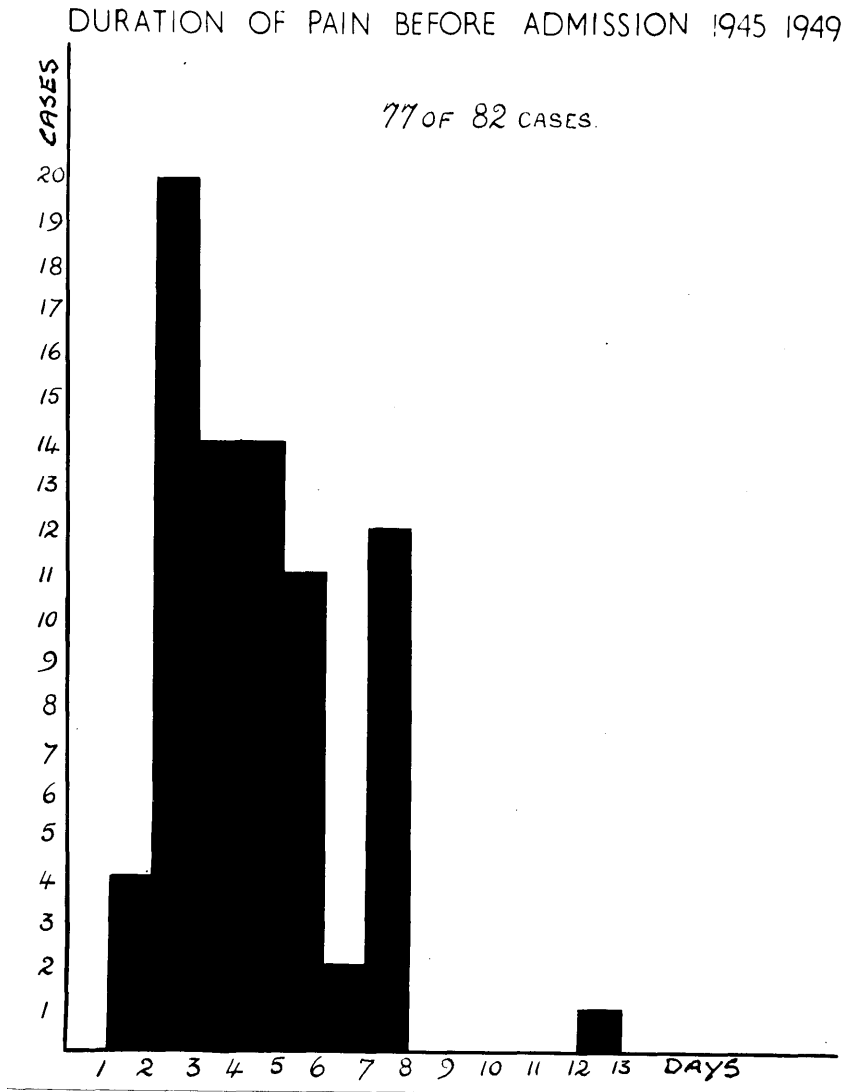
Trauma and Septic Focus   There was a history of trauma in 37 cases (45%) and evidence of a septic focus was found in 27 (32%).

Bacteriology   Blood culture was positive in 39 cases (47%).   The infecting organism (grown from blood or pus) was a staphylococcus in 80 cases;   infections due to streptococcus and pneumococcus each occurred once.

Bones affected   The common sites were again the tibia and femur and the incidence /

incidence of bones affected is shown in graphic form in Figure 24.

Figure 24

SITE AND MORTALITY.

1945 - 1949

Bar chart titled "SITE AND MORTALITY. 1945-1949" with legend: open square = NUMBER, filled square = DEATHS. Y-axis from 5 to 35. Bars for: TIBIA, FEMUR, HUMERUS, RADIUS, ULNA, PELVIS, MANDIBLE, RIB, TARSUS, META-TARSUS, SCAPULA, VERTEBRA, FRONTAL.
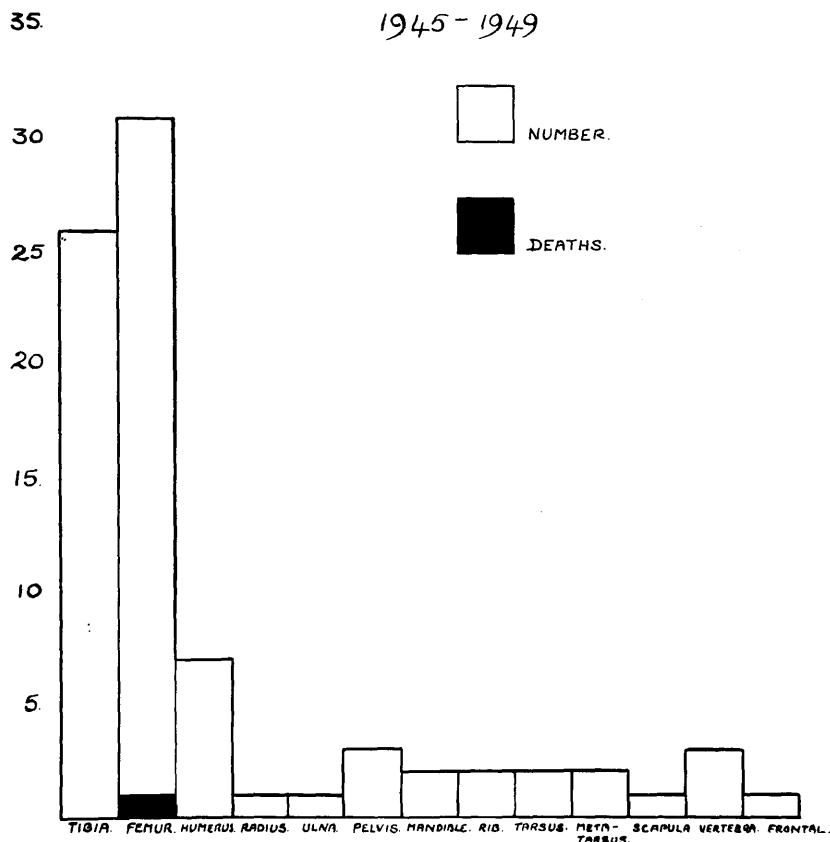
<u>Clinical Course</u>   In acute haematogenous osteitis, the response of

septicaemia to penicillin was neither immediate nor dramatic.   General

improvement was usually slowly progressive from the start of treatment but the

patient remained ill for several days.   Pyrexia continued for about a week,

resolving slowly by lysis.   The blood culture, if initially positive, has been

sterile by the third day in all cases except Case 47, in which the organism was

insensitive to penicillin.   In over 80% of cases in this group pus was present

under the periosteum or in the soft tissues on admission, but neither the

temperature chart nor the leucocyte count was a reliable criterion for assessing

the /

the local condition of the limb.   Careful examination of the limb, repeated

marrow aspiration and accurate radiographic observation were all necessary

when assessing the progress of the bone lesion.   With careful immobilisation

and relief of tension by surgical intervention when indicated, severe pain

was rarely present in penicillin-treated cases after the second day of

treatment.   Swelling due to soft tissue oedema usually subsided within seven

days.   Swelling of longer duration raised the suspicion of persistent deep pus.

<u>Duration of stay in hospital</u>   The duration of in-patient treatment varied

from twelve to one hundred and eighty days and this is shown in graphic form

in Figure 25.   Over 70 per cent of the cases were home within six weeks.

<div align="center"><u>Figure 25</u></div>

DURATION OF STAY IN HOSPITAL.

1945 — 49   81 CASES
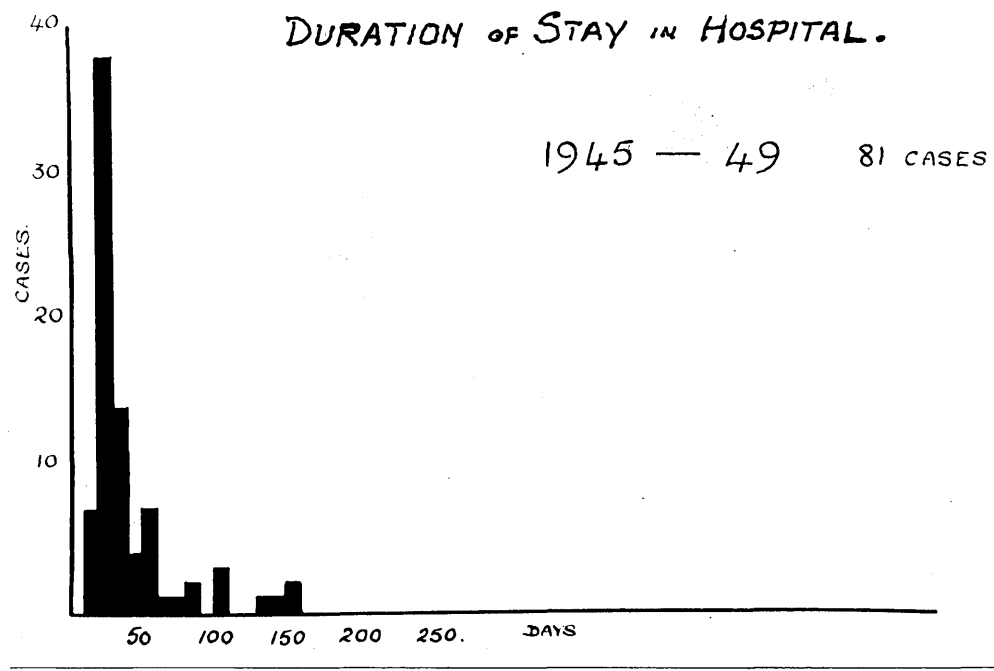
<u>Radiographic Changes</u>   The usual sequence of radiographic changes in penicillin

treated osteitis are now well known and have been described elsewhere

(Dennison 1948).

Generally /

Generally speaking, there was a striking absence of dense involucrum formation (c.f. Figure 11 Group I and Figures 17 and 18 Group II) so that the radiographic changes were more readily seen than in the days before the introduction of penicillin. During the first few days, soft tissue oedema was seen (Figure 16). About the tenth day there was usually evidence of raising of the periosteum and about the fourteenth day a translucent area of decalcification could be seen in the affected metaphysis. From this time onwards new subperiosteal bone was seen and this bone spread for varying distances down the shaft. About twenty-one days patchy decalcification was evident in the metaphysis and usually this decalcification was progressive over a period of months. The appearance of decalcification was exaggerated by the generalised decalcification which is seen in an immobilised limb. After four weeks sequestrum formation was shown by the appearance of areas of increased density. Small sequestra were usually absorbed (Figure 26). Figure 27 shows the importance of positioning in radiography. Even in the most satisfactory cases (Case 24, treated with penicillin without surgical intervention) there was a surprising increase in girth although intervening films showed little evidence of new subperiosteal bone formation (Figures 28 and 29).

Altemeier and Helmsworth (1945), Higgins et al (1947) and Beerman (1948) all reported cases in which the course of disease was typical of acute osteitis but radiographic changes never occurred to confirm the diagnosis. We have all seen such cases and must admit that early therapy may so limit bony changes that they are never sufficiently extensive to be seen by X-ray.

Mortality /

Figure 26

Case 8.   Osteitis of tibia

(a) cavity and sequestrum formation, four months after onset.
(b) absorption of sequestrum and consolidation of cavity
    fourteen months after onset.

Figure 27

Case 22.   Osteitis of femur

(a) five months: cortical sequestrum absorbing.
(b) seven months: cortical sequestrum apparently absorbed.
(c) nine months: sequestrum still present.
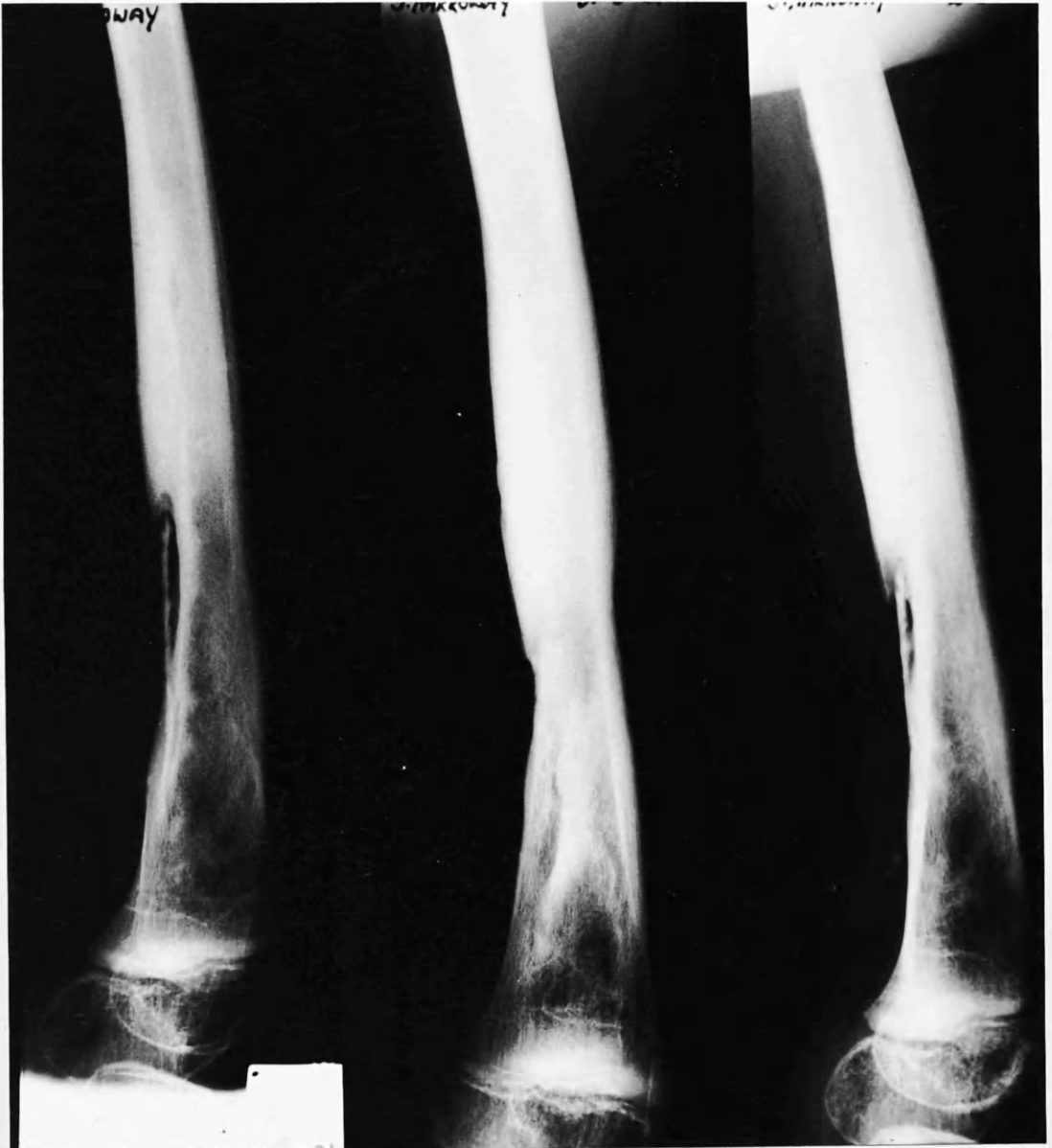
Figure 28

Case 24. Osteitis of right humerus

        (a) on admission: no evidence of bone change.
        (b) tenth day: translucent area upper metaphysis.
        (c) three weeks: patchy decalcification in shaft.

Figure 29.

Case 24. (continued).   Osteitis of right humerus.

        (a) <u>5 weeks</u>:   subperiosteal new bone formation; small
                             cavities with sequestra in shaft.
        (b) <u>3 months</u>: bone recalcified with absorption of cavities
                             and sequestra.
        (c) <u>6 months</u>: no evidence of active disease; sclerosis of
                             shaft and increase in girth (<u>c.f.</u> 28 (a))

<u>Mortality</u>   Of the 82 cases, one died (1.2%).   The organism in this case
was a penicillin-resistant staphylococcus and the case will be discussed
more fully later (Part III, Case 48).   Results reported from other centres
are shown in Table XI.

<div align="center">TABLE XI</div>

<div align="center">Results in penicillin-treated acute osteitis *</div>

Author	Cases	Deaths	Mortality (per cent)
Altemeier & Helmsworth (1945)	34	1	2.9
McAdam (1945)	40	1	2.5
Trueta (1946)	30	0	Nil
Butler (1946)	14	0	Nil
Hudson (1946 a)	37	2	5.4
Higgins et al (1947)	31	0	Nil
Dennison (1948)	30	0	Nil
Tucker & Hollenberg (1948)	39	0	Nil
Wilkinson (1948)	50	0	Nil
Present Series (Group III)	82	1	1.2

*   The reports of Higgins, Dennison and Wilkinson deal with infants and
children;   the others are mixed groups of children and adults.

<u>Autopsy Findings</u> (Case 48).   There was no pus in the hip joint.   A
subperiosteal abscess extended for seven centimetres below the great trochanter.
There was no naked eye evidence of bone focus in the upper femur.   There was
a large septic spleen and pyaemic abscesses in both lungs.

<u>Complications</u>   The complications in the 81 surviving cases were as follows –
arthritis (11 joints), limb lengthening (13 cases), pathological fracture
(8 cases) /

(8 cases), sequestrum formation requiring surgical intervention (15 cases), pericarditis (1 case), stress fracture of a metatarsal (1 case) and subluxation of the axis (1 case).

The major findings, methods of treatment, dosage and duration of penicillin administration and results in the 82 cases in the group are analysed in Appendix I.

PART III

PRESENT DAY TREATMENT AND COMPLICATIONS.

PART III

PRESENT DAY TREATMENT AND COMPLICATIONS

INTRODUCTION

In this section osteitis as seen in Group III is discussed in further detail. The introduction of penicillin has so altered the course of the disease that osteitis as seen in Groups I and II can already be relegated to past history and detailed discussion can serve no useful purpose.

The present day methods and the more common difficulties in treatment will now be discussed and the complications of the disease as seen in the penicillin-treated group will be presented.

TREATMENT

The aim of treatment is to control septicaemia and to reduce tension in the local bone focus. The relief of tension serves the threefold purpose of easing pain, lessening absorption and preserving the blood supply of the bone. If the infecting organism is penicillin-sensitive and penicillin therapy is instituted early, these objects should be achieved without surgical intervention (Florey and Florey 1943). Unfortunately, the average duration of local pain was four and a half days before admission to hospital and in 68 of the 82 penicillin treated cases, pus was present under the periosteum or in the soft tissues on admission and surgical intervention was necessary. It is disappointing that cases come to hospital no earlier

to-day /

to-day than they did fifteen years ago.

Treatment is considered under three headings; general treatment of the patient, penicillin administration, and operative procedure.

GENERAL TREATMENT   This comprises restoration of fluids, electrolytes and proteins and immobilisation of the affected part.   Even if pus is obviously present in the soft tissues, the extremely ill child is not taken to the operating theatre at once.   Penicillin is administered intravenously (after removing blood for culture) and an intravenous plasma drip is set up.   If the capillary circulation is poor the child is placed in an "Oxygenaire" type of oxygen tent and suprarenal exhaustion countered by such preparations as Eucortone or desoxycorticosterone acetate (D.O.C.A.).   In the absence of redness and gross oedema of the part it is hoped that both local pain and signs of toxaemia will abate or at least not become more severe.   If the pain and toxaemia do not abate, one must presume that either there is pus under tension in the bone or under the periosteum or that the organism is not sensitive to penicillin.   Exploration soon settles the first point;   until the bacteriologist's report on sensitivity is received one can only attack the other problem by "blunderbus therapy".   If the patient cannot swallow, sulphonamide (soluthiazole) is given intravenously.   In one extremely ill patient streptomycin was given prophylactically until the organism was reported "penicillin sensitive" (Case 80).   Aureomycin and chloromycetin have not been used in the treatment of osteitis in this series.

Immobilisation   The immobilised limb must be available for inspection and should not be enclosed in a plaster case during the first fourteen days of treatment (Butler 1946).   In two early cases (11 and 17) an unsuspected soft /

soft tissue abscess formed under a plaster case and evacuation of pus was unduly delayed. A fibre abduction splint is used in osteitis of the humerus; the forearm bones are immobilised in a plaster of Paris gutter and later in a fibre or "perspex" splint; skin traction is used for pelvic and upper femoral lesions and a posterior plaster of Paris gutter or padded Cramer wire splint for all other lesions of the lower limb. Immobilisation is continued after the acute phase to avoid pathological fracture as the bone becomes progressively decalcified. During this period, a sling is used for the upper limb, a walking caliper for femoral lesions and plaster of Paris for other lesions of the lower limb. Immobilisation is continued until radiographic examination shows satisfactory recalcification and this may take many months. It is essential, however, to differentiate post-inflammatory decalcification from decalcification due to prolonged immobilisation. This is done by radiographic examination of the other bones of the immobilised limb. Too prolonged immobilisation delays restoration of trabecular structure.

PENICILLIN ADMINISTRATION   Those of us who had the opportunity of using penicillin before its general release were impressed with our responsibility to ensure that the clinical diagnosis was accurate and supported by bacteriological evidence, not only of the organism responsible but also of its sensitivity to penicillin. In the early cases in Group III only small quantities of penicillin were available and it was necessary to exercise the strictest economy in its use. So that the value of penicillin could be assessed in acute osteitis, the early cases were treated as far as was clinically justifiable with penicillin alone and no sulphonamides were given in the first 30 cases (Dennison 1948).

Penicillin /

Penicillin administration was started as soon as the clinical diagnosis was made and after blood was withdrawn f or culture. During the first twelve months of this period (Cases 1-23 - Appendix I) penicillin was given by continuous intramuscular drip, 100,000 units in 100 c.c. of sterile saline each twenty-four hours, using the Eudrip No. 3 apparatus (McAdam et al 1944). Administration was continued for nine to fourteen days. A therapeutic blood level was found in each specimen of blood assayed (Buchanan 1946). Although this was probably the most economical method of giving penicillin it was never popular with the nursing staff because - (1) an ill and restless child needed constant supervision to ensure that the needle remained in place; (2) the needle in the thigh caused discomfort and restricted movement; older children stated their preference for intermittent injection; (3) the rate of flow was often difficult to control and after repeated sterilisation the apparatus required more frequent attention; (4) despite the reinsertion of the needle in new positions every second day sterile "abscess" formation was not uncommon. Continuous infusion was therefore abandoned in favour of intermittent injection.

Following the procedure of Florey and Florey (1943) intramuscular injections were given at three-hourly intervals. At the same time, penicillin blood levels were assessed after injections at four, five and six-hourly intervals. The modified slide-cell method of Bigger and his colleagues (1944) was used in these estimations. Our personal standard of adequate blood bacteriostasis to the standard H. strain Staphylococcus aureus (Fleming 1946) was set at inhibition in a dilution of 1 in 2 (0.06 units/c.c.) at the end of the period being investigated. We failed to confirm the therapeutic levels maintained by Buchanan (1946) at the end of the six-hour period (Table XII).

TABLE XII /

TABLE XII

Serum Inhibition after an injection of 50,000 units
of Penicillin.

Case	At 3 hours	At 4 hours	At 5 hours	At 6 hours
22	Complete at 1 in 4	Complete at 1 in 2	Partial in undiluted serum	No inhibition
23	Complete at 1 in 2	Complete in undiluted serum	Partial in undiluted serum	No inhibition
24	Complete at 1 in 4	Complete at 1 in 2	Partial in undiluted serum	No inhibition
27	Complete at 1 in 8	Complete at 1 in 4	Complete in undiluted serum	Partial in undiluted serum
28	Complete at 1 in 4	Complete at 1 in 2	Complete at 1 in 2	Complete in undiluted serum
29	Complete at 1 in 8	Complete at 1 in 4	Partial in undiluted serum	No inhibition
30	Complete at 1 in 16	Complete at 1 in 4	Complete in undiluted serum	Partial in undiluted serum

Adequate serological levels at 3 and 4 hours in all cases; inadequate levels at 5 hours in 4 cases; therapeutic level in one case at 6 hours; c.f. Buchanan (1947).

Irrespective of age and body-weight, it was the exception to obtain complete inhibition of the standard staphylococcus beyond four hours (Figure 30).

Figure 30 /

Figure 30

Average result of bacteriostatic estimations of serum after single intramuscular injection of penicillin.

FIGURE 30

AVERAGE RESULT OF BACTERIOSTATIC ESTIMATIONS OF
SERUM IN ALL AGE GROUPS AFTER A SINGLE INTRA –
MUSCULAR INJECTION OF PENICILLIN.

HOURS AFTER SINGLE INTRAMUSCULAR INJECTION.
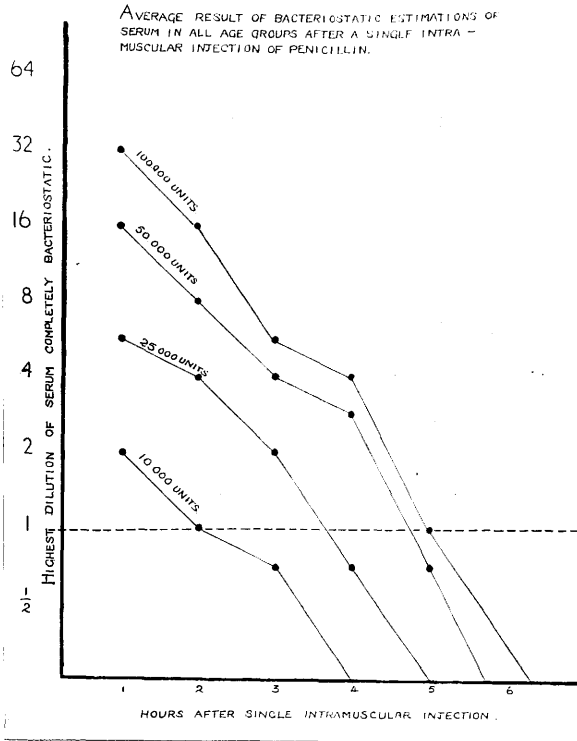
If the individual dose was less than 30,000 units, injections were given at

three-hourly intervals; doses of 30,000 units and over were given at four-

hourly intervals (Dennison 1948).   The dosage and duration of administration

presented a serious problem.   Bodian (1945) advocated a dose of 1,000 units

per lb. body weight each twenty-four hours by intramuscular injection.

Buchanan (1946) in the Royal Hospital for Sick Children, Glasgow, found that

such doses were insufficient to maintain a constant therapeutic level in the

blood and reported that 2,000 units per lb. per twenty-four hours were

necessary.   Knowing little about "degrees" of penicillin resistance, I

decided to double this dose.   5,000 units and its multiples were much more

convenient for dispensing purposes and it was therefore decided that we would

use /

use a daily dose of 5,000 units per lb. body weight. Using an approximate average weight for each age group the scheme shown in Table XIII was drawn up as a guide for the resident medical staff (Dennison 1948).

TABLE XIII

Scheme of Penicillin Dosage used as a guide to
Resident Medical Staff.

Age Group	Dose each 24 hours	Frequency and Route
Birth — 3 months	80,000 units	Three-hourly by mouth
3 months — 6 months	80,000 units	Three-hourly by intramuscular injection
6 months — 12 months	120,000 units	Three-hourly by intramuscular injection
1 year — 5 years	200,000 units	Three-hourly by intramuscular injection
5 years — 10 years	300,000 units	Four-hourly by intramuscular injection
10 years — 12 years	450,000 units	Four-hourly by intramuscular injection

Penicillin is maintained in the Ward refrigerators in strengths from 10,000 up to 1,000,000 units per c.cm. in pyrogen free sterile water.

Although these doses have been frequently exceeded they have served as a guide to an ever changing medical and nursing staff for almost four years.

For comparative purposes, doses suggested by other authors in the treatment of osteitis are shown in Table XIV.

TABLE XIV. /

TABLE XIV

Author	Penicillin Dosage
McAdam (1945)	100,000 units daily by drip for 21 days (with marrow control)
Bodian (1945)	1,000 units/lb/24 hours for 7 - 14 days.
Compere et al (1945)	15-20,000 three-hourly until temperature is normal for five days
Hudson (1946)	60,000 units three-hourly for 10 - 12 days.
Self (1948)	50-100,000 units three-hourly until infection under control.
Wilkinson (1948)	50,000 units three-hourly (+ 0.2 - 0.25 gms. sulphadiazine/Kgm. body-weight/diem) for 10 - 14 days.
Tucker & Hollenberg (1948)	500,000 units/diem for 28 days
Altemeier & Wadsworth (1948)	20-100,000 units three-hourly for 21 days +
Beerman (1948)	50,000 units three-hourly for 14 - 28 days.
Trueta (1948)	400,000 units/diem for first three days
	300,000 units/diem fourth day.
	200,000 units/diem fifth day and onwards.
Drijvers (1949)	300-500,000 units/diem + sulphonamides
Stocker (1949)	300,000-1,000,000 units/diem + sulphonamides + local administration of penicillin.

Until July 1946 penicillin administration was stopped when septicaemia was controlled and in the first 23 cases (Appendix I) it was given only for periods of nine to fourteen days. Following the experience of Aird (1945) and McAdam (1945) with marrow cultures it was decided to perform routine marrow punctures on the seventh, fourteenth and twenty-first days or until the marrow was sterile (Dennison 1948). Until February 1947 (Case 33) /

(Case 33) all marrow cultures were reported sterile on the fourteenth day but penicillin was continued for a further seven days. It was then found that penicillin sensitive staphylococci could be grown from the marrow after twenty-one days of apparently adequate penicillin administration (Appendix II, Cases 33 and 35). The implications of this finding are discussed later.

At this period two methods of treatment were adopted in cases of subacute osteitis (not included in the cases under discussion). In both groups intermittent injections were given for ten days (until septicaemia was controlled). In the first group, the bone infection was attacked by a modification of the intermittent method of treatment of staphylococcal infections suggested by Bigger (1944, 1 & 2). In the other group, penicillin was given in a dose of 100,000 units three times a day from the eleventh to the twenty-first day, this being based on experimental work on penicillin levels in bone cavities after sequestrectomy and conforming to the work of Florey et al (1946) on wounds. These methods have been described elsewhere (Dennison 1948) but they were not persevered with as the details required too much supervision and apparently offered no advantages over the more routine method shown in Table XIII.

The frequent intramuscular injections of penicillin preparations cause pain and unhappiness to many of the children. We have followed with interest the many attempts to prolong the therapeutic action of a single injection, by delayed absorption or by delayed excretion. The disadvantages (Dennison 1948) of the oil and wax preparation described by Romansky and Rittman (1944) were overcome by the introduction of an insoluble salt of procaine and penicillin (Jones and Shooter 1948, and Carson et al 1949).

Like /

Like Emery, Stewart and Stone (1949) we found that blood levels were too variable for reliance to be placed on once daily injections. Satisfactory levels were invariably found at twelve hours and the preparation was occasionally used in acute osteitis to allow an exhausted child a complete night's rest. Using procaine penicillin with aluminium monostearate (Emery, Rose et al 1949) more consistent blood levels were maintained but not infrequently the minimum desired level of 0.06 units per ml. was not found at twenty-four hours. A new preparation of procaine penicillin G in aqueous suspension is at present under trial in the hospital. "Caronamide" - 4' - carboxyphenylmethane-sulphonanilide - (Beyer 1947) inhibits the tubular excretion of penicillin, but as it is possible that it may cause renal damage in some cases (Hunter et al 1948) this compound has not been used in the surgical division of the hospital.

Although the various procaine penicillin preparations are used in less acute staphylococcal infections and in the Out-Patient Department, it is doubtful if they have any place in the treatment of acute osteitis.

OPERATIVE PROCEDURES   Once an abscess has formed it cannot be sterilised by the general administration of penicillin, and so long as cases of acute osteitis continue to arrive at hospital with pus under the periosteum or in the soft tissues, surgery cannot with impunity by discarded completely. Surgical procedure has been discussed fully elsewhere (Dennison 1948) and only a brief outline is given here.

Aspiration   In spite of reports to the contrary (Higgins et al 1947) I have personally found that aspiration is rarely successful in evacuating pus in acute osteitis. The pus may be too thick to pass through the needle or

through /

through the nozzle of the syringe.   After aspirating pus as thoroughly as possible, it is instructive to leave the needle in position and to cut down on the abscess; the quantity of residual pus is usually considerable.   In osteitis of the tibia, pus frequently collects between the tibia and fibula rather than on the subcutaneous surface as one might expect.   It is difficult to aspirate pus adequately from this inter-osseous position.

Incision   After incision of a soft tissue or subperiosteal abscess, pus is evacuated as completely as possible by gentle swabbing and by breaking down loculi with the gloved finger.   The soft tissues are then insufflated with penicillin-sulphathiazole powder and the wound is sutured round a wide-bore needle inserted into the deepest part of the wound.   When suturing is complete penicillin is instilled down the indwelling needle, the needle is removed and a dry dressing applied.   No sulph-granulomata have followed the practice of insufflating the wound with penicillin-sulphathiazole powder.

One must be prepared to re-open an occasional wound as the cavity may refill from the metaphyseal focus.   In osteitis of the lower end of the femur the subperiosteal abscess is sometimes extensive and in such cases it is my practice to suture the wound, leaving a narrow bore perforated rubber tube leading into the depths of the cavity.   If necessary, the tube is brought out through a posterior stab wound to ensure dependant drainage of the popliteal fossa.   Penicillin is instilled down the tube at the conclusion of the operation and the tube is occluded with a sterile spigot.   After two hours , the spigot is removed and the tube drained into a sterile test tube. The instillation of penicillin followed by drainage two hours later, is repeated each morning for about three days; the tube is then removed. Theoretically /

Theoretically, the tube should remain in situ until the drained fluid is sterile, but if it is left for more than three or four days the resultant sinus may take some time to heal. There is also the risk of secondary infection with a penicillin resistant organism. Bact. coli and B. proteus have been grown from the sinus track in cases of chronic osteitis but in no case has the secondary invader reached the underlying bone.

Bone drilling   Bone drilling should rarely be necessary but less harm will be done by bone drilling followed by primary sutures of the skin, than by incomplete relief of tension. If pus is present in the soft tissues or under the periosteum, the tension in the bone has probably been relieved. If acute pain persists after simple incision or at a later stage if one suspects that the blood supply to the bone is inadequate, drill holes without elevating the periosteum will at least give an alternative blood supply and will also allow local instillation of penicillin. Metaphyseal decompression (Tucker and Hollenberg 1948) should certainly be carried out if there is any suggestion of tension within the bone.

Guttering and "saucerisation" have no place in the modern treatment of acute osteitis. Diaphysectomy should never be necessary but in two cases of extensive osteitis of a rib the necrotic bone was removed and the wound sutured (Cases 38 and 49, Appendix I).

Arthritis   Pyogenic arthritis in an associated joint has been treated by aspiration and local instillation of penicillin. In only one case was it necessary to open a knee joint to evacuate pus (Case 73). Although parenteral penicillin may reach the cavity of an inflamed joint, an effective concentration /

concentration cannot be guaranteed by systemic administration.   Following the aspiration of as much fluid as possible it is our custom to instil one mega-unit of penicillin in a volume of two millilitres.

UNSATISFACTORY CASES

All centres can now show a high percentage of successful results in acute haematogenous osteitis treated with penicillin.   The 82 cases in this series are analysed in Appendix I but I feel that more can be learned from a more detailed analysis of those cases which did not proceed uneventfully to a satisfactory conclusion.   Since 1945 there have been 14 such cases and 13 surviving cases are discussed in some detail in Appendix II.   They can be divided into three groups.

Group A   Cases inadequately treated.

Group B   Cases in which the blood supply to the bone was seriously interrupted - (1) by raising of the periosteum,

(2) by thrombosis of the nutrient artery (Figure 2).

Group C   Cases in which the causal organism was resistant to penicillin.

Group A   In the first 23 cases treated in the unit penicillin was administered by continuous intramuscular drip.   The average duration of administration of penicillin was eleven days and the average total dose was only 1.3 mega units.   Coagulase positive staphylococci were grown from the blood in 13 cases and in 13 obvious pus was present in the soft tissues on admission.   By present standards both the total dosage and duration of penicillin administration were inadequate.   And yet 12 cases proceeded uneventfully to recovery and have been followed up for at least three years.

All /

All have full joint movements, there have been no recurrences, and although the bone architecture is not completely restored to normal in all cases there is no evidence of bone disease in any.   Case 5 developed scarlet fever on the twenty-fourth day and will be discussed later.   The remaining 9 cases constitute Group A and they will be discussed in some detail in Appendix II. In this group there were two major errors.   Early cases were treated without surgical intervention and cases 4, 11, 14 and 17 were immobilised in a complete plaster of Paris case shortly after admission.   Although the temperature fell to normal and pain disappeared, subperiosteal and soft tissue abscesses formed quietly and undetected and irreversible bone damage occurred.   Recurrent abscesses required evacuation in cases 4 and 11 and Figures 31 and 32 illustrate the consequent increase in length of the affected limb.   Sequestrectomy was required in cases 14 and 17.   The second mistake was our failure to recognise the importance of primary suture.   In cases 8, 15 and 19, packing of the wound prevented restoration of the periosteal blood supply and led to sequestrum formation.   Figures 33 to 35 illustrate the sequence of radiographic changes in case 15.

Group B   From July 1946 penicillin was given by intermittent injections in a dose of 5,000 units per lb. body weight each 24 hours.   Penicillin administration was continued for three weeks or until the marrow was sterile. Until December 1949 a further 60 cases were treated.   Surgical intervention was required in all but 4 cases.   There must have been interference with the blood supply to the bone in all cases, but in 4 this interference was obvious from radiographic appearances, marrow punctures and ultimate sequestrum formation.   If the blood supply is cut off, penicillin cannot reach the bone focus in therapeutic doses.   Cases 33, 35, 58 and 72 are discussed in some

detail /

Figure 31

Case 4.   Osteitis of left femur.   X-ray shows increase
          in length and girth of left femur following osteitis
          of upper end twenty-nine months previously.

79.

Figure 32   Case 14   Osteitis of right femur.   Photographs show 2.5 cms. increase in length of affected limb with pelvic tilt and scoliosis, corrected by 2.5 cms. block under foot on sound side.
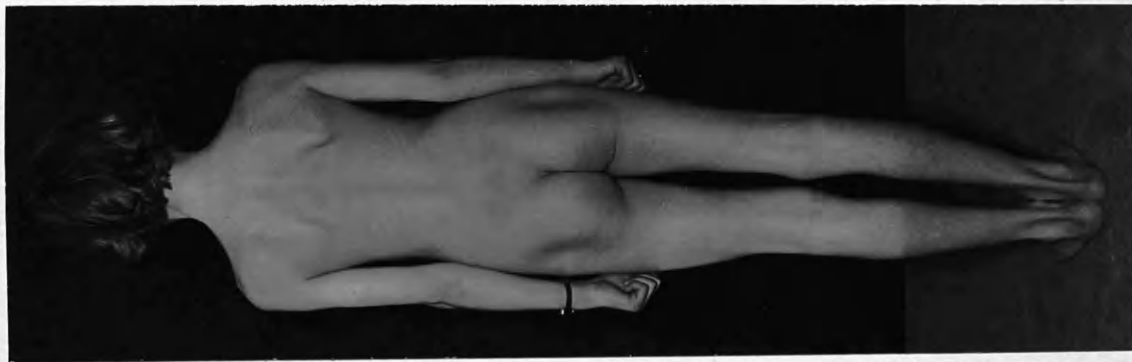
Figure 33

Case 15.   Osteitis of right tibia.

   (a) three weeks: gross decalcification and new bone formation.
   (b) two months: extensive sequestrum formation.
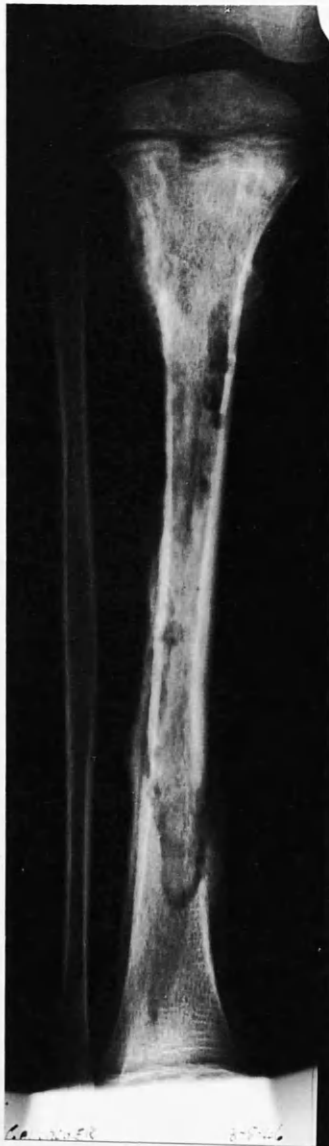
Figure 34

Case 15 (continued).   Osteitis of right tibia

     (a) formation of large cortical sequestrum following
         secondary suture three months previously.
     (b) tibia well consolidated nine months after onset.

Figure 35

Case 15 (continued). Osteitis of right tibia. X-ray of
both tibiae on one film eighteen months after
onset showing sclerosis of right tibia and increase
in length of both tibia and fibula.

detail in Appendix II. Figure 36 shows a typical bipolar infection of
the femur (Case 58). Marrow puncture at this time showed that no penicillin
was reaching either metaphysis, although the child was receiving 1,000,000
units of parenteral penicillin daily.

Group C   To date, only one case has fallen into Group C.   In the others
the infecting organisms have been sensitive to penicillin in approximately
the same degree as the standard Oxford staphylococcus.

Case 48. S.M. Female aged four years.

The child was admitted to hospital on 24th October 1947.   She was
very ill and septicaemia concealed the localising signs.   Movements of the
right hip joint were resented and tenderness appeared to be most marked over
the great trochanter.   The leg was immobilised by skin traction and after
withdrawing blood for culture, penicillin therapy was started.   Coagulase
positive staphylococci were grown from the blood;   the erythrocyte
sedimentation rate was 88 mm. in the first hour.   She was given 25,000 units
of penicillin three-hourly during the first day but as her condition had
deteriorated on the second day the dose was increased to 75,000 units.
Under light general anaesthesia the hip joint was explored by needle but no
pus was found.   0.25 mega-units of penicillin were injected into the joint.
Exploration of the soft tissues by needle was also negative and marrow
puncture revealed apparently normal marrow (a penicillin resistant
staphylococcus was subsequently grown from this specimen of marrow).   0.25 mega
units of penicillin were injected into the marrow cavity.   On the third day
the staphylococcus grown from the blood was reported insensitive to
penicillin.   With a final concentration of approximately 1,000,000,000
organisms per ml. the staphylococcus was resistant to 200 units of penicillin
per /

Figure 36

Case 58. Bipolar osteitis of left femur showing
pathological fractures of upper and lower ends.

per ml.   Streptomycin was not available for non-tuberculous cases at this
time and the patient was given an approximate total of 7.5 gms. of
soluthiazole in a plasma drip.   During the third and fourth days a further
1.6 mega units of penicillin were administered, but she died on the evening
of the fourth day.

Necropsy   There was no pus in the hip joint.   A subperiosteal abscess
extended for 7 cms. below the great trochanter.   The marrow puncture needle
had passed through the middle of this abscess but the pus was too thick to
be aspirated.   On splitting the femur there was no naked eye evidence of the
focus in the upper end of the femur.   There was a large septic spleen and
pyaemic abscess in both lungs.

Subcultured, the staphylococcus remained resistant to 200 units of
penicillin per ml. for a period of nine months.

Remarks   This case followed the same course as 30 per cent. of the cases
seen in the hospital before the introduction of chemotherapy.   It is unlikely
that more radical surgery would have influenced the progress of the case.
The necropsy findings were similar to those found in pre-penicillin cases
dying within the first week.   The metaphyseal focus was so small at this
stage that the chance of striking it with a bone drill was remote.

Such as case might now be saved with streptomycin (Jefferey et al
1949) or aureomycin.   The problem of the penicillin resistant staphylococcus
is discussed very briefly in Part IV.

COMPLICATIONS

The complications of acute haematogenous osteitis which occurred

in /

in Group III are shown in Appendix I and some of them are discussed in Appendix II.   I think that some complications are avoidable, but so long as cases continue to arrive in hospital at a relatively late stage of the disease, other complications are inevitable.   The important complications encountered in the penicillin-treated cases will now be considered briefly.

Arthritis   Pyogenic arthritis occurred in 11 of the 81 surviving cases in Group III.   All joints were involved by direct extension from an adjacent metaphysis.   Case 5 developed scarlet fever on the twenty-fourth day of his illness and was transferred to a fever hospital.   There he developed multiple lesions and now has a bony ankylosis of the right ankle.   In Case 10 there is gross irregularity of the lower femoral epiphysis.   In the other 9 cases there is complete restoration of joint movement.   One joint (Case 72) was treated by open drainage;   the other joint infections were treated by aspiration and penicillin instillation.

Rammelkamp and Keefer (1943) suggested that synovial membrane was a barrier to the passage of penicillin from the blood stream.   In a small series of war wounds of the knee joint, I found a level of penicillin in each joint following intramuscular injections of penicillin and in 3 cases with haemarthrosis, the joint penicillin reached that of the blood.   It is unwise to depend on this level alone and in the traumatic cases parenteral administration was supplemented by intra-articular injection of 100,000 units of penicillin.   Similarly in pyogenic arthritis one cannot depend on a level obtained via the blood stream and after aspiration of pus, penicillin is instilled in doses from 100,000 to 1,000,000 units.   In one case aspiration and penicillin instillation had to be repeated twice and in Case 72 after four aspirations followed by penicillin replacement the knee joint was opened

to /

to evacuate thick pus and large fibrin clots.   In this case the wound healed by first intention and full movement was restored within two months.

Sympathetic effusion occurred into other joints in the group. Straw coloured fluid was aspirated and penicillin instilled.   In these cases the aspirated fluid was reported sterile and such cases are not considered further in this report.

The infecting organism was a coagulase positive staphylococcus in all cases of arthritis in the group.   The percentage of recovery to full function is gratifyingly high.   Before the introduction of antibiotics, staphylococcal arthritis in children led to ankylosis of the joint in 50 per cent of the cases.   The prognosis was much better in streptococcal joint infections (White 1935).

Limb Lengthening   In 24 infections of long bones treated during 1945 and 1946 (Dennison 1948) measurable increase in length (1-3 cms.) occurred in 13 (50%), followed up for a period of at least three years.   In some, this lengthening did not become apparent for almost a year after the onset of the acute bone infection (Figure 37) while in one patient (Case 8) lengthening of 2 cms. eighteen months after onset (Figure 38) increased to 2.5 cms. after four years (Figure 39), there being no clinical or radiographic evidence of active bone disease noted during this period.   Since January 1947 (Case 32 et seq.) no increase in length of more than 1 cm. has been observed.

The increase in girth of a long bone following osteitis is well known but there is little literature describing the increase in length following prolonged bone infection.   Gross increase in girth and length is uncommon in penicillin-treated cases but in the earlier cases of the

penicillin /

Figure 37 Case 22 Osteitis of left femur. Photographs show increase in length of left leg and pelvic tilt corrected by 1.5 cm. block under foot on sound side. X-ray film shows increase in length and girth of left femur.
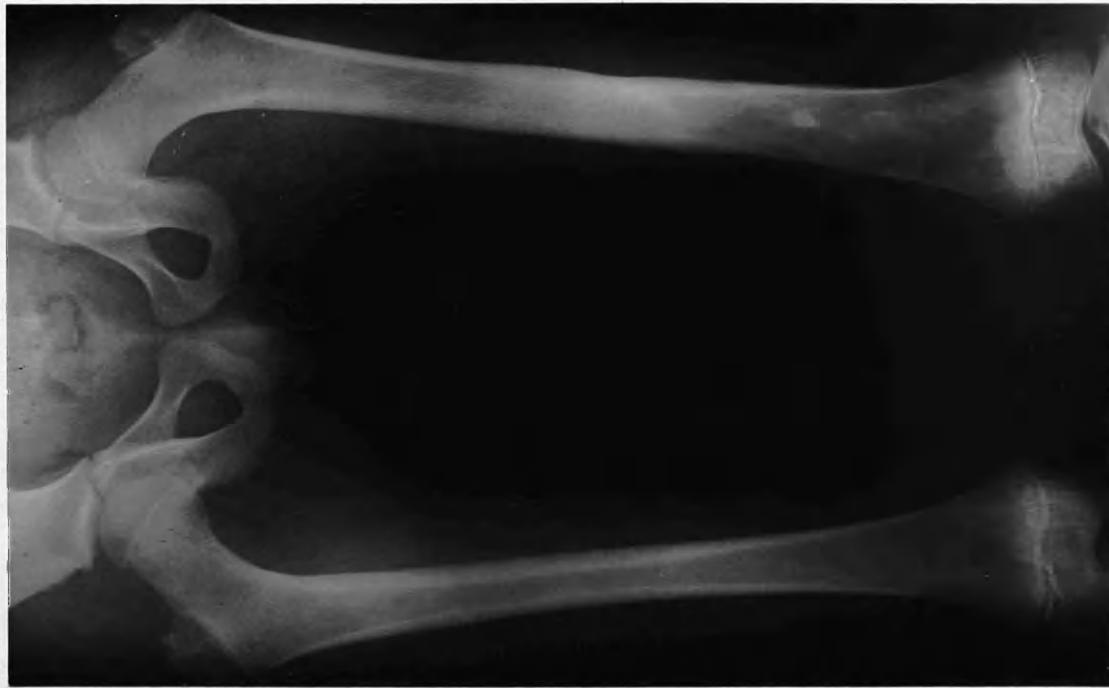
Figure 38 Osteitis of right femur. Eighteen months after onset, photographs show increase in length of right leg with pelvic tilt corrected by 2 cm. block under foot on sound side. X-ray film shows increase in length and girth of right femur.
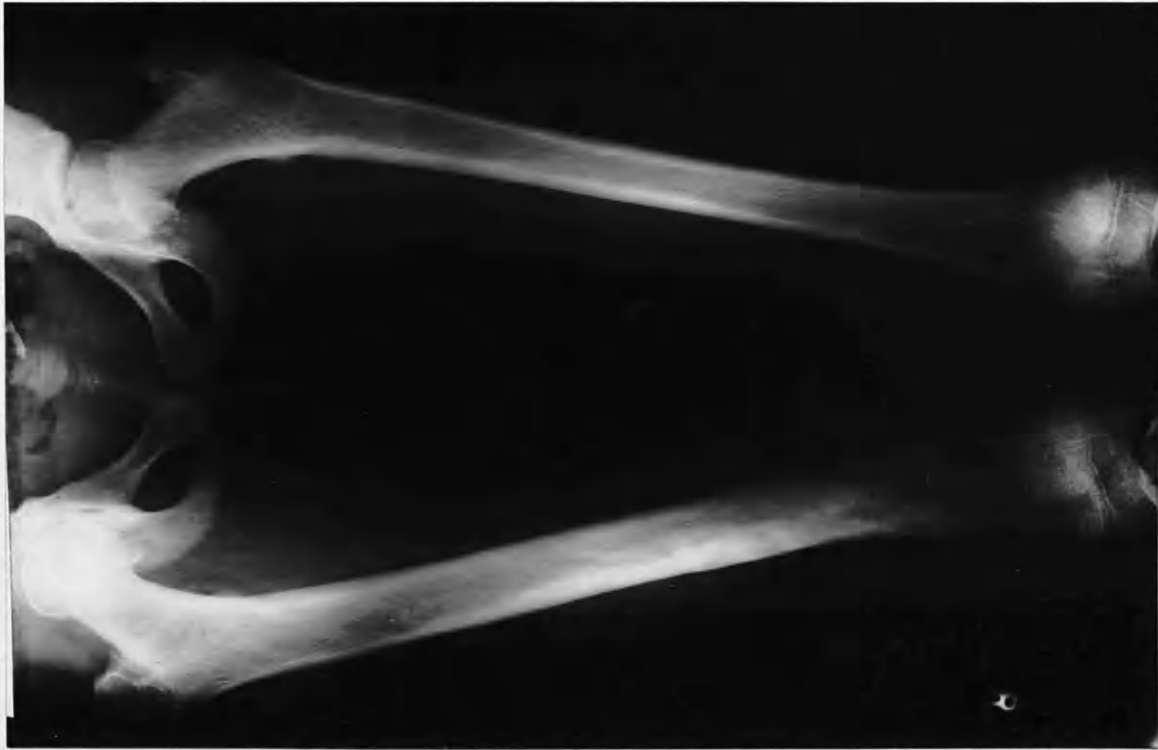
Figure 39.

Case 8 (continued). Osteitis of right femur. Four years after
onset photographs show scoliosis and genu valgum partially
corrected by 2 cm. block under foot on sound side.

penicillin series however, failure to perform primary suture led to cavity
and sequestrum formation in a number of limbs and examples of the resulting
overgrowth have been shown in Figures 30, 31, 32 and 38.   Gross lengthening
of the femur following infection of all three long bones of the lower limb
is shown in Figure 40 (Case 5).   Unless an epiphysis is damaged the growth
in length is symmetrical and where only one or two paired bones is diseased
the increase in length affects both bones equally (Figure 35).

Pathological Fracture   Despite our awareness of the risks of pathological
fracture in the decalcified bone in penicillin-treated osteitis (Agerholm
and Trueta 1946, Aird 1946, Dennison 1948 et al), this complication occurred
on seven occasions.   These cases showed gross decalcification and the
fractures appeared almost inevitable in spite of apparently adequate
immobilisation.   Admittedly immobilisation was temporarily abandoned to allow
radiography to be carried out and in at least 3 cases I am convinced that
fracture did in fact occur during a visit to the X-ray department.   The
diagnosis has always been made by radiography.   The displacement was usually
negligible and there was no pain to indicate the moment of fracture.   The
fractures have all united but rather slowly and with little callus formation.

Sequestrum formation   Sequestrum formation necessitating surgical
intervention occurred in 14 cases.   Case 5 developed scarlet fever on the
twenty-fourth day after commencement of treatment of osteitis of the femur.
On his return from a fever hospital twelve weeks later the infection had
spread by metastases to the tibia and fibula of the same limb and the ankle
joint had been destroyed by arthritis.   Multiple sequestrectomies were
required before the disease was finally eradicated.   All cases in Group III
have /

Figure 40   Osteitis of left femur with metastasis in left tibia and fibula following scarlet fever. Photographs show gross lengthening of left leg and pelvic tilt, partially corrected by 2.5 cm. block under foot on sound side.   X-ray film shows increase in length of left femur with cavity, sequestrum and healing pathological fracture.
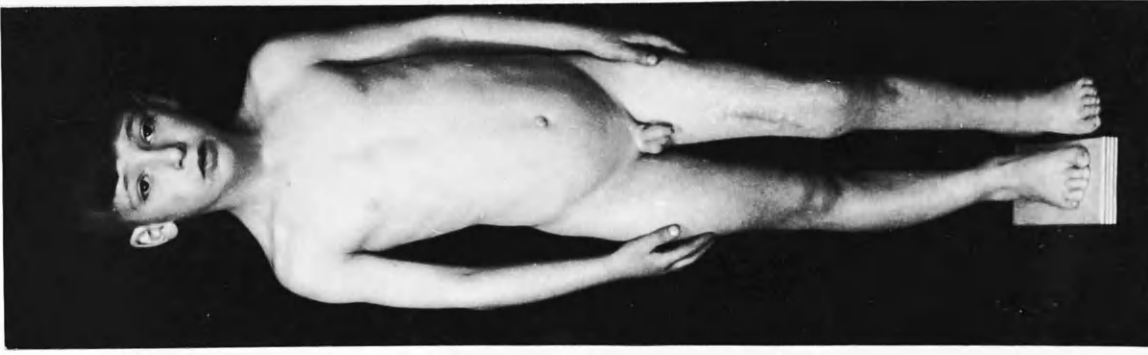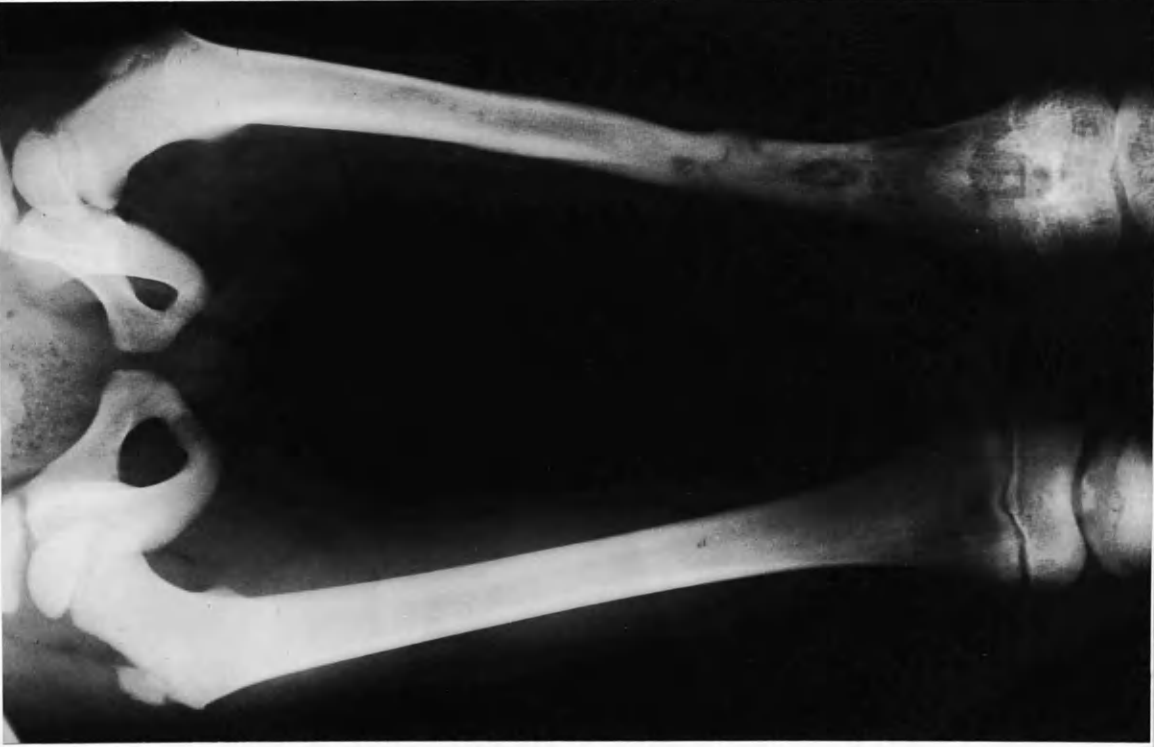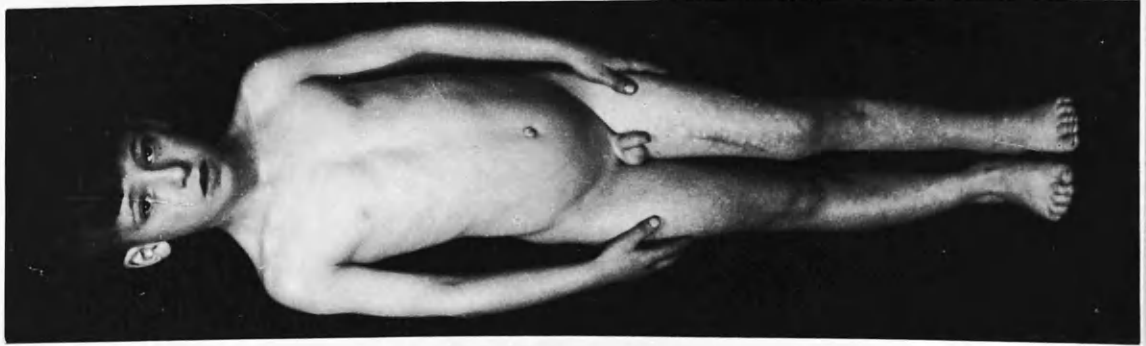
have been reviewed during April and May 1950 and there was no clinical or
radiographic evidence of active bone disease or sequestrum formation in any.

<u>Pericarditis</u>   Although this complication only appeared once (Case 82) it
is a reminder that penicillin has not lessened our responsibility for precise
diagnosis.

<u>Case 82</u>   The patient, a male aged 6 years, was admitted on 30th November 1949
in a comatose condition.   He was given penicillin and soluthiazole, placed
in an "Oxygenaire" oxygen tent and an intravenous plasma drip commenced.
When his general condition had improved a subperiosteal abscess over the left
tibia was evacuated and the wound sutured.   Shortly after his return to the
ward he collapsed and showed severe cyanosis and a failing capillary
circulation.   A dramatic recovery followed administration of Cortrophin (an
early adrenocorticotrophic hormone, provided by Organon Laboratories for
experimental purposes).   Suprarenal replacement therapy was continued by
adding Eucortone (A. & H.) to the intravenous drip.   There was no evidence
of disease in other parts of the skeleton, in the pericardium or in the
respiratory tract at this time.

After forty-eight hours, the child's condition ceased to cause
anxiety but he was given streptomycin and sulphatriad until the causal
staphylococcus was reported sensitive to penicillin.   Irregular pyrexia was
still present at fourteen days and in view of continuing oedema of the leg
the tibia was drilled to allow re-vascularising and to allow instillation of
penicillin into the metaphysis.   The following day a more thorough
examination revealed enlargement of the heart and radiography confirmed the
diagnosis of pericarditis.   Attempted aspiration was unsuccessful and
penicillin /

penicillin therapy was continued for a further two weeks, and on
1st January 1950 there was no clinical or radiographic evidence of enlargement
of the heart.   Further recovery was uneventful.

Subluxation of the Axis   Case 32 was admitted with osteitis of the second
cervical vertebra.   After sixteen days in hospital he was noticed to be
holding his head in the torticollis position.   The head was held rigidly,
slightly in front of the normal plane, tilted towards the right shoulder with
the chin pointed to the left.   Any attempt at passive movement was resented
and the child appeared more apprehensive than he had been previous to the
development of the torticollis.   A clinical diagnosis of hyperaemic
subluxation was made and radiography showed decalcification of the lamina of
the second cervical vertebra with subluxation of the second on the third
vertebra.   The head was immobilised in a "Minerva" type of plaster of Paris
splint and almost immediately the child lost his appearance of apprehension.
The plaster collar was later replaced by a reinforced leather support and
immobilisation was continued for four months when radiography showed healing
with fusion of the second and third cervical vertebrae in the subluxated
position.   Three years after onset there was no evidence of subluxation
(Figures 41A and 41B).

I have previously described the condition of hyperaemic subluxation
of the atlas (Dennison 1939) but I have never before seen an inflammatory
subluxation of the axis.   Case 34 suffered from osteitis of the atlas, and
developed a retropharyngeal abscess.   This patient seemed a likely candidate
for the classical type of hyperaemic subluxation of the atlas but with strict
immobilisation this complication was prevented.

Other /

Figure 41.

Case 32. Osteitis of axis.

        (a) Osteitis of lamina of C.2 with forward
            subluxation of C.2 on C.3 (7.2.47).
        (b) Fusion of laminae of C.2 and C.3. No
            evidence of subluxation (3.2.50).

Other Complications   Adherent scars developed in two cases only and these have both been excised with satisfactory results.   Genu valgum developed in two cases.   Case 8 is discussed in Appendix II.   In Case 26 the deformity was due to epiphyseal damage and the progress of the condition can be followed in the radiographs shown in Figure 42.   The deformity in this case is now fully corrected.   Case 30 made an uneventful recovery from osteitis of the left femur but fourteen months later he reported with osteochondritis of the opposite hip (Perthe's disease).   He was treated by prolonged bed rest and after a further two years the condition was radiologically "healed" with minimal deformity.   Case 19 developed a stress fracture of the third metatarsal thirteen months after the onset of osteitis of the femur on the opposite side.   This case is illustrated and discussed briefly in Appendix II.

Figure 42   Case 26.   Osteitis of right tibia.
(a) two weeks :   decalcification of upper tibia.
(b) five weeks :   subperiosteal new bone formation.
(c) seven months :   overgrowth of medial tibial condyle causing genu valgum.
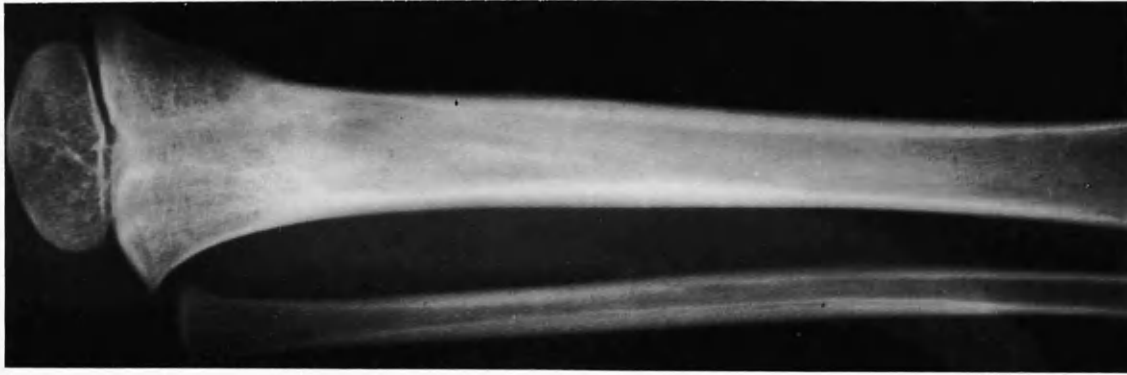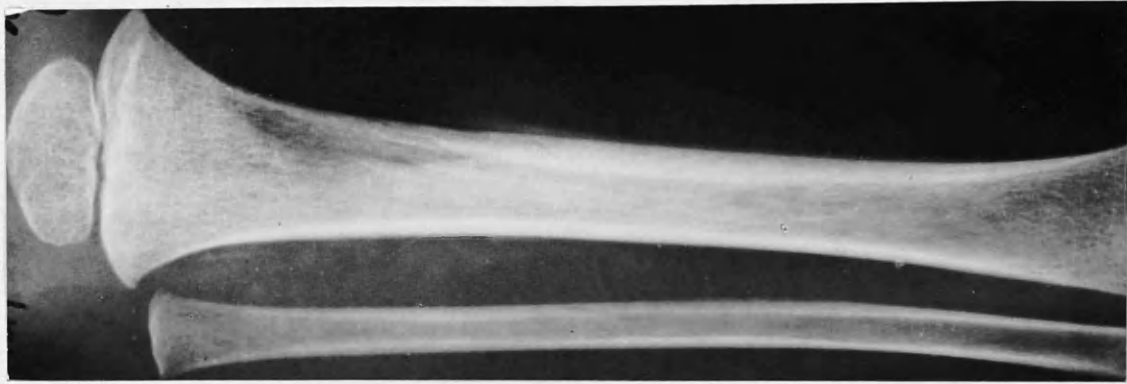
PART IV

DISCUSSION ON ACUTE OSTEITIS INCLUDING EXPERIMENTAL DATA.

PART IV.

INTRODUCTION

It is now proposed to discuss the problem of acute osteitis against the background of fact already presented. In the consideration of the disease as a whole, it is necessary to introduce further experimental data suggested by various problems which have arisen during the investigation. It is convenient to discuss this section under three headings - Aetiology, Treatment and Results.

AETIOLOGY

Incidence   The disease known as acute haematogenous osteitis (vide "Definition": Part I, Introduction) varies not only from district to district but also with the resistance of the individual patient, with the virulence of the invading organism and with the massiveness of the dose. It has therefore been difficult to compare reports from different centres. Even in Glasgow, Stevenson (1946) found it impossible to compile figures of any value from the city's teaching hospitals. The patients in all three groups of the present series have come from the same geographical area (West and North-West Scotland) which is served by the Royal Hospital for Sick Children, Glasgow.

At surgical meetings, in medical journals and in standard text books one has heard and read about the diminishing incidence of osteitis during the past two decades (Ogilvie 1932, Wakeley 1932, Romanis and Mitchiner 1932, Butler 1940, Bailey and Love 1946, and many others). In the Royal Hospital for /

for Sick Children, Glasgow, evidence that this is so is unfortunately lacking and there has been little change in the incidence of the disease since the beginning of the century (White 1937). By the courtesy of Mr. J.M. Mason Brown I have been able to obtain the figures of true acute haematogenous osteitis from another large children's hospital (Brown 1950) and in Table XV they are compared with the figures of the present series.

TABLE XV

Annual Incidence of Acute Osteitis 1936 - 1949

Year	Royal Hospital for Sick Children, Edinburgh.	Royal Hospital for Sick Children, Glasgow.
1936	12	16
1937	7	14
1938	4	12
1939	5	22
1940	20	11
1941	9	7
1942	9	8
1943	18	14
1944	16	18
1945	18	20
1946	13	19
1947	20	19
1948	53	20
1949	27	12
1936-1949	231	212

<u>Social Incidence</u>   According to Trueta (1948) the incidence of osteitis is low /

low where the standard of cleanliness is high.   In the industrial areas of Scotland there is still appalling overcrowding and in some of the rural districts which the hospital serves living conditions are shocking.   From personal visits, from information supplied by the patients' doctors and from investigations by the hospital almoners, it was established that unsatisfactory home conditions existed in 57 (70%) of the 82 penicillin-treated cases. Mitchell (1928) stated that there is a definite class distinction manifest in the child who is affected by osteitis and Stevenson (1946) found that acute osteitis was rarely encountered in private consulting practice.   Stevenson also reported the incidence of the disease from two well-known public schools - Repton: 4 cases of osteitis in twenty-four years, out of a yearly population of children under eighteen of almost five hundred.

Rugby: 4 cases in thirty-eight years, out of a total yearly schoolboy population of five to six hundred.

Bailey and Love (1946) state that osteitis is almost unknown in naval schools although minor injuries and infected abrasions are common (vide infra - Septic Foci and Trauma).   From Salzburg, Dominig (1947) reported that the rural population is more susceptible to osteitis than are the city inhabitants. This he ascribed to poorer living conditions in rural districts.

__Age and Sex__   The Royal Hospital for Sick Children admits infants and children up to the age of twelve years and in the 212 patients admitted with acute osteitis between 1936 and 1949 the disease occurred in all age groups (Figure 43).

<div align="center">

Figure 43 /

</div>

Figure 43

AGE INCIDENCE   1936 1949
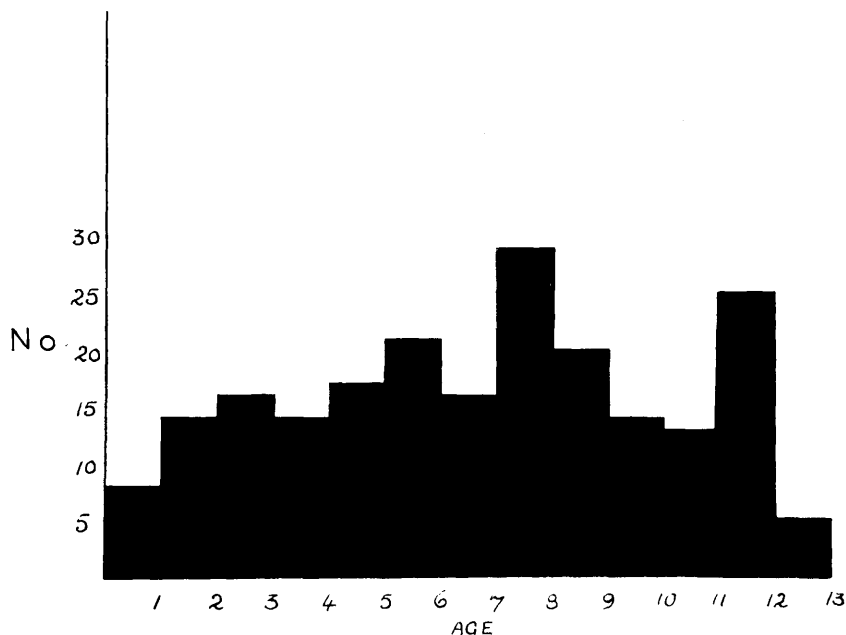
The proportion of males to females was approximately four to three (Table XVI).

TABLE XVI

The Ratio of Males to Females in Groups I, II and III

		Males	Females
Group I	1939 - 1940	43	32
Group II	1941 - 1945	31	24
Group III	1945 - 1949	48	34
Total	1936 - 1949	122	90

These figures are similar to those published by White (1937) from the same hospital and in Table XVII they are compared with figures from other centres.

TABLE XVII /

TABLE XVII

Age and Sex Incidence in Acute Osteitis.

Centre	Author	No. of Cases	Age Incidence	Ratio of Males to Females
Edinburgh	Fraser (1924)	400	8-12 years	6 males to 1 female
	(1926)	200	3-10 years	4 males to 1 female
London	Ogilvie (1928)	51	Average 12.9 years	4 males to 1 female
	Pyrah & Pain (1933)	262	5-14 years	2 males to 1 female
Paris	Fèvre (1933)	115	4-16 years	2 males to 1 female
Glasgow	White (1937)	200	5-10 years	7 males to 5 females
	Present Series (1936-1949)	212	2-12 years	4 males to 3 females

Osteitis occurs most commonly during a period of active bone growth. Trauma is common during this period and is probably more common in boys than girls.

Septic Foci and Trauma   The accepted aetiology is that a child suffering from a symptomless bacteriaemia, arising from such septic foci as boils, septic abrasions, infected teeth and tonsils, is subjected to some minor trauma to the delicate vascular metaphysis. There was a definite history of injury to the affected limb within fourteen days of onset of osteitis in 99 of the 212 patients (46%) and evidence of a septic focus in 76 (35%). The incidence of traumata and septic foci in each group is shown in Table XVIII.

TABLE XVIII /

TABLE XVIII

Incidence of Trauma and Sepsis in Groups I, II, III.

		Trauma	Per cent	Septic Focus	Per cent
Group I	1936 - 1940	41	53	27	36
Group II	1941 - 1945	21	38	22	40
Group III	1945 - 1949	37	45	27	32

Similar figures are given by Self (1948) from the Babies Hospital, New York. In 138 cases there was a history of preceding trauma in 20 per cent and evidence of a septic focus was found in 33 per cent. As osteitis never follows a simple fracture, one must postulate that solution in the continuity of a bone allows release of tension in the region of the fracture haematoma.

It is well-known how infection can lie latent for long periods in childhood. In the common inguinal adenitis of infancy and childhood the primary focus is frequently healed before the glandular infection becomes apparent . It is hardly surprising that an obvious primary septic focus is found in such a small percentage (35%) of cases of osteitis. The initial lesion is often healed and forgotten for two or three weeks before the onset of the disease. The daily bumps and twists to which the normal child subjects himself may be similarly forgotten. It is unusual to find any local evidence of trauma and it is possible that the upset in metabolism which so often follows a fright or injury (usually called a bilious attack and treated with castor oil) may lower the child's resistance to infection.

Bones affected. The bones of the lower extremity are most liable to infection (Fraser 1926 et al) and the tibia and femur are by far the most common /

common sites for osteitis.   This is possibly explained by the greater
liability of the lower limb to trauma.   The bones affected in the present
series are shown in Table XIX along with the sites given in other well
known series.

Organism   The causal organism was a coagulase positive staphylococcus in
202 cases, that is 95 per cent. of the entire series.   Of the remaining
10 infections 7 were streptococcal and 3 pneumococcal (Table I, page 15).

DISCUSSION ON AETIOLOGY (including experimental work).   From the foregoing
observation it would appear that a metaphyseal focus of infection follows
minor trauma in a susceptible subject with a staphylococcal bacteriaemia.
During the past three years, various experiments have been performed in an
attempt to establish the aetiological factors in haematogenous osteitis.

Following a suggestion by Professor Lendrum (1948), the titre of
anticoagulase in the plasma of eight cases of osteitis from Group III was
assayed by Dr. Milne of the Pathology Department of the Western Infirmary,
Glasgow.   In no case was there any titre of anticoagulase.   In one patient,
coagulase was injected subcutaneously at three day intervals over a period of
three weeks.   At the end of this period, a normal titre (1 in 150) of
anticoagulase was present and this titre has remained for a period of six
months.   It is possible that an inherited or environmental deficiency in
anticoagulase may be one of the factors which render a patient susceptible to
staphylococcal infections including haematogenous osteitis.   By killing the
staphylococcus at a relatively early stage of infection it is possible that
penicillin may prevent the development of immunity in a patient already
susceptible to staphylococcal infection.

It /

	Fraser (1926)	Eglivie (1928)	Pluett (1928)	Moore (1932)	Henley (1932)	(1935)	(1945)	(1946)	(1948)	Series (1926-1942)
Tibia	87	24	13	7	23	96	15	7	26	67
Femur	32	12	7	8	30	92	13	15	29	72
Humerus	20	4	4	6	16	17	3	2	13	20
Radius	10	-	3	3	4	14	1	1	1	6
Ulna	18	-	2	2	10	3		1	2	4
Pelvis	6	4	4	5	2	2	4	3	4	8
Tarsus	10	2	-	-	5	5	3	1	-	5
Metatarsus	-	1	2	-	-	2	-	3	-	5
Mandible	-	-	1	-	-	1	-	-	-	5
Maxilla	-	-	-	-	-	-	-	-	-	3
Zygoma	-	-	-	-	-	-	1	1	-	1
Fibula	6	4	4	3	3	26	-	3	3	5
Vertebrae	4	-	1	1	-	1	-	-	-	3
Clavicle	-	-	-	2	2	2	-	-	-	1
Rib	-	-	1	-	-	-	1	1	-	5
Scapula	4	-	2	2	2	-	-	-	-	2
Skull	2	-	1	-	-	-	-	-	-	1
Carpus	1	-	-	3	-	-	-	-	-	-
Metacarpus	-	-	1	-	-	-	-	-	-	-
Phalanges	-	-	-	-	-	1	-	-	-	-
Multiple	-	-	-	-	-	-	-	-	-	1
	200	51	40	40	100	262	40	37	78	212

It has long been accepted (Lexer 1894, Hobo 1903) that certain anatomical peculiarities (page 13) lead to infection of the metaphysis of a long bone.   The efficacy of penicillin has re-opened the question of the relative importance of each group of vessels contributing to the vascular anastomoses of the metaphysis.   At least one group of vessels must be intact to ensure an adequate concentration of penicillin in the bone focus.   I therefore attempted to demonstrate the commonly accepted vascular anastomoses in the metaphysis.   Stained sections of the human metaphysis revealed a mass of large sinuses but no individual vessels could be traced.   Sections of periosteum from different age groups (removed in the post-mortem room over a period of two years) suggested that the periosteum was highly vascular in infancy and became more fibrous in the older age groups.   The blood vessels were on the outer aspect of the periosteum and at wide intervals branches passed inwards to the apparently avascular cortex.   I then attempted to demonstrate the vessels by injecting dyes and radio-opaque substances, both in the fresh cadaver and in freshly amputated limbs but without success. During 1948 I sought the help of colleagues in the University Departments of Anatomy, Physiology, Zoology and Veterinary Surgery.   No one in any of these departments had ever seen the vascular anastomoses in the metaphysis of a long bone.   Using Monastral fast Blue (Imperial Chemical Industries), fine suspensions of barium sulphate or latex, many intra-arterial injections were made in cadavers of all available age groups in the post-mortem room of the Royal Hospital for Sick Children, Glasgow.   Injections were also made in animal cadavers (guinea pig, rabbit, dog, red deer and horse).   In these experiments I had the co-operation of Dr. MacDonald, Pathologist to the Royal Hospital for Sick Children, Glasgow, and Mrs. Smith, Anatomist to Glasgow University Veterinary School.   In no case were the vessels adequately outlined.

Dos Santos /

Dos Santos (1947) described arteriography in the diagnosis of bone tumours but Barclay (1947) failed to devise a technique suitable for micro-arteriography of the normal bone (1948). Lexer and his colleagues (Lexer 1903, Lexer et al 1904) published stereographs of X-rays of various adult bones injected with mercuro-turpentine. Since adopting a modification of the technique of these workers I have obtained a successful injection in every case (Figure 44). A suspension of mercury in turpentine pigmented with Monastral fast Blue was injected into the femoral artery of infant cadavers. The bones were decalcified and X-rayed before and after stripping the periosteum. The specimens were then cleared with methyl salicylate. After clearing the decalcified bone, cartilage and fatty marrow were transparent, while the red marrow and injected vessels remained opaque.

Anatomical facts alone will not provide a satisfactory basis for the clear understanding of the pathology of osteitis. Using dogs Johnson (1927) demonstrated that the nutrient artery supplied mainly the central medulla and the inner cortex, the metaphyseal vessels supplied the metaphyseal region while the periosteal system was responsible only for the outer cortex. Adult dogs were used in these experiments and our findings so far suggest that the relative importance of the three sources of blood supply may be very different in the growing child and in the adult. Under appropriate animal licences, our experiments continue.

Haematogenous osteitis is rare, if not unknown in wild and domestic animals (Stevenson 1946, Weipers 1948) although many animals are vulnerable to staphylococcal infection. The experiments of Hobo (1921) have been repeated and finely ground Indian ink (Higgin's ink) has been injected into the ear vein /

Figure 44

X-ray film of decalcified tibia and fibula from an infant of three months, injected with suspension of mercury in turpentine. The periosteum with its injected vessels has been removed.

vein of young rabbits. In the first group the animals were sacrificed three hours later and the particles were found in the lung, liver, spleen and long bones. In the tibia (the bone of choice in our experiments) the particles were evenly distributed throughout the medulla. In the second group the animals were sacrificed after six hours. Again the particles were widely distributed but in the tibia the particles were strikingly less in the metaphysis. Although only a small proportion of the particles were intracellular, the findings suggest that the diaphysis is richer in phagocytic elements than the metaphysis. This apparent lack of phagocytosis in the metaphysis may be an important factor in determining the site of osteitis.

Using twelve week old rabbits, 1 ml. of an emulsion of coagulase positive staphylococcus (containing approximately 1,000 million organisms) from a case of acute osteitis was injected into the ear veins. The first animal was sacrificed after two hours and marrow cultures taken immediately after death showed coagulase positive staphylococci in the centre of the shaft and in the metaphysis. In an animal sacrificed after six hours staphylococci were grown from the metaphysis only. A third rabbit was sacrificed at thirty-six hours (the animal was very ill and obviously dying). At autopsy there was a pleural effusion and coagulase positive staphylococci were grown from this fluid. Staphylococci were also grown from the liver, lung, spleen and bone marrow. When smaller quantities of the bacterial emulsion were injected, the results were unpredictable and in several rabbits there was no evidence of local or general infection. There is a considerable difference in susceptibility in individual rabbits to the Staphylococcus aureus (De Navasquez 1950). Doses of approximately 500 to 1,000 million bacteria per c.c. caused death at intervals ranging from one to four days while doses of 50 to 200 million /

million produced only a transient bacteriaemia.   Five animals which
survived intravenous innoculation of Staphylococcus aureus were killed three
or four weeks later.   Three showed pyelonephritis while two showed small foci
in the lungs and liver.   No bone lesions were found.   One animal was given
a second innoculation (approximately 200 million organisms) two weeks after
the initial injection.   This rabbit died four days later and at necropsy
abscesses were found in the liver, lungs, kidneys, bones and joints.   In no
other experimental animal have abscesses been found in the bones.   One young
adult (six months old) rabbit developed a septic arthritis two weeks after
intravenous injection of (approximately) 400 million staphylococci.   The
experiments continue.

Similar experiments were performed by Bancroft (1921) and
Robertson (1927) and the latter, from both animal and clinical observation,
reported that –

1. Organisms introduced into the blood stream are deposited, among other
    places, in the long bones.

2. In bones there is very active phagocytosis except in the metaphysis.

3. Organisms produce inflammatory centres in the metaphysis independent of
    trauma.

4. It is impossible to produce a general infection of the medulla by a simple
    innoculation of organisms into the blood stream.

5. Trauma may determine a local infection.

6. Growing bones develop abscesses of the type of osteomyelitis within them.
    Adult bones do so but rarely.   In the presence of a bacteriaemia, adults
    may produce an arthritis.

TREATMENT

The treatment of osteitis throughout the ages has been reviewed briefly in the historical section and the contemporary methods adopted in Groups I and II of the present series have been described. With the introduction of penicillin the change in reaction of the patient was so remarkable that the local changes in the bone were neglected or considered inevitable. It was quickly recognised that failure to obtain a satisfactory result was the fault, not of the drug, but of the clinician in charge of the case. The suitability of a case for penicillin treatment, the exact line of treatment, the prognosis and the final assessment of the result depend on exact clinical and bacteriological diagnosis. In fact, the clinician's responsibility for a precise diagnosis has increased rather than lessened. Even in a comatose patient the affected metaphysis can usually be located, but a thorough general examination must be carried out, paying particular attention to other parts of the skeleton, the respiratory tract and the pericardium. While many observations are essential to ensure adequate treatment of a case of acute haematogenous osteitis, any single observation can be deceptive. For example, a patient can appear perfectly well and apyrexial while gross bone changes are taking place quietly and painlessly. Following is shown a copy of the instructions pinned up in each surgical side room for the guidance of the resident staff of the hospital (Table XX). It has been in use since 1946. The Osteitis Form (Appendix IV) has been in use since 1945 and when filled in from the information on the case notes, these forms provide the information shown in Appendix I.

TABLE XX /

TABLE XX

Routine of investigation and treatment of cases of acute
Osteitis for guidance of resident, medical and nursing staff.

1. Routine history and examination (vide osteitis proforma, Appendix IV).

2. Blood for culture and for Ca., P., phosphatase and E.S.R.

3. W.B.C.

4. Then penicillin therapy instituted as below (based on dose of 5,000
    units/lb. body weight/24 hours).

Age Group	Dose each 24 hours	Frequency and Rate
Birth - 3 months	80,000 units	3 hourly by mouth
3 months - 6 months	80,000 units	3 hourly by intramuscular injection
6 months - 12 months	120,000 units	3 hourly by intramuscular injection
1 year - 5 years	200,000 units	3 hourly by intramuscular injection
5 years - 10 years	300,000 units	4 hourly by intramuscular injection
10 years - 12 years	450,000 units	4 hourly by intramuscular injection

(Penicillin in Ward refrigerators in strengths of 10,000, 15,000, 25,000,
50,000, 75,000, 100,000, 500,000 and 1,000,000 units per c.cm.)

5. Limb immobilised (do NOT enclose in P.O.P. case).

6. Blood Culture 1st, 2nd, 3rd days or until culture is sterile.

7. Marrow Culture 14th, 21st and 28th days, or until sterile (THEATRE).
    Penicillin level on marrow assayed at same time. Marrow Ca., P. and
    phosphatase.

8. Case reviewed daily with special reference to pain, temperature and local
    condition.

9. Operation only under penicillin umbrella.

10. Penicillin continued for 21 days or until marrow sterile.

11. X-ray. If lesion in doubt - immediate (after giving penicillin), 7th, 10th,
    14th, 21st and 28th days; 2, 3, 4 and 6 months and thereafter as required.

To /

To ensure a satisfactory result, that is to say, to control septicaemia, to prevent the development of metastatic foci and to induce resolution of the initial bone focus without cavitation or sequestrum formation -

1. Penicillin administration must be begun early (before serious damage to the blood supply with irreversible bone damage) and the dosage must be adequate.

2. The organism must be sensitive to penicillin.

3. Treatment must be continued until metaphyseal culture is reported sterile (Marrow puncture).

4. Subperiosteal or soft tissue abscesses must be evacuated and the wound sutured.

1. <u>Penicillin Administration</u>   The dosage and duration of penicillin administration still presents problems.   It is generally accepted (Eagle 1948) that maximum bactericidal effect is achieved by quite low concentrations of penicillin (for Staphylococcus aureus about 0.1 unit per ml.) and that no increase beyond this will accelerate it.   In fact, higher concentrations may be a positive disadvantage because in the case of some strains of staphylococcus increase in concentration actually reduces the bactericidal effect.   The theoretical ideal is to maintain a constant optimum level of 0.1 units per ml.

This level of penicillin has been maintained in the blood stream using the scheme of dosage outlined in Part III, p. 70, namely an approximate dose of 5,000 units per lb. body weight each 24 hours.   The penicillin level in the marrow bears no constant relationship to the level in the blood stream and marrow puncture is essential to confirm a therapeutic level in the marrow.

This /

This procedure is also essential to control the duration of penicillin administration and a separate paragraph is devoted to consideration of marrow puncture.

2. Penicillin Sensitivity   The organisms in Group III (staphylococcus 79, streptococcus 2, pneumococcus 1) were, with one exception, sensitive to penicillin in approximately the same degree as the Oxford H. Staphylococcus. The fate of the child with the penicillin-resistant organism (Case 42) has been described in Part III (p. 83) and following this case I read with increasing dismay the reports from other centres of the ever-increasing incidence of penicillin-resistant staphylococci (Spink et al 1944, Barber 1947, Barber and Rozwadowska-Dowzenko 1948, Nichols and Needham 1949).   Barber and Whitehead (1949) reported the frequency of occurrence of penicillin-resistant strains of staphylococci in 1946, 1947 and 1948 as 14 per cent, 38 per cent, and 59 per cent.   In our hospital, however, the bacteriologist (Studzinsky 1950) informs me that the incidence of resistant strains has remained constant at 14 per cent. since the introduction of penicillin in 1945.   Moreover, in our unit, only three pathogenic penicillin-resistant strains of staphylococcus have been isolated during the past three years. Each was sensitive to streptomycin.

Many clinicians do not realise that the degree of resistance when measured in the laboratory may vary many hundredfold according to the size of the inoculum used, probably depending on penicillinase * formation (Gibson and Parker 1948).   For example, the staphylococcus isolated from Case 42 was resistant /

* Abraham & Chain (1940) found that certain penicillin-insensitive organisms contain an enzyme-like substance which destroys penicillin.   This substance they called penicillinase.   It can be prepared by filtration of a week-old culture of a suitable organism - usually a coliform bacillus.

resistant to 200 units per ml. when there was a final concentration of approximately 1,000,000,000 organisms. Using a small inoculum (approximately 1,000,000 organisms) the staphylococcus was resistant to only 5 units per ml. (The other two resistant strains - from a septic finger and an abscess of the abdominal wall - were equally resistant and no strains showing a minor degree of resistance have been encountered.)

After withdrawing blood for culture, forty-eight hours elapse before a report is received on the penicillin-sensitivity of the infecting organism. In the acutely ill child one must consider the possibility of a penicillin-resistant infection. If the clinical condition of the patient has not improved after twenty-four hours of penicillin therapy (combined if necessary with metaphyseal decompression) sulphonamides are given. In one instance (Case 82), streptomycin was administered for ninety-six hours. Aureomycin has recently been used successfully in penicillin-resistant staphylococcal osteitis in this hospital. Nichols and Needham (1949) and Beigelman and Rantz (1950) reporting the increasing frequency of penicillin-resistant staphylococci, state that all their strains have been sensitive to aureomycin. Jacobs and Jacobs (1949) and Egan (1950) have reported the successful use of aureomycin in the treatment of osteitis of the mandible. I have found no literature describing the use of chloromycetin in osteitis.

When assessing the probable effect of penicillin in any particular case, the clinician must not rely too much on the bacteriologist's report. The bacteriologist's test tube is very different from the human body and there are at least three problems which the bacteriologist cannot at present answer -
1. How many organisms is penicillin likely to encounter in the body in any given infection?
2. /

2. Do staphylococci produce penicillinase at the same rate _in vivo_ as _in vitro_?

3. What is the optimum level of penicillin in the blood stream?
The aid of the laboratory is essential in assessing the action of antibiotics but the results of the laboratory tests must not be applied too rigidly in the treatment of disease.

3. <u>Marrow Puncture</u>   By aspiration of the infected marrow, McAdam (1945) showed that neither the temperature chart nor the leucocyte count was a reliable criterion of the time of sterilization of infected bone. After considerable hesitation I decided that repeated marrow puncture was the only method by which I could obtain some idea of the state of the metaphysis. During 1946, it was performed in suitable cases in theatre and was repeated on the 7th, 14th and 21st days (Dennison 1948) and from Case 22 onwards this procedure became part of the routine of investigation.   Until February 1947 (Case 33) no marrow fluid was reported infected after the 14th day of treatment, and a routine of twenty-one days penicillin treatment was adopted.   In Case 33, however, a penicillin sensitive Staphylococcus aureus was grown from the marrow fluid until the thirty-eighth day of treatment.   It was therefore obvious that penicillin must be continued until the marrow fluid was reported sterile.   From this period onwards, the fluid withdrawn from the metaphysis was divided and put into two test tubes.   One specimen was sent for bacteriological examination and the other was assayed for its penicillin content.   In Case 35 a report came back on the twenty-fifth day that the specimen contained penicillin-sensitive coagulase positive staphylococci and that there was no level of penicillin one hour after an intramuscular injection of penicillin.   At marrow puncture a week later marrow fluid was aspirated but /

but before withdrawing the marrow puncture needle 500,000 units of penicillin were instilled into the marrow. The next specimen was reported sterile. Following this experience, penicillin was instilled in every case before withdrawing the marrow puncture needle.

Absence of a penicillin level in the marrow fluid within a reasonable period of the last intramuscular injection indicates interference with the blood supply so that penicillin cannot reach the affected area. This may be remedied by local instillation of penicillin. On three occasions I have supplemented this method by multiple drilling. This not only allows instillation of penicillin, but theoretically, young granulation tissue will grow down the drill holes and thus provide an alternative blood supply.

Lest a high penicillin level in the specimen should eliminate the organisms, during the past year penicillinase has been added to the test tube whose contents will be examined bacteriologically. Usually the penicillin level in the marrow is at least as high as the blood level.

The technique of the operation is simple. Under light general anaesthesia a marrow puncture needle of suitable length with the stilet and guard in place, is made to pierce the skin and firm cortex in the region of the metaphysis. With pressure and a rotatory movement the needle is inserted in an oblique direction towards the epiphysis until resistance ceases and the point lies in the metaphysis. The procedure is simple until the age of six years but in older children penetration of the firm cortex requires considerable force. Fluid is aspirated into a 10 c.c. syringe and varies from blood through sero-sanguinous fluid to frankly purulent material.

4. /

4. <u>Evacuation of Subperiosteal and Soft Tissue Abscess.</u>   So long as cases continue to arrive in hospital with pre-formed pus, so long will surgical intervention by necessary.   The methods of surgery described in Groups I and II of the present series have no place in the modern treatment of acute osteitis and surgery has now become the handmaiden of penicillin.   Bone drilling should rarely be adopted as a primary operation but less harm will be caused by drilling followed by primary suture than by incomplete relief of tension.

<div align="center"><u>RESULTS</u></div>

To those of us who were called upon to treat acute haematogenous osteitis before the introduction of penicillin, it is obvious that we are now working in a new era.   During the period under review more and more attention has been given to maintenance of fluid and electrolytic balance.   By 1936 intravenous therapy had replaced the subcutaneous and rectal routes in maintaining normal fluid balance and during the war years plasma became available and gradually replaced or supplemented glucose-saline.   These factors must be taken into consideration when evaluating the results of chemotherapy and antibiotics.   The mortality in Group I (1936-1940) was 30 per cent; in Group II it fell to just over 12 per cent. but there was no reduction in the duration of stay in hospital.   In this second group, the course of fever appeared shorter, the metastases were fewer but healing was no more rapid and the degree of bone destruction appeared to be similar to that in Group I.   In the last 82 (penicillin-treated) cases of Group III there has been one death - a mortality of 1.2 per cent.   The mortality in each group is compared in Figure 45.

<div align="center"><u>Figure 45</u> /</div>

Figure 45

Deaths from acute osteitis in Groups I, II and III

MORTALITY

1936–1949

35%

30%

25%

20%

15%

10%

5%

GROUP I   GROUP II   GROUP III
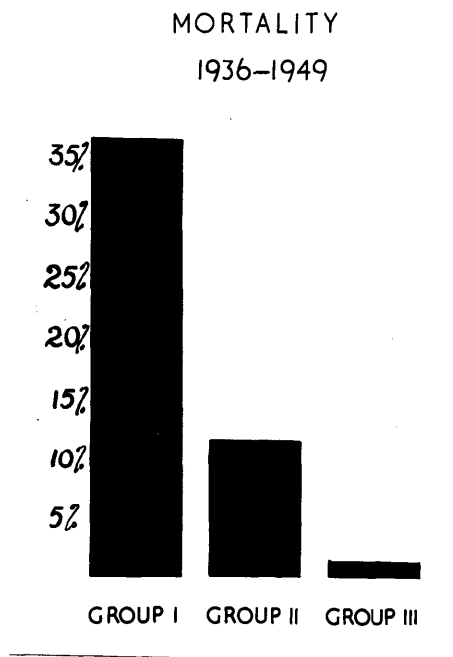
While the improvement in the death rate is quite obvious the improvement in the morbidity rate can never be demonstrated so dramatically. Some indication of the reduced morbidity is given by Figure 46 which shows the duration of in-patient in the three groups.

Figure 46 /

Figure 46.

Duration of stay in hospital in Groups I, II and III

DURATION OF STAY IN HOSPITAL

1936 — 40   40 CASES.

1941 — 1945   48 CASES.

1945 — 49   81 CASES
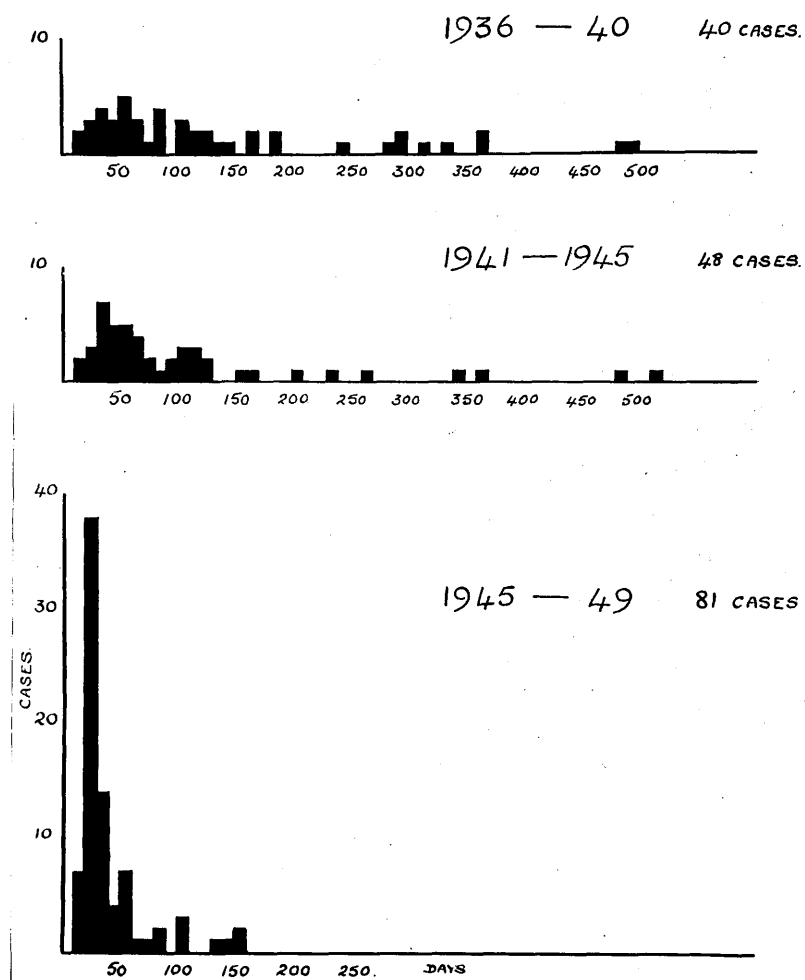
__COMPLICATIONS__   Although metastatic lesions have become rare, the single case

of pericarditis in Group III is a reminder that penicillin has not lessened

our responsibility for thorough examination and precise diagnosis.   Pyogenic

arthritis is still a common complication of acute osteitis (11 of 82 penicillin-

treated cases) but all joint infections have been from direct extension from an

adjacent bone focus and no metastatic joint infections have occurred.   The

late /

late results, however, are different. Bisgard (1932) reported 51 cases of pyogenic arthritis occurring in a series of 217 cases of acute osteitis. In this series only 13 per cent. of joints regained a good range of movement while 65 per cent. became ankylosed. White (1935) in our own hospital reported ankylosis in 50 per cent. of cases of staphylococcal arthritis; the prognosis was better in streptococcal joint infections. All joint infections in Group III of the present series were staphylococcal and yet the only ankylosed joint occurred in Case 5 who developed scarlet fever twenty-four days after the onset of staphylococcal osteitis of the femur.

The complications which occurred in all three groups have been considered in Parts II and III but three of them still present problems and require further discussion. These problems are –

1. The progressive decalcification which almost inevitably takes place following treatment of acute osteitis with penicillin;

2. Sequestrum formation;

3. Limb lengthening following osteitis.

Bone Decalcification following penicillin-treated Osteitis   The most striking radiographic change in penicillin-treated osteitis is the progressive decalcification and relative absence of involucrum formation. I have suggested elsewhere (Dennison 1948) that the removal of the stimulus of continuing infection by sterilisation of the bone explains the absence of dense involucrum formation. As a corollary, the appearance in the X-ray film of excess formation of new subperiosteal bone indicates that the bone is still infected.

During /

During experiments to determine the causal factor responsible for the low tissue specificity possessed by cartilage and cornea, Bacsich and Wyburn (1947) implanted control homografts into the same host.   Among these controls was bone from the rib of the donor animal.   In six guinea pig hosts the subcutaneous bone homografts were removed in three to five days and the host tissue was sectioned and examined after twenty-one days.   In three cases (Wyburn and Bacsich 1947) new bone formation had occurred around the cavities formerly occupied by the bone grafts.   In each of these three cases infection had occurred.   It was suggested that the release of the osteogenetic stimulus would be facilitated by increased enzymatic activity due to infection. Slessor and Wyburn (1947) later implanted bone homografts in the subcutaneous tissue of guinea pigs for three weeks.   There was no bone formation in the host.   I implanted bone homografts into the subcutaneous tissue of the abdominal wall of four guinea pigs.   In two of the animals I injected 0.5 c.c. of an inoculum of coagulase positive staphylococci into the region of the graft.   One animal died of septicaemia after two days;   the other showed evidence of mild local sepsis, but the graft was not extruded and the animal was sacrificed after three weeks.   In the remaining two guinea pigs I injected 1 c.c. of hyaluronidase (Hyalase, Benger) into the region of the graft.   The animals were sacrificed after three weeks.   In none of the animals was there an evidence of new bone formation in the cavity occupied by the graft.   These experiments will be repeated.

Meyer, Dubos and Smyth (1936) first described hyaluronidase as a bacterialytic component which hydrolysed the polysaccharide of vitreous humour and umbilical cord (hyaluronic acid).   Duran-Reynals (1942) states that hyaluronidase is an aggressive device for bacteria which is directed against host /

host tissue. It is associated with such offensive or toxic agents as the salivary glands of the shrew and venoms of snakes (Chain and Duthie 1940) and with fibrolysins and coagulase of streptococcus and staphylococcus (Bellis 1943, Cuncliffe et al 1945). Although the organisms infecting the guinea pigs of Bacsich and Wyburn were not known (Bacsich 1949) it is quite likely that infection was streptococcal or staphylococcal.

Hyaluronidase hydrolyses chondroitin sulphate and ossification is characterised by rapid local disappearance of chondroitin sulphate and concurrently by the appearance of large amounts alkaline phosphatase (Sylven 1947a). It is possible that the removal of acid chondroitin sulphate is a prerequisite for the action of bone forming osteoblasts. The precipitation of lime salts is directed by alkaline phosphotase. Within a few days of fracture the phosphatase content of the haematoma increased to six or eight times the normal level (Botterell and King 1935), and Moog (1944) reports large increase of alkaline phosphatase in newly formed bone. In my limited experience there was no apparent increase in phosphatase in the marrow fluid aspirated in cases of acute osteitis.

I therefore put forward the hypothesis that in penicillin-treated osteitis the staphylococcus is destroyed, thus removing the source of hyaluronidase with its osteogenic stimulus. There is thus no gross new bone formation which one always expected in staphylococcal infection of bone. In 1949 I obtained a supply of hyaluronidase by the courtesy of Schering laboratories and I intended to inject this substance into the decalcifying bone following acute osteitis. Unfortunately hyaluronidase as a spreading factor is intimately concerned in the mechanism of bacterial invasion (Duran-Reynals 1928). /

1928). I have not had sufficient confidence to inject this substance locally into a decalcified bone.   The manufacturers are at present devising a suitable preparation of hyaluronidase which I can insert under the periosteum of an experimental animal.   I also hope to assess the effect of different solutions of hyaluronidase on bone formation in a chick embryo. As no two cases of osteitis are comparable it would be difficult to assess the experimental effect of injected hyaluronidase on decalcification.

The erythrocyte sedimentation rate has been measured in a number of cases in Group III (Appendix III).   Not only was it high during the acute phase of the disease, but it remained high for at least three weeks and had no apparent relationship to the clinical condition of the patient (Dennison 1948). In both adults (Quast and Wilberg 1948) and children I have noted a high erythrocyte sedimentation rate in patients with severe fractures, particularly where there is extensive soft tissue damage.   In this type of case, however, the sedimentation rate fell to normal levels within ten days.   Numerous substances can be used to promote erythrocyte aggregation and of these certain are present in infections which accelerate sedimentation (Nichols 1945). Viscosity of the blood is one of the variables with which the sedimentation rate is increased, although it is usually an increase in fibrinogen (Helm 1943) which increases both the sedimentation rate and the viscosity.   Hyaluronic acid is a generally distributed form of viscosity-enhancing substance.   By adding hyaluronic acid to blood (Meyer et al 1945) the sedimentation rate is increased.   The introduction of hyaluronidase (to human blood in vitro and to rats' blood in vivo) restores the elevated rate to normal.   I have only recently investigated this phenomenon and have only had the opportunity of carrying out the investigation in two cases of osteitis and in two controls. In /

In each case the sample of venous blood was divided into two parts and 1 c.c. of hyaluronidase (Hyalase, Benger) was added to one specimen. The results are shown in Appendix III. The investigation continues.

Parenteral penicillin does not diffuse into a normal joint but in a damaged joint (Jones 1948) or in pyogenic arthritis associated with osteitis, a therapeutic level is often found in the joint cavity. Hyaluronidase has not yet been isolated from normal synovial fluid (Sylven 1947b) but hyaluronic acid is present. Organisms in contact with the synovia produce a considerable amount of hyaluronidase which can be measured by McClean's test for estimating the potency of antihyaluronidase (Auquier 1949). Hyaluronidase in a joint infected by the staphylococcus may, by exercising its spreading effect, allow diffusion of parenterally administered penicillin into the joint.

The physiologist, the biochemist and the micro-anatomist regard the problem of bone formation each in their own way. The subject is too vast for more than a brief survey but some distinct facts are presented as being pertinent to this thesis.

In spite of intensive investigation which has been directed towards the problem of ossification, we remain ignorant on two of the salient points, namely, the mechanism by which calcium is deposited in the organic bone matrix and the immediate stimulus which leads to the formation of bone in a given location.

Bone is formed either as a result of a local chemical phenomenon, or it is the product of specific bone cells (osteoblasts) which have the capacity of laying down bone (Macewen 1912).

Bone /

Bone is largely calcium phosphate which is insoluble in a fairly alkaline medium. Robinson (1923) discovered that bone contained a ferment phosphatase which will decompose the soluble salts of phosphosic esters to give free phosphate ions. The latter trap calcium if available, resulting in a local deposit of calcium phosphate if the environment is fairly alkaline. Three factors are thus of importance in ossification and therefore in bone disease, namely, serum calcium, the local concentration of organic phosphate and the concentration of phosphatase. Key (1934) failed to stimulate osteogenesis after implanting either calcium carbonate or calcium phosphate into bone defects. A local depot of implanted calcium is thus of no value in stimulating bone formation. Much work has been done on phosphatase, both in the laboratory and at the bedside, but from the clinical point of view most of it has been disappointing.

Following the work of Morris and his colleagues (1937) and Peden (1937) in this hospital, on plasma phosphorus and phosphatase in childhood, it was found that there was an increase in phosphatase during the healing of fractures. During a period of six months estimations of serum calcium, plasma phosphorus and phosphatase were made in all cases of acute osteitis (9 cases in all). No significant changes were observed in the values for serum calcim and the plasma phosphorus values were no higher than in a comparable series of fracture cases. Morris and his colleagues used the method of Jenner and Kay (1932) and found that plasma phosphatase in healthy children varied between 3.0 and 10.0 units with an average value of 6.92. In the present investigation the method of King and Armstrong (King 1946) was used and the figures in Table XXI are all within normal limits (Cantarow and Trumper 1949). Duvoir et al (1935) using the method of Bodansky (1933) found normal /

normal levels in acute osteitis and increased levels in chronic osteitis.

TABLE XXI

Case	Calcium (mgms.%)	Phosphorus (mgms.%)	Phosphatase (K.A. units)		
	On admission	On admission	On admission	After a week	After 4 weeks
52	12.1	4.3	8.3	6.6	7.2
54	10.4	4.1	6.1	8.9	-
55	9.4	2.8	10.8	-	7.8
56	10.5	3.2	11.8	-	9.9
57	10.0	6.4	8.5	5.7	13.3
58	10.1	2.6	10.4	10.2	13.3
59	10.0	3.0	12.0	9.1	-
60	10.0	5.1	8.8	10.4	-
61	9.0	3.0	21.3	-	-
63	-	2.6	10.4	10.2	

Taylor (1935) regards strain as the stimulus to the formation of phosphatase by osteoblasts. Decalcification following hyperaemia is not so much decalcification as a hindrance of recalcification by excessive removal of phosphatase. Bone is laid down along the lines of strain resulting in the mechanically optimum pattern of the trabeculae in cancellous bone and the hollow compact shafts of the long bones. The cancelli in the end of a femur, for example, are disposed along the lines of the greatest pressure and tension. D'Arcy Thomson (1941) compares the pressure and compression lines of the femur to the theoretical stress-diagram of an engineer's crane.

During the phase of decalcification in osteitis, the trabecular structure as seen radiographically is grossly altered in many cases. When

recalcification /

recalcification commences the trabeculae are laid down fortuitously in any direction within the substance of the bone and not until weight bearing takes place are obliquely placed trabeculae acted upon and moved away by the shearing force.   In no case in this series have I seen the "normal" trabecular pattern restored in less than two years.   Prolonged immobilisation delays recalcification and restoration of trabecular structure.

Whatever their underlying cause, the radiographic changes are due to a combination of decalcification followed by recalcification, and bone destruction of varying degree followed by bone synthesis.

Sequestrum formation   Bancroft (1921) and later Starr (1922) induced chemical osteitis by inserting capillary tubes containing croton oil into the medulla of the long bone of an experimental animal.   Involucrum and extensive sequestrum formation followed.   These sequestra were always absorbed and were replaced by new bone.   Bancroft postulated that the sequestra in haematogenous osteitis would be similarly absorbed if it were possible to sterilise them.   This in fact does occur (Dennison 1948) but in my experience only small sequestra have been absorbed.   Conversely, all sequestra in Group III which required surgical removal grew coagulase positive staphylococci. So long as cases continue to arrive late at hospital there will be interference with blood supply with death of portions of the bone.   Without a blood supply parenteral penicillin will fail to reach such dead fragments and in some instances the infected sequestrum will remain and give rise to future trouble. As in ununited fractures with sclerosis, bone drilling will lead to hyperaemic decalcification (Watson Jones 1943) and in some cases may provide a new route for penicillin and allow sterilisation of a segment of bone whose blood supply has /

has been interfered with (Case 70).

<u>Limb Lengthening</u>   The effects of alteration in circulation on growth of bone has interested many observers.   In recent works on bone disease and fractures, however, there is little reference to the known facts of changes in osteogenesis produced by circulatory derangement.   Many observers have recorded clinical improvement in the repair of bone in the presence of venous stasis and Stanley (1849), Paget (1853), and V. Bergmann (1868) have shown that any long-continued inflammatory process will be followed by increase in length and thickness of the bones.   Bier (1905) in his book on hyperaemia denies that he is the inventor of stasis hyperaemia and he gives a comprehensive historical review of the subject.

During the past five years I have noted increase in length and girth of long bones in conditions other than osteitis.   The following conditions showing increase in length of the lower limb have all bone seen in Mr. White's wards at the Royal Hospital for Sick Children.

1.   Increase of 2 cms. following transverse fracture of the femur.

2.   3 cms. increase in length associated with diffuse haemangioma (congenital arterio-venous fistula).

3.   2 cms. increase in length following recurring haemarthrosis of one knee in a haemophilic patient.

4.   Increase of 2.5 cms. following severe laceration of the thigh associated with compound fracture of the femur.

5.   Increase in length of 1 cm. associated with sepsis in a severe burn of one leg.

6.   2.5 cms. increase in length of the affected leg following synovial tuberculosis of the hip joint.

Many /

Many surgeons have noted overgrowth of the lower limb in a young adult suffering from severe varicose veins (Greig 1920). Although I have seen this phenomenon, I could never prove that the "increase" in length was not a congenital anomaly.

Leriche and Policard (1926) have suggested an indirect vascular effect on bone growth by the sympathetic nervous system. In the Sick Children's Hospital we have now come to expect increase in length of the leg by at least 1 cm. following unilateral lumbar ganglionectomy.

It can be seen that increased blood supply, either venous or arterial, may lead to increase in length of a limb. In osteitis this is due to continued hyperaemia caused by an infected sequestrum in most cases. And yet, where one of two paired bones is diseased, the increase in length affects both bones equally (Figures 19, 20 and 35). The hyperaemia must therefore affect the soft tissues and increase the blood supply throughout the segment. Sequestrectomy has been performed in 15 cases in Group III and in every case coagulase positive staphylococci have been grown from either the sequestrum or the surrounding granulation tissue. Sterile sequestra are eventually absorbed (Bancroft 1921) but an infected sequestrum must be removed surgically. Advantage of this knowledge was taken in Case 58. Following pathological fractures of the upper and lower ends of the femur, the patient exhibited 1 cm. shortening of the affected limb (Figure 47). Radiography revealed a cavity and sequestrum formation and at operation on 12th February 1949 three small infected sequestra were removed and a fourth was deliberately left _in situ_ to promote bone growth. This remaining sequestrum was removed on 4th October 1949 and Figure 48 shows both legs the same length.

The /

Figure 47 Case 58   Photographs show shortening of left leg and slight pelvic tilt – corrected by 1 cm. block under left foot. X-ray film shows coxa vara following fracture of the neck of the left femur, sclerosis of shaft and cavitation in lower quarter.
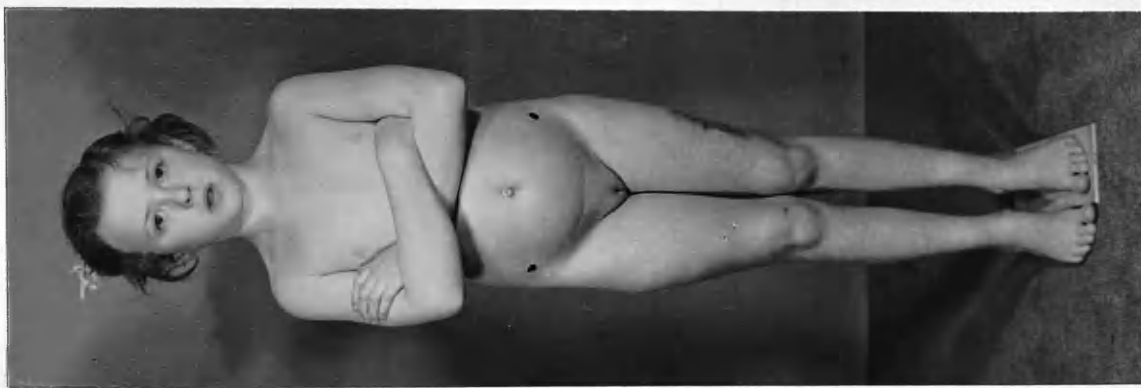
Figure 48   Case 58 (eight months later).   Legs of equal length.   X-ray film shows femora of equal length; increase in girth, sclerosis and partial consolidation of cavities.

The stimulus activated by the hyperaemia gradually passes off and in the growing child moderate increase in length is rectified within five years. Increase in length up to 2.5 cms. is no longer apparent by the time adult life is reached, presumably because growth ceases earlier in the overgrown limb. I have recently examined four young adults who were patients in Group I and in whose case histories increase in length of the lower limb had been noted. (Unfortunately no photographs were taken in this earlier group and no accurate measurements were recorded). In none was there any measurable difference in the length of the two limbs, although radiography still revealed considerable increase in girth of the affected bones.

With the accurate records now kept and with photographs available, it should eventually be possible to report accurately on the ultimate fate of the long limb of many of the Group III patients thus afflicted.

In the meantime it must be remembered that the growing child can compensate for the long limb by such postural defects as scoliosis (Figure 24) and genu valgum (Figure 38) and constant watch must be kept as these deformities develop insidiously if suitable raising is not applied to the footwear of the normal leg.

SUMMARY AND CONCLUSIONS.

SUMMARY AND CONCLUSIONS

In the foregoing parts, various aspects of acute haematogenous osteitis have been reviewed and 212 cases admitted to one of the surgical units of the Royal Hospital for Sick Children, Glasgow, between 1936 and 1949 have been surveyed.   This survey offers a unique opportunity of assessing the various therapeutic agents in three comparable groups of patients.   In Group I, 75 cases treated before the introduction of effective chemotherapy are presented.   The mortality in this group was 36 per cent. A similar review is made of 55 cases treated with sulphathiazole.   These cases constitute Group II and the mortality in this group was 12.7 per cent. In Group III, 82 cases treated with penicillin are presented.   The mortality was 1.2 per cent. and all cases in this group are analysed in Appendix I.

The present day treatment has been outlined and factors leading to unsatisfactory results have been discussed with illustrative cases presented in Appendix II.

In Part IV, various aspects of the disease presented in the preceding parts are analysed and discussed under Aetiology, Treatment and Results.   The aetiology of acute haematogenous osteitis is not fully understood and experimental data have been introduced in an attempt to solve certain aetiological problems.   Penicillin dosage, duration of penicillin treatment and the problems of "penicillin sensitivity" are discussed and the importance of marrow culture as a control to penicillin therapy is stressed. The results of treatment in the three groups are compared and three complications which present problems in the penicillin-treated group are discussed.

The /

The present review shows no diminution in the incidence of acute haematogenous osteitis in the area served by the Royal Hospital for Sick Children, Glasgow.   The incidence of the disease appears to be associated with poor living conditions.   Osteitis appears in all age groups admitted to the hospital and the disease is slightly more common in males.   Sixty-five per cent. of cases occur in the femur and tibia.   The causal organism is a coagulase positive staphylococcus in ninety-five per cent. of cases.

Until ten years ago, the disease was essentially "surgical" and the final outcome was determined largely by the ability of the patient's natural resources to localise the infection and to combat effectively the hostile organisms and their deleterious effect upon his tissues.   Despite all forms of surgical intervention a third of the affected children died.   In those who survived the result could only be measured in terms of tissue sacrifice, impairment of function and the time-consuming loss of social and educational life.

Effective sulphonamide therapy reduced the mortality to just over twelve per cent. but there was little alteration in the morbidity of the disease.

With the introduction of penicillin the response to treatment, although not immediate, was dramatic.   The blood culture, if initially positive, becomes sterile within three days and although the patient may remain seriously ill for some days, improvement is slowly progressive from the time treatment starts.   Even with associated joint involvement, a full recovery of function may be expected in the affected limb, if the organism is penicillin-sensitive /

sensitive, if subperiosteal pus is evacuated early and if there is no gross interference with the blood supply to the affected metaphysis. The duration of penicillin therapy is controlled by the results of marrow culture and repeated marrow punctures are performed in every case of acute osteitis. An increasing incidence of penicillin-resistant staphylococci has been reported from many centres but fortunately these organisms are still rare in the surgical division of this hospital. One acute bone infection caused by a penicillin-resistant staphylococcus ended fatally. The newer antibiotics should prevent the repetition of such a tragedy. Delay in evacuation of pus, inadequate penicillin dosage or insufficient duration of treatment may all lead to cavitation or sequestrum formation and if these conditions are not treated early, to limb lengthening. Sequestra, if sterilised, will be absorbed. Coagulase positive staphylococci have been cultured from all sequestra which required surgical removal. In spite of the increased attention that is being paid to the teaching of paediatrics, it is regrettable that cases in Group III presented for treatment even later than those in the two earlier groups.

Treated sufficiently early and intensively with penicillin, the acute stage of haematogenous osteitis should not require surgical intervention even of the relatively minor degree carried out in Group III cases. Owing to the anatomical peculiarities of bone, its blood supply is particularly vulnerable to pyogenic infection. With the antibiotics at present available it is essential to retain an adequate blood supply to the focus of infection, not only to prevent destruction of bone tissue in varying degrees but also to prevent recurrence of infection from a focus which may lie latent for many years. To know this disease, we must try to understand the normal functioning /

functioning of bone as well as its normal and pathological histology. It has become incumbent upon us to attempt the diagnosis of the condition before irreversible structural changes have occurred and to treat the disease with an intelligent concept of the physiological factors underlying the deviation from health. I have briefly reviewed some of the problems of bone formation in so far as they affect bone infection. To explain the progressive decalcification which so often follows the penicillin treatment of acute osteitis I have suggested (1948) that the removal of the stimulus of continuing infection by sterilisation of the bone focus prevents dense involucrum formation. The destruction of the staphylococcus removes a source of hyaluronidase which experimental findings suggest may be concerned with bone formation. The continuing high erythrocyte sedimentation rate could also be due to lack of hyaluronidase. The investigations and experiments are continuing and my efforts will be particularly directed to solving the problem of the detailed blood supply of the long bone of the child. Although the arterial tree of the tibia has now been demonstrated more detailed knowledge of the blood supply of long bones in different age groups is required. Haematogenous osteitis occurs only in man and there may be some anatomical explanation for the vulnerability of the actively growing metaphysis of the child.

Throughout the surgical division of the hospital there has been a striking betterment in mortality statistics during the period under review. When evaluating the results of chemotherapy and antibiotics in osteitis we must consider the factors which have brought about this improvement in the results of paediatric surgery in general. There has been a gradual increase in the number of those who devote the main part of their time to the problems of /

of surgery and anaesthesia in childhood. The paediatric surgeons and anaesthetists work in close collaboration with their medical colleagues and meet them in a much wider common field than exists for those who work only with adults. Consequently there has been more detailed pre-operative and post-operative care, particularly in the maintenance of normal fluid and electrolytic balance. Finally, two further factors have helped greatly towards the improved results. Plasma became available for the first time during the war years and more recently the modern oxygen tent has proved to be a very satisfactory method of providing a high oxygen atmosphere for the acutely ill child.

Penicillin is the most valuable single agent available for the treatment of acute haematogenous osteitis, but the acknowledged advances listed above have played an important part in controlling this scourge of childhood.

ACUTE HAEMATOGENOUS OSTEITIS IN CHILDHOOD

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The Bibliography is divided into two sections for convenience. The first section subserves the historical background of osteitis. The second section contains all the other references quoted.

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APPENDIX I

Analysis of eighty-two cases of acute haematogenous osteitis treated with penicillin.

ANALYSIS OF EIGHTY-TWO CASES OF SEPTICAEMIC OSTEITIS TREATED
WITH PENICILLIN.

Case No.	Sex.	Age. Years.	Site.	Days ill.	Blood Culture.	Pus.	Complications.	Surgical Treatment.	Route.	Penicillin Total Dose (Mega Units)	Dura-tion (Days)	Days in Hos-pital.	Radiographic Appearances.	Result.
1945.														
1	M	6	Both tibiae	6	Sterile	Staph aureus	–	Aspiration	I.M. Drip	1.4	14	71	2 weeks: raised periosteum: decalcification both tibiae. 6 weeks: gross decalcification both. 3 months: Recalcification and sclerosis.	Well at five years. Full function.
2	F	7½	Ilium	7	Sterile	Staph aureus	–	Incision of abscess.	I.M. Drip.	1.2	12	36	1 week: osteitis ilium. 3 weeks: gross decalcification with extra and intra-pelvic abscess. 5 months: no evidence of osteitis.	Well at three years. Full function.
3	M	6½	Femur (lower)	3	Staph aureus	–	–	Immobilisation	I.M. Drip.	1.2	12	21	2 weeks: raised periosteum. 3 weeks: patchy decalcification. 3 months: "healed osteitis". 4 years: no bone lesion.	Well at four years. Full function.
4	M	6	Femur (upper)	4	Staph aureus	–	Recurrent abscess at 2½ years, 3 years and 4 years.	Immobilisation	I.M. Drip.	1.0	10	21	2 weeks: raised periosteum. 3 weeks: decalcification neck of femur. 16 weeks: well calcified tiny cortical sequestrum 5 years: sclerosis upper end femur.	At five years no evidence of disease. ¾" lengthening.
5	M	3	Femur (lower)	1	Staph aureus	Staph aureus	✗ Scarlet fever 24th day: met-astes to tibia and fibula. Multiple sequestra.	1) Immobilisation 2) Multiple sequestrect-omies.	I.M. Drip.	1.4	14	✗ 24	2 weeks: raised periosteum. 3 months: cavities femur and tibia: sequestra fibula. 17 months: pathological fracture following saucer-isation. 5 years: sclerosis femur tibia and fibula.	At three years 1½" lengthen-ing of affect-ed limb. At five years no lengthening.

Case No.	Sex.	Age Years.	Site.	Days Ill.	Blood Culture.	Pus.	Complications.	Surgical Treatment.	Route.	Penicillin Total Dose (Mega Units)	Duration (Days)	Days in Hospital.	Radiographic Appearances.	Result.
6	M	4½	Tibia	7	Staph aureus	–	–	Immobilisation.	I.M. Drip.	0.9	9	38	3 weeks: patchy decalcification. 8 weeks: gross decalcification. 16 weeks: recalcifying. 8 months: "healed osteitis". 3 years: no evidence of bone disease.	Well at three years. Full function.
7	M	9	Calcaneus	2	Sterile	Staph aureus	–	Incision of abscess eighth day.	I.M. Drip.	1.1	11	35	1 week: decalcification. 20 weeks: decalcification and cavities. 8 months: "healed osteitis". 2 years: sclerosis.	Well at two years. Full function.
8	F	10	Femur & metatarsal.	7	Sterile	Staph aureus	1.Arthritis of knee. 2.Sequestrum formation.	Aspiration knee: incision foot and thigh. Sequestrectomy at 18 months.	I.M. Drip.	0.9	9	22	1 week: decalcification of femur and metatarsal. 12 weeks:cavity with sequestrum formation. 2 years: sclerosis of femur.	At five years: 1" lengthening affected leg: unilateral genu valgum.
9	M	10	Tibia	4	Sterile	Staph aureus (Marrow Culture)	–	Immobilisation.	I.M. Drip.	1.1	11	20	2 weeks: raised periosteum: patchy decalcification. 4 months: Decalcification lower end tibia. 1 year: slight sclerosis tibia.	At 4½ years – no clinical or radiographic abnormality. Full function.
10	F	7½	Tibia	4	Staph aureus	Staph aureus	–	Incision and bone drilling	I.M. Drip.	1.0	10	25	2 weeks: decalcification. 4 weeks: gross decalcification. 4 months:cavity with sequestrum. 14 months: sequestrum absorbed: cavity consolidated.	At 4½ years – ½" lengthening and slight genu valgum.
11	F	3	Tibia	4		Staph aureus	Recurrent soft tissue abscess at 9 months and 28 months.	Immobilisation.	I.M. Drip.	1.1	11	14	1 week: Raised periosteum. 3 weeks: patchy decalcification. 3 months: small cortical sequestrum. 3 years: no evidence of osteitis.	Well 3½ years after onset. Full function.
12	F	3/52	Femur	4	Staph aureus	Staph aureus	Arthritis of knee.	Aspiration of hip and knee: incision of soft tissue abscess.	I.M. Drip.	1.1	11	32	2 weeks: effusion of hip & knee: raised periosteum. 1 month: destruction lower femoral epiphysis. 1 year: gross deformity lower end of femur.	At 4½ years: 1" shortening movements of knee full and painless.

Penicillin

Case No.	Sex.	Age Years.	Site.	Days Ill.	Blood Culture.	Pus.	Complications.	Surgical Treatment.	Route.	Total Dose (Mega Units)	Duration (Days)	Days in Hospital.	Radiographic Appearances.	Result.
1946.														
13	F	2/12	Third lumbar vertebra.	12	–	Staph Aureus	Flaccid paralysis both legs on admission.	Incision of abscess and primary suture.	I.M. injection.	0.264	11	25	2 weeks: osteitis. 2 months: no evidence of osteitis.	Slight drop foot (R) at 7 months. (Child not traced).
14	F.	7	Femur & metatarsal.	2	Sterile	Staph Aureus (From Sequestrum)	Sequestrum formation.	1.Immobilisation. 2.Sequestrectomy at 21 months.	I.M. Drip.	1.1	11	55	3 weeks: gross decalcification and raised periosteum. 2 months: decalcification and involucrum formation. 6 months: cavity and sequestrum formation. 3 years: sclerosis and lengthening ? cavity.	Well at 4 years apart from ¾" lengthening.
15	M.	6	Tibia (Bi-polar)	5	Sterile	Staph Aureus	Sequestrum formation.	1.Incision and bone drilling. 2.Sequestrectomy at 6 months.	I.M. Drip.	1.1	11	14	3 weeks: raised periosteum: decalcification entire shaft. 2 months: large sequestrum. 9 months: tibia well consolidated.	Well at 3 years apart from ½" lengthening.
16	M	5	Tibia (Bi-polar)	2	Staph Aureus	Staph Aureus	Acute supp.otitis media. Convulsions. Pneumonia.	Incision, bone drilling and suture third day.	I.M. Drip.	1.0	10	82	3 weeks: decalcification. 2 months: new bone formation: decalcification. 9 months: no evidence of bone disease.	Well at four years. Full function.
17	M	6¾	Femur (Lower)	5	Sterile	Staph Aureus	Sequestrum formation.	1.Immobilisation. 2.Aspiration at 8 weeks. 3.Sequestrectomy at 6 and 18 months.	I.M. Drip.	2.3	21	69	2 weeks: raised periosteum patchy decalcification. 5 months: cortical sequestrum. 3 years: sclerosis and slight lengthening.	Well at four years. Negligible lengthening. Full function.
18	M	4½	Ischium	7	Staph Aureus	Staph Aureus	Extra and intra pelvic abscess.	Aspiration and local installation of penicillin X2	I.M. Drip.	1.2	12	85	1 week: effusion right hip. 3 weeks: decalcification right ischium. 4 weeks: osteitis ischium-pelvic abscess. 4 months: healed osteitis.	Well at four years. Full function.

Case No.	Sex.	Age. Years.	Site.	Days Ill.	Blood Culture.	Pus.	Complications.	Surgical Treatment.	Route.	Penicillin Total Dose (Mega Units)	Penicillin Dura-tion (Days)	Days in Hos-pital.	Radiographic Appearances.	Result.
1946. 19	F	9	Femur (lower)	2	Staph aureus	Staph aureus	Arthritis knee sequestrum formation March fracture at 13 months.	1.Aspiration knee: incision abscess 2.Sequestrectomy at 6 months.	I.M. Drip.	1.0	10	25	10 days: raised periosteum decalcification. 8 weeks: gross decalcific-ation. 3 months: cavity and sequestrum. 3 years: slight sclerosis.	Well at 4 years. Full function.
20	F	10	Fibula& femur (lower)	5	Sterile	Staph Aureus (from marrow cult-ure)	-	Immobilisation.	I.M. Drip.	1.4	14	28	2 weeks: decalcification lower femur. 4 weeks: increased decalcification. 10 months: no evidence of disease.	Well at 4 years. Full function.
21	F	7½	Tibia (upper)	2	Staph aureus	Staph aureus	Sequestrum formation.	1.Incision and bone drilling. 2.Sequestrectomy at 6 months.	I.M. Drip and inject-ion.	2.35	11	18	2 weeks: raised periosteum patchy decalcification. 4 weeks: sequestrum. 1 year: pathological fracture. 18 months: fracture consolidated.	Well at 33 months. Failed to report again.
22	M	10	Femur (lower)	3	Staph aureus	Staph aureus	Sequestrum formation.	1.Incision and bone drilling. 2.Sequestrectomy at 28 months.	I.M. Drip and inject-ion.	1.4	9	35	2 weeks: raised periosteum. 3 weeks: decalcification. 4 weeks: sequestrum. 32 months: sclerosis only. 3 years: increase in girth in length.	Well at 3½ years apart from ½" length-ening.
23	M	8	Femur (lower)	2	Staph aureus	Staph aureus	-	Incision and bone drilling.	I.M. Drip and inject-ion.	1.7	9	22	2 weeks: raised periosteum. 4 weeks: decalcification. 1 year: sclerosis only.	Well at 3 years. Full function.
24	F	8	Humerus	2	Staph aureus	-	-	Immobilisation.	I.M. inject-ion.	1.6	8	13	10 days: decalcification. 3 weeks: raised periosteum and decalcification. 6 months: healed osteitis.	Well at 3½ years. Full function.

P e n i c i l l i n

Case No.	Sex.	Age Years.	Site.	Days Ill.	Blood Culture.	Pus.	Complications.	Surgical Treatment.	Route.	Total Dose (Mega Units)	Duration (Days)	Days in Hospital.	Radiographic Appearances.	Result.
25	M	1.7/12	Femur	3	Staph Aureus	–	–	Immobilisation	I.M. injection.	1.1	21	27	2 weeks: raised periosteum. 3 weeks: patchy decalcification. 6 months: healed osteitis.	Well at $3\frac{1}{2}$ years. Full function.
26	M	$2\frac{1}{2}$	Tibia (lower)	7	Sterile	Staph aureus	–	Incision and suture.	I.M. injection.	2.3	21	23	2 weeks: raised periosteum, and patchy decalcification. 4 weeks: increased decalcification. 6 months: sclerosis only: genu valgum.	Well at 3 years. No evidence of genu valgum.
27	F	7	Tibia (lower)	2	Staph aureus	Staph aureus	Sequestrum formation	1.Incision. 2.Sequestrectomy at 10 months.	I.M. injection.	2.1	21	22	2 weeks: raised periosteum: patchy decalcification. 4 weeks: increased decalcification. 4 months: cavity and sequestrum formation. 3 years: sclerosis only.	Full function at $3\frac{1}{2}$ years.
28	M	7	Femur (lower)	5	Sterile	Staph aureus	–	Incision and suture.	I.M. injection.	7.8	23	27	3 weeks: subperiosteal new bone. 7 weeks: gross decalcification. 2 years: sclerosis only.	Full function at $2\frac{1}{2}$ years.
29	M	$11\frac{1}{2}$	First meta-tarsal	4	Staph aureus	Staph aureus	–	Incision and primary suture	I.M. injection.	8.4	21	25	3 weeks: early decalcification. 4 weeks: increased decalcification. 4 months: consolidating well. 3 years: bone structure normal.	Well at 3 years. Full function.
30	M	5	Femur (upper)	4	Sterile	Staph aureus	Perthe's disease of opposite hip 1 year after onset of osteitis.	Incision and primary suture	I.M. injection.	3.9	20	22	2 weeks: early decalcification. 3 weeks: new bone formation. 1 year: no evidence of bone disease.	Healing Perthe's disease (right): Normal bone trabeculation left femur at 3 years.

P e n i c i l l i n

Case No.	Sex.	Age. Years.	Site.	Days ill.	Blood Culture.	Pus.	Complications.	Surgical Treatment.	Route.	Total Dose (Mega Units)	Dura-tion (Days)	Days in Hos-pital.	Radiographic Appearances.	Result.
31	M	3	Humerus (upper)	3	Staph aureus	Staph aureus	–	Incision and primary suture	I.M. inject-ion.	6.3	21	27	2 weeks: raised periosteum. 4 weeks: decalcification. 5 months: consolidating. 3 years: no abnormality.	Well at 3 years. Full function.
1947. 32	M	6	Second cervical vertebra	?	Haem. Strept-ococcus	–	Subluxation of of C2 on C3.	Lumbar puncture Immobilisation	I.M. inject-ion.	6.3	21	144	2 weeks: osteitis of lamina of C2. 3 weeks: subluxation of C2 on C3. Destruction of lamina of C2. 1 year: healed with fusion of C2 and C3.	Well at 3 years. Full function.
33	F	8	Tibia (lower)	4	Staph aureus	Staph aureus	–	Incision and primary suture	I.M. inject-ion.	9.95	33	50	10 days: raised periosteum and decalcification. 3 weeks: gross decalcific-ation. 2 months: consolidating. 2 years: no evidence of osteitis.	Well at 3 years apart from 3/4" lengthening.
34	F	6/12	Atlas	?7	–	Staph aureus	Pyaemic abscess	Aspiration of pyaemic abscess	I.M. inject-ion.	2.16	22	46	10 days: osteitis of atlas. 3 weeks: decalcification of atlas and retropheringsal abscess. 2 months: recalcifying. 1 year: atlas symmetrical.	Well at 2 years. Full function.
35	F	6	Ilium	6	–	Staph Aureus (from marrow puncture)	–	Immobilisation and local penicillin	I.M. inject-ion (1) 8.1 (2) 3.6 Total:- 11.7		29) 12)	48	1 week: soft tissue oedema. 2 weeks: patchy decalcifica-tion. 5 weeks: gross decalcifica-tion. 3 months: chronic osteitis.	Full function at 1 year ilium thick. Failed to report again.

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Case No.	Sex.	Age. Years.	Site.	Days ill.	Blood Culture.	Pus.	Complications.	Surgical Treatment.	Route.	Total Dose (Mega Units)	Duration (Days)	Days in Hospital.	Radiographic Appearances.	Result.
36	M	10	Femur (lower)	5	-	Staph aureus	-	1. Aspiration 2. Incision and suture.	I.M. injection.	13.95	31	35	10 days: raised periosteum. 3 weeks: early decalcification and subperiosteal new bone. 2 months: recalcifying. 3 years: apparently normal.	Well at 3 years. Full function.
37	M	7	Femur (lower)	2	Staph. aureus	Staph aureus	-	Incision and suture	I.M. injection.	14.4	32	37	2 weeks: decalcification and raised periosteum. 4 weeks: gross decalcification. 4 months: early re-calcification. Cortical sequestrum. 2 years: sclerosis sequestrum absorbed.	Well at 3 years. Full function.
38	F	8.3/12	Rib (12th.)	3	-	Staph aureus	Pneumothorax	Removal of 12th rib and suture	I.M. injection.	8.1	21	33	1 week: no evidence of 12th rib: fluid and air left chest. 1 month: lung fully expanded.	Well at 2 years. No disability.
39	M	7	Tibia (Bipolar)	4	Staph aureus	Staph aureus	-	1. Incision and suture (lower end. 2. (3 days) incision & suture (upper end)	I.M. injection.	6.7	21	25	2 weeks: raised periosteum & patchy decalcification. 3 weeks: increased decalcification. 4 months: consolidating. 2 years: slight sclerosis and lengthening.	Full function at 2½ years apart from ½" lengthening.
40	M	12	Tibia (upper)	1	-	Staph aureus	-	Incision, drilling and suture.	I.M. injection.	6.6	22	25	2 weeks: raised periosteum and patch of decalcification upper end. 3 weeks: general decalcification. 2 months: recalcifying.	Well at 2 years. Full function.

Penicillin

Case No.	Sex.	Age. Years.	Site.	Days ill.	Blood Culture.	Pus.	Complications.	Surgical Treatment.	Route.	Total Dose (Mega Units)	Duration (Days)	Days in Hospital.	Radiographic Appearances.	Result.
41	M	7	Femur (lower)	3	-	Staph aureus	-	Incision and Suture.	I.M. injection.	6.66	20	25	2 weeks: raised periosteum. 1 month: patchy decalcification. 3 months: consolidating. 2 years: sclerosis and slight lengthening.	Full function at 2½ years apart from ⅜" lengthening.
42	F	11	Humerus	2	-	Haemolytic streptococcus.	-	Incision, drilling and suture.	I.M. injection.	7.0	21	23	2 weeks: raised periosteum. 3 weeks: early decalcification. 3 months: early sclerosis. 2 years: no evidence of disease.	Well at 2½ years. Full function.
43	M	11	Tibia (upper)	4	Sterile	Staph aureus	Arthritis of knee.	Aspiration of knee. Incision and suture.	I.M. injection.	8.87	25	30	2 weeks: raised periosteum. 3 weeks: patchy decalcification. 2 months: gross decalcification. 2 years: no evidence of disease.	Well at 2½ years. Full function.
44	F	8	Tibia (lower)	7	Sterile	Staph aureus	-	Incision, drilling and suture.	I.M. injection.	7.2	24	27	10 days: raised periosteum and translucent patch. 3 weeks: subperiosteal new bone: patchy decalcification. 2 months: early re-calcification. 2 years: no evidence of disease.	Well at 2½ years. Full function.

Penicillin

Case No.	Sex.	Age. Years.	Site.	Days ill.	Blood Culture.	Pus.	Complications.	Surgical Treatment.	Route.	Total Dose (Mega Units)	Duration (Days)	Days in Hospital.	Radiographic Appearances.	Result.
45	M	8	Humerus & femur	? treated elsewhere as poliomyelitis	–	Staph aureus	Pathological fractures upper humerus and lower femur.	Incision and suture thigh and arm.	I.M. injection.	8.76	27	152	On admission:decalcification humerus and femur. 2 weeks: gross decalcification. 3 weeks: pathological fractures femur and humerus. 1 year: sclerosis femur and humerus.	Well at 2½ years. Full function arm and leg.
46	M	4	Femur (upper)	? treated elsewhere as poliomyelitis	–	Staph aureus (marrow puncture)	Pathological fracture neck of femur.	Immobilisation	I.M. injection.	5.4	27	29	On admission:decalcification and pathological fracture. 2 months: fracture united coxa vara. 6 months: sclerosis and coxa vara.	Well at 2½ years. Radiographic evidence of coxa vara.
47	M	9	Metatarsal (3rd.)	2	Staph aureus	Staph aureus	Pathological Fracture	Incision and suture.	I.M. injection.	4.1	13		No radiographic changes for 3 weeks. 3 weeks: decalcification and raised periosteum. 2 months: pathological fracture. 6 months: soundly healed.	Well at 2 years. Full function.
48	F	4	Femur (upper)	4	Staph aureus Penicillin resistant.	Staph aureus	Pyaemia and death fourth day.	Aspiration and local insillation of penicillin.	I.M. injection.	2.0	4	4	2nd day: N.A.D.	Died 4th day.
49	F	2/52	Rib (7th)	?	–	Pneumococcos	–	Aspiration and local instillation of penicillin. 1 week excision of rib and suture.	I.M. injection.	1.53	17	22	7 days: osteitis 7th rib.	Transferred to physicians for treatment of cretinism.

P e n i c i l l i n

Case No.	Sex.	Age. Years	Site.	Days ill.	Blood Culture.	Pus.	Complications.	Surgical Treatment.	Route.	Total Dose (Mega Units)	Duration (Days)	Days in Hospital.	Radiographic Appearances.	Result.
50	M	1¼	Tibia	7	–	Staph aureus (Marrow Culture)	–	Immobilisation.	I.M. injection.	1.6	15	26	<u>1 week</u>: soft tissue oedema. <u>2 weeks</u>: raised periosteum. <u>1 month</u>: sclerosis. <u>1 year</u>: slight sclerosis.	Well at 2 years. Full function.
<u>1948.</u> 51	F	2/52	Femur (lower)	3	–	Haem-olytic Strept-ococcus.	Arthritis of knee.	Aspiration of knee. Immobilisation.	I.M. injection.	0.8	8	12	<u>1 week</u>: effusion knee. <u>2 weeks</u>: raised periosteum. decalcification. <u>1 month</u>: increased decalcification <u>1 year</u>: normal bone structure.	Well at 2 years. Full function.
52	M	4	Femur (lower)	7	Staph aureus.	Staph aureus.	Arthritis of knee.	Aspiration of knee. Incision and suture.	I.M. injection.	5.67	21	38	<u>On admission</u>: Arthritis knee. <u>2 weeks</u>: raised periosteum. Destruction epiphysis. <u>3 weeks</u>: subperiosteal new bone: fragmentation epiphysis. <u>2 years</u>: epiphysis not yet normal.	Coarse crepitus knee: ½" lengthening. No disability.
53	F	10	Frontal.	2	–	Staph aureus.	–	Aspiration.	I.M. injection.	2.4	8	13	<u>2 weeks</u>: area translucency. <u>3 weeks</u>: increased translucency. <u>2 months</u>: recalcifying. <u>6 months</u>: no evidence of disease.	Well at 2 years.
54	F	2	Ulna.	5	Staph aureus.	Staph aureus.	–	Incision and suture.	I.M. injection.	3.45	23	33	<u>1 week</u>: Translucency. <u>2 weeks</u>: gross decalcification: subperiosteal new bone. <u>1 month</u>: gross new bone formation: decalcification. <u>1 year</u>: ulna thick and sclerotic.	Full function at 2 years. ¼" increase in length.

Penicillin

Case No.	Sex.	Age Years.	Site.	Days ill.	Blood Culture.	Pus.	Complications.	Surgical Treatment.	Route.	Total Dose (Mega Units)	Duration (Days)	Days in Hospital.	Radiographic Appearances.	Result.
55	M	3½	Femur (lower)	3	Staph aureus	Staph aureus	-	Incision and suture.	I.M. injection.	8.75	21	35	10 days: raised periosteum. 1 month: decalcification. 6 months: well consolidated. 1 year: sclerosis and ¼" lengthening. 2 years: ¼" lengthening.	Well at 2 years. ¼" increase in length.
56	M	7	Humerus	4	-	Staph Aureus (Marrow of humerus. Puncture)	Pathological fracture neck	Incision and suture.	I.M. injection.	7.3	28	55	1 week: translucent area. 2 weeks: raised periosteum: decalcification throughout. 2 months: consolidating. 1 year: sclerosis.	Well at 2 years. Full function.
57	F	10	Tibia (lower)	2	Staph aureus	Staph aureus	Arthritis of ankle.	Aspiration of ankle. Incision and suture.	I.M. injection.	27.0	25	30	10 days: raised periosteum. 2 weeks: subperiosteal new bone. 3 weeks: increased decalcification. 3 months: consolidating. 2 years: apparently normal.	Well at 2 years. Full function.
58	F	7	Femur (Bi-polar)	2	Staph aureus	Staph aureus	Pathological fractures: sequestrum formation. Shortening of affected leg.	1. Incision and suture. 2. Sequestrectomy at 9 months and 16 months.	I.M. injection.	40.8	34	179	2 weeks: patchy decalcification and raised periosteum. 3 weeks: bipolar infection. 5 weeks: fracture neck femur. 2 months: supracondylar fracture femur. 5 months: sequestra. 2 years: "healed" osteitis.	Well at 2 years. Full function. No shortening.
59	M	6	Femur (upper)	5	-	Staph aureus (from hip & marrow puncture).	Arthritis hip.	Aspiration of hip: marrow puncture and instillation of penicillin.	I.M. injection.	8.1	27	51	1 week: raised periosteum. 2 weeks: area translucency. 3 weeks: patchy decalcification. 2 years: sclerosis around great trochanter.	Well at 2 years. Full function.

Penicillin

Case No.	Sex.	Age. Years.	Site.	Days ill.	Blood Culture.	Pus.	Complications.	Surgical Treatment.	Route.	Total Dose (Mega Units)	Duration (Days)	Days in Hospital.	Radiographic Appearances.	Result.
60	F	3½	Radius	2	-	Staph aureus	-	Incision, drilling and suture.	I.M. injection.	4.225	21	23	1 week: raised periosteum. 3 weeks: patchy decalcification and new bone formation. 3 months: consolidating. 2 years: sclerosis with increase of girth and length.	Well at 2 years. Full function.
61	M	7	Humerus	2	Staph aureus	Staph aureus	-	Incision, drilling and suture.	I.M. injection.	9.44	22	23	10 days: raised periosteum. 2 weeks: translucent area. 3 months: consolidating. 23 months: restoration to normal.	Well at 23 months. Full function.
62	M	9	Mandible	5	-	Staph aureus	Sequestrum formation.	1. Incision and suture. 2. Sequestrectomies at 3 months and 7 months.	I.M. injection.	7.8	26	28	1 week: patchy decalcification throughout. 1 month: multiple sequestra. 3 months: consolidating sequestra. 18 months: sclerosis and irregularity of mandible.	Well at 22 months: palpable Irregularity of bone. No disability.
63	M	9	Tibia (upper)	3	-	Staph aureus	-	Incision and suture.	I.M. injection.	6.9	23	28	2 weeks: raised periosteum. 3 weeks: patchy decalcification. 3 months: consolidating. 22 months: sclerosis upper tibia.	Well at 22 months. Full function.
64	M	5	Tibia (lower)	3	Staph aureus	Staph aureus	-	Incision and suture.	I.M. injection.	6.6	22	41	12 days: patchy decalcification and raised periosteum. 3 weeks: subperiosteal new bone: decalcification. 2 months: patchy sclerosis. 18 months: very slight sclerosis.	Well at 18 months. Full function.

Penicillin

Case No.	Sex.	Age. Years.	Site.	Days ill.	Blood Culture.	Pus.	Complications.	Surgical Treatment.	Route.	Total Dose (Mega Units)	Dura-tion (Days)	Days in Hos-pital.	Radiographic Appearances.	Result.
65	M	7½	Mandible	4	-	Staph aureus	Sequestrum formation.	1.At 14 days - extraction of mol-ar tooth and cur-ettage. 2.Sequestrectomy at 4 months.	I.M. inject-ion. Sulphi-atriad for 7 days.	11.2	14	33	10 days: area translucency. 3 weeks: extensive de-calcification. 1 month: sequestrum formation. 1 year: mandible irreg-ular and sclerotic.	Occlusion of jaws poor: otherwise well.
66	F	12½	Femur (lower)	3	Staph aureus	Staph aureus	-	Incision,drilling and suture.	I.M. inject-ion.	8.9	24	51	10 days: raised periosteum. 3 weeks: patchy decalcific-ation. 3 months: consolidating. 18 months:residual sclerosis.	Well at 18 months. Full function.
67	F	1.3/12	Humerus (Upper)	?	-	Staph aureus (from marrow puncture)	-	Immobilisation in abduction.	I.M. inject-ion.	2.6	21	24	1 week: decalcification. 2 weeks: increased decalcification. 2 months: consolidating. 18 months:structure normal.	Well after 18 months: Full function.
68	M	10.10/12	Femur (Lower)	2	Staph aureus	-	-	1.Immobilisation. 2.Multiple drill holes at 6 weeks and local penicillin.	I.M. inject-ion.	10.45	21	38	2 weeks: decalcification. 1 month: extensive decal-cification. 3 months: extensive decal-cification. 18 months:very slight sclerosis.	Well at 18 months: Full function.
69	M	2.1/12	Calc-aneus.	7	-	Staph aureus	Acute supp-urative otitis media at 6 weeks.	Incision,drilling and suture.	I.M. inject-ion.	20	34	107	2 weeks: decalcification. 1 month: decalcification and new bone formation. 6 months: well consolidated. 18 months: "normal".	Well at 18 months. Full function.

Penicillin

Case No.	Sex.	Age. Years.	Site.	Days ill.	Blood Culture.	Pus.	Complications.	Surgical Treatment.	Route.	Total Dose (Mega Units)	Duration (Days)	Days in Hospital.	Radiographic Appearances.	Result.
70	F	10.11/12	Femur (lower)	5	Staph aureus	Staph aureus	–	Incision, drilling and suture.	I.M. inject-ion.	20	34	151	10 days: raised periosteum and area of translucency. 3 weeks: subperiosteal new bone: decalcification. 10 months: consolidating well. 17 months: slight sclerosis.	Well at 17 months. Full function.
1949. 71	M	5.11/12.	Femur (lower)	2	Staph aureus	Staph aureus	Arthritis of knee.	Aspiration of knee: incision and suture of thigh.	I.M. inject-ion.	2.1	21	23	10 days: area of trans-lucency. 2 weeks: raised periosteum. 1 month: decalcification. 6 months: sclerosis.	Well at 16 months. Full function.
72	M	8½	Femur (lower)	3	Staph aureus	Staph aureus	Arthritis of knee: Sequestrum formation.	1. Aspiration of knee: incision & primary suture. 2. Open drainage of knee. 3. Sequestrectomy at 9 months.	I.M. inject-ion.	37.2	38	107	3 weeks: decalcification and new bone formation. 3 months: increased decalcification. 6 months: cortical sequestrum. 17 months: residual sclerosis.	Well at 17 months: 1 cm. increase in length of leg.
73	F	8	Tibia (lower)	5	–	Staph aureus	–	Incision and suture.	I.M. inject-ion.	27	22	28	10 days: raised periosteum and patchy decalcification. 2 months: patchy decalcific-ation lower tibia. 6 months: consolidating. 15 months: residual sclerosis.	Well at 15 months. Full function.
74	F	1	Femur (lower)	4	–	Staph aureus	Pathological fracture lower femur.	Aspiration and skin traction.	I.M. inject-ion.	7.2	28	33	1 week: decalcification. 2 weeks: pathological fracture. 1 month: extensive decalcification. 6 months: no evidence of bone disease.	Well after 13 months. Full function.

Penicillin

Case No.	Sex.	Age. Years.	Site.	Days ill.	Blood Culture.	Pus.	Complications.	Surgical Treatment.	Route.	Total Dose (Mega Units)	Dura-tion (Days)	Days in Hos-pital.	Radiographic. Appearances.	Result.
75	F	7	Tibia (lower)	2	–	Staph aureus	–	Incision and Suture.	I.M. Inject-ion.	16.8	26	29	2 weeks: raised periosteum 3 weeks: patchy decalcific-ation. 4 weeks: increased decalc-ification. 6 months: consolidated. 1 year: 1 c.m. increase in length.	Well at 1 year: 1 c.m. increase in length.
76	M	6	Tibia (lower)	1	Staph aureus	Staph aureus	–	Incision, drilling and suture.	I.M. inject-ion.	6.3	21	28	1 week: translucent area metaphysis. 3 weeks:subperiosteal new bone. 4 months: consolidating. 1 year: slight sclerosis.	Well at 1 year: Full function.
77	M	7.9/12.	Femur (lower)	3	Staph aureus	Staph aureus	–	Incision and suture.	I.M. inject-ion.	12.6	21	57	2 weeks: raised periosteum and patchy decalcification. 1 month: increased decalcification. 6 months: consolidating. 10 months: well consolidated.	Well at 10 months: 1 c.m. increase in length.
78	M	1	Scapula	2	–	Staph aureus	Stubborn anaemia re-quiring blood trans-fusion.	Aspiration.	I.M. inject-ion.	6.48	18	36	2 weeks: decalcification. 4 weeks: fracture. 2 months:increased decalcification. 10 months: no evidence of disease.	Well after 10 months.

Penicillin

Case No.	Sex.	Age. Years.	Site.	Days ill.	Blood Culture.	Pus.	Complications.	Surgical Treatment.	Route.	Total Dose (Mega Units)	Duration (Days)	Days in Hospital.	Radiographic Appearances.	Result.
79	F	7	Tibia (upper)	7	–	Staph aureus	–	Incision, drilling and suture.	I.M. injection.	6	20	27	10 days: raised periosteum. 2 weeks: early decalcification. 3 months: decalcification. 9 months: consolidating.	Well at 9 months: Full function.
80	M	1.9/12	Tibia (Upper)	1	Staph aureus Lumbar puncture to eliminate meningocaecemia.	Staph aureus	–	Incision, drilling and suture.	I.M. injection. Streptomycin 3.6 gms. over 6 days.	13.05	24	25	10 days: raised periosteum: area translucency. 3 weeks: patchy decalcification. 3 months: recalcifying. 6 months: sclerosis.	Well at 9 months. Full function.
81	F	8	Tibia (Bi-polar)	5	Staph aureus	Staph aureus	Pathological fracture: sequestrum formation.	1. Incision, drilling and suture. 2. Sequestrectomy at 6 and 9 months.	I.M. injection.	13.1	21	137	3 weeks: generalised decalcification. 2 months: sequestra. 6 months: pathological fracture.	Well. In P.O.P. following sequestrectomy.
82	M	6	Tibia	2	Staph aureus	Staph aureus	1. Pericarditis. 2. Sequestrum formation.	1. Incision and suture. 2. Sequestrectomy at 6 months.	I.M. injection.	13.95	39	44	2 weeks: raised periosteum: area of translucency. 3 weeks: pericarditis. 1 month: extensive decalcification and new bone formation. 4 months: involucrum formation around sequestrum.	At 6 months in P.O.P. following sequestrectomy.

APPENDIX II

Details of unsatisfactory cases mentioned in

Part III

Group A.   Cases inadequately treated.

Group B.   Cases in which the blood supply

                  was seriously impaired.

APPENDIX II

Details of unsatisfactory cases discussed in
Part III.

GROUP A.   CASES INADEQUATELY TREATED.

Case 4.   A.M., male aged 6 years.   Osteitis of upper end of left femur.   Blood culture, coagulase positive staphylococcus.   Limb immobilised. No surgical intervention.   Penicillin 100,000 units daily for ten days; total 1 mega unit.   In hospital for twenty-one days.   Remained well for twenty-nine months when he was re-admitted with a large painless soft tissue abscess of the thigh.   X-ray showed a sclerotic femur with some irregularity in the region of the great trochanter and a tiny free sequestrum.   Abscess incised; sequestrum removed;   wound healed uneventfully after primary suture. Coagulase positive staphylococci were grown from the pus.   The affected limb showed 1.25 cms. increase in length (Figure 30).   Six months later, re-admitted with soft tissue abscess of thigh.   Radiography revealed no sequestrum and there was no naked eye abnormality of the femur.   The organism was again a coagulase positive staphylococcus.   The wound healed uneventfully.

Child remained well and radiography shows restoration of bone architecture five years after onset.

Remarks   It is interesting that infection should lie latent in a small sequestrum for twenty-nine months.   If sterile, such a sequestrum would be absorbed (Bancroft 1921).

Case 8 /

Case 8.   J.P., female aged 10 years.   Osteitis of lower end of right femur and arthritis of knee.   Blood culture, coagulase positive staphylococci.   Treatment: Pus aspirated from knee-joint and penicillin instilled.   Soft tissue abscess incised, wound packed with vaseline gauze and limb immobilised.   900,000 units of penicillin administered over nine days. Patient discharged with wound healing after twenty-two days.   Small cortical sequestrum discharged spontaneously at four months.   Wound remained soundly healed thereafter for eighteen months when a sinus appeared.   X-ray showed large sequestrum at site of original operation wound.   The sinus was excised and the sequestrum removed (sequestrum grew coagulase positive staphylococci). Wound sutured and healed by first intention.   Affected limb showed less than 1 cm. increase in length.   Three years after onset the affected limb was 1.25 cms. longer than the healthy one (Figure 37).   Four years after onset the affected leg showed 2.5 cms. increase in length and pelvic tilt and scoliosis were marked and genu valgum had developed (Figure 38).   X-ray showed only slight sclerosis.

Remarks   The major fault was the packing of the wound as this prevented restoration of the periosteal blood supply.   The growth stimulus continued between the third and fourth years when there was no apparent bone focus on X-ray.   At present the shoe on the sound side is raised 2 cms;   the other shoe is wedged on the inner side.   She wears a knock-knee splint at night.

Case 11.   P.G., female aged 3 years.   Osteitis of left tibia. Blood culture sterile.   The limb was immobilised in plaster of Paris and 1 mega unit of penicillin was administered over ten days.   The temperature remained normal after six days.   The plaster was removed after four weeks and there /

there was an area of fluctuation over the upper end of the tibia.

Aspiration was unsuccessful.   X-ray showed typical patchy decalcification of

the metaphysis and subperiosteal new bone.   The fluctuation had disappeared

by the sixth week.   Two months later movements were full but X-ray showed a

small cortical sequestrum.   The patient then removed from Glasgow and failed

to report again.   Nine months after the original operation she was admitted

to the Royal Hospital for Sick Children, Edinburgh, with a subperiosteal

abscess.   This was evacuated and sutured and the child was once more lost

sight of until she reported nineteen months later with a soft tissue abscess.

X-ray revealed no bone lesion.   After evacuation of pus (staphylococcus aureus)

the wound healed uneventfully.   She remains well three and a half years after

onset (Mason Brown 1950).

Remarks   The duration of penicillin administration was inadequate.

Evacuation of pus over the upper end of the tibia would have relieved tension

and might have prevented sequestrum formation.   It is a serious mistake to

enclose the limb in plaster of Paris in the early days of the illness.   It

took us some time to realise that surgical removal of preformed pus is

essential to prevent progressive destruction of bone.

        Case 14   S.E., female aged 7 years.   Osteitis of right femur.

Blood culture sterile.   Limb immobilised in plaster of Paris and 1.1 mega

units of penicillin administered over eleven days.   The clinical recovery was

uneventful but radiographic changes were gross.   There was little disability

and no sinus formation, but at twenty-one months sequestrectomy was performed

because of swelling of the lower thigh.   The wound healed uneventfully.

Coagulase positive staphylococci were grown from the granulations.   Three

years /

Three years after onset there was 2 cms. lengthening of the affected limb
(Figure 31) and X-ray revealed a small cavity in the lower third of the femur.

Remarks   The mistakes made in this case were the same as in Case 8.

Case 15   J.G., male aged 6 years.   Osteitis of right tibia.
Blood culture sterile.   Large subperiosteal abscess extending over two-thirds
of length of the tibia evacuated and wound packed.   1.1 mega units of
penicillin administered over eleven days.   The limb was immobilised in plaster
of Paris to mid-thigh.   At three weeks X-ray showed gross decalcification and
new bone formation (Figure 33A), and at two months two-thirds of the shaft
appeared to form a sequestrum (Figure 33B).   Secondary suture was performed
under a penicillin "umbrella" at three months.   At six months the X-ray showed
only a large cortical sequestrum (Figure 34A).   Sequestrectomy was performed
and plaster of Paris re-applied.   The wound healed uneventfully and at nine
months the tibia was well consolidated (Figure 34B).   X-ray at eighteen months
showed 1.25 cms. increase in length of the affected tibia with a corresponding
increase in the fibula of that leg (Figure 35).

If one compares Figures 32B and 34 the result is highly satisfactory.
In pre-penicillin days the radiographic appearance in Figure 32B would have
made one consider diaphysectomy.   As in Case 7, the faults were (1) failure
to close the wound, (2) inadequate penicillin therapy.

Case 17   J.S., male aged 6.9/12 years.   Osteitis of left femur.
Blood culture sterile on admission.   The limb was immobilised and penicillin
administered by continuous intramuscular drip.   The boy was very ill and his
temperature did not settle until penicillin had been given for twenty-one days.

Total /

Total penicillin 2.1 mega units.   At fifty-seven days 35 c.c. of staphylococcal pus were aspirated from the thigh.   He remained in hospital for sixty-nine days.   Six months after onset a cortical sequestrum was removed at operation.   Eighteen months later he reported with pain in the thigh.   X-ray revealed a sequestrum.   Sequestrectomy was performed and coagulase positive staphylococci were grown from the sequestrum.   There was 2 cms. lengthening of the limb at this date.   Four years after onset the lengthening had been reduced to less than 1 cm. and X-ray revealed a slightly sclerotic femur but no evidence of active disease.

Remarks   Leveuf and Laurence (1947) advocate delayed evacuation of pus in septicaemic cases.   The result in this case does not support their claims.

Case 19   C.H., female aged 9 years.   Osteitis of right femur. Blood culture, coagulase positive staphylococcus.   Pus aspirated from right knee joint;   subperiosteal abscess evacuated by incision, periosteum found widely stripped.   Wound lightly packed.   Penicillin given by intramuscular drip - 100,000 units daily for ten days.   The wound healed and she was dismissed in a long plaster case after twenty-five days.   In spite of instructions to remain in bed, she clamped a skate on to her plaster and went roller skating.   Decalcification increased for three months and radiography revealed a cavity in the lower femur with small sequestra.   Six months after onset sequestrectomy was performed.   Penicillin sensitive staphylococci were grown from the several minute sequestra.   The wound healed uneventfully but her movements were restricted by a walking caliper for a further two months. Full movement was restored to the knee joint eleven months after the original infection.

Thirteen /

Thirteen months after onset, she reported complaining of pain in the right foot with swelling of the dorsum of the foot. Radiography at this visit and during the following two months revealed the typical changes of a March fracture of the third metatarsal (Figure 49).

At eighteen months there was 1.5 cms. increase in length of the affected leg. The difference in length gradually decreased until three years after onset there was no measurable difference and radiography revealed only slight sclerosis of the right femur.

Remarks   The duration of penicillin administration was inadequate. It is always difficult to keep a healthy child in bed. With this knowledge, a high plaster of Paris is obviously a dangerous method of fixation of a decalcifying femur, and after this case a caliper splint was fitted to patients with lesions of the femur.

The significance of the infected sequestra was considered in the section on "Bone Lengthening". Stress fracture of a metatarsal is an unusual condition in childhood and this case and one other case of March fracture in a child seen subsequently in the unit are discussed fully elsewhere (Macpherson 1950). I have been able to trace only three other cases in the literature. Zeitlin and Odessky (1935) report a stress fracture of the metatarsal in a girl of ten years; Childress (1946) reports a case in a child of seven and Rutter (1947) described March fracture in a child of four years.

Case 21   E.P., female aged $7\frac{1}{2}$ years. Osteitis of right tibia. Blood culture, coagulase positive staphylococcus. Comatose on admission. Limb immobilised and penicillin 25,000 units injected six-hourly (at five and five- /

Figure 49

Case 19   Female aged 10 years.   X-ray shows a typical
stress fracture of the third metatarsal.

five-and-a-half hours there was no inhibition of the Oxford staphylococcus in undiluted serum). _Treatment_: (thirty-six hours after admission). Incision, no soft tissue abscess. Incision of periosteum, pus under tension. The periosteum had been elevated over entire length of tibia. The metaphysis was drilled and penicillin instilled. The wound was sutured and healed uneventfully. After operation penicillin was administered by continuous drip - 0.5 mega units daily for three days and then 0.1 mega units for seven days. Total penicillin 2.35 mega units. Child dismissed in plaster of Paris after eighteen days. Cavitation and sequestration were obvious on X-ray two months after onset and at six months sequestrectomy and saucerisation were carried out and the cavity filled with bone chips from the overlying cortex. The limb was immobilised in a mid-thigh plaster but twelve months after onset an incomplete pathological fracture was seen on X-ray. The fracture healed rapidly. She was clinically well at thirty-three months but the tibia was still sclerotic.

Remarks Six-hourly injections of penicillin failed to maintain a therapeutic level in the blood. The duration of penicillin administration was probably inadequate.

Case 22 J.H., male aged 10 years. Osteitis of left femur. Blood culture, staphylococcus aureus. Arthritis of knee. Pus from knee joint aspirated and 0.5 mega units of penicillin instilled. (The pus contained 0.5 units of penicillin per ml.). Thigh incised - pus under pressure under periosteum; bone drilled and 75,000 units penicillin instilled into marrow. Wound sutured with indwelling perforated tube. 1.5 mega units administered by intramuscular drip over nine days and 25,000 units were instilled down /

down the indwelling tube twice a day for ten days. The resulting sinus after removal of the indwelling tube was not soundly healed for three weeks. A cortical sequestrum was obvious on X-ray at four weeks. The sequestrum gradually became smaller and at eight months had apparently been absorbed. Two months later the sequestrum re-appeared (Figure 27). At twenty-eight months a soft tissue abscess appeared and the sequestrum was removed at operation. Healing was uneventful and at thirty-two months there was no evidence of bone disease, but the affected femur was sclerotic and the limb almost 2 cms. longer than the sound limb (Figure 32).

Remarks The result was quite satisfactory considering the short course of penicillin. The radiographs (Figure 29) show the importance of positioning in radiography. If the indwelling "penicillin tube" is retained for longer than four days the resulting sinus is difficult to heal.

GROUP B. CASES IN WHICH THE BLOOD SUPPLY TO THE BONE
WAS SERIOUSLY IMPAIRED.

Case 33 M.G., female aged 8 years. Osteitis of right tibia. Blood culture grew staphylococcus aureus. Child was very ill on admission and the affected leg was red, hot and swollen. There was a large soft tissue abscess between the tibia and fibula and the periosteum had been raised over the entire shaft of the tibia. The wound was sutured with an indwelling tube and 100,000 units of penicillin instilled. The limb was immobilised in a plaster of Paris gutter. 10 mega units were given over forty days by four-hourly injections. The fluid aspirated from the indwelling tube was sterile after five days and the tube was removed. The wound healed uneventfully. /

uneventfully.   Marrow punctures were performed on the 14th, 21st and 28th days.   Coagulase positive staphylococci were grown from the aspirated fluid and there was no inhibition of the standard Oxford staphylococcus in the undiluted fluid.   Before withdrawing the marrow needle on the 28th day, 0.5 mega units of penicillin were injected into the marrow cavity.   On the 35th day the aspirated fluid was sterile and there was a level of 0.5 units of penicillin per ml.   The patient was discharged in a mid-thigh plaster on the 50th day.   Immobilisation was continued for a further two months. Eighteen months after onset the tibia showed slight sclerosis and the affected leg showed 2 cms. lengthening.   She was still well three years after onset.

Remarks   The marrow fluid showed no level of penicillin at fourteen, twenty-one and twenty-eight days (see also Case 35).   In all succeeding cases penicillin was injected into the marrow fluid before withdrawing the marrow puncture needle, in case parenteral penicillin was not reaching the affected area.

Case 35   A.R., female aged 6 years.   Osteitis of ilium.   Blood culture, sterile on admission.   There was a burn over the upper thigh and iliac crest following the application of a Kaolin poultice at home so that marrow puncture could not be performed for five weeks.   Marrow puncture 5 cms. below the iliac crest produced 25 ml. of purulent fluid and no level of penicillin.   100,000 units of penicillin were instilled.   A week later 5 ml. of sterile purulent fluid were aspirated from the marrow and on receipt of the bacteriologist's report on this fluid parenteral administration of penicillin was stopped.   13 mega units were administered over forty-four days.   Gross decalcification of the left ilium was present on discharge at forty-eight days. Bimanual /

Bimanual rectal examination under an anaesthetic revealed gross thickening of the blade of the left ilium.

Recovery was uneventful but the ilium was still thickened at two years.

Remarks   As in Case 33, parenteral penicillin did not reach the affected bone.

Case 58   M.H., female aged 7 years.   Osteitis of left femur. Blood culture, coagulase positive staphylococci.   Very ill and delirious. 0.25 mega. units of penicillin intravenously and a plasma drip started before taking the child to theatre.   At operation no pus was found in soft tissues, but on incising periosteum over lower end of femur blood-stained pus under great tension was evacuated.   The periosteum had been stripped over the lower third of the femur and the bone looked white and avascular.   After frosting the soft tissues with penicillin-sulphathiazole powder wound closed with indwelling tube and 1.25 mega units of penicillin instilled.   As the capillary circulation was failing 10 c.c. of Eucortone were added to the drip before the child left theatre.   On return to the ward she was given 1 mega unit of penicillin four-hourly intramuscularly for four days, and soluthiazole gms. IV in the plasma drip.   She was nursed in an oxygen tent for two days.   After four days her condition had greatly improved and the drip was stopped. Penicillin was continued parenterally in a dose of 1 mega unit daily.   As the organism was of the same order of sensitivity as the standard staphylococcus no further sulphonamide was given.   The marrow fluid aspirated from the lower femoral metaphysis was reported sterile at three weeks but there was no level of penicillin in spite of an intramuscular injection an hour before theatre. At four weeks the marrow fluid showed a few pus cells, no organisms and no level /

level of penicillin in either upper or lower metaphysis.   2 mega units of penicillin were injected into the marrow before withdrawing the needle. Parenteral penicillin was continued for thirty-four days and a total of 40.8 mega units was given.   Radiography at this stage revealed a bipolar infection and in spite of continued skin traction a pathological fracture of the neck of the femur was apparent at six weeks (Figure 36).   Jaundice appeared at this stage and homologous serum hepatitis was diagnosed. Immobilisation was continued but at eleven weeks X-ray revealed a fracture of the distal end of the femur.   The affected limb showed 1.25 cms. shortening (Figure 46).   Both fractures united uneventfully.   At nine months a sinus appeared in the thigh.   This was excised under penicillin and three small sequestra were removed.   A fourth sequestrum which had not separated was deliberately left - in the hope of encouraging bone lengthening (vide supra). The wound healed uneventfully and seventeen months after onset the limbs were of equal length (Figure 47).   The remaining sequestrum was then removed.

Remarks   Owing to the risk of pathological fracture no marrow puncture was performed after four weeks.   In such a case it would have been instructive to investigate the marrow from the intervening apparently healthy shaft as well as from both metaphysis.   In this case it is interesting to speculate on the relative importance of the nutrient artery, the periosteal vessels and the metaphyseal vessels in maintaining the blood supply to the bone.

Case 72   K.W., male aged 8.4/12 years.   Osteitis of lower right femur.   Blood culture, coagulase positive staphylococcus grown from the blood January 7th to January 11th.   Very ill on admission.   After giving penicillin pus was aspirated from the knee joint and penicillin instilled.   An extensive subperiosteal abscess was evacuated and the periosteum was found to be completely /

completely stripped from the lower half of the femur.   In view of the size

of the abscess cavity the wound was sutured around an indwelling rubber tube.

The knee was aspirated again on the third and fourth days.   On the fifth day

the leg was still grossly swollen and the wound was re-opened and watery pus

and thick "curds" evacuated from the completely bare popliteal aspect of the

femur.   An indwelling tube was inserted through a stab wound in the popliteal

fossa and the operation wound was completely sutured.   Three days later the

child was still very toxic and the knee joint was widely opened, flushed out

with warm saline and sutured after instilling a million units of penicillin.

The indwelling tube in the popliteal fossa was removed.   All wounds healed

uneventfully and marrow puncture on the fourteenth day of treatment produced

sterile fluid.   Marrow punctures were performed again on the twenty-first and

twenty-eighth days, on each occasion an hour after intramuscular injection of

50,000 units of penicillin.   The aspirated fluid was sterile on both occasions

but there was no measurable level of penicillin in the fluid.   1.25 mega units

were injected into the marrow cavity on the thirty-fifth day.   Radiography

showed gross decalcification of the femur and at five months sequestrum

formation was obvious.   Sequestrectomy was performed eight months after onset

and the child is now well with full movement of the knee and no clinical or

radiographic evidence of bone disease (sixteen months after onset).   The

affected limb shows almost half an inch lengthening.

<u>Remarks</u>   The blood supply was cut off from the lower femur by gross elevation

of the periosteum and probably by thrombosis of the nutrient artery.   This

was demonstrated by the absence of inhibition of the standard staphylococcus

by undiluted marrow fluid and by the radiographic changes and sequestrum

formation /

formation.   Even with heavy pressure dressings I doubt if it is possible to restore the continuity of the periosteum to the popliteal aspect of the femur in such a case.   Pus and serum inevitably gravitate to this region from the metaphyseal focus and from the walls of the subperiosteal abscess cavity.

APPENDIX   III

Erythrocyte sedimentation rate in acute haematogenous osteitis.

APPENDIX III

A. <u>The Erythrocyte Sedimentation Rate in Osteitis (Westergren)</u>

<div align="center">E.S.R.</div>

Case	On admission	2nd week	3rd week	5th week
J.G.	88	90	54	-
J.S.	80	-	48	28
C.H.	92	-	-	40
E.P.	78	-	-	-
J.H.	80	92	48	30
D.K.	72	-	40	-
R.C.	70	88	52	-
L.McI.	95	-	50	-
K.W.	54	92	63	-
W.W.	65	50	-	35
N.McL.	104	97	-	48
J.H.	66	-	42	-
A.McD.	60	-	54	-
W.M.	68	-	48	-
A.G.	78	85	50	45

B. <u>The effect of Hyaluronidase on the Erythrocyte Sedimentation Rate</u>

Case	Disease	Venous blood	Venous blood - Hyaluronidase
D.T.	Osteitis of fibula	E.S.R. 1st hr. 36	E.S.R. 1st hr. 3
W.W.	Osteitis of tibia	E.S.R. 1st hr. 65	E.S.R. 1st hr. 5
A.M.	Tuberculous arthritis of knee	E.S.R. 1st hr. 18	E.S.R. 1st hr. 16
D.B.	Extensive scald	E.S.R. 1st hr. 28	E.S.R. 1st hr. 22

APPENDIX IV

Osteitis proforma as used in Mr. White's unit,

Royal Hospital for Sick Children, Glasgow.

OSTEITIS

Name ....   <u>Age</u>:   <u>Sex</u>:   <u>Month</u>:

Address ....   <u>Admitted</u>:

Site ....:....................   <u>Discharged</u>:

Result ....   <u>Days in hospital</u>:

<u>History</u>:   Days ill: <u>Injury</u>:   Septic focus:

<u>Examination</u>: T.   P.   R.   Toxaemia: Oedema:
             Erythema: Joint: Metastases:
             W.B.C.
             Complications:

    Blood Culture   1.   Blood Ca.:
       (date)   2.   P.:
                    3.   Phosphatase:

    Marrow Culture 1.   Marrow Ca.:
       (date)   2.   P.:
                    3.   Phosphatase:
                    4.

<u>Treatment</u>: Method of Immobilisation:

<u>Penicillin</u>: Solution: Oily Suspension: Oral: Drip:
            I.M. Injection:
            Dose 1st 24 hours: Total Dose: Duration (days):

<u>Surgical</u>:   Aspiration :   Incision of abscess:
            Incision of periosteum: Bone drilling:
            Primary Suture: Secondary Suture:
            Local Chemotherapy:

<u>Radiological</u>   1.
<u>Appearances</u>: 2.
   (date)   3.
               4.
               5.
               6.

APPENDIX V

Methods of surgical intervention in Groups I and II.

APPENDIX V

Methods of surgical intervention, deaths and cause of death,

1936 - 1945

Group I - 1936 - 1940

Treatment		Cases	Deaths	Cause of Death
No surgical intervention	1936	1	1	Septicaemia
	1937	1	1	Septicaemia
	1938	0	0	-
	1939	1	1	Septicaemia
	1940	0	0	-
Simple Aspiration	1936	3	1	Pyaemia *
	1937	0	0	-
	1938	1	1	Pyaemia *
	1939	1	1	Pyaemia *
	1940	1	0	-
Incision of Periosteum	1936	4	2	Pyaemia *; oedema of glottidis
	1937	3	0	-
	1938	3	0	-
	1939	3	0	-
	1940	3	2	Both pyaemia *
Drilling	1936	6	3	All pyaemia *
	1937	9	3	All pyaemia Two *
	1938	4	1	Pyaemia
	1939	10	2	Both pyaemia
	1940	7	2	Both pyaemia *
Guttering	1936	2	1	Septicaemia and shock
	1937	1	0	-
	1938	4	1	Pyaemia *
	1939	7	4	All pyaemia *
	1940	0	0	-
Delayed Diaphesectomy	1936	1 fibula	0	-
	1937	2 both tibiae	0	-
	1938	0	0	-
	1939	1 tibia	0	-
	1940	0	0	-

* Confirmed at autopsy.