Gentamicin-PMMA beads
Proefschrift
der verkrijging van de graad van doctor in de geneeskunde
aan de Katholieke Universiteit te Nijmegen, op gezag van
de Rector Magnificus Prof. Dr. J.H.G.I. Giesbers
volgens besluit van het College van Dekanen in het
openbaar te verdedigen op woensdag 29 juni 1983 des
namiddags om vier uur

door

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geboren te Breda

Drukkerij Cliteur, Amsterdam
To the memory of my father
This treatise is the product of an investigation that was made possible by help from many sides. The need for the investigation was felt when in 1977 gentamicin-PMMA beads became available for clinical study in the Netherlands. It was desired to test obtained elsewhere and to enquire more thoroughly into the safety of the preparation.

The clinical part of the study was carried out in the department of orthopaedics of the St Radboud Hospital of the RC University of Nijmegen (RCUN). The investigation was initiated by the head of this department, Prof Dr Th J G van Rens. Prof Dr G C J van der Ploeg provided aid and advice on matters of bacteriology. Their stimulating interest was a great support to the author and contributed much to the value of the study.

In the processing of the many data of the retrospective part of the clinical study, H A Dekkers has been extremely helpful. The preparation of the data for the computer and the dialogue with it were performed very accurately by A Rentjes, and their statistical analysis was carried out thoroughly and profoundly by J A M van Druten (RCUN Department Medical Statistical Advisory Service).

The pharmacokinetic and nephrotoxicologic parts of the investigation have become an essential element of the study, owing entirely to the inspiring contribution by Dr T B Vree, head of the department of clinical pharmacokinetics and toxicology of the department of clinical pharmacology (Head Prof Dr E van der Kleijn) of the RCUN. Due to his critical and original approach, this part of the study went beyond the mere determination of some concentrations. The other members of his laboratory team were equally enthusiastically helpful.

This part of the investigation necessitated a large number of samples of blood and urine. For their collection, the willing cooperation of test subjects and patients was indispensable, and the aid of the nursing staff of the wards and operation rooms of the department of orthopaedics of inestimable value.

All assays were carried out at the central medical laboratory ABL of Assen, where the dedication and the rapid, accurate work of B Jongman-Nix and P J M Guelen rendered it possible for numerous data to be obtained in a short time.

The study of possible ototoxic side effects could be carried out with the aid and advice of P L M Huygen. The investigation was performed with the help of M G M Nicolasen in the ORL department of the RCUN (head Prof Dr P van den Broek).

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- Marlu Ackermans: drawings
- Ed Noyons: drawings
- Henk Berns: graphs (Chapters 2, 9, 10)
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- Cor de Bruin: cover photograph
- Helmi Leegstraten: typed the manuscript marvellously fast, accurate and without losing her good sense of humour.

The English translation was prepared by C Visser (in cooperation with M Henkes), Eindhoven. The book was printed by Cliteur Printers, Amsterdam.

Many persons have helped by giving their time and attention to serve as sounding boards, which resulted in valuable additions and criticism. This applies in the first place to the staff and assistants of the RCUN department of orthopaedics. It also particularly holds true of Dr H Wahlig, Dr A Grieben, Dr K. Klemm and Dr K H Muller. Where nephrological aspects are concerned, it also applies to Prof Dr A W Mondorf and Prof Dr M E de Broe.

The support by my wife and children would have sufficed for several manuscripts more.
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Chapter 1. Introduction

In spite of growing knowledge of their pathogenesis and treatment, skeletal infections continue to cause patients to suffer severely, treating surgeons to experience repeated frustrations and the costs of health care to rise substantially. Notwithstanding the therapeutic possibilities offered by antibiotics, 15 to 30% of all cases of haematogenous osteomyelitis turn into chronic osteomyelitis (Norden et al, 1970; Waldvogel et al, 1970).

After 'clean' orthopaedic operations, postoperative infection occurs in approx 1 to 5% (Lidgren, 1973; Lidgren and Lindberg, 1972, 1974, Altemeier et al, 1976, Burri, 1979, Muller, 1981). Implantation of a hip endoprosthesis is followed by a deep infection in approx 2 to 4%. Frustrations and the costs of health care to rise substantially.

The total number of infections per year increases because a) the number of accidents involving fractures is rising, b) increasing numbers of orthopaedic operations are being performed with implantation of osteosynthesis material or endoprostheses, c) in spite of all efforts, infections always occur in a few percent of all operations on the skeleton.

In the United States in 1976, approx 80,000 total hip prostheses and 40,000 total knee prostheses were implanted (Hori et al, 1978). Huskies estimates that in the near future the number of articular prostheses implanted globally each year will amount to 300,000 and that 2.4 million people will be living with an artificial joint (Huskus, 1979).

The Dutch Medical Records Foundation (Stichting Medische Registratie, SMR) reports that in the Netherlands the number of endoprostheses implanted annually is gradually rising. The number of the principal types of endoprostheses implanted in the Netherlands was 11,484 in 1980 as against 8,000 in 1977, an increase by 44% in four years. In 1977, 5,391 hip and 643 knee prostheses were implanted, as against 7,364 and 1,127, respectively, in 1980 (Table 1.1). In 1977, of the total hip prostheses, 214 were removed in toto and 49 in part, for reasons not specified. For 1980, these figures were 357 hip prostheses removed in toto and 153 removed in part.

If we estimate that of all total hip prostheses implanted, 4% will become infected, we find that of the total number of hip prostheses implanted in the Netherlands in 1980, 295 are infected. For the United States in 1976 we find 3,200 infected prostheses, and globally there are at present 96,000 patients who have to consider the possibility that their prosthesis is, or has been infected.

Some idea of the total number of osteosynthesis performed may be gained from the numbers of operations at which osteosynthesis material was removed. These amounted to 12,090 in 1977 and to 15,271 in 1980, a 26% rise in four years.

The number of cases of osteomyelitis that has been treated in the Netherlands may be roughly estimated on the basis of the number of operations involving 'sequestrectomy'. The principal operations are listed in Table 1.1. From 1977 to 1980 there has been a rise from 364 to 606, or 66%.

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>ARTHROPLASTY</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>elbow</td>
<td>826 2</td>
<td>31</td>
<td>41</td>
</tr>
<tr>
<td>total knee</td>
<td>866 2</td>
<td>643</td>
<td>1127</td>
</tr>
<tr>
<td>hip cup</td>
<td>856 6</td>
<td>40</td>
<td>128</td>
</tr>
<tr>
<td>head-neck</td>
<td>856 7</td>
<td>1894</td>
<td>2823</td>
</tr>
<tr>
<td>total hip</td>
<td>856 8</td>
<td>5391</td>
<td>7364</td>
</tr>
<tr>
<td>total extraction total hip</td>
<td>854 3</td>
<td>214</td>
<td>357</td>
</tr>
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<td>partial extraction total hip</td>
<td>854 4</td>
<td>49</td>
<td>153</td>
</tr>
<tr>
<td>SEQUESTRECTOMY</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>humerus</td>
<td>810 4</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>fingers/metacarpals</td>
<td>830 1</td>
<td>32</td>
<td>46</td>
</tr>
<tr>
<td>hip/thigh</td>
<td>850 4</td>
<td>109</td>
<td>167</td>
</tr>
<tr>
<td>tibia/fibula</td>
<td>860 3</td>
<td>152</td>
<td>246</td>
</tr>
<tr>
<td>ankle/foot</td>
<td>870 5</td>
<td>57</td>
<td>129</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>REMOVAL OF MATERIALS</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>hip nail</td>
<td>880 0</td>
<td>779</td>
</tr>
<tr>
<td>intramedullary nail</td>
<td>880 1</td>
<td>1112</td>
</tr>
<tr>
<td>plate + screws</td>
<td>880 2</td>
<td>6492</td>
</tr>
<tr>
<td>cerclage</td>
<td>880 3</td>
<td>723</td>
</tr>
<tr>
<td>epiphyseal staples</td>
<td>880 4</td>
<td>192</td>
</tr>
<tr>
<td>other</td>
<td>880 5</td>
<td>2791</td>
</tr>
<tr>
<td>+ 9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>12090</td>
</tr>
</tbody>
</table>

Table 11 Numbers of various types of operations performed in 1977 and in 1980. The table shows the type of operation and its code as used by the Netherlands Medical Records Foundation. The numbers of the operations indicate the major and accessory operations performed in hospitals associated with the Medical Records Foundation. Extrapolation enables estimation of figures for the Netherlands as a whole (for 1977, multiply by 1.11; for 1980 by 10.5).

<table>
<thead>
<tr>
<th>Year</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1975</td>
<td>1860</td>
</tr>
<tr>
<td>1976</td>
<td>1970</td>
</tr>
<tr>
<td>1977</td>
<td>2146</td>
</tr>
<tr>
<td>1978</td>
<td>2056</td>
</tr>
<tr>
<td>1979</td>
<td>2231</td>
</tr>
<tr>
<td>1980</td>
<td>2196</td>
</tr>
</tbody>
</table>

Table 12 Numbers of cases of osteomyelitis in the Netherlands from 1975 to 1980 inclusive. The figures refer to the main or accessory diagnoses at discharge recorded by the Medical Records Foundation, coded as acute, subacute and chronic osteomyelitis (codes 720.0, 720.1 and 720.2), with exclusion of osteomyelitis of the jaw, nasal sinuses and mastoid. The figures have already been extrapolated to 'total Netherlands'.
Some impression of the number of cases of osteomyelitis may also be gained from the diagnoses at discharge that listed osteomyelitis, acute or subacute, with exclusion of infection of nasal sinuses, jaws and mastoid bone. As Table 1.2 shows, from 1975 to 1980 there has been a rise from 1,860 to 2,196 patients. After 1977, there has been hardly any rise. In this connection it should be kept in mind that these figures reflect just the numbers of admissions because of osteomyelitis, not the numbers of patients or of operations.

Most skeletal infections necessitate several operations and as a rule they heal only after many years of treatment. It is every surgeon’s duty to do all he can to prevent infection, and it is a challenge to keep the proportion of postoperative infections at a minimum. Every new therapy for which it is claimed that it favourably affects the results of treatment of an infection deserves attention and critical study. This is the more pressing if the therapy not only improves the cure rate but also reduces the patients’ discomfort during treatment.

One new method of treatment for which the above advantages are being claimed is that with gentamicin-PMMA beads. Their use has gained currency in the last few years, mostly in Germany and largely in skeletal infections.

This study is intended to assess the value of the gentamicin-PMMA beads as a method of local antibiotic treatment by comparing their effects with those of other methods of treating infections used up to now. The study is divided into three parts:

The first part comprises the study of the literature describing the qualities of antibiotic-containing cement, of gentamicin and of gentamicin-PMMA beads. It also includes a detailed discussion of the infections in which attention is focused in orthopaedic surgery: osteomyelitis and infected endoprostheses. Their pathogenesis, diagnosis and various methods of treatment are described and discussed to the extent necessary to define the role of the new local antibiotic treatment.

The second part reports a study of the results of the treatment of infections in patients. A group of patients treated with gentamicin-PMMA beads and studied prospectively is compared with a group of patients treated by other methods, studied retrospectively.

The third part of this report contains a study of the possible side effects of gentamicin during treatment of an infection with gentamicin-PMMA beads. For this purpose, an attempt has been made to gain insight into the pharmacokinetics of the gentamicin-PMMA beads. To be able to assess nephrotoxicity, we first had to evaluate, in experiments and at operations, a sensitive parameter, viz. β2-microglobulin. Finally, audiological and vestibular examinations have been carried out in some patients to evaluate the effect on hearing or equilibrium.
Chapter 2. Osteomyelitis

2.1 Introduction

Infections are often compared to battles between parasite and host, the outcome depending on the parasites' virulence and number on the one hand and the host's defensive forces on the other (Fig. 2.1). Much then depends on the place where the battle is fought.

DEFENCE OF THE HOST

sclerosing osteomyelitis of Garré
Brodie's abscess
osteomyelitis albuminosa of Poncet
recurrent osteomyelitis
acute osteomyelitis
septic osteomyelitis

VIRULENCE OF MICRO ORGANISM

endogenous osteomyelitis
chronic (§ 2.2)
pyogenous osteomyelitis
acute
osteomyelitis
exogenous osteomyelitis (§ 2.2.3)
chronic
non-pyogenous osteomyelitis (§ 2.2.4)

Figure 2.1 This figure shows schematically how the equilibrium between the host's defensive force and the virulence of the microorganism determines the type of osteomyelitis (from Fanconi, 1967).

Osteomyelitis constitutes an autonomous, pathological and clinically well-defined entity. The pathophysiological and anatomical properties of the osseous tissue are of decisive importance for the occurrence and the course of the infection. These qualities also have important implications for the treatment of osteomyelitis and for the evaluation of the results of their treatment.

2.2. Histological and pathogenetic aspects of osteomyelitis

Bone may be regarded as an organ, in which the various hard and soft constructive elements constitute a functional unit. Its inflammation is not restricted to one of these elements but involves all compartments of the bone. Osteomyelitis is an inflammation of the entire osseous tissue.

A characteristic feature of osseous tissue is that unlike other organs, it behaves relatively passively and reacts slowly to infection (Konn and Postberg, 1970, Konn and Böhm, 1974).

An inflammation that starts in the medullary cavity will only at a relatively late stage cause histologically discernible signs of inflammation in the cancellous tissue, cortex and periosteum. An inflammation that at first manifests itself mostly in the periosteum becomes histologically visible in the medullary cavity only much later.

Clinically and histologically, distinctions may be made on the basis of the stage of the inflammation and of certain clinical evolutive types (Table 2.1)

<table>
<thead>
<tr>
<th>Type</th>
<th>Pathogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>acute</td>
<td>endogenous osteomyelitis</td>
</tr>
<tr>
<td>endogenous osteomyelitis</td>
<td>chronic (§ 2.2)</td>
</tr>
<tr>
<td>pyogenous osteomyelitis</td>
<td>acute</td>
</tr>
<tr>
<td>osteomyelitis</td>
<td>exogenous osteomyelitis</td>
</tr>
<tr>
<td>non-pyogenous osteomyelitis</td>
<td>chronic</td>
</tr>
</tbody>
</table>

Table 2.1 Classification of osteomyelitis by pathogenesis, indicating the paragraphs in which the various types of osteomyelitis are discussed

2.2.1 Acute haematogenous osteomyelitis

In acute pyogenus inflammation, we find polymorphonuclear leukocytes in the bone, also, as a reaction to the bacteria. Just as in other tissues, interstitial oedema and rupture of capillaries occur in bone, also. This process, which runs its course in a few days, does not differ from cellular or humoral mechanisms in other infected tissues (Enneking, 1979). Specific of the osseous tissue, however, is the effect of the rising pressure of the exudate inside the unyielding Haversian canals. This deprives the osteocytes of their blood supply. The rising pressure leads to rapid spread of the infection in the medullary canal and along the Volkmann's and haversian canals through the frequently thin and porous cortex.

Studies by Hobo have shown that the vasa nutentia at the level of an epiphyseal disc make a sharp bend and widen into sinusoids, with the vascular diameter increasing from 8 to 15 - 60μ. As a result, the blood flow slows down, producing a likely site for bacteria to settle. In addition, it is believed that development of an infection is facilitated by the fact that the endothelial cells in the afferent tracts of the metaphyseal vessels have no or insufficient phagocytizing properties (Waldvogel et al., 1970) (Fig. 2.2).

The pattern of the spread of the inflammation is determined by the local anatomical situation which depends appreciably on the patient's age. Trueta describes the typical course of acute haematogenous osteomyelitis. He demonstrates that the evolution of the inflammation is determined by various vascular patterns in the bone which in their turn depend on the patient's age (Trueta, 1959; Trueta, 1968). On the basis...
of the course, three age groups can be distinguished: children below one year, children from 1 to 16 years and adults (Fig. 2.3).

**Below the age of one year**, a few blood vessels enter the epiphyseal disc. Subchondrally, these epiphyseal vessels also show sinusoid dilations, just as in the metaphysis. Consequently, when acute haematogenous osteomyelitis occurs in a baby, it is often associated with arthritis and severe damage to the epiphyseal cartilage. Another characteristic finding at this age is formation of a massive involucrum, due to the fact that the periosseum is raised by the exudate, and later by pus which penetrates the thin cortex. The raised periosseum again forms new bone. Sometimes, the periostum is separated along the entire length of the diaphysis (Fig. 2.3).

Between the ages of 8 and 18 months, an avascular barrier develops in the epiphysis in humans, as demonstrated for the femoral head by Trueta (1968). This is the reason why in the age group between approx. one and 16 years, the epiphysis remains unaffected by the inflammation (Fig. 2.3). A massive involucrum develops, however. Thrombosis of the arteria nutritia on the one hand and separation of the periostum on the other deprive the cortex of, respectively, its endosteal and periosteal blood supply, resulting in large cortical sequestra. The firm fixation of the periostum to the bone at the level of the epiphyseal disc prevents subperiosteal spread in the direction of the joint (Hart, 1937). Where the metaphysis extends to inside the articulation, as is the case in the hip and the shoulder, its intra-articular position after penetration of pus through the thin periostum may lead to rapid development of arthritis (Fig. 2.4).

Whereas in the child the site of predilection of haematogenous osteomyelitis is the richly vascularized metaphysis of the most rapidly growing long bones, in the adult the sites of predilection are the vertebral bodies and the pelvis. In adults, the rapid spread of the infection along the entire length of the bone and the absence of large sequestra with involucrum are typical. The periostum is so firmly attached to the bone that it can no longer be easily separated from it. Also, the absence of epiphyseal discs

**Figure 2.2** Schematic representation of the vascularization of the metaphysis (from Hobo, according to Trueta, 1968). Sinusoidal dilations of the vasa nutritia at the level of epiphyseal disc might be the sites where bacteria settle because of local deceleration of the blood flow.

**Figure 2.3** Relationship of the age and the pattern of spread of a haematogenous osteomyelitis. It is only between the ages of approximately one year and sixteen years (b) that the epiphyseal disc constitutes an effective barrier against spread of the inflammation from the metaphysis to the joint. In younger children (a), blood vessels penetrate the epiphyseal disc. In adults (c), the epiphyseal disc is absent.
facilitates the occurrence of articular inflammations (Trueta, 1959). Furthermore, there is fairly rapid spread to soft parts due to the exudate breaking through the periosteum. Also, the tendency to chronicity of the inflammation is far stronger than in the child (Fig. 2.3).

From the histological point of view, several stages of inflammation exist side by side in chronic osteomyelitis. Depending on the predominance of a particular histological image, several types of osteomyelitis are distinguished.

**Exudative-aggressive chronic osteomyelitis**

Just as in acute pyogenic osteomyelitis, there are concentrations of leukocytes, fibrin, exudate and abscesses. The trabeculae are devitalized and delimited by granulation tissue with predominance of the osteoclastic activity.

**Chronic persistant osteomyelitis**

Here, we find connective tissue rich in cells and fibres with infiltrates of lymphocytes and plasma cells. The trabeculae show osteoblastic activity with young fibrous bone. This chronic type is further subdivided into the little-active form, with few cells and little transformation of bone, and the strongly active form, which is richer in cells and constitutes the transition form to the exudative aggressive form.

**Cicatrized chronic osteomyelitis**

Here, there is predominance of scar tissue, with few nuclei and numerous fibres. Here and there, however, there exist small abscesses, possibly the cause of exacerbation of this chronic osteomyelitis (Könn and Böhm, 1974). Macroscopically, the soft parts surrounding the osteomyelitic focus contain fistulous ducts, which are frequently ramified. In the fistulous duct we find cavities and old small abscesses, and often several, mostly small sequestra. The scar tissue is most strongly developed close to the skeleton but extends into the soft parts, fairly often involving the neurovascular bundle. Inflammation of the vascular wall may lead to obliterating endangitis or thrombosis of the vessels.

Access to the focus of infection through the circulation is increasingly abolished and the inflammatory process is 'autonomized'. The problems of ischaemia and inaccessibility of the chronic osteomyelitic focus are characteristic and of essential importance for the treatment (Trueta, 1968; Könn and Böhm, 1974).

**2.2.3. Exogenous osteomyelitis**

The term ‘exogenous osteomyelitis’ designates osteomyelitis caused by an external infection, a trauma or an operation. Histologically, there is no essential difference between exogenous osteomyelitis and endogenous, haematogenous osteomyelitis. For exogenous traumatic osteomyelitis, certain authors, especially in the German literature, prefer the term ‘osteitis’ (Lexer, 1936; Popkirov, 1971; Burri, 1979). This preference is argued by stating that ‘osteitis’ indicates better that all parts of the osseous tissue are involved. Allegedly, to many, the term ‘osteomyelitis’ means only haematogenous osteomyelitis (Hierholzer, 1970). However, opponents of the term ‘osteitis’ use the same argument: osteomyelitis indicates better that all constructive elements are involved in the inflammation (Könn and Postberg, 1970; Rehn, 1974). This is a frequent topic of discussion at congresses (Hierholzer and Rehn, 1971).
Histologically, exogenous osteomyelitis has virtually the same characteristics as haematogenous osteomyelitis. One important difference is, however, that in exogenous osteomyelitis there is a normergic reaction, in contrast to haematogenous osteomyelitis, which generally causes a hyperergic tissue reaction. In exogenous osteomyelitis, sequestra in the form of devitalized bone fragments may be present from the onset of the inflammation. Popkirov calls these 'pseudo-sequestra' (Popkirov, 1971). Here again, the acute and the chronic form cannot be distinguished sharply. No histological examination of an early stage of exogenous inflammation is believed to have been reported (Hierholzer, 1970; Könn and Böhm, 1974).

Burri states that aggressive exudative osteomyelitis hardly ever occurs after bone surgery: only in case of infection when an intramedullary nail is used. In that case, the infection spreads rapidly throughout the bone marrow, resulting in a medullary phlegmon with sequestration of the interior portion of the cortex due to destruction of the endosteal blood supply. Infections after other osseous operations more often show the picture of plasmocellular 'osteitis' (Burri, 1970). The microscopical image of this as described by Burri is identical to that of the above-mentioned chronic persistent osteomyelitis. One important difference from endogenous osteomyelitis is that the exudate, produced during the acute phase of exogenous osteomyelitis, can escape through the defects in the cortex, so that the intra-osseous pressure does not rise, no ischaemic lesions occur and spread in the skeleton is less extensive. An abscess develops around the fracture or the osteotomy surfaces. Local reabsorption occurs. This is even stronger if there is interfragmentary instability. If there is adequate interfragmentary compression, consolidation of a fracture or osteotomy in the presence of an inflammation may nevertheless proceed fast, with formation of much periosteal callus (Burri, 1979).

2.2.4 Non-pyogenic osteomyelitis
An important category in osteomyelitis, which is different histologically as well, is that caused by non-pyogenic causative agents. These include fungi, viruses and certain bacteria. The most important group in this category is tuberculous osteomyelitis. The inflammation is characterized by absence of the acute response of the body with oedema and haemorrhage. Rather, the reaction takes the form of lymphocytes, plasma cells and epithelioid histiocytes forming giant cells. The destruction of the bone here is the consequence of this granulomatous reaction and not of high intraosseous pressure with ischaemia (Enneking, 1979). Accordingly, no sequestra are formed. This granulomatous reaction is not specific of tuberculosis; granulation tissue with epithelioid histiocytes is also seen in brucellar and fungal infections (Putschar, 1976). The principal differences between pyogenous and non-pyogenous osteomyelitis result from the fact that in the non-pyogenous form the reaction is less acute so that less sequestration occurs, no involucrum is formed and the continuous destruction of the bone is pre-eminant (Enneking, 1979).

2.3 Clinical picture and course of osteomyelitis
2.3.1 Acute haematogenous osteomyelitis
Three stages can be distinguished, on the basis of the degree of extension of the process (Trueta, 1968).

Stage 1. Severe, constant pain is felt far below the surface and can sometimes be pin-pointed by the child with one finger. This 'one-finger' test over the metaphysis is the only symptom at the onset of the disease, apart from the pain. Occasionally, it has been preceded by a recent infection or minor trauma (Nade, 1974).

Stage 2. As soon as pus is being formed in the medulla and sub-periosteally, the pain grows more severe and the tenderness on palpation more pronounced. The children display variable degrees of sickness, from mild malaise to severe toxemia.

Stage 3. As soon as pus reaches the surrounding soft parts, the classical local signs of inflammation develop, such as pain, warmth, redness and fluctuation. This third, decisive stage as a rule occurs within two to three days. Arthritis of the adjacent joint readily develops in a baby; also in a child, if the metaphysis of the proximal humerus or proximal femur is affected. Hydrops in an adjacent articulation may give rise to confusion; it often develops as the result of a sympathetic reaction.

Antibiotic treatment has reduced the formerly high mortality from 15 to 30% to approx 1% (Ferguson, 1973). Since 1951, penicillin-resistant staphylococci have changed the situation: osteomyelitis more often becomes multifocal, the patients more often are younger children (especially neonates) and septicaemias are more severe (Gilmour, 1962).

However, a major problem since the introduction of antibiotics is the masking of the symptoms. The diagnosis at an early stage is very difficult and often uncertain. As a result, the treatment initially is often symptomatic and sometimes inadequate. Antibiotics change the natural course of the disease. Although the mortality has admittedly decreased, morbidity has not. Because the correct diagnosis is made later, complications such as aseptic necrosis and destruction of the infantile hip occur more often. Making the correct diagnosis during the first few days is of extreme importance (Hart, 1937; Heckman, 1955; Trueta, 1959; Harris, 1960; Gilmour, 1962; Tronzo and Dowling, 1962; Blockey and Watson, 1970; Ferguson, 1973; Nade, 1974 and Mollan and Piggot, 1977).

Every case of pain in a child, associated with tenderness near a metaphysis and with signs of infection should be regarded as an acute haematogenic osteomyelitis until the contrary is proved.

2.3.2 Subacute osteomyelitis
If there is equilibrium between the parasite and the host, the inflammation may remain limited as to localization and symptoms. It is then called subacute osteomyelitis or primary chronic osteomyelitis. Kulowski then speaks of an arrestive form, in contrast to the abortive form, in which the host wins the fight, or the suppressive form in which
subacute osteomyelitis can be distinguished.

a **Brodie's abscess**
A small cavity develops, usually in the diaphysis of the tibia without an acute clinical picture. This cavity contains granulation tissue, no pus. Brodie's abscess may also be regarded as a form of primary subacute osteomyelitis (Kandel and Mankin, 1973) (cf e).

b **Antibiotics osteomyelitis**
Also known as cold, indolent or smouldering osteomyelitis (Popkirov, 1971). This form of osteomyelitis has been described by Popkirov during treatment of osteomyelitis with antibiotics. The clinical course is mild, often without clinical symptoms of infection.

c **Plasmocellular osteomyelitis**
Also sometimes called Poncet's osteomyelitis albuminosa. Instead of pus, a serous, viscous, oily fluid is formed in the medullary cavity. The course is quiescent, the localization is usually the femur. The most frequent causative agent is Staphylococcus aureus (Popkirov, 1971, Exner, 1970).

d **Garre's sclerosing osteomyelitis**
This is a non-pyogenous osteomyelitis with a decisively chronic course. A characteristic feature is thickening and densification of the bone, sometimes leading to occlusion of the medullary cavity. Formerly, the ostitis osteoma was considered to belong to this form (Popkirov, 1971, Kahn and Pntzker, 1973). Osteomyelitis in the jaw has been alleged to occur more often as sclerosing osteomyelitis. Some clinicians doubt whether this form of osteomyelitis really exists.

e **Primary subacute pyogenous osteomyelitis** (Harris and Kirkaldy-Willis, 1965, Brit med J, Leading article, 1969, Gledhill, 1973 and Kandel and Mankin, 1973) This type of osteomyelitis is encountered often in East-Africa and Nigeria. It is believed that in East-Africa, osteomyelitis assumes this form in approx. two-thirds of all cases. There is no acute onset and no systemic reaction. The subacute course is attributed to the low virulence of the causative agent (usually Staphylococcus aureus, coagulase-positive) or to raised immunity of the host. The cavity brought about by the osteomyelitis is localized in the metaphysis and extends to the diaphysis. It is filled with granulation tissue, usually not with pus. Sequestra sometimes occur. This subacute form may also be localized primarily in the epiphysis (Green et al, 1981).

f **Chronic recurrent multifocal osteomyelitis**
This osteomyelitis develops gradually with moderately severe systemic symptoms of infection, and runs a subacute or chronic course. The condition flares up from time to time, for an average of six years. It is localized in the metaphyses of the long bones. The cause and pathogenesis are unknown. The histological picture sometimes resembles that of a mononuclear plasmacellular osteomyelitis but no causative agent has ever been demonstrated. The multifocal nature is reminiscent of salmonellar osteomyelitis or sickle-cell infarctions. So far, no therapy has been able to influence the course. The prognosis is favourable (Solheim et al., 1980).

2.3.3 **Chronic pyogenous osteomyelitis**
Chronic osteomyelitis is characterized by its protracted course and by the rarity of spontaneous recovery. Its persistence and its recurrent character have prompted certain dicta that express despondence because of this chronic nature: 'once osteomyelitis, always osteomyelitis', and 'osteomyelitis is a time-bomb that keeps ticking all your life'.

It is rare for spontaneous expulsion or reabsorption of a sequestrum to lead to spontaneous cure. Treatments are characterized by a usually high recurrence rate. Recurrence after periods of up to 80 years duration have been reported (Dodd, 1962). The average duration of the disease is several decades, and often, numerous surgical interventions and long courses of antibiotic treatment are necessary.

The extremity has a characteristic appearance with several, often deeply retracted scars and one or several sinuses. The soft parts around the osteomyelitic focus are greatly scarified and the skin is often dystrophic. As a rule, pus is secreted in small quantities and most patients learn to cleanse the sinus themselves. The presence of the sinus, however, frequently constitutes a severe psychic stress (Lidgren and Torholm, 1980).

Most patients with chronic osteomyelitis feel hardly any pain. However, early closure of a sinus resulting in congestion of pus causes pain as the pressure in the sinus rises and in addition frequent general inflammatory systems. When pain develops in a still discharging sinus, the possibility of malignant degeneration of the epithelium of the fistulous duct should be seriously considered.

Fibrosarcoma, reticulum cell sarcoma, adenocarcinoma, basal cell carcinoma and plasmocytoma may originate from a chronic fistula that has been present for a few decades. The frequency is believed to amount to approx. 0.4% (Waugh, 1952, Sedlin and Fleming, 1963, Popkirov, 1968, Lidgren, 1973, Johnston and Miles, 1973). Akbarnia et al., 1976, Brewer et al., 1976, Dranert et al., 1976)

The bone may be locally sensitive to tapping. More deep-seated parts of the skeleton such as the femur, however, are often little accessible to physical diagnostics. Pain in a bone is not necessarily due to an inflammation. It may also be caused by an intraosseous venous hypertension. This higher intraosseous blood pressure occurs as a sequela in inactive osteomyelitis and may be compared to the higher intra-osseous blood pressure in arthritis (Lidgren and Torholm, 1980).

There are gradual transitions to non-suppurative forms of osteomyelitis. The diagnosis may then become difficult, with mild pain and some loss of function as the only symptoms. Other clinical indications may be entirely absent.

2.4. **Diagnostics**

2.4.1 **Introduction**
To make the diagnosis, but particularly also to follow the evolution of the osteomyelitis, quantifiable data are required. It is especially in cases of chronic exacerbating osteomyelitis that the need is felt of more objective observation than is possible with the clinical eye which often fails short. Objective data are also important for the evaluation of the results of a treatment and for comparison of results. Acute osteomyelitis during the first few days...
and data are discussed below. BSR plotted on a semi-logarithmic scale runs a linear course (from Figure 2.5). After an uncomplicated operation, the evolution of the BSR, determined often enough, generally proves the only really useful parameter to establish the course of the healing.

Some authors determine antibody titres in osteomyelitis and ascribe diagnostic value to their findings (Lack and Towers, 1962; Hedstrom and Kamme, 1973). The antibodies produced against staphylococci can be demonstrated by means of indirect haemagglutination assay (IHA), with determination of antibody titres against the staphylococcal antigen groups A, B and F. These antibodies occur in healthy subjects, but the titres are raised in acute staphylococcal infections. Hedstrom and Kamme in 20 patients found a good correlation between the IHA titre and the clinical course of exacerbation and regression (Hedstrom and Kamme, 1973). Interestingly, S and G. Hierholzer found that in chronic staphylococcal infections the function of the phagocytising cells is reduced. With recovery, this function of the phagocytes increased again (S. and G. Hierholzer, 1979, 1980). The same authors showed that probably during the transition from the acute to the chronic form of osteomyelitis, the leukocytes are impaired in their binding to the particles to be phagocytised, owing to functional reduction of the necessary receptors. They were unable to establish whether the reduced phagocytising function is a cause or a consequence of the osteomyelitis. Eid in 90 patients with acute haematogenous osteomyelitis found an indication of a depression of the normal immune response to infection (Eid et al, 1980).

Cartridge in 23 patients with acute haematogenous osteomyelitis always observed a 'neutrophil dysfunction' compared with a control group (Cartridge et al, 1981).

2.4.4 Roentgenology
Roentgenological examination is of great importance in all skeletal diseases. In infections, however, it should be kept in mind that before skeletal alterations become visible, a lytic or osteoblastic process had been in progress for an appreciable length of time. Bone atrophy only becomes visible after loss of 30 to 50% of the minerals. For instance, an osteoid margin of a width of 10 μ takes 10 days to be formed (Waldvogel et al, 1970).

In acute haematogenous osteomyelitis, no roentgen abnormalities are present during the first few days. A normal X-ray of a bone in a child that has acutely become painful and tender suggests the diagnosis of acute haematogenous osteomyelitis (Trueta, 1968)

Roentgenologically, a swelling of the soft parts at the level of the metaphysis becomes visible first. Sometimes, it includes a clear area brought about by accumulation of pus (Fig. 2.6). It is only on the 10th to 12th days that the first roentgen abnormalities of the skeleton become visible (Hart, 1937; Hlenck, 1972; Edeiken and Hodes, 1973; Ferguson, 1973, McAllister, 1974). At that stage, irregular lytic areas become visible in the metaphysis, sometimes preceded by a 'smoky' aspect (Tachdjian, 1972). This is followed soon by the subperiosteal spread which leads to an involucrum and cortical sequestrum. The first lytic lesions then grow visible; sclerosis only develops after one month (Waldvogel, 1970*). Different causative agents allegedly bring about more or less distinguishable roentgen abnormalities (Ferguson, 1973). In general, in osteomyelitis...
Figure 2.6  X-ray film at an early stage of haematogenous osteomyelitis of the proximal femur (a) and the distal radius (b) At this stage of the inflammation, only a small subperiosteal abscess is visible.
not influenced by antibiotics, the roentgen lesions run the following course:

- rarefaction: the structure becomes less dense.
  Osteoporosis with periosteal reaction

- destruction: loss of structure, sequestra and reaction of periosteum

- repair: ossification, hyperostosis and osteosclerosis (Flach, 1970).

Exogenous osteomyelitis differs from haematogenous osteomyelitis in that in the former, early periosteal lesions are diagnostically irrelevant (Burri, 1979). Medullary bone destruction is not clearly visible. There may be massive accumulation of pus in the medulla without any visible radiological manifestation (Butt, 1973).

It is only when an osteomyelitis has been present for approx two weeks that clear areas and periosteal reactions occur. In florid infections, clear areas develop around implants (Müller, 1978), and in case of a medullary nail, small round lytic areas occur, followed by extensive destruction along the entire nail (Burri, 1979).

In chronic active osteomyelitis, the progressive destruction leads to formation of sequestra. Pseudo-sequestra, unlike true sequestra, do not retain the dense, sclerotic structure unless they fail to be revitalized and are transformed into true sequestra (Müller, 1978; Burri, 1979). In chronic inactive osteomyelitis there are hyperostosis and numerous subperiosteal bone formations.

Antibiotic treatment causes a significantly different roentgenological image, due to less periosteal reaction, reduced sequestration and suppressed reconstructive changes (Flach, 1970; Müller, 1978).

In order to obtain adequate roentgenological information in osteomyelitis, the plain X-rays are best made in four projections (Rehn, 1974). With osteosynthesis material in situ, it is advisable to look for the optimal projection under image-intensifier control. The variably sclerotic areas in the bone often necessitate X-rays with different exposures (Fig. 2.7).

In the presence of a sinus, fistulography should always be performed, but sometimes the fistulous duct is inadequately visualized owing to contrast medium leaking away with insufficient pressure during the contrast injection as the result. Sepsis after fistulography has been reported (Halpern et al., 1979). The CT-scan may supply valuable supplementary data, just as the planigram. It is especially in osteomyelitis with sclerosis that X-ray films with different exposures provide more information, as in this patient with chronic osteomyelitis after an empyema of the medullary cavity of the tibia.

**Figure 2.7** It is especially in osteomyelitis with sclerosis that X-ray films with different exposures provide more information, as in this patient with chronic osteomyelitis after an empyema of the medullary cavity of the tibia.

2.4.5. Scintigraphy

Scintigraphy provides important information on osseous processes. The problem is to interpret this information. In the technetium scan, the distribution of Tc$^{99m}$-MDP is influenced by the regional blood distribution and by uptake into the bone matrix (Kahn et al., 1979). A rapid initial phase reflects vascularization, a slower second phase the immature bone formation (Davies and Galasko, 1977). Thus, technetium reacts to remodelling of the bone, for which it is essential that an adequate amount of sound bone is present to incorporate the radionuclide (Hughes, 1980). The precise mechanism of the uptake of technetium by the skeleton is still a mystery. A part is adsorbed to the hydroxyapatite crystals of the bone (Jones and Cady, 1981). Accordingly, the technetium scan does not constitute a specific parameter of inflammation. The gallium scan allegedly does react specifically: to the presence of leukocytes instead of to vascular permeability. Deyssine et al. in 6 patients saw good correlation of the evolution to the infection with 13 gallium scans. Control patients showed that postoperative haematomas did not cause positive gallium scans. They found no false-negative scans in osteomyelitis (Deysine et al., 1975).

As a general rule, in osteomyelitis the scan reveals abnormalities sooner than a roentgenogram (Scoles, 1980). It is believed that the increased activity in osteomyelitis is due to vascular hyperactivity rather than to osteogenesis. A raised intraosseous pressure, however, reduces the blood supply so that scintigraphy no longer shows increased local activity (Scoles et al., 1980). Sometimes, there even occurs a local cold spot, which turns hot again after spontaneous or surgical decompression (Jones and Cady, 1981).
2.5 Bacteriology

Bacteriological examination is an important part of the diagnosis and for this reason is discussed separately.

2.5.1. Gram preparation

Specimens collected for cultivation may yield direct information when examined microscopically after staining. The morphological findings obtained at microscopical examination, combined with the clinical symptoms, often permit a tentative conclusion concerning the identity of the causative agent. This permits a somewhat more informed choice of the antibiotics to be administered while awaiting the results of the culture.

2.5.2. Culture

The culture is the key element in the diagnosis and treatment of osteomyelitis. A correct collection technique and knowledgeable interpretation of the results of the culture are of great importance in this respect.

Numerous micro-organisms are described in the literature as possible causative agents of osteomyelitis. The frequency distribution of the bacteria varies greatly from one group of patients to another, depending on the type of osteomyelitis, the localization and probably the culturing technique, as well (Table 2.2).

A number of authors have pointed out that as a rule the bacteria present in sinuses are not the same as those in the more deepseated focus of infection. In the sinus tract, namely, contamination often leads to a mixed flora, whereas in the deeper layers, a mono-infection often persists. Accordingly, Popkirov advocates bacteriological examination at several levels: ‘bakteriologische Schichtaufnahme’ (bacteriological tomography) (Popkirov, 1971).

Mackowiak et al. in an important investigation studied the relationship between the culture from the sinus tract and the culture from deep-seated tissue obtained at operation (Mackowiak et al., 1978). They studied the results of cultivation in 40 patients with osteomyelitis. Thirty-six patients at operation had a mono-culture. The 183 cultures from fistulous material of these 35 patients in only 81 cases (44%) grew the same bacteria as found in the deep tissue. In 33 cultures (18%), the bacterium, although present, was dominated by other bacteria. The longer a sinus had been present, the more often the fistulous culture differed from the deep culture: the discrepancy rate rose from 18% to 69%.

It is therefore never possible to attach diagnostic value to any micro-organism cultured from a sinus, not even when the culture is pure. In Mackowiak’s study, one exception to this rule was Staphylococcus aureus. If this species was present in a fistula, it was present in the deep culture as well in almost 80% of the cases. On the other hand, if the deep culture revealed Staphylococcus aureus, this species was demonstrable in the sinus in only 44%. If the culture from the sinus repeatedly contained the same species, there was slightly more correlation with the species in the deep tissue, especially when enterobacteriaceae were involved. This discrepancy between cultures from the fistula and the deep tissue has been confirmed by several authors. Robson and
Heggars (1969) in deep wound biopsies found a mono-infection in 87% and a mixed infection in 13%. Exudate from the sinus revealed 52% mixed infections. Other authors found mixed and mono-infections at various ratios (Table 2.3).

Table 2.2 Review of literature data concerning percentages of causative agents cultured in osteomyelitis. Where authors did not state percentages, these have been calculated. Percentages may add up to over 100% because the causative mechanisms of mixed infections are listed separately.

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<td>Kayser et al. '81</td>
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<td>Vecsei '81</td>
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Table 2.3 Review of literature data concerning distribution of mixed and mono-infections and of sterile cultures in patients with osteomyelitis.
2.5.4. Anaerobic infecting organisms

In interpreting cultures and collecting culture material, it should be kept in mind that osteomyelitis may be caused not only by all bacteria but also by many fungi and viruses. A group that in recent years has been brought back from oblivion is that of the anaerobic bacteria. Many authors do not report any anaerobic infecting organisms but often they do report a relatively large number of sterile culture findings (Table 2.3). Anaerobic bacteria demand much of transport media and organization of transport (Dingeldein, 1979; Lodenkämper and Rühlicke, 1974; Nettles et al., 1969).

In the body, anaerobic bacteria are found in the intestine but on many other mucous membranes, as well. Transient subclinical bacteriaemia caused by these anaerobes are believed to be very frequent (Lodenkämper and Löhr, 1971). Bacteria readily pass through mucous membranes, especially when the latter are changed under the influence of hormones, allergies, infections, etc. Haematogenous infections due to anaerobic bacteria are less rare than used to be believed (Lodenkämper and Rühlicke, 1974), but anaerobes are frequent in non-haematogenous infections, as well (Lewis et al., 1978; Nettles et al., 1969). They grow slowly and have a long incubation period. In cultures, growth is often only to be observed after one week and it is believed that too many cultures are reported to be sterile as the result of premature evaluation (Nettles et al., 1969). In patients with a very ill-smelling wound with much necrosis, the possibility of an anaerobic infection should be seriously considered.

2.5.5. Cell wall deficient bacteria

Certain bacteria under the influence of antibiotics develop alterations of the cell wall: protoplasts, spheroplasts and L-types. The absence of the cell wall prevents antibiotics from destroying this type of bacteria (penicillins, cephalosporins), whereas the bacteria can still be influenced by antibiotics with a different mechanism of action (e.g. aminoglycosides). The L-types are probably not pathogenic themselves, but they may survive in spite of antibiotic treatment, thus constituting a latent microbe. They can also reproduce and sooner or later return from the latent to the original bacterial form. Culturing these special bacterial types has to be done in special osmotic conditions. Gordon (Gordon et al., 1971) describes four patients, three of whom had metallic implants in situ. One patient had several different metals. Possibly there is a connection with so callad abacterial osteitis due to metallosis (Contzen, 1970, 1973).

Rosner describes one patient with osteomyelitis caused by an L-phase variant of Staphylococcus aureus (Rosner, 1968).

In all patients with sterile discharge (without antibiotic treatment), the presence of L-forms should be suspected.
Since the diagnosis of anaerobic and cell wall defective bacteria is difficult and has frequently been inadequate, the role of the two types as causative agents of osteomyelitis is uncertain. Both bacterial types are characterized by a low virulence. Also, most publications report a large number of sterile cultures. A correlation between these sterile cultures and incomplete bacteriological diagnosis in osteomyelitis may well exist. This might be one of the explanations of the chronic recurrent character of an osteomyelitis with frequently long latent periods.

2.6 Treatment

2.6.1 Historical survey up to the late 19th century

The earliest signs of osteomyelitis have been found in Neanderthals of the Last Glacial Age (Bishop, 1960). The earliest references to the treatment are to be found in the Smith Papyrus of 5000 to 3000 B.C. (Picket, 1935). Treatment at the time consisted of splints and dressings of various compositions. For a long time, live wood embers were placed on the wound to provoke a kind of defence reaction. Hippocrates apart from rest recommended application of dressings: not on but beside the wound (Picket, 1935); necrotic tissue should not be removed but allowed to slough spontaneously (Burri, 1979). Galenus (131 B.C.) appreciated pus as a sign of healing: pus bonum et laudabile. Celsius (100 A.D.) preferred a more active treatment, and recommended removal of the 'carious' bone with a red hot iron till healthy bleeding bone was exposed. During the subsequent centuries, intervention and abstinence were alternatingly recommended.

Paré (1510-1590) and Jaubert (circa 1570) urged a more active management than just dressing: pain, flexion, inflammation and defects are matters that surgeons should not leave entirely to nature. Due to a shortage of oil, Paré fortuitously detected that a dressing had an expected good effect on a gunshot wound and was less pathogenic and necrotising than boiling oil, although the dressing consisted of a mixture of egg-yolk, oil of roses and turpentine (Orr, 1922).

Burri describes how his predecessor, Secultus (1595-1645) in Ulm treated osteomyelitis according to rules that still apply today, with sequestrectomy and rest with elevation (Burri, 1979).

Jacob van de Haar in Holland described in the 18th century how 'festering and corruption in the hollow of the shinbone' might be cured by 'trepanning'. He considered decompression of the wound essential as long as 'bone corruption' was still present, and he prevented premature closure of fistulae by introduction of a few grains (Van de Haar, 1797).

William Hey (1736-1819) also preferred sequestrectomy and open drainage to cauterization (Picket, 1935). Removal of necrosis and sequestra in the treatment of osteomyelitis appears to be generally accepted, and constitutes a symptomatic therapy, where lack of insight into the cause of osteomyelitis bars the way to more causal treatment. Van de Haar, for instance, still thought that the main cause was a 'commotion' of the bone, impairing its blood supply by the 'internal marrow lining', the later endostem. As a result, he said, the internal 'pipe' died and separated from the outer part (Van de Haar, 1797).

Early in the 19th century, confusion arose about the differential diagnosis of the various types of osteomyelitis, osseous tuberculosis and various osseous tumours. Brodie (1783-1862) in 1832 described a tibial abscess and its treatment (Rang, 1968). In 1853, Chassaignac described the difference between osseous typhus and the more benign osteomyelitis, with amputation and drainage as the respective therapeutic consequences. Osteomyelitis was defined as an autonomous clinical entity by Chassaignac in 1854 (Picket, 1935; Knapstein, 1962), but according to others by Lannelongue in 1879.

2.6.2 Antiseptics

It was only toward the end of the 19th century that a more causal therapy was rendered possible by two important discoveries:

The first of these was Pasteur's discovery in 1864 of anaerobic and aerobic bacteria. In 1880, in an osteomyelitis abscess, he identified the same bacterium as in a furuncle: 'Osteomyelitis is the furuncle of the bone'. Further progress was booked by Lister (1827-1912), who applied one of Pasteur's measures to inhibit the growth of micro-organisms: disinfection. He tried to prevent postoperative infection by using many antiseptics, later mostly carbolic acid. He gathered his first experiences with the treatment of complicated fractures which were treated locally with carbolic acid tampons and with plaster. In addition to this prophylactic use of antiseptics, they were also increasingly applied to combat existing inflammations. According to Orr, however, this 'listerism' has done the treatment of osteomyelitis no good. Surgeons neglected the prophylactic aspects of the infections too much, became confused by the multiplicity of antiseptics and regarded treatment of infection too much as a battle between micro-organisms and antiseptics (Orr, 1922). This reliance on the hoped-for magic powers of a new method, whilst essential surgical principles were ignored, could be observed once more, with all its features, shortly after World War II, when antibiotics were expected to oust the problem of infection from the globe and to turn osteomyelitis into an 'internal' disease.

While, as described above, rest and sequestrectomy as part of the debridement have long been accepted in the treatment of osteomyelitis, in the last one hundred years it has become clear that in addition, two factors are of decisive importance for that treatment: stabilization and the prevention of cavitation.

2.6.3 Stabilization

H. Winnet Orr (1922) was the first to emphasize the importance of stabilization. In advocating his then new, personal therapy, he stressed the drawbacks of earlier methods, not an uncommon practice at any time: his scapegoat was the excessive use of antiseptics, 'listerism'. His therapy also comprised a solution of the cavitation problem. The treatment consisted of:

1. Combating local infection by asepsis or antisepsis. Complete curettage was not considered necessary: the patient can handle part of the infection by himself.
2. Adequate drainage.
3. Postoperative dressing with vaseline tampons, to be changed only at fairly long intervals and sometimes introduced into the cavities as well.
4. Rest ensured by adequate immobilization in a plaster cast.
Like so many therapies for osteomyelitis, this ‘Orr method’ also was based on war experience (Orr, 1922). Appreciable shortening of hospitalization and incapacity was mentioned as the advantage of this new method (Kulowski, 1931). The same arguments were to be advanced later for other new methods, by advocates of the suction drainage system and gentamicin-PMMA beads.

Stability as an essential part of the treatment of infections has been and is still being emphasized by many, particularly by the AO-group (Arbeitsgemeinschaft für Osteosynthesefragen, Association for the study of internal fixation) (Müller and Rehn, 1978; Burri, 1979). The advantage of preserved stability is considered to outweigh the disadvantage of the presence of a foreign body, viz. osteosynthesis material (Willeenegger, 1973; Hierholzer et al., 1974; Burri, 1973, 1979; Schneider, 1979).

Further research will be required, however, to gain more insight into the role of stability in the treatment of infections. The results of experiments in animals by Harms and Van de Berg to some extent support clinical experience regarding stability and infection (Harms and Van de Berg, 1976).

2.6.4. Prevention of cavitation
The cavitation which in osteomyelitis results from the destructive infection itself and from the curettage has often been regarded as one of the main causes of recurrence. In the skeleton, the rigid structure of the bone keep walls from collapsing so that cavities persist. Many ways have been proposed to solve this problem. Prevention of cavities was achieved by smoothing the overhanging walls, changing the shape of a plug, followed by primary closure of the skin. Dresmann implanted plaster with a 5% carbolic acid solution. The stimulating effect of plaster on bone growth was disappointing (Dresmann, 1893). This stimulation of bone growth may be better in non-infected areas (Häuptli, 1952). Löhr mixed plaster with cod liver oil (Löhr, 1934) in the expectation that the oil would influence the mesenchymal cells more favourably than antiseptics. Some of the other packing materials that have been used are copper amalgam, iron, lead, aluminium, cement, clay, glass, ivory, calcium, gelatin, paraffin and vaseline (Popkirov, 1971).

Of the autoplastic materials the first one to be mentioned is the ‘feuchter Blutschorf’ (moist blood crust). The earliest users of this technique were Neuber in 1896 and Schede in 1889. For the first time, the cavity was no longer plugged with gauze: after removal of the tourniquet (in use since 1873), the cavity filled with blood. This coagulum was left intact to become organized beneath the crust.

Failures were frequent, however (Neuber, 1896). Addition of antiseptics failed to improve the results. In later years, blood was mixed with antibiotics to form the so-called antibiotic plug, sometimes mixed with fibrinous products (Winter, 1951; Winter et al., 1953; Maday and Horvath, 1959; Bikfalvi and Ecke, 1960; Ecke et al., 1960; Axhausen, 1961, 1965).

Obliteration of the cavities was also achieved by invagination of the skin (Neuber, 1896; Schulten, 1896). In the epiphyseal region, the skin had to be fixed with a nail (Fig. 2.10). Pedicled skin flaps, cutaneo-periosteal flaps and muscle flaps were also used (Knight and Wood, 1945; Kelly, 1946; Stark, 1946; Springerum, 1949; Evans and Davies, 1969; Horwitz, 1973; Shannon et al., 1973). This method had the drawback that often much sound bone had to be sacrificed, so that it could not be applied close to articulations. Also, the resulting weakening of the bone sometimes led to fracturing, so that the osteomyelitis was replaced by an infected pseudarthrosis. Another technique was to cause the walls to collapse (‘feuillet du livre = book page—Brunet and Bertaux, 1975; ‘Einklappungsmethode’ = folding-in technique—Schulten, 1896) (Fig. 2.9), or the ‘Knochenverschiebeplastik’ (= bone displacement plasty—Popkirov, 1971). These techniques, also, can only be applied in the diaphyseal region.

Many ingenious attempts have been made to prevent dead space in osteomyelitis by packing the cavity. Often, use was made of substances intended to combat the infection locally or to stimulate bone growth. Thus, in the evolution of treatment of osteomyelitis there runs a direct line from the disinfected sponges used by Hamilton in 1881 (Picket, 1935) and the packing of cavities with gentamicin-PMMA beads. The implanted materials may be divided into alloplastic and autoplactic substances (Popkirov, 1971).

The alloplastic substances were often implanted in the shape of a plug, followed by primary closure of the skin. Dresmann implanted plaster with a 5% carbolic acid solution. The stimulating effect of plaster on bone growth was disappointing (Dresmann, 1893). This stimulation of bone growth may be better in non-infected areas (Häuptli, 1952). Löhr mixed plaster with cod liver oil (Löhr, 1934) in the expectation that the oil would influence the mesenchymal cells more favourably than antiseptics. Some of the other packing materials that have been used are copper amalgam, iron, lead, aluminium, cement, clay, glass, ivory, calcium, gelatin, paraffin and vaseline (Popkirov, 1971).

Essential in the history of osteomyelitis are the development and improvement of surgical techniques in the early 20th century: curettage with sequestrectomy, rest, saucerization and packing of cavities are interventions that have mostly proved themselves empirically. The discovery of bacteria and the use of antiseptics failed to improve the therapeutic results in osteomyelitis to the large extent expected. Before antibiotics became available after World War II, one other curious therapy has been used side by side with those described above: maggot therapy.

2.6.5. Maggot therapy
A particular part in the treatment of osteomyelitis has been played by maggot therapy. Military surgeons observed on battlefields that wounds were covered in crawling fly grubs. Larrey, of Napoleon’s army, reported that they did no harm (Picket, 1935). Similar observations were made during the American Civil War. Baer, however, noted that the maggots were not only harmless but even exerted a positive...
Figure 2.10 Obliteration of the residual cavity in treatment of osteomyelitis of a femur. Imagination of skin with musculature, fixation with adhesive plaster. In the metaphyseal region, a nail is necessary for fixation (from Neuber, 1896).

influence on the local appearance of the wound and on the patients' general condition. In 1917 he saw two soldiers with complicated femoral fractures of seven days' standing. Both patients were in good condition and the wounds showed fresh granulations. He kept this observation in mind for ten years, before in 1928 he ventured to use maggots therapeutically himself. He worked out a method to breed and feed maggots under sterile conditions. After débridement and haemostasis, the wound was packed with maggots. Since maggots retain their larval shape for only seven days, they had to be replaced regularly (Baer, 1931). The method was used on a large scale in the United States during the period between the two World Wars (Buchman and Blair, 1932; Buchman, 1934).

The effect of the method may be due to the removal of necrotic tissues, although maggots cannot eat devitalized bone (Buchman and Blair, 1932): with this method, also, surgical debridement remains essential. In Europe, the maggots therapy apparently evoked too much disgust; it was hardly ever used (Schürch, 1933). The beginning of the antibiotic era rendered this therapy obsolete.

2.6.6. Antibiotics

When antibiotics are used to combat infections, they have to be present in the infected tissue at sufficiently high levels to be able to inhibit or destroy the infecting micro-organism. When an antibiotic is administered orally or parenterally, it is distributed over various types of tissues in the body. The levels reached in those various tissues vary, and depend among other things on the type of the tissue, the properties of the antibiotic and the vascularization.

Generally, the antibiotic concentration attained in bone is appreciably below the serum level. We find, for instance, that after a single dose of flucloxacillin, the levels of the antibiotic that can be demonstrated in bone vary from 11.6% (in the cortex) to 15.6% (in the spongy bone) of the serum level (Unsworth et al., 1978). This so-called serum:bone ratio has been reported for cefalotin and cefamandole as 6% and 12.8%, respectively (Schurman et al., 1980).

Kolczun and Nelson studied the bone levels of oxacillin, lincomycin and cefalotin after various doses (Kolczun and Nelson, 1974). They found that after various different doses of oxacillin and lincomycin there were fixed serum:bone ratios of 16:1 and 6:1, respectively. In the case of cefalotin, this ratio was not fixed, but decreased as the serum level rose. It was especially with lincomycin that it was possible to attain a sufficiently high concentration in a bone, necessary to exceed the MIC (minimum inhibitory concentration) of staphylococci.

Norden also observed that the bone level of antibiotics was lower than the serum level. In osteomyelitis bone, however, he frequently found higher concentrations than in normal bone. In the treatment of rats with osteomyelitis, he was able to sterilize the infected bone in one-half of the cases. However, this success rate was considerably lower when a sequestrum was present (Norden, 1971). Hierholzer studied fusidic acid and found that the penetration was less in chronically inflamed bone tissue than in sound bone. Just as in sequestra, the penetration of antibiotics is also less good in cavities filled with pus and necrotic débris (Hierholzer et al., 1974).

Waldvogel saw good therapeutic results when patients were treated with antibiotics in large doses, resulting in sufficiently high serum levels. Waldvogel observed that when patients with haematogenous osteomyelitis were treated with sufficiently large doses, 96% were cured, as against 17% of those treated inadequately, with insufficient dosage. In the treatment of recurrences of haematogenous osteomyelitis, these proportions even amounted to 50% and 0%, respectively (Waldvogel et al., 1970).

Some authors attach importance not only to the type of antibiotic, the dosage and the administration interval, but also to the duration of the treatment. Hedström considered it necessary to administer large doses of antibiotics for long periods of time. He subjected 40 patients to protracted antibiotic treatment (long-term treatment, LTT): cloxacillin or lincomycin was given for six months to longer than one year. He obtained a lower recurrence rate, which, however, still amounted to 29%; cure in these cases was achieved by secondary sequestrectomy, abscess drainage or removal of osteosynthesis material (Hedström, 1969, 1974). Hagen saw frequent recurrences even with LTT (Hagen, 1978).

If antibiotics are administered systemically, some important factors are the serum level, the tissue perfusion, the diffusibility of the antibiotic and its affinity to the tissues (Wysocki, 1974). The tissue concentrations required amount to three to ten times the minimum inhibitory concentration (MIC) of the bacterium, and these high levels tend to be
2.6.7. Suction drainage

Markoe in 1880 published results of treatment of osteomyelitis; he also criticized 'Mr Lister' and proposed thorough, accurate drainage with irrigation of the wound. The wound was irrigated four times daily with carbolic acid (Markoe, 1880).

Carrel in 1915 described an irrigation method with hypochlorite (NaClO): 'Dakin's fluid'. Every hour or every other hour, he instilled the hypochlorite solution through drains, at first intermittently ('instillation intermittente'), later continuously (Carrel, 1915; Dakin, 1915). Smith-Petersen in 1934 designed cannulae to be inserted into the wounds and connected to a drain. By means of an instillation system he initially instilled Dakin's fluid, later a penicillin solution.

The advantages of this method were the possibility of primary closure of the wound and loss of less serum than used to be lost before with the open granulating wound (Smith-Petersen et al., 1945) (Fig. 2.11).

It was especially Willenegger who strongly advocated the use of the irrigation system. First he used penicillin but subsequently he recommended adding chloramphenicol to the irrigation fluid (Willenegger and Roth, 1962; Willenegger, 1963). The irrigation fluid is instilled gradually into the infected area and drained by a vacuum suction system. Some years later, he replaced physiological saline by Ringer solution and reduced the duration of the irrigation. One important effect of the irrigation system is the mechanical cleansing of the wound. According to Willenegger and other authors the antibiotic needs only to be added to the irrigation fluid for two to four days. The total duration of the irrigation-drainage system should be one to a maximum of three weeks (Willenegger, 1970, 1973, 1979; Willenegger et al., 1970; Polster and Samimi, 1979; Burri and Van de Werken, 1981). The irrigation system has been used by many, with numerous variations: intermittent or continuous, with or without changes of the direction of the flow (Grace and Bryson, 1950; Dombrowski and Dunn, 1965; Compere et al., 1967; Dilmaghani et al., 1969; Anderson and Horn, 1970; Kelly et al., 1970; Taylor and Mandsley, 1970; Hertel and Albrecht, 1968; Lawyer and Eyring, 1972; Clawson et al., 1973; Law, 1975; Meyer et al., 1975; Fasol and Schmid, 1976; Mitra and Grace, 1956; Boda, 1979; Geneste et al., 1979; Kawashina et al., 1980; Lehnhardt, 1980).

2.6.8. Cancellous bone graft

The cancellous bone graft has a twofold purpose in the treatment of osteomyelitis: to fill the cavity and to provide stability. Chase and Herndon (1955) have published a very detailed, well-documented survey of the history of bone auto- and homografting and the results obtained. Ollier in 1867 laid the scientific foundation for bone grafting, emphasizing the importance of the periosteum (Ollier, 1867). During the first few years, the transplantation material used was mostly autologous cortical bone; later, use was also made of homologous or heterologous bone, sometimes denatured (Orell, 1937). Especially during World War II, cancellous bone graft was practised increasingly.

Prigge in 1946 described the first use of this technique in osteomyelitis (Prigge, 1946). He arrived at this application because at sites such as the proximal tibia, the calcaneus and the distal radius, a muscle graft was not adequately feasible. The first part of the treatment consisted of débridement and saucerization. The cavity was temporarily packed with gauze, into which a penicillin solution was instilled. Subsequently, the greater part of the cavity was filled with chips of cancellous bone. The wound was then closed, leaving a small opening, the extremity was immobilized in a plaster cast and postoperatively, penicillin was administered systemically for one to two weeks. Thus grew up a combination treatment with débridement, irrigation, antibiotics, immobilization and packing of the cavity. Prigge considered the method to be not indicated in tibial defects larger than three centimetres, in the femur or at other sites where a muscle-flap graft is feasible. Coleman and others in 1946 published their data on cancellous bone grafting in osteomyelitis. They performed the operation in one session. The wound was closed immediately and antibiotics were administered systemically and locally into the wound, sometimes mixed in with the bone chips. They were of the opinion that cancellous bone, unlike cortical bone, offers good resistance to infection (Coleman et al., 1946). In
the Netherlands, De Grood in 1947 described two patients treated according to this technique (De Grood, 1947).

The addition of antibiotics to the cancellous bone has been studied by Graig Gray and Elves: they observed that chloramphenicol and polybactrin spray exerted an adverse influence on the cancellous bone (Graig Gray and Elves, 1981).

Papineau in 1973 described a cancellous bone grafting method for osteomyelitis. He carried out this procedure in a minimum of two stages. In order to obtain an optimally clear view of structures to be excised, the débridement if necessary was also performed in several stages. Between operations, the wound was not closed but plugged with antibiotic-containing gauze. Irrigation was performed if necessary. Subsequently, cancellous bone chips were supplied in generous amounts and antibiotics given systemically for four to six months. A stable state was created by means of an intramedullary nail, in spite of existing infection (Fig. 2.12). If necessary, a skin plasty was performed to close the wound (Papineau, 1973).

In the French literature, this method has regularly been mentioned up to the present day (Roy-Camille et al., 1974, 1976; Lortat et al., 1977; Piganiol et al., 1979; Miné et al., 1979). In all cases, the cancellous bone graft is only performed after sequestrectomy with stabilization, followed by a waiting period with irrigation as required.

The authors mentioned perform cancellous bone grafts not only to fill cavities but also often as a 'greffe intertibio-péronière' (GITP) or tibia-pro-fibula graft to create a dorsal bony bridge between the tibia and the fibula. Allegedly, this stabilization sometimes suffices to control the infection (Freeland and Mutze, 1976; Miné et al., 1979). Sudman performs cancellous bone graft and débridement at the same session, followed by protracted antibiotic treatment: three to twelve months (Sudman, 1979).

Burri has written a great deal about the role of the cancellous bone graft in the treatment of osteomyelitis (Burri, 1973, 1974, 1979; Burri et al., 1970, 1973, Burri and Henkemeyer, 1971; Burri and Van de Werken, 1982; Spier and Burri, 1977; Van de Werken et al., 1980). His management of osteomyelitis rests on four pillars: stabilization, débridement, irrigation drainage (or other methods) and packing of the defect. The best grafting material is autologous cancellous bone. Homologous bone is slower and less effective in inducing neoformation of bone. Denatured bone is said to have failed in its function of supporter of bone neof ormation, its remodelling taking even more time than the spontaneous refilling of an empty cavity of equal size (Burri, 1979). According to Burri, the indications for a cancellous bone graft in osteomyelitis are an unstable fracture or pseudarthrosis (in which the cancellous bone should be placed as far as possible from the focus of infection) and filling of a defect (after curettage and vitalization of the graft bed).

Cancellous bone grafting is contraindicated in aggressive, purulent osteomyelitis. In this case, the infection should first become less active. If there is no adequately vascularized bed available for the cancellous bone, survival of the graft is insufficient. Van de Werken and others demonstrated that although the cancellous bone does not entirely fail to take in the presence of infection, more of it is lost than in a non-infected region (v.d. Werken et al., 1980).

Interestingly enough, antiseptics are making a comeback (Gilmore, 1977). Modern antiseptics are believed to have better qualities than older ones (Willeweger, 1979; Good, 1979). One of these new disinfectants is Taurolin®. Taurolin is a compound of taurine (ethylamine sulfonic acid) and formaldehyde. It has been reported to exert a favourable influence on chronic osteomyelitis in animal experiments (Götz and Wesch, 1981).

Burri performs peroperative lavage with a 1% solution of Taurolin® in Ringer's solution to reduce the surgical infection rate (Burri et al., 1980). Also, he mixes cancellous bone with collagen and Taurolin® in the treatment of osteomyelitis (Burri and Van de Werken, 1982). This creates a strong resemblance between this therapy and that described by Buchman and Blair (1947), who packed the osteomyelitis cavity with a substance to be absorbed (oxygel with gelatin and thrombin) mixed with penicillin.

Figure 2.12 Cancellous bone grafting by Papineau's technique to bridge a diaphyseal defect in a case of osteomyelitis. Stabilization with a medullary nail (from Papineau, 1973).

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Burri has written a great deal about the role of the cancellous bone graft in the treatment of osteomyelitis (Burri, 1973, 1974, 1979; Burri et al., 1970, 1973, Burri and Henkemeyer, 1971; Burri and Van de Werken, 1982; Spier and Burri, 1977; Van de Werken et al., 1980). His management of osteomyelitis rests on four pillars: stabilization, débridement, irrigation drainage (or other methods) and packing of the defect. The best grafting material is autologous cancellous bone. Homologous bone is slower and less effective in inducing neoformation of bone. Denatured bone is said to have failed in its function of supporter of bone neof ormation, its remodelling taking even more time than the spontaneous refilling of an empty cavity of equal size (Burri, 1979). According to Burri, the indications for a cancellous bone graft in osteomyelitis are an unstable fracture or pseudarthrosis (in which the cancellous bone should be placed as far as possible from the focus of infection) and filling of a defect (after curettage and vitalization of the graft bed).

Cancellous bone grafting is contraindicated in aggressive, purulent osteomyelitis. In this case, the infection should first become less active. If there is no adequately vascularized bed available for the cancellous bone, survival of the graft is insufficient. Van de Werken and others demonstrated that although the cancellous bone does not entirely fail to take in the presence of infection, more of it is lost than in a non-infected region (v.d. Werken et al., 1980).

Interestingly enough, antiseptics are making a comeback (Gilmore, 1977). Modern antiseptics are believed to have better qualities than older ones (Willeweger, 1979; Good, 1979). One of these new disinfectants is Taurolin®. Taurolin is a compound of taurine (ethylamine sulfonic acid) and formaldehyde. It has been reported to exert a favourable influence on chronic osteomyelitis in animal experiments (Götz and Wesch, 1981).

Burri performs peroperative lavage with a 1% solution of Taurolin® in Ringer's solution to reduce the surgical infection rate (Burri et al., 1980). Also, he mixes cancellous bone with collagen and Taurolin® in the treatment of osteomyelitis (Burri and Van de Werken, 1982). This creates a strong resemblance between this therapy and that described by Buchman and Blair (1947), who packed the osteomyelitis cavity with a substance to be absorbed (oxygel with gelatin and thrombin) mixed with penicillin.

Figure 2.13 Schematic representation of remodelling of a cancellous bone graft, used, for instance, to pack an osteomyelitic cavity. Granulation proceeds from the fundus (a). Even when superficial granulation is still only slight, deeper granulation may be far advanced (b). It is only after the granulation reaches the surface of the cancellous bone that the defect is rapidly closed by epithelialization (c).

* Geistlich, Wolhusen, Switzerland.
Chapter 3. The infected endoprosthesis

3.1. Introduction

Infection around an endoprosthesis, for convenience’s sake called ‘infected endoprosthesis’, is regarded in orthopaedics as one of the worst postoperative complications after implantation of an endoprosthesis. As a rule, namely, it heals only after removal of the prosthesis with all cement. Thereafter, restoration of the articular function is usually difficult, sometimes impossible. Another severe postoperative complication is loosening of the prosthesis. The longer hip prostheses, for instance, have been in situ, the higher the incidence of loosening. Some of these loosened prostheses cause enough symptoms to necessitate reoperation.

As will be discussed in this chapter, it is difficult to distinguish between aseptic and septic loosening, which is why so far it has not been possible to make an accurate assessment of the problem of septic and of that of purely mechanical loosening. The matter is further complicated by the alleged fact that an aseptic loosening may turn into a septic complication. Accordingly, both problems: infection and loosening of an endoprosthesis merit discussion.

3.2. Fixation and loosening of the endoprosthesis

Most research into loosening of prostheses has been performed in regard to the hip prosthesis. Prior to the introduction of acrylic cement by Charnley (Charnley, 1960), head-neck prostheses and total hip prostheses were implanted without cement. Many prostheses were subsequently found to be inadequately anchored to the bone, which usually caused pain. Slooff found that out of 53 head-neck prostheses, 56% had become loosened (Slooff, 1970), after a mean follow-up of five years.

Acrylic cement ('bone cement') appeared to be the ideal means of preventing the unwanted mobility between prosthesis and bone. It filled the space between the prosthesis and the bone, enlarging the surface of contact between the two, thus preventing local excessive stress on the bone. This eliminated the 'fretting' between prosthesis and bone which Charnley regards as the main cause of loosening (Charnley and Kettlewell, 1965; Charnley, 1965).

The drawbacks of the use of acrylic cement also became clear, however. The heat produced at polymerization of the cement (50-100°C) and the toxicity of the monomer lead to necrosis in the immediately adjacent osseous tissue (Slooff, 1971; Goebel and Ohnsorge, 1973). This necrosis further impairs the vascularization in the endostem, already damaged during the surgical preparation of the proximal femur. The necrotic layer grows two to three millimeters thick and constitutes the so-called bone-cement interface between the bone and the cement.

Feith concluded from the results of animal experiments that the polymerization heat was the main cause of this necrosis (Feith, 1975).

Huskes assumes on the basis of his calculations that the polymerization heat has to exert its adverse action more indirectly, viz. by strengthening the toxic effect of the monomer (Huskes, 1979) (Fig. 3.1).

Willert distinguishes three phases in the reaction of the body to the acrylic cement:
- the initial phase (two to three weeks) during which the necrotic layer organizes itself,
- the repair phase (three weeks to a few months or sometimes a few years), during which the necrotic layer is eliminated and adjacent bone remodelled,
- the stabilization phase (the last stage).

During this last phase, the bone-cement interface is found to contain a collagenous connective tissue membrane of variable thickness with foreign-body giant cells (Willert, 1973). The ischaemic cortex is gradually revascularized, starting from the subperiosteal region (Slooff, 1971).

In the radiogram, the bone-cement interface is seen as a halo around the cement. The frequency of observation of this halo rises and the size increases as the prostheses remain in situ longer (Harris, 1978; Witt and Hackenbroch, 1976). Witt and Hackenbroch summarise a large number of studies in the literature and find proportions of aseptic loosening of 1.6% after one year, 4% after three years and 8% after eight years. During three to six years' follow-up of personal cases, they saw a distinct halo around the cement in 99.5% in the acetabulum and in 28.5% in the femur. This proportion is almost three times as large as that seen immediately postoperatively (Witt and Hackenbroch, 1976).

Maurer et al. (1977) after four to seven years saw areas of reabsorption in 67% in the acetabulum and in 17% in the femur. In their material, also, most reabsorption zones were progressive from the operation.

Bosch et al. during a follow-up of five years at least saw radiological signs of aseptic loosening in 15.3% of the cases. Unlike others, they saw more loose femoral prostheses than cups, especially when the femoral prosthesis was in the varus position (Bösch et al., 1980).

A possible factor in the widening of the bone-cement interface is disintegration of the acrylic cement by the body (Willert, 1973). Loosening, once started, is inexorably progressive. Mechanical irritation of the interface causes local bleeding, exudate and granulation tissue. This renders the connective-tissue layer thicker and less firm. An unstable implant through this mechanical irritation brings about an inflammatory reaction with all the histological signs of an inflammatory infiltrate, often with necrosis (Szyszkwowic, 1973).

A vicious circle ensues. A thickened granulation layer weakens the anchoring of the prosthesis, increasing instability progressively aggravates the loosening with destruction of bone, which may run a rapid course owing to 'fretting' effects of the prosthesis with the cement (Fig. 3.2). According to Schneider (1979) and Lidgren (Lidgren et al., 1977), instability reduces the defense against infection, offering less virulent bacteria an opportunity to grow. Also, in the presence of a foreign body, cellular and humoral defense allegedly are weakened in their function. Elek and Conen demonstrated that in the presence of a foreign body,
Figure 3.1  At implantation of a metallic implant with the aid of cement in the bone (see a and b), temperatures have been calculated at 12 points, as shown in c. The temperature is plotted as a function of the time at various places (d) or of the distance from the centre at various moments (e). In f, the penetration depth of the 50°C isotherm in the cortex is shown as a function of the time (with permission from Huiskes, 1979).

Figure 3.2  Possible connection between mechanical loosening and infection of a prosthesis. Thermotoxic damage causes formation of granulation tissue that increases owing to fretting and possibly, contamination at operation. This progressive granulation causes progressively increasing destruction of bone. The granulation layer also constitutes an area of reduced resistance to haematogenous infection (from Lidgren et al., 1977, modified version).

Table 3.1  Review of literature data on infections after implantation of a hip or knee prosthesis without use of bone cement as reported by various authors. Just as in subsequent similar reviews of the literature, only the first author is stated where this suffices for the reference. Percentages, where not mentioned by the authors, have been calculated.

<table>
<thead>
<tr>
<th>Author</th>
<th>Total N</th>
<th>Follow up yr.</th>
<th>% Infected</th>
<th>Type of prosthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thompson '54</td>
<td>35</td>
<td>2-6</td>
<td>5.7%</td>
<td>thompson</td>
</tr>
<tr>
<td>Pipkin '55</td>
<td>55</td>
<td>0-6</td>
<td>7.2%</td>
<td>collaron, thomson, judet, sm.P.cup</td>
</tr>
<tr>
<td>Nederveen '56</td>
<td>31</td>
<td>1/2-3 1/2</td>
<td>0%</td>
<td>judet</td>
</tr>
<tr>
<td>Moore '57</td>
<td>159</td>
<td>2-6</td>
<td>0.6%</td>
<td>moore</td>
</tr>
<tr>
<td>Anderson '64</td>
<td>232</td>
<td>1-12</td>
<td>0.4%</td>
<td>thompson, moore</td>
</tr>
<tr>
<td>Sivash '69</td>
<td>164</td>
<td>1-9</td>
<td>4.3%</td>
<td>sivash</td>
</tr>
<tr>
<td>Leddy '71</td>
<td>208</td>
<td>?</td>
<td>5.3%</td>
<td>sm.petersen cup</td>
</tr>
<tr>
<td>McKee '73</td>
<td>16</td>
<td>7</td>
<td>0%</td>
<td>mckee-farrar</td>
</tr>
<tr>
<td>Perry '73</td>
<td>100</td>
<td>2-4</td>
<td>6%</td>
<td>ring</td>
</tr>
<tr>
<td>Ring '73</td>
<td>1045</td>
<td>?</td>
<td>0.7%</td>
<td>ring</td>
</tr>
<tr>
<td>Smith '73</td>
<td>112</td>
<td>1-12</td>
<td>3.6%</td>
<td>moore-gaenslen</td>
</tr>
<tr>
<td>Judet '78</td>
<td>574</td>
<td>?</td>
<td>3.3%</td>
<td>judet</td>
</tr>
<tr>
<td>Lord '79</td>
<td>300</td>
<td>?</td>
<td>2.6%</td>
<td>lord</td>
</tr>
<tr>
<td>Ring '78</td>
<td>1808</td>
<td>1-14</td>
<td>0.5%</td>
<td>ring</td>
</tr>
<tr>
<td>Knesi '79</td>
<td>21</td>
<td>?</td>
<td>11%</td>
<td>knee prosthesis</td>
</tr>
<tr>
<td>Yamamoto '79</td>
<td>91</td>
<td>1-?</td>
<td>1.1%</td>
<td>knee prosthesis</td>
</tr>
</tbody>
</table>
infection occurs with a smaller number of bacteria per milligramme of tissue (Salvati, 1976; Elek and Conen, 1957).

Consequently, the problem of the infected prostheses arises soon. In addition, considerations presented in Chapter 3.5 cause certain authors to assume that owing to inadequate bacteriological diagnostics, a very large proportion of the cases of so-called aseptic loosening are actually cases of septic loosening (Lindberg et al., 1977).

3.3. Clinical picture and course of infection of endoprostheses

The proportion of the endoprostheses which post-operatively are found to be infected varies considerably; it is influenced by the examiner and the follow-up but particularly also by the ways infections are diagnosed and defined. Published papers differ in these respects which renders comparison of the proportions of infection difficult and sometimes useless. Prior to introduction of acrylic cement to fix the hip prosthesis, recorded percentages of infected hip arthroplasties varied from 2% to 7% (Table 3.1). Since the introduction of acrylic cement, recorded percentages vary even more: from 0% to 15%.

However, in most clinics, the proportion fluctuates around 2 to 4%, and limiting the rate of infection to just below 1% appears to be the most that can be accomplished (Tables 3.2 and 3.3).

The symptomatology of the infected prosthesis varies. Generally, a distinction is made between acute and late infections. The late infections may be further subdivided into latent and haematogenous infections (Ahberg et al., 1978). Certain German authors distinguish an early, an insidious and a late infection (Boitzy and Zimmerman, 1969; Weber and Stühmer, 1973; Reichelt and Riedl, 1974). At the Mayo Clinic (Rochester, USA), the Coventry classification is used: stage 1 (acute infection), stage 2 (latent infection) and stage 3 (haematogenous infection) (Fitzgerald et al., 1977).

3.3.1. Acute infections

Infections are called acute when they occur at an early postoperative stage. A period of three to six months has been adopted as the dividing line from late infections (Charnley, 1972; Stadler and Henche, 1976; Müller, 1976; Hunter and Dandy, 1977); others use the date of discharge from hospital (Wilson et al., 1974). Acute infections are divided into superficial and deep infections.

3.3.1.1. The acute superficial infection

The acute superficial infection manifests itself one to two weeks after the operation with wound pain, local signs of inflammation and sometimes, fever with leucocytosis as well (Wilson et al., 1973; Reichelt and Riedl, 1974; Plaue and Städler, 1975). By definition it is an infection with a suprafascial localization. However, spread to deeper tissues and to the prosthesis may be difficult to establish. An untreated superficial infection spreads, but it is believed that with adequate wound treatment the risk of a superficial infection leading to a deep infection is small. Out of 48 early postoperative superficial infections, only five were found to have led to a deep infection (Fitzgerald et al., 1977).

3.3.1.2. The acute deep infection

The acute deep infection is not very frequent and its clinical picture is influenced by the fact that these early post-operative infections are caused by relatively virulent bacteria and are associated with more local and general symptoms than the late infections of prostheses. The condition may run a fulminating course, especially with beta-haematolytic streptococci (Wilson et al., 1973) and with staphylococci (K. Buchholz, 1979).

The hip and thigh region may be slightly swollen; this is rarely accompanied by a superficial infection. The pain is felt deep in the bone. This early postoperative deep infection accounts for 12 to 50% of all postoperative infections according to the literature (Beson and Hughes, 1975; Salvati, 1976; Stadler and Henche, 1976; Amstutz and Kass, 1977; Tönnis and Händel, 1979).

3.3.2. Late infections

Inflammation with late manifestation is a so-called latent or haematogenous infection.

The latent infection allegedly differs from the haematogenous infection in that symptoms, usually pain symptoms, have been constantly present from the time of operation. In other words, there is no symptom-free interval. It is believed that the inflammation has resulted from peroperative contamination and for various reasons has run a smouldering course.

Peroperative wound contamination is a frequent occurrence. Cultures of wound material taken at the end of the operation are positive in approx 30% even of the 'clean operations' (Murray, 1973). According to some authors, wound infection results from contamination that leads to over 10³ bacteria per gramme or millilitre of tissue (Altemeier et al., 1976; Brown, 1977). Presence of a foreign body in the wound increases the risk of inflammation by weakening the local defense (Elek and Conen, 1957; Wilson et al., 1973; Plaue and Städler, 1975; Salvati, 1976). The diminished defense against infection is believed to be the reason why even the less virulent bacteria such as Staphylococcus albus and anaerobics may cause an infection in the presence of a prosthesis. However, infection caused by these less virulent bacteria is often smouldering, with a latent course. In animal experiments, Blomgren was able to infect a prosthesis in the rat using the anaerobic Propionibacterium acnes or a Staphylococcus aureus. In the anaerobic infection there were no macroscopical, micro-radiographic or histological signs of loosening to be seen after seven weeks. This was in contrast to the inflammatory reaction that was always demonstrable four weeks after an infection by Staphylococcus aureus (Blomgren, 1981).

Clinically, a latent infection manifests itself with usually mild pain, as a rule during weight-bearing. Usually, the pain symptoms are present from the operation and are progressive (Ahberg et al., 1978).

A haematogenous spread is assumed to be the cause of an infection of a prosthesis if there has been a frequently protracted–asymptomatic period after the operation. The possibility of haematogenous infection was initially doubted, but many haematogenous infections have since been described with reasonable probability in the literature, bacteriological arguments have been advanced and the possibility has been demonstrated in experiments in animals.

The proportion of total hip prostheses that become infected haematogenously is estimated in the literature at
<table>
<thead>
<tr>
<th>Author</th>
<th>Total number</th>
<th>Follow up (yr)</th>
<th>Infected number</th>
<th>Asept. loosening number</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Charnley '72 (60-61)</td>
<td>118</td>
<td>8</td>
<td>7 %</td>
<td></td>
<td>'dirty-air'</td>
</tr>
<tr>
<td>(60-67)</td>
<td>1723</td>
<td>2</td>
<td>52</td>
<td>3 %</td>
<td>59% anticoag./130 chg./h</td>
</tr>
<tr>
<td>(67)</td>
<td>329</td>
<td>4</td>
<td>4</td>
<td>1.2%</td>
<td>5% anticoag./300 chg./h</td>
</tr>
<tr>
<td>(60-68)</td>
<td>3133</td>
<td>3-11</td>
<td>1</td>
<td>1.6%</td>
<td>mixed group</td>
</tr>
<tr>
<td>(69)</td>
<td>1039</td>
<td>3</td>
<td>0.3%</td>
<td></td>
<td>+ double gloves</td>
</tr>
<tr>
<td>2. Patterson '72</td>
<td>368</td>
<td>¼-4</td>
<td>30</td>
<td>8.2%</td>
<td>9</td>
</tr>
<tr>
<td>3. Almby '73</td>
<td>106</td>
<td>?</td>
<td>2</td>
<td>2 %</td>
<td>7</td>
</tr>
<tr>
<td>4. Bentley '73</td>
<td>101</td>
<td>1-4</td>
<td>3</td>
<td>3 %</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>128</td>
<td>1-4</td>
<td>0</td>
<td>0 %</td>
<td>0</td>
</tr>
<tr>
<td>5. Bergström '73</td>
<td>207</td>
<td>½-3?</td>
<td>1</td>
<td>0.5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>77</td>
<td>½-3?</td>
<td>13</td>
<td>17 %</td>
<td></td>
</tr>
<tr>
<td>6. Buchholz '73 ('64-?)</td>
<td>3205</td>
<td>1-9?</td>
<td>74</td>
<td>2.3%</td>
<td>35</td>
</tr>
<tr>
<td>7. Caron '73</td>
<td>273</td>
<td>¼-4</td>
<td>4</td>
<td>1.5%</td>
<td></td>
</tr>
<tr>
<td>8. Chapchal '73</td>
<td>340</td>
<td>¼-4</td>
<td>0</td>
<td>0 %</td>
<td></td>
</tr>
<tr>
<td>9. Charnley '73</td>
<td>106</td>
<td>9-10</td>
<td>7</td>
<td>6.6%</td>
<td>3</td>
</tr>
<tr>
<td>10. Decoulx '73</td>
<td>574</td>
<td>1-5?</td>
<td>14</td>
<td>2.5%</td>
<td>3</td>
</tr>
<tr>
<td>11. Duparc '73</td>
<td>264</td>
<td>1-?</td>
<td>6</td>
<td>2.2%</td>
<td>14</td>
</tr>
<tr>
<td>12. Ettekar '73</td>
<td>300</td>
<td>2</td>
<td>3</td>
<td>0.4%</td>
<td>3</td>
</tr>
<tr>
<td>13. Enderle '73</td>
<td>334</td>
<td>0-5</td>
<td>6</td>
<td>1.8%</td>
<td>2</td>
</tr>
<tr>
<td>14. Ericson '73 (Carlsson '79)</td>
<td>60</td>
<td>1-1½</td>
<td>2</td>
<td>3.3%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>58</td>
<td>5-6½</td>
<td>14</td>
<td>24 %</td>
<td></td>
</tr>
<tr>
<td>15. Evanski '73</td>
<td>102</td>
<td>½-2½</td>
<td>5</td>
<td>5 %</td>
<td>1</td>
</tr>
<tr>
<td>16. Evans '73</td>
<td>200</td>
<td>2</td>
<td>3</td>
<td>1.5%</td>
<td>2</td>
</tr>
<tr>
<td>17. Freeman '73</td>
<td>339</td>
<td>½-5</td>
<td>13</td>
<td>3.6%</td>
<td>7</td>
</tr>
<tr>
<td>18. Haraldsoo '73</td>
<td>206</td>
<td>0-2½?</td>
<td>3</td>
<td>1.5%</td>
<td>5</td>
</tr>
<tr>
<td>19. Harris '73</td>
<td>127</td>
<td>½-7</td>
<td>1</td>
<td>0.8%</td>
<td>0</td>
</tr>
<tr>
<td>20. Huggler '73 ('62-65)</td>
<td>28</td>
<td>5-8</td>
<td>3</td>
<td>11 %</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>94</td>
<td>1-4</td>
<td>2</td>
<td>2.1%</td>
<td>5</td>
</tr>
<tr>
<td>21. Johnston '73</td>
<td>326</td>
<td>½-2</td>
<td>1</td>
<td>0.3%</td>
<td>2</td>
</tr>
<tr>
<td>22. Krämer '73</td>
<td>251</td>
<td>0-3?</td>
<td>4</td>
<td>1.6%</td>
<td></td>
</tr>
<tr>
<td>23. Kyselka '73</td>
<td>50</td>
<td>?</td>
<td>0</td>
<td>0 %</td>
<td></td>
</tr>
<tr>
<td>24. Langenskiöld '73</td>
<td>116</td>
<td>?</td>
<td>3</td>
<td>2.6%</td>
<td>1</td>
</tr>
<tr>
<td>25. Lazansky '73</td>
<td>501</td>
<td>½-6</td>
<td>4</td>
<td>0.8%</td>
<td>7</td>
</tr>
<tr>
<td>26. Lubinus '73</td>
<td>1350</td>
<td>1-7?</td>
<td>51</td>
<td>3.7%</td>
<td></td>
</tr>
<tr>
<td>27. Leinbach '73</td>
<td>700</td>
<td>½-4</td>
<td>7</td>
<td>1 %</td>
<td>12</td>
</tr>
<tr>
<td>28. Meuli '73</td>
<td>19</td>
<td>?</td>
<td>0</td>
<td>0 %</td>
<td>2</td>
</tr>
<tr>
<td>29. McKee '73 (56-60)</td>
<td>16</td>
<td>7</td>
<td>0</td>
<td>0 %</td>
<td></td>
</tr>
<tr>
<td>('61-64)</td>
<td>100</td>
<td>8</td>
<td>2</td>
<td>2 %</td>
<td></td>
</tr>
<tr>
<td>('65-69)</td>
<td>300</td>
<td>?</td>
<td>12</td>
<td>4 %</td>
<td>24</td>
</tr>
<tr>
<td>('71-69)</td>
<td>100</td>
<td>?</td>
<td>0</td>
<td>0 %</td>
<td></td>
</tr>
<tr>
<td>30. Moczynsky '73</td>
<td>250</td>
<td>½-4?</td>
<td>23</td>
<td>9.7%</td>
<td>4</td>
</tr>
<tr>
<td>31. Müllert '73</td>
<td>175</td>
<td>?</td>
<td>17</td>
<td>10 %</td>
<td></td>
</tr>
<tr>
<td>32. Murray '73</td>
<td>106</td>
<td>¼-4</td>
<td>3</td>
<td>1.9%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>522</td>
<td>¼-4</td>
<td>4</td>
<td>0.8%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>126</td>
<td>¼-4</td>
<td>5</td>
<td>4 %</td>
<td></td>
</tr>
<tr>
<td>33. Safi '73</td>
<td>187</td>
<td>2-8</td>
<td>13</td>
<td>6 %</td>
<td>3</td>
</tr>
<tr>
<td>34. Siegel '73 (64-68)</td>
<td>1409</td>
<td>5-9</td>
<td>44</td>
<td>3.1%</td>
<td></td>
</tr>
<tr>
<td>('69-71)</td>
<td>2609</td>
<td>2-4</td>
<td>21</td>
<td>0.8%</td>
<td></td>
</tr>
<tr>
<td>35. Slot '73</td>
<td>100</td>
<td>1-3</td>
<td>2</td>
<td>2 %</td>
<td>1</td>
</tr>
<tr>
<td>36. Smith et al. '73</td>
<td>3482</td>
<td>¼-2?</td>
<td>58</td>
<td>1.7%</td>
<td>10</td>
</tr>
<tr>
<td>37. Torgerson '73</td>
<td>139</td>
<td>½-3</td>
<td>4?</td>
<td>2.9%</td>
<td>1</td>
</tr>
<tr>
<td>38. Weber '73 ('67)</td>
<td>177</td>
<td>?</td>
<td>12</td>
<td>6.8%</td>
<td></td>
</tr>
<tr>
<td>(Liechti '76) ('70)</td>
<td>243</td>
<td>?</td>
<td>4</td>
<td>1.7%</td>
<td></td>
</tr>
<tr>
<td>('71)</td>
<td>215</td>
<td>?</td>
<td>2</td>
<td>0.9%</td>
<td></td>
</tr>
<tr>
<td>39. Weber et al. '73</td>
<td>1042</td>
<td>1-5</td>
<td>37</td>
<td>3.6%</td>
<td></td>
</tr>
<tr>
<td>40. Wilson '73</td>
<td>100</td>
<td>1½-9</td>
<td>1</td>
<td>1 %</td>
<td>20</td>
</tr>
<tr>
<td>41. Deutman '74</td>
<td>213</td>
<td>0-5</td>
<td>5</td>
<td>2.3%</td>
<td>32</td>
</tr>
<tr>
<td>42. Benson '75</td>
<td>321</td>
<td>¼-5</td>
<td>17</td>
<td>5.3%</td>
<td></td>
</tr>
<tr>
<td>43. Ganz '76</td>
<td>2424</td>
<td>?-2</td>
<td>52</td>
<td>2.1%</td>
<td>230</td>
</tr>
<tr>
<td>44. Gartenmann '76</td>
<td>198</td>
<td>½-1½</td>
<td>0</td>
<td>0 %</td>
<td></td>
</tr>
</tbody>
</table>

Asept. loosening: proph. AB + local AB

idem + after '71 AB-cement

no antibiotics

no antibiotics

AB-cement
Table 3.2  
Review of literature data on percentages of infection of cemented total hip prostheses  Percentages of aseptic loosening, where mentioned in the papers, have been included.

<table>
<thead>
<tr>
<th>Author</th>
<th>Total number</th>
<th>Follow up yr.</th>
<th>Infected %</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petty '75</td>
<td>1045</td>
<td>1-4</td>
<td>2.0%</td>
<td>geometric + polycentric</td>
</tr>
<tr>
<td>Deburge '77</td>
<td>292</td>
<td>?</td>
<td>6%</td>
<td>guepar</td>
</tr>
<tr>
<td>Attenborough '78</td>
<td>221</td>
<td>1-2</td>
<td>1.8%</td>
<td>attenborough</td>
</tr>
<tr>
<td>Aubnot '81</td>
<td>183</td>
<td>1-7</td>
<td>8.3%</td>
<td>guepar</td>
</tr>
<tr>
<td>Cavendish '78</td>
<td>62</td>
<td>?</td>
<td>1.6%</td>
<td>liverpool Mark II</td>
</tr>
<tr>
<td>Lettin '78</td>
<td>100</td>
<td>2-9</td>
<td>3%</td>
<td>stanmore</td>
</tr>
<tr>
<td>Shaw '78</td>
<td>48</td>
<td>?</td>
<td>2%</td>
<td>manchester</td>
</tr>
<tr>
<td>Sheenan '78</td>
<td>135</td>
<td>1-5½</td>
<td>1.5%</td>
<td>sheehan</td>
</tr>
<tr>
<td>Andersen '79</td>
<td>67</td>
<td>?</td>
<td>0%</td>
<td>Mclntosh (42 without cement)</td>
</tr>
<tr>
<td></td>
<td>64</td>
<td>?</td>
<td>15%</td>
<td>guepar, proph. AB</td>
</tr>
<tr>
<td></td>
<td>109</td>
<td>?</td>
<td>2%</td>
<td>marmor, proph. AB</td>
</tr>
<tr>
<td>Cracchiolo '79</td>
<td>211</td>
<td>2-?</td>
<td>2.4%</td>
<td>geometric, polycentric</td>
</tr>
<tr>
<td>Finerman '79</td>
<td>112</td>
<td>1-?</td>
<td>0.9%</td>
<td>anametric</td>
</tr>
<tr>
<td>Insall '79a</td>
<td>220</td>
<td>3-5</td>
<td>1.4%</td>
<td>total condylar</td>
</tr>
<tr>
<td>Insall '79b</td>
<td>461</td>
<td>1-5</td>
<td>1.3%</td>
<td>total condylar</td>
</tr>
<tr>
<td>Kaufer '79</td>
<td>134</td>
<td>1-?</td>
<td>2.2%</td>
<td>spherocentric</td>
</tr>
<tr>
<td>Larsson '79a+b</td>
<td>112</td>
<td>2-?</td>
<td>4%</td>
<td>rheum. arthrits; guepar + geomed</td>
</tr>
<tr>
<td></td>
<td>111</td>
<td>2-?</td>
<td>5%</td>
<td>gonarthrosis, guepar/geomed /st. Georg</td>
</tr>
<tr>
<td>Moreland '79</td>
<td>84</td>
<td>½-2</td>
<td>5%</td>
<td>freeman-swanson</td>
</tr>
</tbody>
</table>

Table 3.3  
Review of literature data on percentages of infection of cemented total knee prostheses

0.3 to 0.5% (Charnley, 1972b; Hunter and Dandy, 1977b; Lidgren et al., 1977; Ahlberg et al., 1978; Lindberg, 1979b)

Ahlberg et al. have collected 19 well-documented cases from the literature and added eight of their own. Blomgren supplements the literature to 61 haemato-genously infected total hip prostheses (Blomgren, 1981). Three other authors have presented data on 14 additional patients, bringing the total to 75 documented cases (Deutman, 1974; Beck, 1977; Hunter and Dandy, 1977a).

Rheumatic patients are believed to run an increased risk of bacteraemia allegedly, spontaneous bacteraemias occur more often in these patients and cause spontaneous arthritis. Also, defense is often weakened due to hypocomplementaemia (Charnley, 1972b; Cristina et al, 1974; del Sel and Charnley, 1979; Fitzgerald et al., 1977); others, however, find no increased risk of infection in rheumatic patients (Lidgren, 1973).

Another important cause of bacteraemia is post-operative catheterization of the bladder, usually performed because of retention of urine in the bladder. Wroblowski...
and del Sel observed a deep infection in 6.2% of 195 patients requiring postoperative catheterization, as against 0.5% in their material as a whole (Wroblewski and del Sel, 1980).

Charnley uttered doubt whether haematogenous infection exists, probably to emphasize the role of peroperative contamination, and reports 31 instances of successful implantation of a total hip prosthesis while an infection was present in the contralateral hip (del Sel and Charnley, 1979). Hunter and Dandy, on the other hand, did observe a haematogenous infection in such a patient (Hunter and Dandy, 1977).

Finally, haematogenous infection appears probable in case of bilateral total hip infection, caused by one and the same agent (Downes, 1977; Hunter and Dandy, 1977).

Furthermore, several investigators succeeded in infecting an endoprosthesys by injecting bacteria into the blood circulation. Elson (Elson et al., 1977) and Marks (1980) observed that haematogenous infections occurred more frequently when the injection was given shortly after the operation. This was confirmed by Blomgren (Blomgren and Lindgren, 1980). He observed that bacteraemias shortly after operation infected a cemented endoprosthesys as often as they infected a cement implant without prosthesis or other injured tissue (e.g. the surgical wound). A cement implant prevented elimination of bacteria by local defense (Blomgren and Lindgren, 1980; Blomgren, 1981). In Blomgren's experiment, in contrast to studies of Elson and of Marks, the prosthesis was made to bear weight physiologically. This resulted in a thicker layer of bone cement granulation beside the prosthesis, which is more realistic. A larger proportion of infections is believed to occur in this thicker interface.

Staphylococcus aureus and the anaerobic bacterium P. acnes caused infection in about the same proportions of the cases (Blomgren, 1981). For therapeutic aspects of this investigation, the reader is referred to paragraph 4.4.

### 3.4. Diagnosis

Just as in osteomyelitis, making the diagnosis of 'infection' is less difficult in acute forms than in a latent infection. However, a major difficulty in endoprosthesys is to establish how far the infection extends, in view of the considerable implications of the diagnosis of 'infection'. Just as in chronic osteomyelitis, the diagnosis is difficult in latent, inactive infection because the symptoms are aspecific. In this instance, also, more objective parameters are needed.

#### 3.4.1. Symptoms

If there is pain after implantation of a prosthesis (especially a total hip prosthesis), the possibility of an infection should be seriously considered (Lazanski, 1970; Fremont-Smith, 1974; Salvati, 1976; Hunter and Dandy, 1977; Amstutz and Kass, 1977). A hip prosthesis should be painless postoperatively (Salvati et al., 1971; Salvati, 1976; Beek, 1977; Ahlberg et al., 1978). Pain occurs predominantly when weight is put on the hip prosthesis (Fitzgerald et al., 1977).
Passive movements of the hip are painful, especially endorotation (Bösch et al., 1980), active movements cause even more pain (P. D. Wilson, 1974). As a rule, there is no local painful palpitation. In severe infection, there is also pain at rest. In general, the pain postoperatively gradually grows worse (Lazanski, 1970).

Other symptoms occur only if the infection flares up. It is only in that case that symptoms such as fever, local swelling and other signs of infection occur, and sometimes a sinus develops. In the latent infection, these infection symptoms are absent and the pain in inflammations is aspecific. The same pain is felt in aseptic loosening. Fever is absent or subfebrile (Wilson et al., 1973; Fitzgerald et al., 1977). The symptoms may be suppressed by antibiotics. Some diagnostic significance might be attributed to this, which the literature, however, fails to mention.

3.4.2 Laboratory
After every uncomplicated operation, the BSR gradually falls to the normal preoperative value. This decrease is linear on a semi-logarithmic scale (Härle, 1979) (Fig. 2.5). After a total hip implantation, the BSR decreases to normal within a few months. Mulier et al. among 147 patients saw normalization after one month in 19 % of the patients, after two months in 73 % and after four months in 93 % (Mulier et al., 1973). Forster and Crawford observed that after total hip implantation normalization occurs after six months, that patients with infected prostheses virtually always have a BSR in excess of 20 mm in the first hour and that in aseptic loosening of the prosthesis, the BSR after six months is usually below 20 mm (Forster and Crawford, 1980). If the BSR remains high postoperatively, this strongly suggests a deep infection, and if a high BSR is observed in cases in which no continuous recording has been possible from the time of operation, a BSR higher than 30 to 40 ml in the first hour is also strongly suggestive of infection (Eftekhar et al., 1973; Breitenfelder and Spranger, 1973; Fremont-Smith, 1974; Wilson, 1974; Benson and Hughes, 1975; Stadler and Henche, 1976; Eftekhar, 1977; Lidgren et al., 1977; Suezawa and Dietschi, 1977; Hunter and Dandy, 1977a and 1977b; Fitzgerald et al., 1977; Carlsson, 1978; Wilson et al., 1978; Hughes et al., 1979; Lindberg, 1979a, Kamme and Lindberg, 1981).

No leukocytosis is ever observed in the absence of acute, systemic symptoms of illness (Eftekhar et al., 1973; Mulier et al., 1973; Wilson et al., 1973; Fremont-Smith, 1974; Fitzgerald et al., 1977; Lindberg, 1979a).

3.4.3 Histological diagnosis
Examination of tissue of the vicinity of the infected prosthesis includes counting of the number of polymorphonuclear leukocytes per square. A large number per square (more than 5 or 2-3+) would constitute a reliable diagnostic criterion for the distinction between septic and aseptic loosening (Wilson et al., 1973; Mirra et al., 1976; Amstutz and Kass, 1977). Eftekhar pays particular attention to the quality of the polymorphonuclear cells (mostly neutrophils): lysosomal activity should be visible. Salvati also studies the polymorphonuclear leukocytes in the aspirate: if there are over 10,000 per ml, and over 25 % in a differentiation, this is highly suggestive of infection (Salvati, 1976). A normal amount of attrition particles allegedly evokes no polymorphonuclear leukocyte response (Mirra et al., 1976).

3.4.4 Roentgenology
In an infection around a prosthesis, no roentgenological abnormalities are visible during the first six weeks. As a rule it takes three to six months for the infection to be recognized in the radiograph (Eftekhar, 1977). The plain radiographs show osteolytic foci along the cement with scalloping of the cortex. Lytic foci can be discerned in the cortex as well; sometimes there is a periosteal reaction, sometimes diffuse irregular cortical thickening and sclerosis (Lazanski, 1970; Eftekhar et al., 1973; Wilson et al., 1973; Benson and Hughes, 1975; Eftekhar, 1977; Dussault et al., 1977). In addition, around the hip joint there is sometimes an osteoporosis that is much more marked than in the contralateral joint, because the pain leads to reduced weight-bearing and consequently to disuse atrophy of the skeleton (Wilson et al., 1973; Enneking, 1981).

The loosening of the prosthesis is revealed by an increasingly broad halo around the cement and sometimes, by dislocation of the prosthesis. Resorption of the calcar also frequently occurs in an uncomplicated total hip prosthesis (Charnley and Cupic, 1973); it is probably due to disuse atrophy (Oh, 1977): the layer of cement presumably causes the stress of weight-bearing to bypass the calcar. In infection, however, the resorption of the calcar is said to be more irregular (Benson and Hughes, 1975).

Mobility of a loosened prosthesis may be demonstrated by X-rays in abduction and adduction, revealing a 'windshield-wiper phenomenon'. Radiographs made under traction may also sometimes show loosening (Deyerle, 1967; Slooff, 1970). Selvik's technique of roentgen stereophotogrammetry may in the future become important for a more exact diagnosis of loosening of prostheses, since it allows more exact demonstration of minute displacement (Selvik, 1974; Van Dijk et al., 1979; Egund et al., 1981; Hanson et al., 1981).

Fistulography supplies information on the course of the sinus tract and fills any abscesses as well. Mostly, it will show contact with the prosthesis (Benson and Hughes, 1975). However, it is not always possible to inject the sinus with adequate pressure; negative findings should be interpreted cautiously.

Evaluations of arthrography differ. Some papers emphasize the useful information it may provide, others deny that it contributes to the diagnosis (Table 3.4). Salvati et al. (1971) among 31 arthrograms of the hip saw only one false-negative and no false-positive arthrograms. Murray and Rodrigo (1975) performed arthrography in 25 painful and 53 asymptomatic hip prostheses. Of the asymptomatic prostheses, 22.6 % proved to have a loosened acetabular cup, as against 0 % of the femoral prostheses. In the group of painful prostheses, 44 % showed loosening. Twelve patients of the symptomatic group were operated: in seven cases, the positive arthrogram as confirmed by macroscopical loosening of the cup. In three patients with a positive arthrogram, this finding was not confirmed at operation, while in three cases with negative arthrograms, operation nevertheless revealed loosening. To sum up: seven correctly positive, three false-positive and two false-negative findings. The authors conclude that loosening is not necessarily painful and that loosening revealed by arthrography is too often not observable at operation (three out of 10 patients). They also conclude that loosening is not more frequent among painful than among asymptomatic hip prostheses.
Dussault et al (1977) found a positive correlation between arthrographic and surgical findings in 19 out of 21 patients (90%). Failure of contrast medium to penetrate between the prosthesis and the bone, however, did not exclude loosening in five out of 25 patients. Suezawa and Dietschi (1977) found a positive correlation of arthrographic and surgical findings in 81% on the acetabular and in 70% on the femoral side.

In contradiction to Fremont-Smith (1974), Amstutz and Kess (1977) and Beck (1977), Lindberg considers arthrography to be of little value out of 20 arthrograms, he found only 20% to be relevant. In his opinion, arthrograms are often difficult to interpret (Lindberg et al., 1977a, Lindberg, 1979) (Table 3.4).

### ARTHROGRAPHY

<table>
<thead>
<tr>
<th>Author</th>
<th>Valuable</th>
<th>Not valuable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fremont-Smith '74</td>
<td>Murray '75</td>
<td></td>
</tr>
<tr>
<td>Salvati '76</td>
<td>Lindbergh '79</td>
<td></td>
</tr>
<tr>
<td>Amstutz '77</td>
<td>Beck '77</td>
<td></td>
</tr>
<tr>
<td>Beck '77</td>
<td>Dussault '77</td>
<td></td>
</tr>
<tr>
<td>Suezawa '77</td>
<td>Turner '79</td>
<td></td>
</tr>
</tbody>
</table>

Table 3.4 Various authors' opinions of arthrography as an aid in the diagnosis of a loose prosthesis

The subtraction technique is said to enhance the quality of the arthrogram (Salvati et al., 1974, Turner, 1979). It requires optimal immobilization of the patient. In addition, the arthrography should be carried out under strict aseptic conditions and intensifying-screen control. Simultaneously with the arthrography, aspiration is carried out for bacteriological examination. According to some authors (Salvati, 1976, Beck, 1977), excessive injection pressure may cause sepsicaemia, just as in fistulography. The value of fistulography, arthrography and aspiration might be increased by taking into account only positive findings, and considering negative findings not to exclude loosening or infection.

**Tomography** may be useful for the detection of slight lytic lesions that are masked in standard radiographs.

**Computed tomography** affords good insight in the interrelationships of the stem of the prosthesis, the bone cement and the cortex. Beck (1977) found that the metal caused too much disturbance, eliminating the contrast between cement and bone. In his material, only pronounced loosening was visible. A modified technique eliminates this disturbance (Dietschi et al., 1979) and reveals the interrelationship clearly. However, owing to the low resolving capacity of computed tomography (approx. 1.5 mm), small cracks in the cement are not shown up.

### 3.4.5 Scintigraphy

The scan makes a useful contribution to the diagnosis of loosening. So far, however, it inadequately allows the differentiation of infection and aseptic loosening.

Just as in osteomyelitis (see Chapter 2.4.5), the $^{99m}$Tc-MDP scan in infection of an endoprosthesis also shows heightened activity over areas with increased vascularization and increased osteogenesis (Galasko, 1977, Davies and Galasko, 1977, Lindberg et al., 1977, Hughes et al., 1978, Khan et al., 1979, Reing et al., 1979, Pearlman A W., 1980). Presence of enough sound bone is a condition of exchange of the radionuclide material (Hughes, 1980).

During an uncomplicated postoperative course after implantation of a hip prosthesis, the scan is positive due to local bone remodelling. When no complications occur, the scan returns to normal after a length of time that varies depending on the isotope used (see Table 3.5).

### SCAN

<table>
<thead>
<tr>
<th>Author</th>
<th>Isotope</th>
<th>Normal after</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bauer '73</td>
<td>$^{85}$Sr</td>
<td>3-10 months</td>
</tr>
<tr>
<td>Wegmann '75</td>
<td>$^{99m}$Tc</td>
<td>3 months</td>
</tr>
<tr>
<td>Feth '76</td>
<td>$^{87m}$Sr</td>
<td>4,3 months</td>
</tr>
<tr>
<td>Tregonning '76</td>
<td>$^{99m}$Tc</td>
<td>9 months</td>
</tr>
<tr>
<td>Lindbergh et al '77</td>
<td>$^{85}$Sr</td>
<td>1-3 years</td>
</tr>
</tbody>
</table>

Table 3.5 Review of literature data on duration of the interval before the scan returns to normal after uncomplicated implantation of an endoprosthesis. Before the end of this period of normalization, scintigraphy is useless for the diagnosis in case of a painful prosthesis
et al., 1979), but in the opinion of Browett et al. (1980), this is just a matter of inadequate documentation.

In gallium scanning, $^{67}$gallium citrate is used. Allegedly, a scan is influenced by increased vascularization, by the protein binding of the gallium and particularly by the binding of gallium to leukocytes (Staab and McCartney, 1978; Re'ing et al., 1979). In that case, the positive scan is caused by migration of the leukocytes to the inflamed area (Staab and McCartney, 1978). However, this migration of leukocytes is diminished under the influence of antibiotic treatment and similarly, a mild inflammation of low virulence, eliciting little reaction, causes a false-negative gallium scan (Re'ing et al., 1979). Blomgren (1981), experimenting in animals, examined five haematogenously caused infections of prostheses and observed a positive gallium scan in three of them. Two scans were false-negative.

Rushton et al. (1982), examining 51 patients with a painful hip prosthesis and 34 control patients, found that the technetium scan ($\text{Tc}^{99m}$-MDP) in combination with the gallium scan did permit accurate distinction between aseptic and septic loosening of the prostheses. In their opinion, a diffuse—in contradistinction to a focal—increase of the uptake in the technetium scan is indicative of an infection. In the 19 infected hip prostheses, the gallium scan was always positive. The value of these findings is reduced by the incomplete data on the bacteriological diagnosis.

For the Indium scan, autologous leukocytes are linked to $^{111}$indium oxinate (Röverkamp et al., 1980) and then re-injected. Since this scan, also, depends on leukocytary activity, it may give a false-negative result in latent infections for the same reasons as the gallium scan does. To recapitulate, at the present stage in case of a painful hip prosthesis, it is advisable first to make a Tc scan. If this is negative, the diagnosis of loosening should be abandoned. If it is positive, the next step should be a $^{57}$rhenium scan which shows good correlation with loosening. For the moment, the scans still appear to offer insufficient aid in the distinction between septic and aseptic loosening.

### 3.5. Bacteriology

#### 3.5.1. Introduction

Just as in osteomyelitis, the bacteriological diagnosis is of great importance in the loosened and the infected prosthesis. That which has been stated in Chapter 2.5 applies equally to the infected prostheses: the relative value of cultures from the sinus tract, the importance of anaerobics and the unknown role of cell wall-deficient bacteria.

Where endoprostheses are concerned, correct techniques of bacteriological diagnosis and correct interpretation of the findings of the bacteriological laboratory are of paramount importance. If, namely, an infection is left untreated because the diagnosis of infection has not been made, rapidly progressive loss of bone will occur. If an endoprosthesis is reimplanted without treatment of the—undiagnosed— infection, reinfection is almost certain to occur.

The recorded percentages of aseptic loosening, which rise to considerable values with the passage of years after implantation of the prosthesis (Witt and Hackenbroch, 1976), might be much lower given correct bacteriological diagnosis. Hunter (Hunter et al., 1979) and Buchholz (Buchholz et al., 1981) are of the opinion that ‘sterile’ loosening is often caused by bacteria even though these are not cultured. Lindberg asserts that in several clinics there have been virtually no observations of aseptic loosening since anaerobic culturing was also carried out. He gives no figures or percentages, however (Lindberg et al., 1977a).

In the study of the problem of loosening of prostheses, where extensive biomechanical research has already solved many mechanical problems, bacteriological examination should also be given more attention, certainly more than it is receiving at present.

#### 3.5.2. Gram preparation

The gram preparation is a useful diagnostic aid according to Eftekar et al. (1973). Others, however, find insufficient correlation with the subsequent culture findings (Hughes et al., 1979). Suezawa and Dietschi found that out of 26 infected hip prostheses, only two had given a positive operative gram preparation. Furthermore, out of 15 positive gram preparations, 11 were subsequently found to be negative after all (Suezawa and Dietschi, 1977).

#### 3.5.3. Cultures

Material for culturing may be collected in two ways: puncture aspiration and open biopsy.

Aspiration by puncturing is best done under image-intensifying control. The puncturing should be performed strictly aseptically, preferably in an operating room (Fitzgerald et al., 1977). The material should be cultured aerobically and anaerobically and arthrography may be carried out at the same time. If the culture is negative but the suspicion of infection is strong, it may be necessary to repeat the aspiration or even to perform an open biopsy (Wilson, 1974; Patel et al., 1976; Hewitt, 1977). If no material can be aspirated, a few ml Ringer’s solution may be injected and re-aspirated (Wilson et al., 1973; Buchholz, 1979). At the same time, a needle biopsy may be taken from the peri-articular tissue, for microscopical examination (Buchholz et al., 1979). Patel and others considered aspiration a useful examination where sepsis was present and a hip infection suspected. After 127 punctures, which included hips not previously operated upon, they saw 26 false-positive results due to contamination, mostly Staphylococcus albus, diphtheroids or streptococci. The contamination could be traced by quantitative bacteriological examination with ‘pour plate’ culturing (Patel et al., 1976) (Table 3.6).

<table>
<thead>
<tr>
<th>Author</th>
<th>Total N</th>
<th>Good</th>
<th>False</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fremont-Smith '74</td>
<td>34</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Patel '76</td>
<td>127</td>
<td>9</td>
<td>26</td>
</tr>
<tr>
<td>P.W. Hughes '78</td>
<td>36</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>M.R. Wilson '78</td>
<td>16</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Buchholz et al. '79</td>
<td>205</td>
<td>151</td>
<td>35 14</td>
</tr>
<tr>
<td>Nelson '80</td>
<td>9</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

Table 3.6 Correlation between the bacteriological findings in aspirated material and the findings at operation according to several authors.
Fremont-Smith (1974) after 34 aspirations encountered 20% false-negative results and no false-positive cultures. It should be noted that of the 23 positive cultures, four were found only in the subculture, after 48 hours. Buchholz found that of the culture results after 205 aspirations, 73% were confirmed at operation. There was a relatively large number of false-negative cultures (35 out of 205 aspirations) (Buchholz et al., 1979).

The peroperative culture may be false-positive or false-negative due to several causes (Table 3.7).

### PEROP. SAMPLES

<table>
<thead>
<tr>
<th>False-positive</th>
<th>False-negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>contamination during operation</td>
<td>preop. antibiotic therapy</td>
</tr>
<tr>
<td>contamination in laboratory</td>
<td>wrong transport media</td>
</tr>
<tr>
<td>sample from fistula</td>
<td>transport too slow</td>
</tr>
<tr>
<td>no multiple samples</td>
<td>judged too early in labor.</td>
</tr>
</tbody>
</table>

Table 3.7 Causes of false-positive or false-negative results of cultures of material collected at operation.

A false-positive culture may result from contamination at operation or in the laboratory. Cultures from ‘clean’ surgical wounds, collected at the end of the operation, are positive in one-third of the cases (Ritter and Stringer, 1981). Murray prepared cultures from 740 capsules at primary implantation of a total hip. Of these cultures, 233 were positive. However, there was no correlation at all with postoperative infection of these prostheses (Murray, 1973, 1974). Fitzgerald saw 23% positive cultures after primary total hip implantation, but only 2 to 3% of the implanted prostheses became infected (Fitzgerald et al., 1973).

Suzawa and Dietschi (1977) observed that the bacteriological diagnosis that had been made pre- and peroperatively (aspiration and preparation, respectively) in 158 cases, subsequently was found to have been incorrect in 15.5% of the cases. Kamme and Lindberg (1981), studying 63 infected prostheses and a control group of 33 hips operated earlier, also found contamination in one-third of the cases. The contamination was not reduced by antibiotics administered preoperatively. Lindberg found 38 contaminations among 319 peroperative biopsies (Lindberg, 1979a). However, when multiple biopsies were taken at operation, contamination was never found in more than three of them. Accordingly, he recommends taking five or six different biopsies for culturing, of tissue adjacent to the cement, for detection of the contaminants: he only regards the hip prosthesis as infected if at least four to five of the biopsies are positive and contain the same causative organism (Lindberg, 1976; Lindberg et al., 1977a; Lindberg, 1979a; Carlson et al., 1978). Ritter and Stringer, also, failed to find a correlation between a positive capsule culture at implantation and subsequent inflammation of the hip prosthesis. They did observe a relationship, on the other hand, if two cultures of material collected at implantation were both positive. Of patients with two positive cultures, 32% developed a postoperative wound problem and 24%, an infection of the hip prosthesis (Ritter and Stringer, 1981).

The above studies justify the conclusion that the role of the contaminant in culturing can be made clear by taking several samples for culturing. Faulty collection techniques increase the degree of contamination. The risk of contamination is minimal if the sample is taken at an early stage of the operation, tissue (biopsies) is examined and every sample is collected with a new, sterile instrument. Contamination by sinus material should be avoided. False-positivity of cultures may also occur in a bacteriological laboratory due to contamination during the processing of the material. Murray sterilized 100 capsules of hips before submitting them. Ten positive culture results were reported for this material (Murray, 1973).

A false-negative result may be due to a number of causes. Delicate bacteria demand much of transport media, transportation speed and laboratory technique. Previously unrecognized anaerobic causative agents exemplify this. Any cell wall-deficient bacteria that may be present necessitate special culturing techniques (10% sucrose). Antibiotics administered pre-operatively increase the risk of false-negative cultures: for this reason, antibiotics should only be administered after collection of the last sample for culturing. Kamme and Lindberg (1981) even recommend cessation of antibiotic treatment six weeks prior to operation.

Since some bacteria grow more slowly than others, the laboratory should not be rash in deciding that there is no growth.

M. E. Müller in two-thirds of the cases of late infections found a Staphylococcus albus or anaerobics and regards these as non-pathogenic (Müller, 1976). Wilson mentions that the coagulase-negative staphylococcus has long been regarded as non-pathogenic (Wilson et al., 1974). However, in neurosurgery and cardiovascular surgery, and later in orthopaedics as well, it has become clear that in the presence of implants these bacteria, also, are pathogenic. For this reason it is incorrect to regard a culture result with Staphylococcus epidermidis or anaerobics as negative.

#### 3.5.4 Causative organism

Infection of a prosthesis is most often caused by a Staphylococcus aureus. Second in the order of frequency is usually Staphylococcus albus (see Table 3.8). Third in the order of frequency is the group of the gram-negative bacteria but this group is nevertheless important in view of the virulent character of the infection. Occasionally, mixed floras are cultured: probably, these originate mostly from sinus material (see Chapter 2.5). They contain as many gram-positive as gram-negative organisms. The percentage of gram-negative infections has grown with the passage of years (Wilson et al., 1973), possibly due to increased prophylactic use of antibiotics (Salvati, 1976).

Anaerobics occur in the intestinal content in large numbers, some 1000 times more than coliform organisms. The skin around the hip as a rule is greatly contaminated by anaerobics (Nobles, 1973; Launder and Hungerford, 1981). The blood circulation also often contains anaerobic bacteria, suggesting the possibility of a haematogenous infection of the prosthesis (Lodenkämper and Stienen, 1955; Lodenkämper, 1969; Stinchfield et al., 1980). According to

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3.6. Treatment

In regard to the treatment of the infected endoprosthesis, important questions are whether an acute or a late postoperative infection is involved, and whether the infection is superficial or deep-seated.

### 3.6.1. Superficial infection

The superficial infection may be regarded as a wound infection and treated as such. Efficacious antibiotic therapy, preferably preceded by identification of the causative organism. The treatment should include adequate relief of haematomas and abscesses (Wilson et al., 1973). If the extent of the process is uncertain, this intervention should preferably be performed as a surgical procedure. Letournel after debridement carries out thorough lavage of the superficial infected area, then uses another set of instruments to inspect the deeper articular region. However, assessment with the naked eye is always uncertain (Letournel, 1969). Examination of a frozen section with a count of the polymorphonuclear leukocytes may provide better information (Amstutz et al., 1977, see paragraph 3.4.3). Beck asserts that conservative treatment of a subcutaneous infection will undoubtedly lead to a deep infection, and describes three cases of this nature. In four other patients, the prosthesis could be saved by rapid wound revision and subcutaneous suction drainage (Beck, 1977).

#### 3.6.2. Acute deep infection

Letournel treats the deep, acute infection at an early stage:  
"réponse précoce" (early reoperation) for "infection précoce" (early infection). Before the operation, however, he allows four to eight days for antibiotic treatment. This should cause the acute signs of infection to disappear. During this preoperative period, the would is repeatedly relieved by puncturing, or a few sutures are removed. He has never observed these few days of postponement to lead to septicemia or spread of the infection. The antibiotics should restrict the infection so that at operation infected tissue can be removed as a whole with a margin of sound tissue. At operation, the scar is resected en bloc and the subsequent operation is time-consuming and gory and requires a good deal of patience and persistence (Letournel, 1969).

At operation, the femoral prosthesis may be temporarily removed to be reimplanted after sterilization (Wilson et al., 1973). After thorough debridement, primary closure of the wound may be performed, a drainage system being left in situ (Weber and Stuhmer, 1973, Wilson et al., 1973; Muller M.E., 1976; Amstutz et al., 1977).

Eftekhar when gram-negative infection occurs leaves the entire wound open (Eftekhar, 1977). Others allow the
Aggressive surgical treatment is reported by several authors. Wilson advises, when drainage is used, to instill 125 ml per hour and to change in- and outlet drains In case of insufficient flow, the drains are withdrawn after preliminary suction (Amstutz et al., 1977). Wilson reduces the duration of suction drainage as much as possible, to four to a maximum of 10 days. He is afraid of superinfection (Wilson et al., 1973).

Antibiotics should be administered intravenously for six to eight weeks and orally for three to six months. Muller M E., 1974, Salvati, 1976, Amstutz and Kass, 1977, Eftekhar, 1977, Hunter and Dandy, 1977) Early, aggressive surgical treatment is reported by several authors to have given good results (Table 3 9) Reichelt and Riedl in 15 early deep infections could leave the prosthesis in situ only four times, but they arrive at the same conclusion early revision (Reichelt and Riedl, 1974).

### Table 3 9  Results of treatment of acute early postoperative deep infections as reported by six authors

<table>
<thead>
<tr>
<th>Author</th>
<th>Total N</th>
<th>Healed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letournel '69</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Henke '73</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Muller '74</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Coventry '74</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Nolan '75</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Amstutz '77</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>43</td>
<td>35</td>
</tr>
</tbody>
</table>

(100%) (81%)

### Table 3 10  Scheme of the various methods of treatment possible in an infected total hip prosthesis. No reference is made to the degree of efficacy of the various techniques

<table>
<thead>
<tr>
<th>CONSERVATIVE</th>
<th>SURGICAL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>antibiotics</strong></td>
<td><strong>prosthesis</strong></td>
</tr>
<tr>
<td><strong>IN SITU</strong></td>
<td><strong>REMOVAL</strong></td>
</tr>
<tr>
<td>REIMPLANTATION</td>
<td>‘GIRDLESTONE’</td>
</tr>
<tr>
<td><strong>ONE-STAGE</strong></td>
<td><strong>TWO-STAGE</strong></td>
</tr>
<tr>
<td>without AB</td>
<td>short period weeks</td>
</tr>
<tr>
<td>AB-cement</td>
<td>(treatment)</td>
</tr>
<tr>
<td>syst AB+/ AB cement</td>
<td>long period months</td>
</tr>
<tr>
<td>(control healing)</td>
<td></td>
</tr>
</tbody>
</table>

3.6.3 Late deep infection

In the treatment of late infection of the prosthesis, no distinction is made between latent and haematogenous infection of the prosthesis. Occasionally, the late infection manifests itself during an exacerbation with acute signs and symptoms. These acute late postoperative infections not rarely run a fatal course and require prompt treatment, as discussed in paragraph 3.6.2. The usual manifestation form of the late infection is less acute. Highly divergent methods of treatment have been described. The treatment may be conservative or surgical. At operation, the prosthesis may be left in situ or removed, in which case reimplantation may be carried out immediately or later (Table 3 10).

3.6.3.1 Conservative treatment

If the patient's life expectancy is limited, or surgery is refused, conservative treatment is indicated (Plaue and Stadtler, 1975). The aim of the treatment is then to relieve the symptoms and to prevent spread of the infection. Relief of pain may be accomplished by the use of crutches. If there is a sinus, it may be irrigated to keep the sinus tract open, but thorough bandaging is necessary to prevent superinfection. Accrual of the infection may be combated for a time with antibiotics. However, antibiotics by themselves can never cure an infection (Plaue and Stadtler, 1975, Salvati, 1976, Hunter and Dandy, 1977). Some patients require a maintenance treatment with antibiotics for the rest of their lives.

Muller proposes to treat the fistulizing, infected prosthesis with antibiotics for three to 12 months, both orally and locally through the sinus tract. This often suppresses the inflammatory phenomena for one to two years, so that time is gained (Muller M E., 1974). Similarly, Hunter and Dandy recommend conservative treatment as long as the wound is dry and the pain, relieved by analgetics and antibiotics, remains bearable (Hunter and Dandy, 1977). Eftekhar states that not every infected prosthesis demands immediate action (Eftekhar, 1977).

An interesting study is that carried out by Lidgren et al. (1977) in which 50 patients with infected hip prostheses were given antibiotics, and the effects were compared with periods during which the patients were not given antibiotics. During the treatment, pain was alleviated and the BSR fell significantly. Most sinuses persisted. Radiological abnormalities were usually not progressive during the treatment. However, in spite of protracted therapy, not a single patient was cured.

3.6.3.2 Surgical treatment

At operation, all granulation and scar tissue should be removed. In particular, the very thick neo-capsule should be excised. There are three reasons for this thorough debridement: the granulation and scar tissues harbour bacteria, the scar tissue is not well accessible to antibiotics because of bad vascularization and this inflexible tissue precludes obliteration of the dead space (Wilson et al., 1973). During the subsequent procedure, some leave the prosthesis in situ while others extract the prosthesis and the cement.

Hewitt states that during debridement the prosthesis may be left in situ and draws the comparison with infections around implants in vascular and neurosurgery. Infections of implants are said to be curable if caused by bacteria of...
low pathogenicity (coagulase-negative staphylococci, diphtheroids, propionibacteria) It is then a condition that the antibiotic therapy should consist of preparations of low toxicity (penicillins, cephalosporins), which sometimes have to be given as long as the patients live If the infection is caused by gram-negative organisms, removal of the implant is considered necessary The results of this treatment are not mentioned, however (Hewitt, 1977)

Nolan only removes the prosthesis when it is loose (Nolan et al, 1975, Coventry et al, 1974) If the prosthesis is still firmly anchored, the infection is treated by debridement, closure of the wound and suction drainage Of the 11 patients treated in this manner, three were cured, three died and in five, the prosthesis had to be extracted at a later stage Accordingly, in a later publication these authors conclude that in view of the disappointing results in a deep infection of the prosthesis, such prostheses should always be extracted (Fitzgerald et al, 1977) Hunter and Dandy made a retrospective study of 135 infected hip prostheses in Canada They concluded that repeated interventions (four operations on the average in their material) aimed at leaving the infected prosthesis in situ proved useless and destroyed the patients' morale (Hunter and Dandy, 1977a)

If extraction of the prosthesis is decided upon, most authors recommend removal of all cement, as well, since residual cement precludes healing of the infection (Buchholz and Gartmann, 1972, Weber and Stuhmer, 1973, Fremont-Smith, 1974, Muller M E, 1974, Plaue and Stadtlr, 1975, Ganz and Meyer, 1976, Clegg, 1977, Eftekhar, 1977, Wilson et al, 1978, Thelen and Steinhauser, 1979) A few authors state that when cement rests are left behind, healing is nevertheless possible (Hunter and Dandy, 1977b, Ahlgren et al, 1980, Petty and Goldsmith, 1980) According to Hackenbroch, cement may be left in situ if absence of infection is certain This appears risky considering the fact that certainty regarding infection is sometimes only reached postoperatively, from cultures (Suezawa and Dietschi, 1977, Hackenbroch, 1979)

Extracting the prosthesis and the cement is usually a laborious and timeconsuming procedure Most authors perform a trochanteric osteotomy Buchholz et al (1979) leave only a thin wall of bone of the greater trochanter Mallory (1978) avoids osteotomy by disinsertion of the abductor at the tip of the trochanter A good description of the technique of removing the cement is given by Stuhmer et al (1979) They designed special chisels to remove the cement Self-tapping extraction instruments have also been developed (Lindner, 1973, Dean Razzano, 1977) Use is also sometimes made of strong, fast-rotating fraises (Harris and Oh, 1978, Turner, 1979) Some early experience of the use of laser to remove cement has been reported (Beacon et al, 1979)

Use of a fibre light source facilitates work deep in the femoral shaft (Amstutz et al, 1976, Eftekhar, 1977) In order to be able to remove all the cement, it may be necessary to make a window in the femur This window as a rule measures one by three cm The corners should be drilled to avoid excessive concentrations of stress at acute angles The site of the window is important to avoid weakening with resulting fracture of the proximal femur Many authors point out the risk of fracture in case of a lateral window (Witt and Hackenbroch, 1976, Amstutz and Kass, 1977, Buchholz et al, 1979, Stuhmer et al, 1979) The window should always be made ventrally or dorsally and, as Buchholz advises, not farther distally than the middle third of the stem of the prosthesis

Clegg (1977) among 30 Girdlestone hips never saw a fracture if the window had been made laterally Hackenbroch mentions that the sawn-out window after extraction may be put back in (Hackenbroch, 1979) Buchholz advises against this, in view of the risk of sequestration (Buchholz and Gartmann, 1973) Some surgeons create a long ventral groove (Muller, 1974, Eftekhar, 1977) which would appear to render re-implantation of a prosthesis practically impossible Only Buchholz still reports reimplantation with this technique (Buchholz and Gartmann, 1973)

Henssge et al (1982) create an elongated ventrolateral window with the aid of pin holes (geplannte ventrolaterale Femurschaftdeckelung = planned creation of a ventrolateral femoral shaft lid) which at reimplantations may be closed and fixed using cerclages

In removal of the acetabular prosthesis, lumps of cement in the pelvis constitute the major problem These, also, should be removed In case of an infected hip prosthesis, they may lead to severe spread of the infection, into the pelvis or farther into the abdomen (Beck, 1977)

A control X-ray is advised to check if all cement has been removed

After extraction of the hip prosthesis, the decision whether or not to reimplant it has to be made If extraction is not followed by reimplantation, the result is a hip joint with absence of the femoral head and neck and usually of the capsule as well This situation is called 'Girdlestone' It is comparable to Girdlestone's primary operation in arthritis of the hip (Girdlestone, 1943) At operation it is attempted to make a good, smooth resection at the level of the intertrochanteric line some surgeons in addition remove the lateral acetabular rim (Muller M E, 1974, Clegg, 1977, Petty et al, 1980) (Fig 3 4)

The stability after resection of the hip joint may be improved by distal displacement of the abductors to the lateral femur (Colonna, 1960, Eftekhar, 1977) Stability may also be achieved by leaving the femoral neck in situ after cup arthroplasty (Soren, 1960) In addition, a subtrochanteric, valgus-inducing osteotomy may provide stability by supporting the pelvis and lengthening the abductors (Witt and Hackenbroch, 1976) However, the osteotomy is inadvisable if the cortex is thin (Witt, 1977)

After extraction of a prosthesis, most authors order six weeks' traction on the leg, and recommend protracted use of a crutch or walking stick during subsequent mobilization The 'Girdlestone' hip is stable to varying degrees and usually reasonably capable of weight-bearing As a rule, however, abductor weakness necessitates use of a crutch or walking stick (Clegg, 1977) The leg as a rule is shortened by four to eight centimeters, necessitating a shoe with a very thick sole and high heel

In most cases, the function of the 'Girdlestone' hip improves during the first year after operation Ultimately, a state of increased exorotation usually persists (Clegg, 1977, Wilson et al, 1978, Ahlgren et al, 1980) The subjective results vary greatly Pain is mostly reported to be mild or absent, but this may be related to the preoperative situation (Haw and Gray, 1976, Clegg, 1977)
3.6.3.3. Reimplantation

A prosthesis may be reimplanted at the same surgical session as the extraction (one-stage) or subsequently (two-stage). If reimplantation is not performed immediately, the interval may be kept short, and is then often used to treat the infection (two to six weeks), or allowed to last longer, to await definite healing of the infection (six to twelve months). The subsequent reimplantation may be carried out with or without antibiotic-containing cement, and with or without systemic administration of antibiotics. Combinations result in a number of possibilities (Table 3.10), which are briefly described with mention of the results (Fig. 3.5).

1. Direct reimplantation
a. Without antibiotics

When at direct reimplantation, antibiotic prophylaxis is refrained from, it is usually omitted because the diagnosis of 'infection' has not been made. Diagnostics, however, is often imperfect. Understandably, direct reimplantations performed in this manner lead to a large percentage of infections. This large proportion of infections, indeed, supports the view that many cases of loosening classified as aseptic actually involved an undiagnosed infection of the prosthesis (Hunter et al., 1977). The percentages of infection of reimplanted prostheses reported in the literature are large (Table 3.11): five out of 64 patients (Hackenbroch jr, 1979), 17% (Dandy and Theodorou, 1975)
Table 3.11 Review of literature data on proportions of infections after first reimplantations of endoprostheses. Absence or presence of infection of the prosthesis, and the therapeutic procedure have been included where mentioned by the authors.

<table>
<thead>
<tr>
<th>Author</th>
<th>Total number</th>
<th>Follow up yr.</th>
<th>Infected %</th>
<th>Remarks (indication, therapy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P. Wilson '73</td>
<td>17</td>
<td>1-4</td>
<td>11.8%</td>
<td>1+2 stage, long-term AB</td>
</tr>
<tr>
<td>2. Fremont-Smith '74</td>
<td>41</td>
<td>½-?</td>
<td>7.3%</td>
<td>1 stage, long-term + high-dose AB</td>
</tr>
<tr>
<td>3. Wilson '74</td>
<td>19</td>
<td>2-5</td>
<td>10%</td>
<td>1+2 stage, long-term AB</td>
</tr>
<tr>
<td>4. Dandy '75</td>
<td>83</td>
<td>?</td>
<td>17%</td>
<td>not infected</td>
</tr>
<tr>
<td>5. Ganz '76</td>
<td>10</td>
<td>¼-¾</td>
<td>70%</td>
<td>2 pat. AB-cement</td>
</tr>
<tr>
<td>6. Beck '77</td>
<td>50</td>
<td>?</td>
<td>36%</td>
<td>data missing</td>
</tr>
<tr>
<td>7. Hunter '77</td>
<td>30</td>
<td>?-5</td>
<td>63.3%</td>
<td>all infected; no AB or AB-cement</td>
</tr>
<tr>
<td>8. Wilson '78</td>
<td>51</td>
<td>?</td>
<td>12%</td>
<td>2 stage; no AB</td>
</tr>
<tr>
<td>9. Hackenbroch '79</td>
<td>64</td>
<td>?</td>
<td>7.8%</td>
<td>not infected</td>
</tr>
<tr>
<td>10. Hunter et al. '79</td>
<td>140</td>
<td>½-?</td>
<td>32%</td>
<td>infected</td>
</tr>
<tr>
<td>11. Hunter '79</td>
<td>65</td>
<td>½-2</td>
<td>39%</td>
<td>infected; AB or AB-cement</td>
</tr>
<tr>
<td>12. Polster '79</td>
<td>109</td>
<td>?</td>
<td>23.3%</td>
<td>100% after fourth reimplantation; different indications</td>
</tr>
<tr>
<td>13. Lindberg et al. 77</td>
<td>92</td>
<td>½-?</td>
<td>16%</td>
<td>infected; 1-stage, AB-cement</td>
</tr>
<tr>
<td>14. Carlsson '78</td>
<td>21</td>
<td>½-?</td>
<td>19%</td>
<td>infected; 2-stage, AB-cement</td>
</tr>
<tr>
<td>15. Josefsson '80</td>
<td>77</td>
<td>½-3½</td>
<td>10% (12%)</td>
<td>infected 1+2 stage, AB-cement</td>
</tr>
<tr>
<td>16. Buchholz '81</td>
<td>68</td>
<td>2-5</td>
<td>24%</td>
<td>infected; 1+2 stage, AB-cement</td>
</tr>
<tr>
<td>17. K. Müller '81</td>
<td>659</td>
<td>½-10</td>
<td>15%</td>
<td>infected; 1-stage, AB-cement</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>2</td>
<td>28%</td>
<td>infected; 21 pat. AB-cement</td>
</tr>
</tbody>
</table>

Table 3.11: Review of literature data on proportions of infections after first reimplantations of endoprostheses. Absence or presence of infection of the prosthesis, and the therapeutic procedure have been included where mentioned by the authors.

b. With systemic antibiotics

Direct reimplantation in infection, with supplementary treatment of the infection by means of postoperative systemic administration of antibiotics is described by authors from the Mayo Clinics and the Hospital for Special Surgery (Wilson M.R. et al., 1978; resp. Wilson P.D. et al., 1973, 1974; Wilson P.D., 1974; Salvati, 1976; Hughes et al., 1979). The antibiotics have to be given in large doses, intravenously for the first few weeks and then orally for three to six months.

Hughes et al describe 13 patients. In the group consisting of these 13 plus 13 other patients subjected to two-stage reimplantation, a recurrence rate of 15.4% was found. Earlier publications from the same clinic mentioned lower recurrence rates due to less strict criteria of infection (Hughes et al., 1979). Fremont-Smith (1974) among 41 patients saw only three recurrences. The number of patients followed up for longer than two years amounted to only 11.

c. With antibiotic-containing cement

Buchholz was the first to perform direct reimplantations under protection of an antibiotic mixed with the cement (see Chapter 4). During the first few years he did not combine this with systemic antibiotics (Buchholz et al., 1981). However, good experiences of Swedish authors who in addition to antibiotic-containing cement administered antibiotics systematically for three to six months post-operatively, convinced him of the value of this regimen (Buchholz, 1979a; Lindberg et al., 1977a; Lindberg, 1979b; Carlson et al., 1978).

Up to the time of writing (mid-1982) no American literature was available on reimplantation with antibiotic-containing cement.

2. Postponed reimplantation

If the infection is fulminant and caused by a virulent...
bacterium, certain authors refrain from direct re-
implantation (Ganz and Meyer, 1976; Hughes et al., 1979).

Others after the extraction of the prosthesis always allow a
shorter or longer interval to treat the infection or to check
whether it is adequately under control (Michel and Spier,
1979; Hovclius and Josefsson, 1979).

Hughes et al. (1979) reimplant the prosthesis after two
to 11 weeks, but they conclude from their material that
results improve with increasing duration of the interval.
Amstutz agrees and proposes a minimal interval of three
months if the causative agent is of low virulence, and a
period of one to two years if a gram-negative bacterium is

M.R. Wilson et al. (1978) saw more recurrence of
infections when reimplantation had been performed after
less than six months. Among 51 patients they saw 12%
recurrences of infection. However, they used no antibiotic-
containing cement, nor did they administer antibiotics
systematically for long perios.

The knee endoprosthesis at revisions causes more problems
than the total hip prosthesis. After the first revision
operation, cancellous bone is often completely absent in the
distal femur and the proximal tibia, so that only a thin cortex
remains (Tönnis and Händel, 1979). Consequently, revision
is only feasible once or twice.

In an acute deep infection of the prosthesis it may be
attempted to save the knee prosthesis by early debridement,
leaving the prosthesis in situ and instituting suction
drainage.

In the late deep infection, the prosthesis should be
removed with all cement. Long ventral windows in femur
and tibia are usually unavoidable in the hinge prostheses.

Reimplantation after treatment of infection is reported only
sporadically in the literature (Insall et al., 1979; Knutson
et al., 1981; Wigren and Kolstad, 1981). Most of these cases
involved a non-hinge prosthesis that is replaced by a hinge
prosthesis if too much bone has been lost. In every case,
however, it is necessary before reimplantation to ascertain
whether an arthrodesis will still be possible if the loosening
occurs again. If this is not the case, no reimplantation should
be performed but arthrodesis should be carried out
immediately (Tönnis and Händel, 1979).

As a general rule, after extraction of a knee prosthesis with
intra-medullary stem (hinge prosthesis, e.g. Guepar), an
arthrodesis will have to follow. On the other hand, after
extraction of a non-hinge prosthesis (e.g. Geomedic)
reimplantation will be possible, usually with a hinge
prosthesis (Knutson et al., 1981).

For arthrodesis of the knee, use may be made of a medullary
nail, a plate with screws, external fixation or a plaster cast
(Brodersen et al., 1979; Lidgren et al., 1981). In case of
infection, external fixation is to be preferred.

Consolidation as a rule is difficult to achieve, owing in
the first place to the extensive bone loss. Hagemann et al.
(1978) observed a consolidation rate of 65%, as against 95%
after primary arthrodesis. In their opinion, it is especially a
marked shortening that is associated with failure of the
arthrodesis.

Failure of an arthrodesis results in a fibrous ankylosis.
This has to be supported by an orthesis, if necessary with
ischial tuberosity loading. If this fibrous ankylosis cannot be
rendered functional, or the infection cannot be controlled
adequately, thigh amputation may become necessary
(Blümlein et al., 1979).
4.1 Introduction

Polymethyl methacrylate (PMMA, 'bone cement') consists of interlinked molecules of methyl methacrylate. At operation the polymer, a powder, is mixed with the liquid monomer. An activator is added to the latter. After mixing of the powder and the liquid, the polymers fuse. This polymerization is an exothermic reaction.

The gentamicin-PMMA beads consist of this polymethyl methacrylate which has been mixed in the factory with gentamicin sulphate before its hardening (see Chapter 5.2). A discussion of the qualities of antibiotic-containing cement will elucidate the possible applications and the mechanism of action of the gentamicin-PMMA beads.

Buchholz attempted to reduce the incidence of infections of hip endoprostheses, especially by eliminating peroperative contamination as far as possible. To this purpose, he wore double gloves and applied a tissue-sparing surgical technique. In addition, however, he made extensive use of locally administered antibiotics: cloths soaked in antibiotics were sutured to the fascia and antibiotic-containing solutions were used for regular lavage of the wound (Buchholz and Gartmann, 1972). The fact that in spite of these measures, infections still occurred (approx. 3% among 1409 prostheses) Buchholz attributes in the first place to haematogenous infections (Buchholz and Gartmann, 1972; Buchholz, 1973). The importance of bacteraemias as a cause of these haematogenous infections had been emphasized to him by Lodenkämper (Lodenkämper, 1969, 1971, 1974).

In developing the antibiotic-containing cement, Buchholz used data obtained from Knappwost. The physical chemist Knappwost, working in Hamburg just as the surgeon, Buchholz and the bacteriologist, Lodenkämper, showed Buchholz how owing to diffusing processes sustained release of various substances from bone cement is possible. Like the residual monomeric component, CuS, for instance, is also released by diffusion from the cement (Buchholz, 1973; Knappwost and Freitag, 1976; Knappwost and Gerlach, 1976). Buchholz mixed four heat-stable powdered antibiotics with bone cement: penicillin G, erythromycin (heptogluconate), rolitetracycline and gentamicin sulphate. The powdered antibiotic was mixed with the powdered polymer followed by mixing and hardening-out with the monomer. In-vitro tests showed that these antibiotics, also, were released into a fluid by a diffusion process, with the exception of the tetracycline (Buchholz and Engelbrecht, 1970).

These findings were confirmed by a study carried out in the same period by Hessert and Rückdeschel: tetracycline was not released from bone cement, but gentamicin and Totocillin® (a combination preparation of ampicillin with dicloxacillin) were (Hessert and Rückdeschel, 1970, 1973). These findings, and the fact that the mechanical qualities of the cement are affected only slightly by addition of the powdered antibiotics (Buchholz and Engelbrecht, 1970) led to increasing use of antibiotic-containing cement. Since that time, additional research has been carried out in the laboratory, in animal experiments and during clinical use, in order to gain more insight into the qualities and possibilities of the various combinations of antibiotics and bone cement.

4.2. In-vitro studies

During in-vitro research, qualitative assays have been carried out to determine what antibiotics will be released from bone cement, and quantitative assays to determine when and at what concentrations these antibiotics diffuse from the bone cement.

4.2.1. Qualitative assays

A small block of antibiotic-containing cement is placed on an agar plate that has been inoculated with a bacterial strain sensitive to the antibiotic in question. After some time, the plate is inspected to see whether around the cement, an area of inhibited growth has formed in the culture that has developed. This occurs if the antibiotic has not been destroyed by the intensive polymerization heat of the cement, if it has not become bound to the cement and if it is released in an effective concentration to nearby bacteria sensitive to the antibiotic (Fig. 4.1).

Figure 4.1 Example of qualitative in-vitro study of antibiotic-containing cement. Diffusion of the antibiotic from a cement cylinder causes an area of inhibition of bacteria on a culture medium.

These tests show that most antibiotics diffuse sufficiently from the cement to cause an area of inhibited growth: penicillins, cephalosporins, aminoglycosides, fucidic acid, clindamycin and lincomycin and streptomycin (Table 4.1). A few antibiotics show no or hardly any area of inhibition, probably due to insufficient heat stability. These are colistimethate and polymyxin B (Chapman and Hadley, 1976), tetracycline (Buchholz and Engelbrecht, 1970) and chloramphenicol (if in Simplex®, Fischer et al., 1977).

The polymerization temperature of the bone cement that is reached during hardening, depends on the thickness of the cement and on the preparation technique: in vivo, local, short-lasting temperatures of 60° to 100° are reached in the cement (Goebe and Ohnsorge, 1973; Huiskes, 1979), while during manufacture of gentamicin beads at the factory, temperatures of 130° to 150° occur (Grieben, 1981).
Antibacterial activity of cement without addition of antibiotics is not probable. Chapman et al. (1976) observed some growth-inhibiting effect of Simplex® cement on certain bacteria. Staphylococcus aureus and Staphylococcus epidermidis. Two-thirds of the number of bacteria mixed with the cement were killed by the polymerization heat or the toxic monomer. Marks et al. (1976) saw no inhibitory effect of Palacos® or Simplex® on Staphylococcus aureus, E. coli or Pseudomonas aeruginosa. Hessert and Ruckdeschel (1970) observed no bacteriostatic effect of cement without antibiotic. Some alternatives to antibiotics or to the cement have been studied, but this has not led to any clinical applications. It has been found, for instance, that various silver salts can also diffuse from the cement (Spadaro et al., 1979), just as CuS (Knappwost and Gerlach, 1976). Silver exerts an antibacterial action by a mechanism that is not yet fully understood (Becker and Spadaro, 1978). CuS in the form of CuSO₄ exerts antibacterial action by interfering with the bacterial protein synthesis. Release of antibiotics from other vehicles is also possible. Gentamicin has occasionally been dissolved in an absorbable matrix for use in ophthalmology (Bloomfield et al., 1978) or for intravaginal or rectal implantation (Toutou et al., 1978) (see par 5.2).

### Quantitative assays

The diffusion of water-soluble substances from bone cement is possible because water in molecular form is incorporated among the macromolecules of the polymethyl methacrylate. The acrylate can incorporate two (Wahlig, 1979, Knappwost and Gerlach, 1976) to five per cent (Levin et al., 1975) by weight of water. The diffusion processes run the same course for all substances, such as for CuS, silver salts, NaCl or antibiotics. The amount of the substance mixed with the cement that is released is proportional to:

1. the surface of the cement (Wahlig et al., 1972; Ruckdeschel et al., 1973, Holm and Vejlsgaard, 1976, Wroblewski, 1977; Schurman et al., 1978, Welch, 1978);
2. the concentration of the antibiotic in the cement (Wahlig et al., 1972, Ruckdeschel et al., 1973; Medcraft and Gardner, 1974; Marks et al., 1976, Welch, 1978);
3. the amount of fluid around the cement (Wahlig et al., 1972; Welch, 1978), and accordingly, the frequency of replacement of the fluid around the cement, or the flow rate of the fluid around the cement.

For the quantitative in-vitro assays, small blocks of cement of known dimensions, usually cylinder-shaped, are submerged for some time in a liquid (broth, plasma, serum, etc.).

### Table 4.1

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of cement</th>
<th>Antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>palacos</td>
<td>Gentamicin</td>
</tr>
<tr>
<td>1. Buchholz et al '70</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>2. Hessert et al '70</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>3. Wahlig et al '72</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>4. Wahlig and Hameister '73</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>5. Wahlig and Dingeldein '80</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>6. Gartenmann '73</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>7. Gartenmann '76</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>8. Ruckdeschel et al. '73</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>9. Sattel et al. '73</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>10. Medcraft et al. '74</td>
<td>??</td>
<td>x</td>
</tr>
<tr>
<td>11. Levin '75</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>12. Chapman et al '76</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>13. Holm et al '76</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>14. Marks et al '76</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>15. Nelson et al '76</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>16. Rosenthal et al. '76</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>17. Elson et al. '77</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>18. Fischer et al. '77</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>19. Hill et al. '77</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>20. Picknell et al. '77</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>21. Wanntske et al. '76</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>22. Quinan et al. '78</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>23. Schurman et al. '78</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>24. Welch '78</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>25. Hoff et al. '81</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

Table 4.1  Review of literature data on in-vitro studies of various combinations of antibiotic-containing cement with antibiotics.
phosphate buffer, NaCl), as a rule at 37°C. After a fixed interval, the fluid is poured off and the cement cylinder is placed in a new liquid, sometimes after preliminary determination of the residual antibacterial activity of the cement block in a culture medium. The concentration of the antibiotic in the bathing fluid is determined (Fig. 4.2). The authors listed in Table 4.1 studied the diffusion of various antibiotics from different types of cement. Table 4.2 shows how much the several quantitative in-vitro assays differ from each other. The composition, amount and temperature of the elution fluid vary, and the same holds true of the frequency of replacement of the elution fluid, the duration of the experiment and the sizes of the cement cylinders. These differences render it impossible to compare the quantitative results of the various determinations with each other, but they do show the constant occurrence of the same diffusion process, in which the above-named factors play a part.

During the first few hours, sometimes the first few days, a very high concentration of the antibiotic in the elution fluid is observed, but this decreases rapidly. Judgements of the length of time during which the antibiotic may be released from the cement vary greatly. It appears, however, that in this respect the dimensions of the test block of cement are of particular importance: Schurman et al. (1978) found that from a disc of cement of 100 μm all the antibiotic had been diffused within one hour. From a thicker disc of 700 μm, only 19% had disappeared from the cement block after one hour. They found that from gentamicin-Palacos® twenty times as much antibiotic diffused during the first hour as during the second hour. One week later, the rate per hour had dropped to one-tenth of that of the second hour.

Wahlig and Dingeldein (1980) found that gentamicin is released from Palacos® for a considerable length of time: even after five years, small constant amounts were still

![Figure 4.2](image)

**Figure 4.2** Scheme of quantitative determination of release of antibiotics from a cement cylinder. From a cylinder of predetermined surface and weight, the antibiotic diffuses to an elution fluid. This elution fluid has a known volume and temperature, and is replaced at preset intervals. The experiment takes a number of weeks to a number of years (see also Table 4.2).

<table>
<thead>
<tr>
<th>Author</th>
<th>Elution fluid</th>
<th>Interval between</th>
<th>Last assay after:</th>
<th>Cement cylinder</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Type</td>
<td>Vol. (ml)</td>
<td>Temp. (°C)</td>
<td></td>
</tr>
<tr>
<td>Buchholz et al. '70</td>
<td>broth</td>
<td>10</td>
<td>37</td>
<td>6-46 d.?</td>
</tr>
<tr>
<td>Hessert et al. '70</td>
<td>NaCl/phosph. buffer</td>
<td>2</td>
<td>37</td>
<td>2/6/24 h.</td>
</tr>
<tr>
<td>Wahlig et al. '72</td>
<td>phosp. buffer</td>
<td>10-50</td>
<td>37</td>
<td>1 d.-months</td>
</tr>
<tr>
<td>Wahlig et al. '80</td>
<td>posph. buffer</td>
<td>20</td>
<td>37</td>
<td>1 d.-months</td>
</tr>
<tr>
<td>Gartenmann et al. '73</td>
<td>NaCl/serum/dextrose</td>
<td>2</td>
<td>37</td>
<td>1 d.</td>
</tr>
<tr>
<td>Gartenmann '76</td>
<td>dextrose</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Rückdeschel et al. '73</td>
<td>posph. buffer</td>
<td>10-50</td>
<td>?</td>
<td>1 d.-weeks</td>
</tr>
<tr>
<td>Sattel et al. '73</td>
<td>?</td>
<td>5-275?</td>
<td>?</td>
<td>48 weeks</td>
</tr>
<tr>
<td>Medcraft et al. '74</td>
<td>plasma</td>
<td>25</td>
<td>33/37 24 h.</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Levin '75</td>
<td>NaCl</td>
<td>1000</td>
<td>37</td>
<td>1-× days</td>
</tr>
<tr>
<td>Chapman et al. '76</td>
<td>NaCl</td>
<td>10</td>
<td>37</td>
<td>1 d.</td>
</tr>
<tr>
<td>Holm et al. '76</td>
<td>serum</td>
<td>?</td>
<td>35</td>
<td>1 d.</td>
</tr>
<tr>
<td>Marks et al. '76</td>
<td>none</td>
<td>--</td>
<td>35</td>
<td>1 d.</td>
</tr>
<tr>
<td>Nelson et al. '76</td>
<td>none</td>
<td>--</td>
<td>35</td>
<td>1 d.</td>
</tr>
<tr>
<td>Rosenthal et al. '76</td>
<td>plasma</td>
<td>1</td>
<td>37</td>
<td>1 d.</td>
</tr>
<tr>
<td>Olson et al. '77</td>
<td>H2O</td>
<td>50</td>
<td>?</td>
<td>1/10/14 d.</td>
</tr>
<tr>
<td>Fischer et al. '77</td>
<td>culture medium</td>
<td>?</td>
<td>?</td>
<td>4 d.</td>
</tr>
<tr>
<td>Hill et al. '77</td>
<td>peptone-H2O</td>
<td>10</td>
<td>37</td>
<td>3-4 d.</td>
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<td>37</td>
<td>3-18 h.</td>
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<td>37</td>
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<td>?</td>
<td>37</td>
<td>1-7 d.</td>
</tr>
<tr>
<td>serum</td>
<td>5</td>
<td>37</td>
<td>1 h.-7 d.</td>
<td>7 d.</td>
</tr>
<tr>
<td>Welch '78</td>
<td>posph. buffer/NaCl</td>
<td>5-10</td>
<td>37</td>
<td>2-7 d.</td>
</tr>
<tr>
<td>Hoff et al. '81</td>
<td>H2O</td>
<td>5</td>
<td>?</td>
<td>1-7 d.</td>
</tr>
</tbody>
</table>

Table 4.2 Review of the literature concerning different experimental protocols in in-vitro study of the release of antibiotics from cement cylinders. (See also Table 4.1.)
4.2.3 Antibiotic-bone cement combinations

In researching the various combinations of antibiotic and cement, Wahlig studied the release of gentamicin from different types of cement. He constantly found that gentamicin and cafazedon\(^*\) were released in larger amounts and for longer periods of time from Palacos\(^R\) than from other types of cement (Wahlig et al., 1972; Wahlig and Buchholz, 1972; Wahlig, 1979; Wahlig and Dingeldein, 1980). Lividomycin (an aminoglycoside), lincomycin and clindamycin were released adequately but in slightly smaller amounts. The diffusion was measured in microgrammes of antibiotic per ml of elution fluid per day and per cement cylinder.

Sattel and Nabert-Bock (1973) also concluded that gentamicin diffused better from Palacos\(^R\) than from CMW bone cement\(^R\) and Simplex\(^R\), but they do not report their findings concerning the diffusion from Simplex\(^R\).

Elson (Elson et al., 1977\(^*\)) found that out of the four types of cement, Palacos\(^R\) showed the best release of fucidin and gentamicin. Picknell (Picknell et al., 1977) found better diffusion of gentamicin from Palacos\(^R\) than from Simplex\(^R\), but no difference between the two types of cement where release of other antibiotics (penicillins, cephaloridine, clindamycin, fusidic acid) was concerned. Hoff, just as Picknell, studied various penicillins and found a better diffusion from Palacos\(^R\) than from Simplex\(^R\) (Hoff et al., 1981).

Marks and Nelson (Marks et al., 1976; Nelson and Marks, 1976) investigated the release from Simplex\(^R\) and Palacos\(^R\); several antibiotics, especially gentamicin, were diffused better from Palacos\(^R\). The supposed explanation is that Palacos\(^R\) has larger pores than Simplex\(^R\). Holm and Vejlsgaard (1976) also saw better release of gentamicin from Palacos\(^R\) than from other types of cement.

Quinian and Mehigan (1978) found that fucidin is released to approximately the same extent from CMW\(^R\), Simplex\(^R\) and Palacos\(^R\). In vitro, release of gentamicin from CMW\(^R\) lasted longest, that from Simplex\(^R\) shortest.

If gentamicin is chosen as the antibiotic, combination with Palacos\(^R\) is the best choice according to the majority of investigations. If a different antibiotic is considered, it is less clear which type of cement has the best qualities.

In studying different antibiotics, Wahlig and Dingeldein (1980) found that of 12 antibiotics, gentamicin and lividomycin diffused best from Palacos\(^R\). Fischer et al. (1977) combined the three types of cement with 14 different antibiotics and observed adequate release in all cases, except for the combination of chloramphenicol with Simplex\(^R\). Levin (1975) studied six different antibiotics in Simplex\(^R\). Cefalotin proved to be released well, clindamycin less well. Gentamicin and erythromycin proved ineffective. Chapman et al. (1976) studied the diffusion from Simplex\(^R\) of ten antibiotics and saw no differences between them.

Welch (1978) concluded that from Simplex\(^R\), gentamicin was released better than cefalotin. Nelson and Marks (1976) found that from Simplex\(^R\), oxacillin was released better than cefalotin and gentamicin. From Palacos\(^R\), on the other hand, the diffusion of gentamicin was better (Marks et al., 1976\(^*\)). Picknell et al. and Hoff et al. focused their attention on the heat-unstable beta-lactam antibiotics. In contrast to what other had expected, several types of penicillin were released well (Picknell et al., 1977; Hoff et al., 1981). Hoff even observed that penicillin was released for a longer length of time from Palacos\(^R\) than gentamicin.

However, the amounts diffusing from the cement in that case are less active than gentamicin. This last finding by Hoff et al. reflects the core of the problem: whether it is rational on the basis of in-vitro studies to decide which antibiotic is released best and from which type of cement.

That Palacos\(^R\) releases several antibiotics well, and especially gentamicin, is confirmed by most investigations. However, comparison of the release rates of different antibiotics is based on investigations that are not comparable quantitatively, and is useless when concentrations of antibiotics are compared with one another. More important than the concentrations themselves is the biological activity of a particular concentration of a particular antibiotic. For instance, 2 μg per ml of antibiotic A may be much more active against Staphylococcus aureus than 6 μg per ml of Antibiotic B. This is why in-vivo studies are so important.

4.3. In-vivo studies

At investigations in vivo, the release of antibiotics from cement has been determined by assay of levels of antibiotics in serum, urine, wound exudate and tissues of laboratory animals and humans. It appears that the findings obtained by in-vitro studies can be extrapolated to the in-vivo situation only with the greatest caution (Marks et al., 1976; Quinian and Mehigan, 1978). On the whole, it could be confirmed that antibiotics are released to the environment and that the rate of diffusion is maximal shortly after the implantation, but the release in vivo proved to persist longer than was to be expected on the basis of certain in-vitro studies.

In the wound exudate, gentamicin concentrations occur that build up in a similar manner as in the elution fluid in in-vitro studies. Koschmieder could aspirate wound exudate through a gentamicin-palacos window in a femur in nine dogs for three weeks. The amounts varied from 0.5 to 5 ml per day. The concentration of gentamicin was determined by a micro-biological method and fell from 20.2 μg per ml on the first postoperative day, via 2.7 μg per ml (seventh
postoperative day), 1.0 μg per ml (14th postoperative day) to
0.01 μg per ml on the 21st postoperative day (Koschmieder
et al., 1973). Wahlig et al were able to obtain wound
exudate for nine days after implantation of gentamicin-
palacos cement in the femur in the dog. The concentrations
of gentamicin varied greatly, from 1.02 to 54.0 μg per ml
(Wahlig et al., 1972; Wahlig and Buchholz, 1972; Wahlig
through a cannula in the bone-cement interface and thus
determined the release of antibiotic from the
cement. They observed protracted release of antibiotic, but
differences from in-vitro assays were considerable

In man, a similar concentration of antibiotic in the exudate is
found, after implantation of a prosthesis, 8 to 64 μg per ml
(Wahlig, 1979), 20 to 10 μg per ml during the first four
postoperative days (Sattel and Nabert-Bock, 1973) or 27 μg
per ml to less than 1.0 μg per ml after seven days (Elson et al.,
1977a) Sattel and Nabert-Bock (1973), puncturing hip joints
of 30 patients after implantation of an endoprosthesis with
gentamicin-palacos, observed that the in-vivo wound
exudate concentrations were influenced by the amount of
cement that was in contact with the wound haematoma at
the level of the cutting plane through the femoral neck
Determinations between the sixth and the 264th
postoperative days showed that after the 50th postoperative
day the concentration in the punctate was always below
0.2 μg per ml All values were constantly obtained by micro-
biological assay methods.

The tissues surrounding implants of antibiotic-loaded

cement show high levels of antibiotic in the haematoma and
to diminishing degrees also in the connective tissue,
cancellous bone and cortex. Concentrations of gentamicin
in tissue were determined in test animals by various
authors: Wahlig et al (Wahlig et al., 1972b; Wahlig
and Buchholz, 1972, 1973; Wahlig and Hameister, 1973; Wahlig,
1979, Wahlig and Dingeldein, 1980), Schurman et al.
(1978), Welch (1978a) and Wannske et al. (1976). In
general, the concentration in tissues is in inverse
proportion to their distance from the cement and to the
length of time elapsed after operation. Tissues that have a
more compact construction, show a lower concentration.

Elson studied the penetration of gentamicin through the
cortex of a cadaver femur. It was found that gentamicin
diffused well through the dead bone, especially if the
cement used had been PalacosR (Elson et al., 1977)
However, the diffusion probably took place through
canalculi, which are present in sclerotic bone but not
necessarily in dead bone

In vivo, good diffusion in the bone proved
demonstrable in humans as well. Assays by Wahlig
and Buchholz (1973) and by Stohr et al. (1973) showed high
levels in cancellous bone and cortex close to the cement, but
a rapid decrease at one to two cm distance. Four days to 69
months postoperatively, it was found in 18 patients that the
highest gentamicin level occurred in connective tissue close
to the layer of cement (Wahlig and Dingeldein, 1980). Hoff
et al demonstrated good diffusion of penicillin and
gentamicin in the rabbit femur, extending into the
outermost layer of the cortex (Hoff et al., 1981

Serum and urine concentrations of the antibiotic indicate how
much is excreted. Determinations of these concentrations
are important because they afford insight into the
pharmacokinetics in test animals and humans, and into
possible toxic side effects.

In contradistinction to the locally high tissue levels,
serum levels prove to be very low. All authors find for all
types of cement and all antibiotics that a few hours after
implantation a maximal serum level is reached, which as a
rule falls to very low levels or even trace level within one day
(Wahlig and Buchholz, 1972, 1973, Marks et al., 1976;
In the serum of patients, the same pattern is observed
(Wahlig and Hameister, 1973; Wahlig, 1979; Wahlig
and Dingeldein, 1980, Elson et al., 1977) Of gentamicin,
98% is excreted by the kidneys. Accordingly, determination of the renal excretion rate of
gentamicin supplies an accurate indication of the amount of
gentamicin released by the cement.

After implantation of a hip prosthesis with gentamicin-
containing cement, Wahlig and Buchholz (1972) observed
gentamicin concentrations in the urine from 0.0 to 1.4 μg/ml
during the first 12 postoperative hours. Within six days, the
level falls to below 1 μg/ml. A later paper reports low
concentrations which, however, remained measurable for
several months (Wahlig and Dingeldein, 1980). However,
not a single publication instead of the urine levels states the
renal excretion rate of gentamicin. The concentration of
gentamicin in the urine samples, namely, depends greatly
on the production of urine by the kidney.

4.4. Experiments in animals

Infections in test animals have been studied to determine
whether antibiotic-loaded cement does indeed protect
against infection by contamination or haematogenous
infection. Elson implanted a cement plug with or without
antibiotic into a rat tibia. The wound was contaminated, or a
haematogenous infection was brought about by intravenous
administration of a bacterial suspension. Gentamicin
provided good protection against contamination by
Staphylococcus aureus, Pseudomonas, Proteus and
streptococci. The haematogenous infection was effectively
prevented by gentamicin-containing PalacosR when the
infection was brought about one half hour postoperatively.
However, when the haematogenous infection was only
brought about six weeks postoperatively, the difference
between gentamicin-containing PalacosR and PalacosR
without antibiotic was less (Elson et al., 1977b) Picknell et
al. implanted amoxicillin-containing SimplexR sub-
cutaneously in mice. A low blood level nevertheless
protected against intraarticular infection with
Staphylococcus aureus (Picknell et al., 1977).

A hemi-arthroplasty mixed with gentamicin-PalacosR
in rat knees was protected adequately against early post-
operative infection (Schurman et al., 1978) In the rat, per-
operative infection of subcutaneously implanted cement
cylinders by E. coli, Pseudomonas and Staphylococcus
aureus was prevented by antibiotic in the cement (Welch,
1978b). Touw observed that bone cement without antibiotic
reduced the resistance to infection of a medullary cavity in
the guinea-pig femur. Antibiotic-containing cement
(gentamicin-PalacosR or SimplexR-erythromycin +
colistine) reduced the risk of infection (Touw, 1980). This
study, just as that by Welch, only shows that contamination
at operation is countered
Blomgren made an extensive study in the rat of the long-term protective effect of antibiotic-containing cement against haematogenous infection of endoprostheses (Blomgren, 1981). In addition he demonstrated that a prosthesis is susceptible to haematogenous infection (Blomgren and Lindgren, 1980a), and that the natural defence against infection is impaired by a prosthesis (1980b). This study shows that in vivo, owing to a falling gentamicin concentration, no protection against a late postoperative haematogenous infection (6 to 8 weeks postoperatively) is possible. This is spite of a residual antibacterial activity of the cement in vitro (Blomgren and Lindgren, 1981).

### 4.5. Clinical results

Among 1138 endoprostheses implanted in a little over four years with the aid of cement without added antibiotics, Buchholz and Engelbrecht (1970) observed 14 infections (1.2%). Subsequent publications show that with longer follow-up the infection rate gradually rises: 3% (Buchholz and Gartmann, 1972), 4.1% (Buchholz, 1973a) and 5% (Buchholz, 1979b) (Fig. 4.3).

![Figure 4.3: Cumulative percentage of infection of 2028 total hips implanted without use of antibiotic-containing cement in the period 1964-1968 (from Buchholz, 1979b). The graph also shows the percentages of infection (*) as stated by Buchholz in successive publications (respectively, Buchholz and Gartmann, 1972; Buchholz, 1973a++) and Buchholz, 1979b). It is clear from the graph that the percentage of infections increases with longer follow-up.](image)

Starting January 1969, antibiotics were added to the cement in Buchholz's clinic: in the first 272 patients, mostly penicillin but also streptomycin, kanamycin or chloramphenicol. At that time there had not yet been any research of the properties of antibiotic-loaded cement (Buchholz, 1973a).

In order to avoid side effects of the above-named four antibiotics, especially allergy, Buchholz subsequently switched to erythromycin. Addition of this antibiotic to the cement was followed by a decrease of the infection rate but also by a shift of the bacterial flora to the anaerobics (Buchholz, 1973a). Pseudomonas infections proved particularly stubborn. Therefore, from 1971, gentamicin was added to the bone cement at all implantations of hip prostheses. It was expected that this addition would result in long-term protection against infection of the prosthesis (Röttger et al., 1979).

On the basis of a very large clinical material, Buchholz et al. illustrate the protective effect of addition of antibiotics to bone cement. To this purpose, the patients were divided into three groups, according to the type of cement used. Especially from 1972, there was a marked decrease of the infection rate, which was ascribed to the admixture of the gentamicin (Buchholz et al., 1979; Buchholz, 1979b) (Fig. 4.4).

![Figure 4.4: The effect of addition of antibiotic to bone cement reflected by the percentages of infection of the total hip prosthesis reported per year after implantation by Buchholz. From 1968, various antibiotics were added, from 1971, gentamicin. This graph, just as Figure 4.3 shows that Buchholz regularly checks the results of his treatment and corrects the percentages of infection. These increase as the follow-up period grows longer (respectively, Buchholz et al., 1977; Buchholz et al., 1979; Buchholz, 1979b).](image)

Wannske and Tcheme (1979) made a prospective study of the value of prophylactic application of antibiotic-loaded cement in 445 patients (476 hip prostheses). If gentamicin-Palacos® was used, the infection rate amounted to 1.1%, without antibiotic-loaded cement to 5.9%. Follow-up ranged from 3.5 to 6 years.

Elson (1979) observed that use of gentamicin-Palacos® reduced the rate of infection after implantation of a hip prosthesis from 2.7 to 0.8%. This was not a prospective study and the follow-up had been short.

Also in a non-prospective study, Thierse compares patients with standard cement (336 patients, 1970-1972) with patients in whom gentamicin-loaded cement had been used (331 patients, 1972-1973). The follow-up was four to five years. In the former group, there were 6.3% early postoperative infections and 4.1% late postoperative infections. The group with antibiotic-loaded cement showed 0.6% early and 0.6% late postoperative infections (Thierse, 1978).

Pfarr and Burri made a prospective study of 800 patients with a follow-up of two years. They alternatingly used cement with and without gentamicin and observed no infections in either group. They did find that the gentamicin-cement group had more periartricular calcifications with a larger radiologic bone cement interface at the acetabulum and BSR's often in excess of 20 mm. The differences were not significant, however (Pfarr and Burri, 1979).

Josefsson in a prospective study of two groups of patients compared the prophylactic effect of the gentamicin-loaded cement with the prophylactic effect of systemic antibiotics (one to 24 hours intravenously before operation and seven to 14 days orally after operation). During a follow-up of one to two years, the gentamicin-cement group showed more superficial infections and fewer deep
infections. However, the percentage of non-infectious loosening was also significantly larger in the antibiotic group. These might have been undiagnosed deep infections (Josefsson, 1980; Josefsson et al., 1981).

Knöringer used Palacos® to close cranial defects in 115 patients. In this group, the infection rate was 6.1%. Infections occur particularly during treatment of frontobasal injuries with opening of the nasal sinuses. Use of gentamicin-Palacos® cement in 53 patients prevented the infection (Knöringer, 1979a, 1979b). The protective effect on cranioplasty after injury was also reported by Stula (1979).

Knöringer and Weidenbach made use of this protective effect of the antibiotic-loaded cement in seven patients treated for osteomyelitis of the roof of the skull: immediately after removal of the sequestered bone, a cranioplasty was carried out with gentamicin-containing bone cement (Knöringer and Weidenbach, 1978).

Once Buchholz had become convinced of the efficacy of the antibiotic-containing cement by the results of its extensive prophylactic application during primary implantation of endoprostheses, he started in 1969 to use it, increasingly, to treat infected prostheses. After removal of the prosthesis with cement, and after debridement, he immediately reimplanted a new prosthesis, using the antibiotic-containing cement.

Earlier, in 1965, he had begun to mix his cement with erythromycin, colistine, cefalotin, carbenicillin, chloramphenicol or penicillin for these reoperations. From 1972, only gentamicin-Palacos® was used (Buchholz and Gartmann, 1972; Buchholz, 1973a). This enabled him to perform reimplantation with growing success in infections with virulent bacteria, such as Pseudomonas and enterococci. In ten publications, ever-larger numbers of patients are reported: from 140 in 1972 to 659 in 1981. Patient data are arranged in various ways in these papers, and the results reported are sometimes contradictory (Buchholz and Gartmann, 1972; Buchholz, 1973a, 1973b, 1973c; Buchholz and Siegel, 1973; Buchholz et al., 1977; Buchholz et al., 1979b; Buchholz et al., 1979c; Röttger et al., 1979; Buchholz et al., 1981).

However, all publications mention that since the use of gentamicin was introduced in 1972, reimplantation was successful in 73 to 85% of the cases. By repeating the exchange of the prosthesis in case of recurrence of the infection, naturally again with debridement, the success rate of treatment of infection increases to an average of 88%. In a few patients, it was even necessary to reoperate five times; this raised the cure rate to 90% (Buchholz et al., 1981). The follow-up in these cases ranged from one to 114 months.

K. H. Müller reports 25 reimplantations in 21 patients; gentamicin-Palacos® was used 19 times in this series. During a follow-up of 21 months, seven recurrences were seen; in four of these, a second reimplantation resulted in healing (Müller, 1981).

Josefsson followed up 68 revised reimplanted prostheses for two to five years: 52 of these were free from infection and six more became so after a second revision (Josefsson, 1980; Carlsson et al., 1978, 1980). This Scandinavian team, who just as Buchholz have much experience of the use of antibiotic-containing cement, compared the results of immediate exchange with two-stage exchange. In 92 and 21 patients, respectively, they observed cure rates of 84 and 81% (Table 3.11). However, 14 of these patients of the one-stage group had only been followed up for less than six months (Lindberg et al., 1977). In a subsequent publication, the conclusion is reached that there was no significant difference between the results of the one-stage and of the two-stage procedure (Carlsson et al., 1980). Lindberg et al. (1977) and Buchholz et al. (1981) are of the opinion that the two-stage procedure, which involves a temporary Girdlestone situation, offers no advantages. The Scandinavian authors in addition to the antibiotic in the cement also administer antibiotics systemically for six months after the operation. Buchholz regards this as an enrichment of the treatment (Buchholz, 1979a).

Both the Scandinavian and the Hamburg authors saw the worst results in infections with gram-negative bacteria, especially Klebsiella and Pseudomonas, and in infections with anaerobic streptococci. Buchholz in cases of this nature attempts to prevent failure of the treatment by adding more gentamicin to the Palacos® cement. The commercially available Refobacin® contains 0.5 g gentamicin per 40 g Palacos®. Buchholz increases the dose to 3 g and, if necessary, depending on the causative agent determined preoperatively, adds other antibiotics: cefalotin, oxacillin, lincomycin and ampicillin (Buchholz et al., 1981). An adverse effect of this addition on the mechanical properties of the cement has to be expected, however.

### 4.6. Conclusion

The efficacy and value of antibiotic-containing bone cement have been demonstrated largely empirically by Buchholz. Its prophylactic use in primary implantation of prostheses is still a matter of debate, and it remains to be demonstrated adequately that its protective effect against contamination is superior to that of other measures such as Charney’s ‘clean air’ protection, or prophylactic systemic administration of antibiotics. The protection against haematogenous infection of a prosthesis in a late postoperative phase is doubted on the basis of experimental research and has been insufficiently proved by clinical studies. Its value at reimplantation, if necessary one-stage, of an infected endoprostheses has been demonstrated convincingly, on the other hand. In-vitro studies show that many antibiotics are released from various types of cement and that a diffusion process is always involved.

In order to be used in bone cement, antibiotics have to fulfill a number of conditions (Wahlig and Buchholz, 1973; Welch, 1978):

1. Good solubility in water
2. Heat stability (50 to 150°C)
3. Protracted stability at 37°C
4. No fixation to cement molecules
5. Small volume
6. Little influence on mechanical properties of the cement.

In addition, the antibiotic should possess the following microbiological qualities:

1. Maximal broad spectrum
2. Bactericial action
3. Activity at small doses (low MIC and MBC)
4. Low primary resistance
5. Low allergy and toxicity.

In-vitro and in-vivo studies show that gentamicin fulfills the above requirements. Its use, particularly in Palacos® is a logical choice.
5.1. Introduction

The results of the use of antibiotic-containing cement in prosthetic surgery prompted a number of surgeons to apply the antibiotic-containing cement in the treatment of osteomyelitis. A favourable effect was expected from the combination of packing the cavity (see par. 2.6.4) and the release of an antibiotic.

Vidal and Allieu used PMMA with antibiotic for massive packing of an osteomyelitic cavity in 17 patients. They report only one bad result. A sterilizing effect of the exothermic polymerization reaction was postulated (Vidal and Allieu, 1969). Jenny reports unsatisfactory results of the same technique and repeats the attempt after adding gentamicin to the cement, again with little success (Jenny et al., 1977; Jenny and Taglang, 1979). Voorhoeve and Stöhr describe 17 patients treated with an antibiotic-containing cement plug (Voorhoeve and Stöhr, 1973; Stöhr et al., 1973). They observed five recurrences, mostly with low dosages of gentamicin. The literature contains no adequate survey of the late results of these methods of treatment. Publications on gentamicin-PMMA beads do explain, on the other hand, why packing the cavity with antibiotic-containing cement was unsuccessful (Klemm, 1977, 1979; Jenny and Taglang, 1979):

1. Drainage of secretion was prevented by the plug and the infection spread in the periphery.
2. After decrease of the antibiotic concentrations, the cement plug continues to act as a foreign body.
3. Removing of the cement plug is difficult and is accompanied by destruction of the bone.
4. Packing the medullary cavity with a rigid cement plug transforms cortical into cancellous bone and disturbs the biomechanical relations, so that fractures occur.

Klemm observed more frequent recurrence of the sinus with a sterile secretion. He regards this as a manifestation of a foreign-body reaction to the cement, and the infection that occurred along the cement cover as a retrograde infection (Klemm, 1977, 1979). These bad results of solid plugs in 1972 prompted Klemm to knead the cement into small spheres before introducing it into the wound. This gave better results than the solid cement plug. Later, the loose spheres were strung on a thread and from 1976, they were manufactured at the factory from Palacos® (firm of Kulzer, Bad Homburg) and gentamicin (Refobacin®, Merck, Darmstadt). When these were used clinically, the following advantages were noticed, especially by comparison with the solid cement plug:

1. Retained possibility of drainage of the secretion
2. Gradual filling of the space between beads by granulation tissue.
3. The beads are easy to remove because they are strung on a thread.
4. Packing with beads was shown by a tension-optical study not to affect the biomechanical properties of the bone.

5. The many small spheres greatly increase the surface of the cement. This leads to release of more gentamicin per unit of time from the same amount of cement (see par. 4.2)
6. Since the cement hardens outside the body, no thermic damage to the patient's tissues is to be expected, and less toxic action of monomer. (Klemm, 1977)

5.2. The beads

The gentamicin-PMMA beads as they are being factory-made since 1976, are spherical with a diameter of 7 mm. They consist of methyl methacrylate-methylacrylate copolymer. One bead of 0.2 g contains 7.5 mg gentamicin sulphate (equivalent to 4.5 mg gentamicin base) and 20 mg zirconium dioxide (radiocontrast medium). In addition, the beads contain a little glycine and a residue of the catalyst, dibenzoyl peroxide (maximally 0.5 %).

The beads are supplied loose (in sets of 10) or strung on a chromium-nickel multistranded thread: 10, 30 or 60 beads to a chain*. The chains measure approx. 1 cm per bead (Wahlig et al., 1977, product information Septopal®, Merck Darmstadt) (Fig. 5.1).

![Figure 5.1 Gentamicin-PMMA beads. The beads are spherical with a diameter of 7 mm. They are supplied singly, or strung on a metal wire, 10, 30 or 60 beads to a chain.](image)

Factory production of smaller beads has so far not proved possible. These smaller beads of 3 x 5 mm, the so-called mini-chains have been hand-made by Asche and used, among other applications, in surgery of the hand (Asche et al., 1979). Not all antibiotics that are released in vitro from test blocks of cement are suitable for admixture to beads. During manufacture of beads at the factory, temperatures of 120 to 150° are reached (Grieben, 1981), so that heat-stability becomes an even more important condition.

There are no publications or reports concerning antibiotic-containing cement beads in other combinations.

* The author is aware that beads strung on a thread should be called strings rather than chains. However, the latter word having gained currency in Anglo-Saxon literature, it has been used throughout this book, also, to avoid confusion.
than gentamicin with Palacos®. On the other hand, antibiotics have been mixed in plaster beads (Mackey et al., 1982): gentamicin, fucidine, cefazolin and lincomycin. These antibiotics are also released from plaster by diffusion to an aqueous environment. The plaster beads need not be removed and are said to contribute to osteoneogenesis in the cavity in the bone (Peltier and Jones, 1978) (see also Chapter 2.6.4).

5.3. In-vitro research

The gentamicin-PMMA beads, also, at in-vitro studies show a diffusion process with the release of gentamicin proceeding as an exponential function. Wahlig et al. in solutions of beads in a phosphate buffer observed a release of gentamicin that showed a half-life during the first 10 days of 3.3 days. During these first 10 days, a total of 1.92 mg gentamicin is released per bead to the surrounding elution fluid (10 beads in 10 ml). On the first day, 200 to 400 μg gentamicin is released per bead and per ml elution fluid (Wahlig et al., 1977).

After replacement of the hand-made beads by factory-made beads, this even rose to 400 to 600 μg per 24 hours on the first day (Wahlig and Dingeldein, 1978; Wahlig et al., 1978; Wahlig, 1979, 1980, 1981). After 40 to 80 days, the release is diminished to 10 μg/bead/day/ml elution fluid.

5.4. In-vivo research

Pharmacokinetic properties and the activity of the gentamicin-PMMA beads have been studied in dogs (Wahlig et al., 1977, 1978; Wahlig and Dingeldein, 1978; Wahlig, 1979, 1980, 1981). Gentamicin-PMMA beads implanted in non-inflamed femurs in 12 healthy dogs show a release rate that is comparable to the findings obtained during in-vivo studies of antibiotic-containing cement in humans (par. 4.3.1). Two to four hours after the operation, a maximal serum concentration of gentamicin is determined that is low: 0.3 μg per ml. The concentrations in the urine are maximal during approximately the first postoperative day (1.5 to 20 μg per ml) but they depend on the urine flow. In the serum, gentamicin is no longer demonstrable after 12 days, in the urine it only becomes non-demonstrable (by a microbiological method) after 115 days. Assays during 10 days postoperatively show a urine concentration of 10 to 18 μg per ml (Wahlig, 1980).

Here, also, the tissues around the beads show a gentamicin concentration that depends on the distance to the beads and on the type of tissue. The highest concentration is found in the haematoma (104 to 212 μg per ml), the lowest in the cortex (0 to 20 μg per gram tissue, moist weight). Cancellous bone immediately beside the beads shows a higher concentration than that at a distance of 2 to 3 cm (see Table 5.1).

The exudate shows a concentration that reaches a peak after about four days and subsequently decreases linearly. Härlé and Ritzerfeld determined the concentrations in five dogs. For nine days, all concentrations in the exudate were higher than 5 μg per ml and maximally 80 μg per ml, for amounts of exudate that ranged from 1.8 to 20.4 ml per day. A decrease of the volume of the secretion is accompanied by an increase of the concentration of the gentamicin in it. The product of volume per day and concentration in the secretion indicates the amount of gentamicin released per day into the secretion. According to Härlé, this diminishes linearly. After 10 days the amount of gentamicin released per day has fallen to only 5% of the original value (Härlé and Ritzerfeld, 1979).

The possibilities of using gentamicin-PMMA beads were tested in 21 dogs with the aid of a femoral osteomyelitis provoked artificially by means of Staphylococcus aureus. Treatment of the inflammation five to seven weeks after infection, with debridement and implantation of gentamicin-PMMA beads resulted in rapid clinical improvement that was confirmed radiologically and scintigraphically. A control group without gentamicin-PMMA beads still showed infection after a few months, even when the inserted foreign bodies had been removed (Wahlig et al., 1978; Wahlig, 1981). PMMA beads not containing gentamicin caused a more severe infection (Wahlig et al., 1977; Wahlig, 1981).

5.5. Clinical research

Clinical applications enabled assay of concentrations of the gentamicin in humans (Dingeldein and Wahlig, 1977; Jenny et al., 1977; Lidgren, 1977; Wahlig et al., 1978; Hedström et al., 1980). Here again, it is always found that the serum level of the gentamicin is low and peaks shortly after operation. In 10 patients, with 80 to 180 beads, the peak always remained below 0.5 μg per ml (Wahlig et al., 1978; Wahlig, 1981).
After implantation of 14 to 90 beads in the soft tissues of seven patients, the serum level was even lower (Wahlig, 1981). The urine concentration of the gentamicin is maximal after two to three days; levels higher than 10 µg per ml have never been measured (Wahlig et al., 1978; Wahlig, 1981). Jenny after one to three months, with gentamicin-PMMA beads in situ still observed urine levels of 0 to 0.7 µg per ml (Jenny et al., 1977) (Fig. 5.2).

![Gentamicin-PMMA beads](image)

**Figure 5.2** Schematic representation of the concentrations of the gentamicin (in µg/ml) in the serum, the exudate and the urine. Data have been culled from the literature and confirmed by personal determinations (see Chapters 13 and 15). The gentamicin concentration is represented logarithmically. This graph, just as Table 5.1 shows that after 10 to 15 days, the concentration of the gentamicin in the exudate has fallen below the minimal inhibitory concentrations of most bacteria. In other words, after this period no influence of the gentamicin-PMMA beads on the healing of the infection is to be expected.

The wound exudate here also showed a very high initial concentration shortly after operation, sometimes decreasing from the beginning, sometimes only decreasing after a peak on the second or third postoperative day. The maximal concentrations determined vary greatly.

Wahlig et al. (1978) report a concentration of 345.6 µg per ml in a patient with 87 beads on the second to third postoperative day, whereas Lidgren determined a maximal concentration of 17.0 µg per ml in a patient with 540 beads on the first postoperative day (Lidgren, 1977).

The concentration in the wound exudate is influenced by the number of beads, the amount of exudate secreted per unit of time and the time elapsed since implantation, as observed during in-vitro studies (Chapter 4). In humans, and during use of gentamicin-PMMA beads, the influence of these variables on the gentamicin concentrations has not been determined with sufficient thoroughness.

In nine patients, Wahlig was able to determine the gentamicin concentration in the tissues, 30 to 70 days after implantation. He observed a distribution of the concentration over the various tissues identical to that in test animals (Table 5.1) (Wahlig, 1979, 1981).

### 5.6. Histological examination

The reaction of the body to the gentamicin-PMMA beads has been tested *in vitro* by culturing fibroblasts from rabbit kidneys on gentamicin-PMMA and, as usual, on glass. This showed the tissue tolerance of gentamicin-PMMA to be very good (Wahlig et al., 1977, 1981). *In vivo* the reaction has been assessed in tissue that could be removed some time after implantation from beside the gentamicin-PMMA beads. By this method, Walter found in 31 biopsies taken two weeks to 24 months after implantation that the gentamicin-PMMA beads often provoke a foreign-body reaction (Walter, 1977).

Bonk and Frieden also saw a foreign-body reaction with giant cells in excision biopsies from 17 patients (Bonk and Frieden, 1979). Böhm and Hörster examined 147 biopsies from 61 patients which implies from a number of patients several biopsies were taken (Böhm and Hörster, 1979). Just as Walther, they found good correlation of the clinical evolution of the inflammation and the histological picture. They observed that, from the histological point of view, the healing process after implantation of gentamicin-PMMA beads does not proceed differently from that of osteomyelitis treated in other ways. However, the course was more rapid, with less inflammatory reaction. These authors, also, observed a foreign-body reaction which, however, did not influence the healing process.

### 5.7. Application and technique

The application, indications, contraindications and results of the treatment with gentamicin-PMMA beads have been explained at several symposia. Four review papers have been published (Contizen, 1977; Burri and Rüter, 1979; Smith, 1980; Van Rens and Kayser, 1981). Where in this chapter general remarks on gentamicin-PMMA beads are not accompanied by references to the literature, these may be found at various places in these review papers.

The use of gentamicin-PMMA beads is always a part of a more comprehensive treatment of the infection. It is only a supplement to other, mostly surgical interventions (Klemm, 1979, 1980*), especially nettoyage and stabilization.

*Nettoyage,* in contradistinction to debridement, also comprises excision of non-osseous pathologically changed tissues (scars, sinuses, granulation tissue) and removal of sequestra and foreign bodies (osteosynthesis material, bone cement) (Nielsen, 1969). Inadequate nettoyage leads to recurrence of the infection. Gentamicin-PMMA beads, also, have disappointed surgeon who attached undue importance to them. History repeats itself: the introduction of antisepsics and antibiotics also let down those who believed that chronic infections would be relegated to the past (par. 2.6).

An exception to the rule of nettoyage is the early postoperative period in infection with osteosynthesis material in situ. Some authors prefer to wait until adequate consolidation is accomplished and leave the osteosynthesis material in situ (Burri, 1979; Müller, 1981; Vecsei and Barquet, 1981). Once there is consolidation, the plate may
Figure 5.3  Treatment of osteomyelitis of a tibia (a) always begins with nettoyage and, if necessary, sequestrectomy (b). Subsequently, stabilization, preferably by external fixation, and implantation of the gentamicin-PMMA beads (c). After 14 days, the gentamicin-PMMA beads are removed and the cavity, if necessary, is packed with cancellous bone (d).

Stabilization may also be achieved with removal of osteosynthesis material and in a defect pseudarthrosis, by making use of external fixation material, especially in diaphyseal regions (Klemm and Vecsei, 1980), in which case the fixation nails have to be inserted outside of the infected area (Härle, 1979b) (Fig. 5.3).

While performing nettoyage, it is constantly necessary to choose between two diciderata: maximal radicality and maximal conservation of skeletal continuity. Information concerning the borderline of vitality of the bone may be obtained in several ways. Disulfine blue\textsuperscript{R} (ICI) stains vital tissues green, while sequestra stand out in white. One hour prior to operation, 30 ml Disulfine blue\textsuperscript{R} solution is injected intravenously in 10 minutes. This technique requires bloodlessness ("Blutleere") of the extremity (Klemm, 1977; Jenny, 1977; Hedström et al., 1980).

Tetracycline is incorporated into vital bone. At operation, it is rendered visible by UV light. It has to be administered orally, 250 mg three times daily on three days during the week before the operation (Enneking, 1979). If no staining of the vital bone is used, the vitality of the bone may be recognized by the punctate bleedings, that are absent in sequestra (Müller and Biebrach, 1979). The bloodlessness of the extremity renders it easier to recognize the borderline of the vitality in the bone. To this purpose, it is advisable not to exsanguinate the extremity entirely by bandaging ("Blutsperre" as distinguished from "Blutleere").

A special problem are the infections after intramedullary fixation. Efficient sequestrectomy of the lamellar sequestra is only possible by drilling out the medullary cavity to 1 mm beyond the dimensions of the nail (Klemm, 1978\textsuperscript{b}; Lidgren and Törholm, 1980).

Endoprostheses in case of infection should be removed completely: all components should be regarded as infected and every residual fragment of cement may cause a recurrence of the infection (see Chapter 4).

During introduction of the gentamicin-PMMA beads it is necessary to insert as many beads as possible into the entire infected area, in order to achieve the highest gentamicin concentration possible in the entire infected region. In this connection it should be kept in mind that the capacity of the gentamicin to diffuse from the beads into the tissues is limited (see par. 5.3). Klemm dusts the wound with thrombin powder to bring about rapid organization of the haematoma, thereby preventing the loss by discharge of gentamicin-containing secretion (Klemm, 1980). Since 1978, after removing a hip prosthesis, he packs the cavity with gauze to reduce the dead space and to prevent excessive blood loss (Klemm, 1980\textsuperscript{b}, 1981\textsuperscript{a}).

The chains of beads should be implanted in such a way that removal remains possible: along a meandering course. The risk that chains catch on each other or on a bony edge should be avoided. For intramedullary introduction, e.g. after removal of an intramedullary nail, there exists a useful special insertion instrument (Fig. 5.4).

A high local gentamicin concentration is achieved optimally by:
1. Implantation of as many beads as possible;
2. Closure of the skin, if necessary with transient use of synthetic skin (e.g. Epigard\textsuperscript{R}, Parke-Davis);
3. Draining sparingly: vacuum drainage should be carried out for a brief period only and soon be replaced by syphoning.

Jenny considers watertight closure of the wound so important that he prefers an open cancellous bone graft if the wound cannot be closed (Jenny et al., 1977). K. H.
Müller, on the other hand, regards retention of secretion as the main cause of recurrence and withdraws it continuously by means of redon or chest pump drainage. In his view, the loss of gentamicin does not cause failure of the treatment and he does not regard open treatment as contraindicated (Müller, 1978; Müller and Biebrach, 1979).

Härle and Ritzerfeld on the basis of determination of concentrations in exudate advise against suction drainage (Härle and Ritzerfeld, 1979).

The chains can be placed in the wound in such a way as to leave the last bead protruding from the skin. Allegedly, this renders it possible to remove the chains more easily and without anaesthesia. It is then necessary to remove the chains after 10 to 14 days. The gentamicin-PMMA bead chains, namely, become soon enveloped in a firm granulation tissue. This anchors the chains in place to a degree depending on their disposition (extended, rolled up) and on the type of surrounding tissue (soft parts, bone). Fixation might be prevented by daily removal of one or two beads, starting on about the seventh day after operation. If removal of the chains is postponed for longer than two to three weeks, surgery is required.

Removal of the beads without anaesthesia and surgery is not generally recommended because it is said to be painful and difficult.

Some authors do not leave the chains protruding from the skin and remove them at a second operation (Müller en Biebrach, 1979; Härle, 1981b).

If surgical after-treatment is necessary, e.g. a cancellous bone graft or reimplantation of a prosthesis, the chains may be left in situ longer, for a few weeks or months. At reoperation, it is then mostly necessary to excise them together with the granulation tissue. Extraction, for instance from a femoral shaft, is no longer possible at that stage.

No adverse effects are known of gentamicin-PMMA beads that have remained in situ permanently. Some patients refuse reoperation for removal of the chains. Then, if a Girdlestone situation exists, the metal wires are found to break (Vecsei, 1981b; Klemm, 1981b) (Fig. 5.5). It happens occasionally that the last bead slips off a chain, particularly in case of removal long after operation. The slight disadvantage of leaving such beads in situ should be weighed against the disadvantages of the frequently extensive intervention necessary to remove such left-behind beads. As a rule, this necessitates the use of an image intensifier (Fig. 5.6).

Combating the inflammation does not require treatment for longer than seven to 10 days, since after this period the gentamicin levels have fallen greatly.

Success of the treatment should be visible at that stage, revealed by rapid covering of genta beads with granulation tissue, rapid attenuation of local signs of infection and decrease of the BSR.
Failure of the treatment is revealed first of all by absent growth of granulation tissue and persistent discharge from the wound. In that case, the treatment should be repeated by another nettoyage and insertion of new gentamicin-PMMA beads.

The result of the treatment cannot be determined by culturing after removal of the genta beads: owing to the high gentamicin concentration, the culture is usually sterile.

Certain authors in addition to the local treatment with gentamicin-PMMA beads also administer antibiotics systemically (Thoma, 1978; Hedström et al., 1980; Weise and Weller, 1980; Härle, 1981a). Others regard this additional systemic stress as superfluous (Jenny and Taglang, 1980; Klemm, 1980a; Vecsei and Barquet, 1981). It is only on particular indications that they consider it desirable to add systemic antibiotics to the local gentamicin treatment. One reason for prophylactic administration is the fact that extensive covering soft parts, as at the thigh or hip, are always contaminated at operation. The gentamicin from beads, buried deep, cannot diffuse adequately in voluminous covering soft parts. Addition of systemic antibiotics for therapeutic purposes is indicated in case of pronounced spread of acute signs of infection in the soft parts, of weak resistance of the patient to infections and of sepsis. In Klemm’s clinical material, additional systemic antibiotics were necessary on these indications in 15% of the cases (Klemm, 1980a).

5.8. Bacteriological aspects

The main purpose of the local treatment with gentamicin-PMMA beads is to reach very high local tissue levels not necessitating high serum levels. When this method of administration is used, it should be kept in mind that concepts such as ‘resistance’ and ‘spectrum’ are relative.

Gentamicin is effective against a wide range of bacteria: both gram-positive and gram-negative and hence is called a broad-spectrum antibiotic. It acts by interfering with the protein synthesis of growing bacteria: it is bactericidal. With the usual dosage and parenteral administration, tissue concentrations of 1 to 4 μg per ml are reached. Bacteria with a MIC (minimum inhibitory concentration) higher than 4 μg per ml are regarded as resistant (Walter and Heilmeyer, 1975). The MBC (minimum bactericidal concentration) is for gentamicin, as a bactericidal antibiotic not much higher than the MIC. At a gentamicin concentration of 4 μg per ml, 80 to 90% of the gram-negative bacteria are inhibited. Streptococci and anaerobics as a rule have a higher gentamicin MIC and then are called resistant.

However, by raising the local gentamicin concentration, it becomes possible to destroy bacteria with a higher MIC as well. Determination of the MIC of a ‘resistant’ bacterium will provide information whether it is possible to destroy such a bacterium by a higher concentration of gentamicin. Accordingly, with this method
of treatment, the term ‘resistance’ should be expressed quantitatively, by determination of the MIC (Kayser and Eberle, 1981).

Dingeldein studied 64 bacteria from culturing material from osteomyelitis patients: 74% of the bacteria had MIC's lower or equal to 4 μg per ml (Dingeldein, 1979). Kayser investigated the sensitivity to gentamicin of 381 strains of enterococci and found that 98% were inhibited by 50 μg per ml gentamicin. Other ‘resistant’ bacterial strains from osteomyelitis patients also usually had a relatively low MIC. A high degree of resistance is rare in his material. He concludes that infections caused by bacteria with MIC's up to 50 μg per ml can be treated with gentamicin-PMMA beads (Kayser and Eberle, 1981).

Resistance to gentamicin is largely due to R-factors. These are resistance factors which as genes may occupy an extra-chromosomal position in the bacterium. These R-factors may be transferred to the same or some other bacterial strain and play an important part particularly in hospital infections (Lode, 1979). With increasing use of gentamicin, growing resistance to it might be feared. However, Dingeldein in a three-year study of 544 patients in Klemm's clinic did not see any increase of the resistance to gentamicin; on the contrary, the resistance to gentamicin of certain bacterial strains even decreased (Dingeldein, 1981).

As the release of gentamicin from the cement tapers off, gentamicin concentrations become low in the long run. She also investigated the effect of such low, subinhibitory concentrations of gentamicin on the development of resistance. The MIC's of the bacteria exposed to these low concentrations remained unchanged (Dingeldein, 1981). This confirmed earlier studies of certain other authors of the influence of subinhibitory concentrations of antibiotics (Lorian, 1978), but was contradictory to the findings of Gialdroni Grassi (1979).

5.9. Indications and contraindications

Klemm regards gentamicin-PMMA beads as indicated in bone infections and infections in the soft parts (Klemm, 1980a). Several authors mention application in acute and chronic haematogenous osteomyelitis, acute and chronic post-traumatic osteomyelitis, infection pseudarthrosis, pinhole sinuses and empyema of the medullary cavity (in: Contzen, 1977; Burri and Rüter, 1979; Smith, 1980 and Van Rens and Kayser, 1981).

Treatment of arthritis is also said to be possible provided it involves the shoulder or the knee (Klemm, 1980a). Gentamicin-PMMA beads have a function in the treatment of infected endoprostheses if replantation is not carried out directly (Walenkamp, 1981; Wilde, 1981). No literature is yet available concerning use of the beads in acute, early postoperative infection of a prosthesis. Technically, a prosthesis left in situ may render introduction of gentamicin-PMMA beads difficult for lack of space. In such cases, suction drainage is to be preferred.

On a number of indications, use of the beads may be called prophylactic. By using them in open fractures, it is attempted to prevent post-traumatic osteomyelitis (Taglang, 1980; Vecsei and Barquet, 1981; Klemm, 1981a). By covering an open cancellous bone graft with gentamicin-PMMA beads, this graft is protected from secondary infection and will be rapidly covered by protective granulation tissue (Schulte and Burri, 1979; Burri, 1979).

Many applications in inflammations of soft parts are also of a prophylactic nature. Eberle concludes that use of gentamicin-PMMA beads at amputations of extremities for diabetic or arteriosclerotic gangrene with phlegmonous inflammation allows a more sparing amputation (Eberle, 1978). Goudarzi reports good results of use of gentamicin-PMMA beads in contaminated gunshot wounds (Goudarzi, 1981).

Hirsch and Güntert (1979) implanted gentamicin-PMMA beads after pneumonectomy to prevent empyema of the residual cavity.

Sachweh observed that implantation of gentamicin-PMMA beads in the cavity after abdomino-perineal rectal amputation resulted in far better wound healing than use of a drainage system (Sachweh, 1979). Prophylactic use of gentamicin-PMMA beads after excision of coccygeal sinuses and in contaminated appendicectomy wounds also reduces the incidence of infections (Sachweh, 1981).

Kampshoff reports good experiences in anorectal fistulae (Kampshoff, 1979).

Wassner treated wound infections with the aid of gentamicin-PMMA beads in 133 patients, mostly with perforated appendicitis and empyema of the gallbladder (Wassner and Drognit, 1978; Wassner, 1981). Seng et al. used gentamicin-PMMA beads in a paranephritic abscess and in a septic necrotic shrunken bladder (Senge et al., 1978). Härle treated 80 patients with various soft-part infections of the locomotor apparatus (Härle, 1980, 1981a). Applications are possible in abscesses of all kinds and localizations: postoperative wound infections, mastitis, septic endometritis, etc. (Klemm, 1980a).

Grieben in a collective study reports applications of gentamicin-PMMA beads in soft parts in 361 patients: 36 times prophylactically, 84 times in postoperative infections and 241 times in primary soft-part infections (Grieben, 1980, 1981a).

No clinical literature on abdominal intraperitoneal application has yet been published. Jonkisz et al. in an unstated number of rabbits implanted gentamicin-PMMA beads in the abdominal cavity. Rapid connective-tissue fixation developed around the beads, with a predominance of young fibroblasts. Gentamicin was demonstrable in the urine, proving that it was being released (Jonkisz et al., 1980). However, this study of intraperitoneal implantations certainly does not justify any recommendations for clinical applications.

On the contraindications, there is no unanimity. Most contraindications are not absolute, and are not endorsed by all authors.

- Osteomyelitis of long standing with severe sclerosis is mentioned as an absolute contraindication to treatment with gentamicin-PMMA beads in Klemm's earliest publication (Klemm, 1977); later, the result is classified as poor (Klemm, 1979) and in more recent publications no more mention is made of the matter (Klemm, 1980a, 1981). It may be important that in some of these patients he did not observe any reaction in the shape of granulation tissue while removing gentamicin-PMMA beads (Klemm, 1980a).

Other authors also regard this form of osteomyelitis as the one most difficult to treat, with the least chance of
- In the treatment of an acute infection with osteosynthesis material in situ, the spread of the inflammation may be arrested. The tips of screws, and the osteosynthesis material which after a few weeks is enveloped in connective tissue are inaccessible to the antibiotic. A chronic infection will certainly not heal without removal of this material (Klemm, 1980). One reason to leave the osteosynthesis material in situ may be to await consolidation, especially in places where application of external fixation is difficult.

- Impossibility to close the wound is regarded by Jenny as a reason to choose some other method of treatment (Jenny et al., 1977). Once in a way, however, the wound is left open on purpose (Müller and Biebrach, 1979).

- Resistance to gentamicin may be a cause of failure of the treatment and hence constitutes a contraindication. It is especially infection by Streptococcus faecalis that is said to be difficult to treat with gentamicin-PMMA beads (Klemm, 1981). If a causative agent shows resistance, the MIC should be determined to find out whether treatment with gentamicin-PMMA beads could be effective (see par. 5.7).

- Allergy to one of the components of the gentamicin-PMMA beads is not an absolute contraindication. Several patients with a positive gentamicin skin test have been treated by Buchholz and Elson with antibiotic-containing cement at reimplantation of a prosthesis. None of them developed a general allergic reaction (Elson, 1979). An allergic reaction to the chromium-nickel wire of the chain is reported in one patient (Grieben, 1981). Briefly, therefore, the risk of allergic reactions is slight and the treatment is simple because the strings can be removed immediately, certainly when they protrude from the skin. There is one case report of a myasthenia-like reaction with polyneuropathy in a patient treated with gentamicin-beads (Martens and Ansink, 1979). Neuromuscular block is a very rare side effect of aminoglycosides, but the neuromuscular transmission is also affected by polymyxin derivatives, tetracyclines and lincomycin derivatives (Booy, 1980).

5.10. Gentamicin-PMMA beads versus irrigation systems

The irrigation system, just as the gentamicin-PMMA beads is only one part of the treatment of an infection (see par. 2.6.7). However, the irrigation system suffers from several important disadvantages.

To function well it requires first-class nursing care, accommodation and technical facilities. Even Willenegger, the promotor of the irrigation system, considers simpler treatment systems desirable (Willenegger, 1979). A retrospective comparison of gentamicin-PMMA beads and an irrigation system was carried out by Asche and Klemm in two groups of 38 patients (Asche and Klemm, 1977; Asche, 1978) and by Kentner in 34 and 44 patients, respectively (Kentner, 1981), while prospective studies were carried out by Iledström et al. (1980) and by Lautenbach (1980). Other authors present arguments without substantiating them by figures. The following arguments are being used in favour of the premise that the gentamicin-PMMA beads are to be preferred to an irrigation-drainage system:

- The patient is no longer chained to the bed and to the drains of the system. Primary closure of the wound as a rule gives a better cosmetic result. The period of bed rest and particularly also that of hospitalization is shortened. Temporary discharge with the beads in situ is possible. When the wound is closed, the patient need not be kept in isolation after a few days.

- The nursing staff is burdened heavily when an irrigation-drainage system is used. Drains, which are prone to clog and leak, necessitate intensive care. The necessity of isolating the patients also creates extra work for the nursing staff. Cleansing and dressing of the wound is necessary only incidentally during gentamicin-PMMA-bead treatment.

- From the bacteriological point of view, drainage systems have severe drawbacks. Superinfection with gram-negative pathogens, especially Pseudomonas, is notorious. The increasing use of gentamicin has not led to an increase of resistance to gentamicin, according to a study by Dingeldein (Dingeldein, 1981). Moreover, improved hygiene and less parenteral administration of antibiotics cause a reduction of the proportion of resistant bacterial strains.
Financially, large amounts can be saved owing to
- shortened hospitalization
- less intensive nursing
- reduced use of parenteral antibiotics and irrigation fluid
- reduction of wound infections by prophylactic use

Asche and Klemm (1977) on the basis of 38 patients calculated that hospital stay was reduced by approx 50%. Patients treated with a drainage system required an average hospitalization of 60 days, those treated with gentamicin-PMMA beads an average of 32 days. The costs involved averaged DM 15,000 and DM 7,000, respectively.

Kentner found that the mean duration of hospitalization was 130 days with a drainage system and 62 days with use of gentamicin-PMMA beads (Kentner, 1981). Sachweh concluded that after abdomino-perineal rectal amputations, the incidence of postoperative infections could be reduced by packing the presacral cavity with gentamicin-PMMA beads. The proportion of postoperative infections that amounted to 69% with a drainage system was then reduced to 20%. This shortened the average duration of the hospital stay from 44 to 21 days. A similar cost reduction by shortening hospitalization was accomplished by using gentamicin-PMMA beads in the wound of an appendectomy when a phlegmonous or perforated appendix was involved. The cost reduction for these appendectomies according to him amounted to DM 1200 per patient (Sachweh, 1981).
6.1. Introduction

Gentamicin belongs to the group of the aminoglycosides. Aminoglycosides are oligosaccharide-like antibiotics that consist of amino sugars interconnected by a glycosidic link. In solution, the amino groups ensure the alkaline character of the compounds.

The sulphates are highly soluble in water and stable at pH 6 to 8 (Lammers et al., 1968; Kagan, 1980). Gentamicin is closely related chemically to sisomicin, tobramycin and netilmicin. It is a fermentation product of Micromonospora purpurea. The commercially available gentamicin consists of three structural analogues: 40% gentamicin C₁, 20% gentamicin C₁₈ and 40% gentamicin C₂ (Lode, 1979).

6.2. Bacterial aspects

The aminoglycosides are characterized by a rapid bacterial action. Aspects of their action in sensitive bacteria are binding to ribosomes in the cell and interference with the protein synthesis. This brings about non-sense proteins and morphological changes of the bacterial cytoplasmatic membrane. Loss of essential cytoplasmatic components causes cellular death (Jackson, 1977; Lode, 1979).

In vitro there is a very broad spectrum of action. Most aerobic gram-negative bacteria are sensitive. The sensitivity to aminoglycosides of the gram-positive aerobic bacteria varies. Most strains of Streptococcus pneumoniae, Streptococcus pyogenes and Streptococcus faecalis (including the penicillinase-producing ones) are resistant. Anaerobic bacteria are not sensitive to aminoglycosides administered in the usual, parenteral way, Bacteroides being especially insensitive (Kagan, 1980). The activity of the aminoglycosides is influenced by, among other things, the pH and the cation concentration.

When gentamicin is administered parenterally, tissue concentrations of approx. 1 to 2 µg per ml are reached. In general, bacteria with an MIC of less than 1 µg per ml are regarded as sensitive, those with an MIC of more than 4 µg per ml as resistant. The bactericidal concentration (MBC) is the same or slightly higher (Walter and Hameister, 1975; Lode, 1979). The nature of bacterial resistance to aminoglycosides varies:

- intrinsic resistance: for instance the incapacity of an aminoglycoside to pass through the cell wall;
- resistance due to mutation. The mutation in question is always a one-step mutation. This kind of resistance to gentamicin has been observed almost exclusively in the laboratory. It has no clinical significance (Wiedemann, 1976);
- enzymatic resistance (often plasmid-coded): in this case, a DNA ring (plasmid) is situated extrachromosomally in the cytoplasm. To this are attached genes (R factors) which cause the insensitivity. This plasmid can be transferred to another bacteria even of a different species (Wiedemann, 1976; Dingeldein, 1979).

6.3. Pharmacokinetics

Since resorption of gentamicin in the digestive tract is minimal, it is administered intramuscularly or intravenously. After intramuscular administration, gentamicin is resorbed fast from the muscles and the peak serum level is reached after 30 to 90 minutes (Jackson, 1977; Lode, 1979).

The distribution in the body is best described by a two-compartment model. We then distinguish a large central compartment and a small peripheral (deep) compartment. As a consequence, the serum level plotted against time forms a biphasic curve with half-lives of two and 112 hours, respectively (Schentag et al., 1977, 1978). The delayed release of gentamicin from the deep compartment causes a very protracted, although slight excretion with the urine. After 24 hours, 85 to 95% of an injected dose of gentamicin has been excreted with the urine (Jackson, 1977).

The central compartment has a distribution volume of 0.15 to 0.30 l per kg, not much larger than the volume of the extracellular water (Jackson, 1977; Lode, 1979). The deep compartment consists of tissues in which gentamicin is accumulated intracellularly. Wahlig et al. demonstrated in dogs and mice that accumulation occurs predominantly in the renal cortex (Wahlig et al., 1974). Accumulation also occurs in the endolymph and perilymph of the internal ear (Federspi et al., 1976, 1977).

In patients with normal kidneys, the non-renal excretion of aminoglycosides amounts to only 2.4% (Dettli, 1976). Virtually all renal excretion probably takes place by glomerular filtration. The renal clearance of gentamicin is 100 ml per minute, based on total plasma concentration. For a protein binding of 20%, the true renal clearance amounts to \( \frac{\text{Cl}_{\text{renal}}}{0.80} \times 100 = 125 \text{ ml per minute} \), which equals the creatinine clearance. The renal clearance of gentamicin is not correlated to urinary flow and \( \text{pH} \), in other words there is no passive reabsorption. Possibly, a small proportion of the aminoglycosides is excreted actively by the tubuli.

Gentamicin is reabsorbed actively in the proximal tubulus. This active reabsorption brings about a gentamicin concentration in the tubular cell that may be over 50 times higher than the serum level (Scherberich et al., 1980). This is probably accomplished by the system that actively reabsorbs aminocoids and protein residues.

6.4. Side effects of gentamicin

6.4.1. Hypersensitivity reactions

Hypersensitivity reactions are possible particularly in the skin and in the haemopoietic system: exanthema, granulocytopenia, anaemia, thrombocytopenia. The reactions are always reversible and are said to occur in 0.3% of patients treated parenterally (Sack et al., 1978).

The cutaneous allergy occurs especially after local application and then is quite frequent. Pirilä et al. among 1760 patients saw allergic skin reactions to local application of the aminoglycoside, neomycin, in 9.8% (Pirilä, 1967). Cross-sensitization occurs frequently with aminoglycosides. An allergic reaction after internal use of gentamicin, and in
the presence of an allergy to neomycin has not been described in the literature, however (Van Joost et al., 1981).

6.4.2. Neuromuscular block
Neuromuscular block is possible owing to influence on the release of acetylcholine (Nielsen and Elb, 1973; Booy, 1980). However, owing to the wide safety margin of the neuromuscular transmission, the effect only manifests itself in patients with neuromuscular abnormalities, e.g. myasthenia gravis. Aminoglycosides also influence muscle-relaxing agents (pancuronium, succinylcholine, NC45) as used in anaesthesia (Rutten et al., 1980). Only five cases of neuromuscular block due to gentamicin have been described, and all these occurred during simultaneous administration of other drugs that also affect the neuromuscular transmission (Martens and Ansink, 1979).

6.4.3. Ototoxicity
Ototoxicity probably results from accumulation of the aminoglycosides in the fluids of the internal ear. These fluids act as a deep compartment and the elimination from the peri- and endolymph is slower than that from the serum. The concentration in these fluids is directly proportional to the dose (Federspil et al., 1976). High concentrations of gentamicin cause destruction of the ciliary cells of the cochlea and of the vestibular labyrinth. This leads to loss of hearing acuity and disturbances of the equilibrium (Igarashi et al., 1971; Waitz et al., 1971; Webster et al., 1971; Jackson and Arcieri, 1971; Brummet et al., 1978; Akiyoshi, 1978; Carrière, 1980). Auditory sensitivity to high tones is affected first, that to lower tones later (Huizing, 1972). Disturbances of the equilibrium may be compensated, especially if they occur gradually.

Ototoxic lesions are said to occur in 1 to 2% of the patients (Jackson and Arcieri, 1971). With growing experience of the use of gentamicin, the frequency of side effects allegedly decreases (Sack, 1978; Lode, 1979). However, when more sensitive tests and prospective studies are carried out, the frequencies are found to be higher (Jackson, 1977; Carrière, 1980).

The possibility of recuperation of the hearing after damage due to gentamicin is very small, unless a very mild lesion is involved (Carrière, 1980). Risk factors are:

- protracted higher concentrations (large surface below the serum level-time curve);
- renal dysfunction;
- use of ototoxic substances in the past;
- simultaneous use of other ototoxic substances;
- neonates are said to be more sensitive to ototoxicity;
- high 'individual susceptibility';
(Bernard et al., 1979a, 1979b; Federspil et al., 1979; Lode, 1979; Carrière, 1980).

6.4.4. Nephrotoxicity
Nephrotoxicity is caused by accumulation of gentamicin in the lysosomes of the proximal tubular cell. Autoradiographic studies show that in the cell there is also some binding to mitochondria and to the nucleus. The accumulation of gentamicin in the lysosomes is believed to cause them to leak enzymes, leading to necrosis of the proximal tubular cell. Accordingly, nephrotoxicity manifests itself with loss into the urine of tubular epithelial cells and enzymes from these cells (Scherberich et al., 1980; Jerauld and Silverblatt, 1980) (Fig. 6.1).

The glomerular filtration is affected by a direct toxic action on the glomerular endothelial cells or by a tubulo-glomerular feedback via the renin-angiotensin II system (Schentag, 1979; Evans et al., 1979).

Here again, with growing experience of the use of gentamicin, the nephrotoxicity during parenteral administration has decreased from 7.7% (1966 to 1967) to 2.9% (1970 to 1973) (Lode, 1979); these figures are based on the serum creatinine level or creatinine clearance as parameters.

Whether nephrotoxicity will occur depends in the first place on the duration of the treatment and on the serum level. It is especially if the minimal serum level is higher than 2 µg per ml and the treatment is protracted that nephrotoxicity is to be expected (Dahlgren et al., 1980). The risk is increased in case of pre-existent damage to the proximal tubulus or reduced renal function (Sensi et al., 1980). Combination with cefalosporins probably increases the nephrotoxicity (Mannion et al., 1981).

Reiner observed in dogs that continuous administration of gentamicin by infusion significantly more...
often had nephrotoxic effects than one single large daily dose. As the principal criterion of nephrotoxicity he regarded a decrease of the creatinine clearance (Reiner et al., 1978).

6.5. Parameters for toxicity of gentamicin

The ototoxicity necessitates control examinations of the hearing and of the organ of equilibrium. Hearing can be measured with adequate sensitivity and good reproducibility with the usual audiological methods. Damage due to gentamicin manifests itself first by loss of sensitivity to high tones (Huizing, 1972; Carrière, 1980). Confusion may result from loss of hearing in case of bad condition, which may be present postoperatively. In that case, however, the loss of hearing affects all frequencies (Carrière, 1980).

Effects on the organ of equilibrium can be determined precisely by measuring nystagmus after stimulation of the organ of equilibrium (posturally or calorically) (Igarashi et al., 1978; Sack et al., 1978). They demonstrated that a raised excretion of AAP in the 24-hour urine may have many different causes: infections, use of cefalosporins or aminoglycosides, renal angiography and urography.

**Sub 3**: β2-microglobulin is a natural body protein that is present in all body fluids. It is the small polypeptide chain of the HLA antigens. It is synthesised by virtually all cells of the body. Being a low-molecular protein, it undergoes complete glomerular filtration. 99.9% of it is reabsorbed in the proximal tubular cells and subsequently metabolised. Its normal serum level is 1 ± 0.2 µg per ml (Vree et al., 1981); it may be raised by increased synthesis or decreased glomerular filtration.

A raised serum level due to increased syntheses of β2-microglobulin is encountered in neoplasia, especially solid tumours and lymphoproliferative diseases and in hepatobiliary, immunological and haematological diseases (Takagi et al., 1980; Beorchia et al., 1981). With increasing age, the median value of the serum level is said to rise: after the age of 70 it is 2.30 µg per ml (Merret et al., 1980).

A rise of the serum level due to decreased GFR occurs, for instance, in case of rejection of a kidney graft (Roxe et al., 1981), but also during use of aminoglycosides, so that the serum level of β2-microglobulin is said to be useful as an early indication of disorders of the GFR (Valsamis et al., 1970; Sethi et al., 1981). However, depression of the GFR in aminoglycoside toxicity is a late manifestation of the nephrotoxicity (Kaloyamides and Pastoriza-Munoz, 1980).

The amount of β2-microglobulin in the urine is normally very small. An increased renal excretion may be due to a raised serum concentration or to disturbance of the tubular reabsorption in hypofunction of the kidney (Evrin and Wibell, 1972; Wibell, 1974; Kult et al., 1974; Revillard, 1979; Vree et al., 1981). This increased excretion into the urine in disorders of the proximal tubular reabsorption makes it a parameter of this renal function (Fig. 11.1).

Just as the excretion of renal epithelial cells and of the enzymes mentioned above, it is a non-specific parameter: tubular dysfunctions of various nature may cause a raised excretion of β2-microglobulin with the urine (Peterson et al., 1969; Hall and Vasiljevic, 1973; Shiroishi et al., 1977; Iesato et al., 1977). The excretion and clearance of β2-microglobulin are also increased in a high urinary tract infection, but in cystitis they are normal (Schardyn et al., 1979).

The non-specific character of β2-microglobulin as a parameter of nephrotoxicity is also confirmed by the fact that its excretion is increased after operations and injuries (Wide and Thorén, 1972) (see also Chapter 11). However, it is a faster-reacting and more sensitive parameter than the others (AAP, enzymes, cylindruria, serum creatinine, creatinine clearance) (Schentag et al., 1978; Schentag et al., 1979).
In the use of gentamicin-PMMA beads, more than in other methods of treatment, the emphasis is on local treatment of the infection. This is a deviation from certain surgical and bacteriological starting points which too often have been accepted as axioma.

The treatment involves the implantation for a few weeks, sometimes a few months, of an antibiotic that when used parenterally has only a narrow therapeutic margin. The side effects of systemically administered gentamicin are admittedly not frequent but if they occur, they are often irreversible. Extra guarantees of safety and certainty about the harmlessness are desirable when a potentially toxic substance is used in situations that are not potentially fatal.

The use of a new method of treatment is adequately justified if its results are better than those of earlier methods. If the results are similar, factors other than the therapeutic results should also be taken into account. On the basis of the study of the literature described in the preceding chapters, the following questions may be asked in regard to the treatment of infections by means of chains of gentamicin-PMMA beads:

1. Is their use in the treatment of infections successful?
2. Is treatment of the infection by means of these chains of beads more successful than other methods of treatment?
3. Are there other aspects of the treatment of infections, apart from the cure rate, on the basis of which the use of gentamicin-PMMA beads is or is not to be preferred? If so, what are they?
4. Do low serum levels of gentamicin affect the kidney, in other words, are nephrotoxic side effects to be expected?
5. Are ototoxic side effects (audiologic or vestibular) to be feared during treatment with gentamicin-PMMA beads?

These questions could be considered on the basis of the experience gained in the treatment of infections in orthopaedic patients. Accordingly, their consideration and answering is limited to use of gentamicin-PMMA beads in infections of the locomotor apparatus, predominantly in osteomyelitis and infected endoprostheses.

Answers to questions 1, 2 and 3 will be sought by studying the data of patients who have been treated with chains of gentamicin-PMMA beads. In addition, these data will be compared with data concerning the treatment and therapeutic results of a group of patients treated by methods other than gentamicin-PMMA beads. The prospective and retrospective studies are reported in Chapters 8 and 9. The comparative statistical analysis is reported in Chapter 10.

Chapters 11, 12 and 13 will be concerned with finding an answer to question 4.

For the investigation of the possible influence on the kidney of gentamicin during treatment with gentamicin-PMMA beads, we have opted for a study by means of ß2-microglobulin assays in serum and urine since this is believed to be a more sensitive parameter than the others. However, in order to be able to answer question 4, three sub-problems have to be solved:

a. Is ß2-microglobulin indeed a sensitive parameter of the effect of gentamicin on the proximal tubular cell? An attempt to obtain an answer to this question from an experiment with three test subjects is described in Chapter 11.
b. Do factors other than gentamicin also influence the excretion of ß2-microglobulin and are these factors relevant to this study? To find an answer to this question, measurements have been carried out in patients who have been subjected to operation but not to treatment with gentamicin; these are described in Chapter 12.
c. Does a treatment with gentamicin-PMMA beads of approximately two weeks' duration influence the renal tubulus, and can this influence be demonstrated on the basis of the renal excretion of ß2-microglobulin? The investigation of this question is described in Chapter 13.

Chapter 14 describes a study of the possible influence on the ear during treatment with gentamicin-PMMA beads (question 5), which included both audiometrical and vestibular examinations.
Chapter 8. Treatment of infections from 1962 to 1977, without use of gentamicin-PMMA beads

8.1. Introduction

The Department of Orthopaedics of the Sint Radboud Hospital (R.C. University) of Nijmegen has been in existence since the autumn of 1961*. It treats patients from the immediate environment, but an important proportion are referred from outside the region. The latter group of patients as a rule has been treated for some considerable time by other orthopaedic surgeons or general surgeons, and many are referred because of complications risen during the treatment, not rarely an infection.

The treatment of infections of the locomotor apparatus is administered, just as all other therapy, by teams and where necessary in consultation with other disciplines. The Department of Orthopaedics had no facilities for isolated nursing or nursing in an infection unit: patients with an infection are treated in the department itself. There, the only form of isolation available was single rooms. Operations are performed in operating rooms reserved for Orthopaedics.

8.2. Treatment of infection from 1962 to 1977

The treatment of infections of the locomotor apparatus was carried out without a fixed protocol, but may be described roughly. To this purpose, the patients are subdivided into three categories: those with osteomyelitis, infected endoprostheses and infections of soft parts.

8.2.1. Osteomyelitis

Haematogenous osteomyelitis was rarely submitted for treatment in the acute phase but usually only when extensive destruction was already present or a chronic stage had been reached. When treatment was possible at an early stage, decompression of the focus of haematogenous osteomyelitis was performed with debridement and, if necessary, sequestrectomy. Until 1977, a local irrigation-drainage system was introduced if possible and parenteral and oral antibiotics were given for long periods of time.

Early postoperative infections in patients with fractures or after elective surgery were treated by nettoyage, large doses of antibiotics and a closed irrigation system or open drainage of the focus of infection. Stable osteosynthesis material was either left in situ or, if possible, replaced by external fixation.

Chronic osteomyelitis was treated by debridement and, if necessary, sequestrectomy, with removal of osteosynthesis material and of any other foreign bodies. The operation was performed without vital staining and usually without exsanguination. In most cases, an irrigation system was introduced and antibiotics were given. Cancellous bone grafting was carried out in cases with large defects or pseudarthrosis, sometimes primarily but mostly after the infection had been treated first. Any muscle and skin grafting required was performed after healing of the infection.

8.2.2. Infection of endoprostheses

The treatment of a painful, loose endoprosthesis consisted in removal of the prosthesis. Up to 1977, it was attempted to differentiate between aseptic and septic loosening with the aid of clinical signs of infection (general, local), of laboratory tests (BSR, if necessary leukocyte differentiation), and of the roentgenographic and scintigraphic findings.

If infection was diagnosed, an irrigation system was introduced after removal of the prosthesis with all cement, and traction was exerted by means of a tuberosity wire. Irrigation-drainage treatment was administered as described in par. 8.3.

Reimplantation of a prosthesis was sometimes performed after treatment of the infection (two-stage reimplantation), i.e. a few weeks after removal of the infected prosthesis. In most cases, however, the patient was first mobilized on the Girdlestone hip and an interval of six to 12 months under out-patient control was allowed to find out whether the inflammation would recur and whether the patient still wanted to be considered for reimplantation.

8.2.3. Inflammation of soft parts

Infection of soft parts were treated in the classical surgical manner. Infected haematomas were drained and evacuated; abscesses were incised and drained; sinuses were explored and excised with their source.

Infections of soft parts were usually accompanied by osteomyelitis or infection of an endoprosthesis. In such cases, the treatment of the osteomyelitis or of the infection of the endoprosthesis was given priority.

8.3. The irrigation-drainage system

The irrigation-drainage system constitutes the principal alternative to gentamicin-PMMA beads in the treatment of infections. Since until 1977 it was an important part of the treatment, the application of this system during that period is described below. Some technical changes were introduced with the passage of years, progressively more emphasis being placed on prevention of ascending infections via the drainage system.

The irrigation fluid used was Ringer's solution with addition of 10 mg Polymyxin-B-Sulphate® and 10 ml Nebacetine® per 500 ml. Under the influence of gravity, the

*Heads: 1961 to 1969: Prof. Dr. G.M. San Giorgi
1969 to 1972: Prof. Dr. G. Chapchal
1972 – present: Prof. Dr. Th.J.G. van Rens
irrigation fluid entered the wound through a ramified infusion system, mostly through two drains. It drained off through a similar ramified system, with usually slightly wider drains, into a closed bag around which a chest pump provided a negative pressure of approx. 25 cm H₂O (Fig. 8.1). The drains were anchored by suturing them to the skin, and the in- and outlet openings were tended and treated with betadine ointment once a day. In principle, all patients received antibiotics parenterally or orally, guided by the result of the peroperative culture. Three times a week, culture material was collected from the outflow drains. Before this material was collected, flushing was carried out for half an hour with 500 ml Ringer's solution. When three cultures in succession remained sterile, the irrigation-drainage was terminated. Other reasons for discontinuing the irrigation-drainage were frequent clogging of the drains and leakage. In principle, irrigation-drainage was never carried out for longer than six weeks. Even if the cultures remained positive, the drainage system was removed after this period.

Figure 8.1 Suction drainage system as used in the department of Orthopaedics of the Sint Radboud Hospital of Nijmegen. Propelled by gravity, an irrigation fluid flows into the wound through a ramifying system. Outflow is through thicker drains which join and lead the irrigation fluid into a closed bag. This bag is enclosed in a glass bottle in which a chest pump maintains a negative pressure. This creates a controllable suction force on the outflow side of the drainage system, permitting the system to remain closed.

8.4. The follow-up

In order to evaluate the results of the treatment of infections from 1962 to 1977, data were collected on all patients who during that period had been treated for an infection without use of gentamicin-PMMA beads. Patients who belonged to this category but in addition had received treatment with gentamicin-PMMA beads after 1977, have been classified in the group described in Chapter 9.

8.4.1 Method

The aim was to obtain as complete a picture as possible of all patients subjected to operation. To this purpose, the names of all patients who might have been treated for an infection, were collected from the administration of the operation room. Examination of the case reports revealed that 198 patients had been treated for osteomyelitis, a possibly infected prosthesis or an inflammation of soft parts. From every file, the data were collected and after coding stored in the computer. These data, arranged by patient and by operation, are listed in Table 8.0. For every operation, all data were coded separately.

The course of the healing, the presence or absence of recurrences and the ultimate result were evaluated by interpretation of the notes in the patients' case reports.

8.4.2 Material

In slightly over 15 years, 198 patients were treated, one of them bilaterally. These patients' data (sex, origin, localization) are listed in Table 8.1 and Fig. 8.2.

The diagnoses were classified into four main groups: osteomyelitis, infected endoprosthesis, infection of soft tissues and 'non-infected' (Table 8.2). The last-mentioned category comprises the patients in whom treatment for infection had been instituted on the basis of the clinical picture but in whom the cultures, after removal of the painful and sometimes loose prosthesis proved sterile. Also, these patients' files did not contain enough hard evidence (clinical examination, laboratory, roentgen, scan) of the presence of an infection. As proof of infection of an endoprosthesis were regarded the presence of a sinus or abscess, BSR values repeatedly higher than 30 mm in the first hour (and not due to some other cause) and positive culture of material removed at operation.

Radiological abnormalities were not a condition. Scans, when made, were always positive but this did not in itself constitute proof of infection.

Isolated infections of soft parts did occur but most of these infections were associated with osteomyelitis or infection of the endoprosthesis (Table 8.2).

All four main diagnostic categories were divided into sub-groups (see Table 8.3). If a patient's diagnosis was changed in the course of the treatment, the patient was categorized on the basis of the diagnosis made at the start of the treatment.

In the 198 patients with the 199 localizations treated, 345 operations were carried out. Table 8.3 in addition to the number of infections treated shows how many operations were required for each diagnostic category.

The figures shown do not include any after-treatments, such as cancellous bone grafts, reimplantation and arthrodeses.

At every operation, several treatments were performed.

These treatments are listed in Table 8.4 which shows in what percentage of the 345 operations the treatment in question was carried out. The table also shows what after-treatments have been performed in these patients. These after-treatments were carried out not to combat infection but to create a better useful extremity. These after-treatments have not been included in Tables 8.3 and 8.4 because the operations listed in these tables were performed to combat the infection. Tables 8.5 and 8.6 provide information on the causative agents encountered in the patients. Four mixed infections, all the causative agents found are listed separately. The percentage listed indicates in how many per cent of the 345 operations the microorganism was cultured. The proportions of mono- and
PER PATIENT

1. General
   - patient number
   - group number
   - date of birth
   - sex
   - origin: own/referred
   - result: healed/not healed, amputation/uncertain, deceased, unknown
   - at follow-up: BSR tendency to decrease?
     - sinus absent?
     - recent culture sterile?

2. Dates
   - date accident or elective operation
   - date first manifestation of infection
   - dates operations 1 to 6 inclusive
   - dates recurrences 1 to 5 inclusive
   - date healed (recurrence-free)
   - date last examination or follow-up examination

PER OPERATION

3. Diagnosis
   - main diagnosis: osteomyelitis/infection of prosthesis/infection of soft tissues/not infected
   - subdiagnosis
   - localization: nos. 1 and 2
   - left/right
   - osteomyelitis: cause:
     - haematogenous/injury/fracture ± operation/± complicated/ elective operation
   - type:
     - infected pseudarthrosis/pinhole sinus/decubitus/arthrodesis
   - fixation: int.fix./ext.fix./intramedullary fix./others
   - stable/ unstable
   - endoprostheses: type:
     - total hip/double cup/head-neck/Girdlestone/Guepar/Geomedic/knee arthrodesis/others
   - soft tissues:
     - type:
       - abscess/postoperative haematoma/sinus/others

4. Treatment
   - systemic antibiotics
   - genta beads
   - other local antibiotic
   - debridement
   - irrigation system with antibiotic
   - sequestrectomy
   - irrigation system without antibiotic
   - abscess drainage
   - cancellous bone graft open
   - extraction of endoprostheses
   - cancellous bone graft closed
   - removal of cement rest
   - tamponade
   - removal of fix. mat.
   - muscle/periosteum/skin graft
   - stabilization
   - amputation
   - other
   - sub irrigation system
   - duration in weeks
   - superinfection after × weeks
   - leaking drains
   - clogged drains
   - reoperation drains
   - reason of termination
   - sub genta beads
   - number of beads
   - duration in situ
   - extraction technique

5. After-treatment
   - cancellous bone graft
   - arthrodesis
   - reimplantation of prosthesis
   - Girdlestone

6. Causative agent

Table 8.0 Data of every patient and of every operation of a patient that have been recorded and studied.
mixed infections in the several main diagnostic categories are also shown. In calculating the percentage, the 'non-infected group' was left out of account. Finally, the table shows what proportion of the cultures was negative in spite of the presence of an infection.

There were several reasons why no causative agent could be mentioned (Table 8.5). Sometimes the data failed to make clear which of the bacteria encountered had actually caused the inflammation (12%). Also, data were sometimes unreliable or incomplete (19%). Cultures were sometimes sterile when antibiotics were used (1%). Finally, sterile cultures were seen while clinically the infection was certain (11%).

The evolution of the disease is reconstructed with the aid of a time scale that shows the main dates (Table 8.7). These dates show how long a sub-clinical or manifest inflammation was present, and what were the durations of the periods of treatment, postoperative healing, freedom from recurrence and follow-up. For the main diagnostic categories, these periods are listed in Table 8.9, in which the figures refer to the numbers of months. The median age in years at the time of the first operation is shown in Table 8.8.

The duration of stay in hospital and in the nursing home is shown in Table 8.10 for each main diagnostic category. The figures refer to the duration of hospital and nursing-home stay in months, added per patient for all operations together.

8.5. Results

With a median follow-up of three years after the last operation, 72% of the patients were free from recurrences during a median period of 28 months (see for results Table 8.11, for the distribution of the follow-up periods, Table 8.9). Excluding, for the calculation, the results of patients in the category 'non-infected endoprostheses', since we are concerned here with the treatment of infections, we find a proportion of 76% patients free from recurrence. Failure of the treatment is recorded for 14%, which includes the patients subjected to an amputation. Healing was uncertain in 10% of the patients. The largest proportion of freedom from recurrence was obtained in patients with infection of an endoprosthesis (83%), the smallest proportion in patients with osteomyelitis (72%).

As mentioned above, during the period with which this study was concerned (1962-1977), these 198 patients have been subjected to 345 operations for treatment of an infection. In addition, 61 after-treatments have been necessary. 38% of the patients required more than one operation for the treatment of the inflammation (Table 8.12). Treatment of the infection was relatively difficult particularly in patients with an infected pseudarthrosis, an infected knee prosthesis or osteomyelitis (Table 8.3). Infected pseudarthrosis required slightly over three operations on the average, the other two diagnostic categories an average of two operations.

Patients in whom an infected endoprosthesis was treated constituted a special group. Table 8.13 shows how the treatment proceeded in 34 patients with a deep infection of a total hip prosthesis. Six times, a treatment was instituted without removing the prosthesis in toto. In all these cases, the treatment failed and the prosthesis had to be removed at a later stage. When in-toto removal of the prosthesis had been performed immediately (28 patients), reimplantation was successful in 12 out of 14 cases. Unfortunately, the records did not show whether antibiotic-containing cement had been used in all cases. Ultimately, the treatment of the infections of 34 total hip prostheses resulted in a Girdlestone or arthrodesis 19 times, and in successful reimplantation 15 times.

Table 8.9 presents a survey of the durations of the total courses of the disease. Of the 199 localizations treated, the data are included to the extent they are known. The numbers of unknown localizations can be found by subtracting the figure listed under 'total' from 199. For instance, of 44 localizations treated the duration of the subclinical infections was unknown (199-155). The durations are rounded off downwards to whole months. As a result, for instance, the median duration of surgical treatment (c) is always 0 months. The table also clearly shows, for instance for this duration of surgical treatment, the difference between mean duration and median duration. This difference is sometimes considerable, because in calculating the mean durations the extreme values have been included. Influence of these extreme values on the median duration is much less. Examination of the data shown in Table 8.9 prompts a number of remarks:

- Patients with osteomyelitis as a rule already show the symptoms shortly after the operation or the accident. The median duration of this period: the subclinical infection: is one month. The median duration of the interval before operation (a + b) is 14 months. The mean durations of these periods differ even more owing to a few extremely long periods of manifest infection (b) in cases of haematogenous osteomyelitis.

- In patients with an infected endoprosthesis, the infection is diagnosed after a mean period of nine months (period a).

On the average, the operation is carried out eight to 10 months later.

- In the main diagnostic category with aseptic loosening of the prostheses, the onset of the symptoms on the average follows 21 months after implantation of the prosthesis (median period 14 months, period a). Here, also, operation was also performed approximately nine months later. Median age is highest in this group of patients (Table 8.8).

Table 8.10 shows the durations of the stays in hospital and in the nursing home, rounded off downwards to whole months, that were necessary for the treatment of the 199 localizations in the 198 patients: hospital months, nursing-home months and total. The figures represent the totals per patient of all admissions required for all treatments listed in Tables 8.3 and 8.4. We find that the median duration of intramural care is longest for infected endoprostheses, viz. not less than one year.

For osteomyelitis patients this amounts to six months, for soft-part infections to three months and for non-infected, revised prostheses, to 11 months. Where the long duration of treatment after revision of an articular prosthesis is concerned, it makes little difference whether a septic or an aseptic loosening was involved. In the septic cases the period spent in hospital is relatively longer than that spent in the nursing home.
8.6. Discussion

Within the restrictions characteristic of a retrospective study, examination of the medical files of these 198 patients nevertheless affords good insight, particularly in the evolution of the condition in these patients. The most interesting data are those that concern patients with osteomyelitis or with an infected endoprosthesis.

The restrictions of this study imply that no information could be obtained apart from that which had been recorded in the medical files. Accordingly, maximal attention has been paid to the so-called 'hard data': dates, ages, operation protocols, culture results, laboratory lists, etc. Even when only a medical file is studied, the subjective notes in the case history often clearly reveal the manifestation of a recurrence, and its moment of onset. Even so, the results in the follow-up still have to be classified as uncertain in 10% of the cases.

### Table 8.15

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Healed</th>
<th>Follow-up</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Harris '60</td>
<td>45</td>
<td>71%</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>2. Blockey + McAllister '70</td>
<td>113</td>
<td>81%</td>
<td>1-8yr</td>
<td>surgical + AB</td>
</tr>
<tr>
<td>3. Blockey + McAllister '72</td>
<td>38</td>
<td>89%</td>
<td>&gt;14mn</td>
<td>acute haem.osteom.:</td>
</tr>
<tr>
<td>4. Mollan + Piggot '77</td>
<td>93</td>
<td>81%</td>
<td>3mn-12yr</td>
<td>muscle, skin graft</td>
</tr>
<tr>
<td>5. Petersen et al. '80</td>
<td>73</td>
<td>93%</td>
<td>1-11yr</td>
<td>muscle, skin graft</td>
</tr>
<tr>
<td>6. Gillespie + Mayo '81</td>
<td>655</td>
<td>80%</td>
<td>4-33yr</td>
<td>muscle graft, AB</td>
</tr>
<tr>
<td>7. Baer '31</td>
<td>89</td>
<td>45%</td>
<td>1-2yr</td>
<td>maggots</td>
</tr>
<tr>
<td>8. Kulowski '31</td>
<td>130(154)</td>
<td>76%</td>
<td>9-19mn</td>
<td>'Orr' method</td>
</tr>
<tr>
<td>9. Prigge '46</td>
<td>61(64)</td>
<td>94%</td>
<td>&gt;7½mn</td>
<td>muscle graft</td>
</tr>
<tr>
<td>10. Rowley '59</td>
<td>58</td>
<td>83%</td>
<td>3mn-7/4yr</td>
<td>muscle, skin graft</td>
</tr>
<tr>
<td>11. Horwitz '73</td>
<td>40</td>
<td>83%</td>
<td>½-3½yr</td>
<td>saucerisation</td>
</tr>
<tr>
<td>12. Shannon et al. '73</td>
<td>68</td>
<td>68%</td>
<td>5-22yr</td>
<td>saucerisation + skin graft</td>
</tr>
<tr>
<td>13. Brunet + Berteaux '75</td>
<td>54(58)</td>
<td>85%</td>
<td>1-10yr</td>
<td>muscle graft, AB</td>
</tr>
<tr>
<td>14. Grace + Bryson '50</td>
<td>45</td>
<td>69%</td>
<td>1-5yr</td>
<td>local AB -solution</td>
</tr>
<tr>
<td>15. Winter '51</td>
<td>56(61)</td>
<td>93%</td>
<td>-</td>
<td>AB -bloodplug</td>
</tr>
<tr>
<td>16. Axhausen '61</td>
<td>11</td>
<td>82%</td>
<td>-</td>
<td>AB -plug</td>
</tr>
<tr>
<td>17. Axhausen '65</td>
<td>27</td>
<td>82%</td>
<td>-</td>
<td>AB -plug</td>
</tr>
<tr>
<td>18. Hurley et al. '66</td>
<td>20</td>
<td>50%</td>
<td>6yr</td>
<td>local AB perfusion</td>
</tr>
<tr>
<td>19. Rowley '70</td>
<td>29</td>
<td>86%</td>
<td>7mn-4½yr</td>
<td>AB</td>
</tr>
<tr>
<td>20. Organ '71</td>
<td>16</td>
<td>63%</td>
<td>9mn-3½yr</td>
<td>AB</td>
</tr>
<tr>
<td>21. Paus '71</td>
<td>50</td>
<td>80%</td>
<td>4-33mn</td>
<td>AB-long-term treatment</td>
</tr>
<tr>
<td>22. Hedström '74</td>
<td>36</td>
<td>90%</td>
<td>3-36mn</td>
<td>AB</td>
</tr>
<tr>
<td>23. Becker et al. '78</td>
<td>14(15)</td>
<td>80%</td>
<td>-</td>
<td>Silver ions</td>
</tr>
<tr>
<td>24. Schurman + Wheeler '78</td>
<td>46</td>
<td>57%</td>
<td>-</td>
<td>AB</td>
</tr>
<tr>
<td>25. Burri + Henkmeyer '71</td>
<td>25</td>
<td>92%</td>
<td>1-6yr</td>
<td>cancellous bone graft</td>
</tr>
<tr>
<td>26. Burri '73</td>
<td>200</td>
<td>95%</td>
<td>1-20yr</td>
<td>cancellous bone graft</td>
</tr>
<tr>
<td>27. Roy Camille et al. '76</td>
<td>46</td>
<td>70%</td>
<td>1½yr</td>
<td>'Papineau'</td>
</tr>
<tr>
<td>28. Lortat et al. '77</td>
<td>41</td>
<td>61%</td>
<td>4mn-2yr</td>
<td>'Papineau'</td>
</tr>
<tr>
<td>29. Miné et al. '79</td>
<td>68</td>
<td>80%</td>
<td>-</td>
<td>'Papineau'</td>
</tr>
<tr>
<td>30. Pigniol '79</td>
<td>33</td>
<td>91%</td>
<td>-</td>
<td>'Papineau'</td>
</tr>
<tr>
<td>31. Burri '79</td>
<td>79</td>
<td>92%</td>
<td>1-20yr</td>
<td>cancellous bone graft</td>
</tr>
<tr>
<td>32. Sudman '79</td>
<td>13</td>
<td>92%</td>
<td>9mn-3yr</td>
<td>cancellous bone graft</td>
</tr>
<tr>
<td>33. Dombrowski + Dunn '65</td>
<td>22</td>
<td>77%</td>
<td>-</td>
<td>suction drainage</td>
</tr>
<tr>
<td>34. Dilmaghani '69</td>
<td>24</td>
<td>87%</td>
<td>½-5yr</td>
<td>suction drainage</td>
</tr>
<tr>
<td>35. Anderson + Horn '70</td>
<td>75</td>
<td>68%</td>
<td>-</td>
<td>Orr + suction drainage</td>
</tr>
<tr>
<td>36. Kelly et al. '70</td>
<td>40</td>
<td>80%</td>
<td>2-8yr</td>
<td>suction drainage + suction drainage</td>
</tr>
<tr>
<td>37. Taylor + Mandsley '70</td>
<td>12</td>
<td>68%</td>
<td>2½-3½yr</td>
<td>suction drainage + suction drainage</td>
</tr>
<tr>
<td>38. Lawyer + Eyring '72</td>
<td>12</td>
<td>92%</td>
<td>&gt;2yr</td>
<td>suction drainage</td>
</tr>
<tr>
<td>39. Clawson et al. '73</td>
<td>97</td>
<td>74%</td>
<td>½-5yr</td>
<td>suction drainage</td>
</tr>
<tr>
<td>40. Hagen '74</td>
<td>62</td>
<td>74%</td>
<td>3mn-10yr</td>
<td>suction drainage</td>
</tr>
<tr>
<td>41. Kelly et al. '75</td>
<td>186</td>
<td>80%</td>
<td>5yr</td>
<td>suction drainage</td>
</tr>
<tr>
<td>42. Boda '79</td>
<td>103(125)</td>
<td>33%</td>
<td>&gt;2yr</td>
<td>suction drainage</td>
</tr>
<tr>
<td>43. Burri '79</td>
<td>121</td>
<td>89%</td>
<td>1-20yr</td>
<td>suction drainage</td>
</tr>
<tr>
<td>44. Geneste et al. '79</td>
<td>115</td>
<td>94%</td>
<td>&gt;16mn</td>
<td>suction drainage</td>
</tr>
</tbody>
</table>

Table 8.15 Review of the literature on results of treatment of various types of osteomyelitis. Cure rates, and in some cases the follow-up, have been calculated where necessary.
In regard to the interventions carried out at the operations, a distinction should be made between a number of interventions that were performed nearly always, and a number of interventions from among which subsequently a choice had to be made. The first intervention then consisted of debridement, sequestrectomy, abscess drainage and/or removal of fixation material or prosthesis (Table 8.4). Subsequently, an irrigation system with antibiotics was used frequently (24%) and antibiotics were administered systematically in most cases (70%). Packing of cavities was carried out occasionally (16%). Cancellous bone grafting, packing with tampons, skin or muscle grafting.

An irrigation-drainage system was used 87 times in these 198 patients, and another 14 times in the patients described in Chapter 9. The data concerning these 101 applications of irrigation-drainage systems are shown in Table 8.14. Although in principle a duration of six weeks was aimed at, most irrigation systems proved to have functioned for no longer than two to three weeks. In a substantial proportion, problems with the drains necessitated discontinuation. Culturing of the material collected three times a week revealed a superinfection in 27 patients, mostly after two weeks. Twenty-one times, the irrigation had to be discontinued in spite of a positive culture. Only 57 of the 101 irrigation-drainage systems were removed after the culture had become negative.

These findings corroborate the trend in the literature to reduce the total duration of the irrigation-drainage system to one to a maximum of three weeks (Willenegger, 1970, 1973, 1979; Willenegger et al., 1970; Polster and Samimi, 1979; Burri and v d Werken, 1981). Fear of superinfections proved not unfounded in our patients, either, and problems with the drains also occurred frequently.

The results of the treatment of osteomyelitis (72% free from recurrence during a median follow-up of 33 months) is comparable to the, admittedly widely divergent, results of the authors listed in Table 8.15. Most authors approach a cure rate of about 80%, some one of over 90%.

It should be noted, however, that often it is not made clear precisely what is meant by ‘follow-up’. Most authors appear to mean the period from the last operation to the follow-up examination (period d + e in Table 8.9). Greater importance attaches to the period of freedom from recurrence (period e in Table 8.9). In our material, the mean follow-up after treatment of the osteomyelitis amounted to 43 months. However, the period free from recurrence was 35 months: a difference of eight months, on the average.

The result of the treatment of infected endoprostheses (83% free from recurrence during a median follow-up of 37 months) may be compared with the results of reimplantations as reported by various authors and summarized in Table 3.11. However, our results should preferably be compared only with those reported in the nine publications, in which it is established with certainty that it was indeed infected endoprostheses that had been treated.

### DATA ON PATIENTS

**Total number of patients:** 198

<table>
<thead>
<tr>
<th>Sex</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>men</td>
<td>110</td>
<td>56</td>
</tr>
<tr>
<td>women</td>
<td>88</td>
<td>44</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Origin</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>own</td>
<td>66</td>
<td>33</td>
</tr>
<tr>
<td>referred</td>
<td>129</td>
<td>65</td>
</tr>
<tr>
<td>unknown</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

**Total number of localizations:** 199

<table>
<thead>
<tr>
<th>Localization</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>left-sided</td>
<td>95</td>
<td>48</td>
</tr>
<tr>
<td>right-sided</td>
<td>97</td>
<td>49</td>
</tr>
<tr>
<td>central</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>unknown</td>
<td>1</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Table 8.1 Data on patients from the follow-up of the period 1962-1977

### DATA ON PATIENTS

**Total number of patients:** 90

<table>
<thead>
<tr>
<th>Sex</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>men</td>
<td>46</td>
<td>51</td>
</tr>
<tr>
<td>women</td>
<td>44</td>
<td>49</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Origin</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>own</td>
<td>49</td>
<td>54</td>
</tr>
<tr>
<td>referred</td>
<td>41</td>
<td>46</td>
</tr>
</tbody>
</table>

**Total number of localizations:** 93

<table>
<thead>
<tr>
<th>Localization</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>left-sided</td>
<td>47</td>
<td>51</td>
</tr>
<tr>
<td>right-sided</td>
<td>45</td>
<td>48</td>
</tr>
<tr>
<td>central</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 9.1 Data on patients from the study of the period 1977-1981
DATA ON TREATED LOCALIZATIONS CLASSIFIED BY DIAGNOSIS

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number</th>
<th>%</th>
<th>With infection of soft tissues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteomyelitis</td>
<td>39</td>
<td>58</td>
<td>88 (of 115 = 77%)</td>
</tr>
<tr>
<td>infection of endoprosthesis</td>
<td>41</td>
<td>21</td>
<td>15 (of 41 = 37%)</td>
</tr>
<tr>
<td>infection of soft tissues</td>
<td>34</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>not infected</td>
<td>9</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>199</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

Table 8.2. Number of localizations treated during the period from 1962 to 1977, classified according to the main diagnosis. Soft-tissue infections occurred not only isolatedly (34) but also in other main diagnostic group (103).

DATA ON TREATED LOCALIZATIONS CLASSIFIED BY DIAGNOSIS

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number</th>
<th>%</th>
<th>With infection of soft tissues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteomyelitis</td>
<td>39</td>
<td>42</td>
<td>31 (of 39 = 79%)</td>
</tr>
<tr>
<td>infection of endoprosthesis</td>
<td>41</td>
<td>44</td>
<td>13 (of 41 = 32%)</td>
</tr>
<tr>
<td>infection of soft tissues</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>not infected</td>
<td>9</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>93</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

Table 9.2. Number of localizations treated during the period from 1977 to 1981, classified according to the main diagnosis. Soft tissue infections occurred not only isolatedly (4) but also in other main diagnostic groups (44).

Table 8.3. Localizations treated during the period 1962 to 1977, classified according to main diagnostic groups and diagnostic subgroups. The table lists the numbers of localizations and the numbers of operations required for those localizations. These figures are presented separately for the infected pseudarthroses and the pinhole sinuses.

Table 9.3. Localizations treated during the period 1977 to 1981 classified by main diagnostic groups and diagnostic subgroups. The table lists the numbers of localizations and the number of operations required for those localizations. The data concerning the infected pseudarthroses and the pinhole sinuses are presented separately.
### Table 8.4 Review of the treatments performed at the 345 operations during the period from 1962 to 1977. The percentages indicate how often the (after-)treatment was carried out at the 345 operations: 345 = 100%. As a rule, several treatments were carried out at one operation.

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>systemic antibacterial treatment</td>
<td>243</td>
<td>70</td>
</tr>
<tr>
<td>systemic prophylactic treatment</td>
<td>1</td>
<td>0,3</td>
</tr>
<tr>
<td>debridement</td>
<td>232</td>
<td>67</td>
</tr>
<tr>
<td>sequestrectomy</td>
<td>99</td>
<td>29</td>
</tr>
<tr>
<td>removal of cement rest</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>abscess drainage</td>
<td>75</td>
<td>22</td>
</tr>
<tr>
<td>prosthesis removed in toto</td>
<td>51</td>
<td>15</td>
</tr>
<tr>
<td>prosthesis removed in part</td>
<td>3</td>
<td>0,9</td>
</tr>
<tr>
<td>fixation material removed</td>
<td>70</td>
<td>20</td>
</tr>
<tr>
<td>stabilization</td>
<td>30</td>
<td>9</td>
</tr>
<tr>
<td>gentamicin-PMMA beads</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>other local antibiotic</td>
<td>29</td>
<td>8</td>
</tr>
<tr>
<td>irrigation system with antibiotic</td>
<td>84</td>
<td>24</td>
</tr>
<tr>
<td>irrigation system without antibiotic</td>
<td>3</td>
<td>0,9</td>
</tr>
<tr>
<td>cancellous bone grafting open</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>cancellous bone grafting closed</td>
<td>26</td>
<td>8</td>
</tr>
<tr>
<td>tamponade</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>muscle/skin/peristeal graft</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>amputation</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>other</td>
<td>10</td>
<td>3</td>
</tr>
</tbody>
</table>

### After-treatments

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>cancellous bone grafting</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>arthrodesis</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>reimplantation</td>
<td>26</td>
<td>8</td>
</tr>
<tr>
<td>Girdlestone</td>
<td>21</td>
<td>6</td>
</tr>
</tbody>
</table>

### Table 9.5 Review of the causative agents cultured at the 345 operations of the period from 1962 to 1977. This figure includes the operations of endoprostheses which subsequently proved to be non-infected. The percentages show in how many per cent of the 345 operations, the bacterium in question was encountered in a mixed or mono-culture: 100% = 345.

<table>
<thead>
<tr>
<th>Causative agent</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus pen.-resistant</td>
<td>106</td>
<td>31</td>
</tr>
<tr>
<td>Staphylococcus aureus pen.-sensitive</td>
<td>43</td>
<td>13</td>
</tr>
<tr>
<td>Staphylococcus albus</td>
<td>33</td>
<td>10</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>30</td>
<td>9</td>
</tr>
<tr>
<td>Proteus (nn.)</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Proteus vulgaris</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Esch. coli</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>enterobacteriaceae (nn.)</td>
<td>3</td>
<td>0,9</td>
</tr>
<tr>
<td>Enterobacter</td>
<td>2</td>
<td>0,6</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>2</td>
<td>0,6</td>
</tr>
<tr>
<td>anaerobic bact. (nn.)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bacteroides fragilis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>anaerobic gram+ cocci</td>
<td>1</td>
<td>0,3</td>
</tr>
<tr>
<td>other anaerobic bact.</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>other causative agents, or determination of agent not possible</td>
<td>42</td>
<td>12</td>
</tr>
<tr>
<td>sterile</td>
<td>39</td>
<td>11</td>
</tr>
<tr>
<td>sterile during use of antibiotic</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>unreliable or incomplete</td>
<td>67</td>
<td>19</td>
</tr>
</tbody>
</table>

### Table 9.5 Review of the causative agents cultured during the period from 1977 to 1981 at 147 operations (including the operations for the non-infected prostheses). The percentages show in how many per cent of the 147 operations, the bacterium in question was encountered in a mixed or mono-culture: 100% = 147.

<table>
<thead>
<tr>
<th>Causative agent</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus pen.-resistant</td>
<td>51</td>
<td>35</td>
</tr>
<tr>
<td>Staphylococcus aureus pen.-sensitive</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Staphylococcus albus</td>
<td>27</td>
<td>18</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Proteus (nn.)</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>1</td>
<td>0,7</td>
</tr>
<tr>
<td>Proteus vulgaris</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Esch. coli</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>enterobacteriaceae (nn.)</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Enterobacter</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>anaerobic bact. (nn.)</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Bacteroides fragilis</td>
<td>1</td>
<td>0,7</td>
</tr>
<tr>
<td>anaerobic gram+ cocci</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>other anaerobic bact.</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>other causative agents, or determination of agent not possible</td>
<td>25</td>
<td>17</td>
</tr>
<tr>
<td>sterile</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>sterile during use of antibiotic</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>unreliable or incomplete</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
### Table 8.6 Distribution of the mono- and mixed cultures and sterile cultures of the period 1962 to 1977 classified on the basis of the main diagnosis.

<table>
<thead>
<tr>
<th>Main diagnosis</th>
<th>Mono</th>
<th>Mixed</th>
<th>Neg.</th>
<th>Total</th>
<th>%</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>osteomyelitis</td>
<td>58</td>
<td>17</td>
<td>26</td>
<td>100</td>
<td>55</td>
<td>35</td>
</tr>
<tr>
<td>infection of endoprostheses</td>
<td>58</td>
<td>9</td>
<td>33</td>
<td>100</td>
<td>57</td>
<td>33</td>
</tr>
<tr>
<td>infection of soft tissues</td>
<td>50</td>
<td>8</td>
<td>42</td>
<td>100</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>not infected</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>55</td>
<td>14</td>
<td>31</td>
<td>100</td>
<td>42</td>
<td>100</td>
</tr>
</tbody>
</table>

### Table 9.6 Distribution of the mono- and mixed cultures and sterile cultures of the period 1977 to 1981 classified on the basis of the main diagnosis.

<table>
<thead>
<tr>
<th>Main diagnosis</th>
<th>Mono</th>
<th>Mixed</th>
<th>Neg.</th>
<th>Total</th>
<th>%</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>osteomyelitis</td>
<td>55</td>
<td>35</td>
<td>10</td>
<td>100</td>
<td>69</td>
<td>31</td>
</tr>
<tr>
<td>infection of endoprostheses</td>
<td>62</td>
<td>20</td>
<td>18</td>
<td>100</td>
<td>65</td>
<td>20</td>
</tr>
<tr>
<td>infection of soft tissues</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>not infected</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>56</td>
<td>25</td>
<td>19</td>
<td>100</td>
<td>147</td>
<td>147</td>
</tr>
</tbody>
</table>

### Table 8.7 Time scale of the case history. Markings indicate the main dates (1 to 5 inclusive), and the main periods (A to E inclusive).

- 1 date of injury or elective operation
- 2 date of first manifestation of the inflammation
- 3 dates of operations 1 to X inclusive
- 4 date declared 'cured' (recurrence-free)
- 5 date of last examination or follow-up examination

<table>
<thead>
<tr>
<th>Period</th>
<th>Marking</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>A</td>
<td>period of sub-clinical infection</td>
</tr>
<tr>
<td>B</td>
<td>B+C+D</td>
<td>total duration of the infection</td>
</tr>
<tr>
<td>C</td>
<td>C+D</td>
<td>total duration of treatment of the infection</td>
</tr>
<tr>
<td>D</td>
<td>D+E</td>
<td>follow-up period</td>
</tr>
<tr>
<td>E</td>
<td>A+B</td>
<td>duration of anamnesis</td>
</tr>
</tbody>
</table>

### Table 8.8 Median ages of the patients at the time of their first operations, expressed in years. These patients have been treated during the period 1962 to 1977.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Median age</th>
</tr>
</thead>
<tbody>
<tr>
<td>osteomyelitis</td>
<td>32</td>
</tr>
<tr>
<td>infection of prosthesis</td>
<td>65.5</td>
</tr>
<tr>
<td>infection of soft tissues</td>
<td>30</td>
</tr>
<tr>
<td>not infected</td>
<td>70</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>40</td>
</tr>
</tbody>
</table>

### Table 9.8 Median ages of the patients at the time of their first operations, expressed in years. These patients have been treated during the period 1977 to 1981.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Median age</th>
</tr>
</thead>
<tbody>
<tr>
<td>osteomyelitis</td>
<td>31</td>
</tr>
<tr>
<td>infection of prosthesis</td>
<td>65</td>
</tr>
<tr>
<td>infection of soft tissues</td>
<td>42</td>
</tr>
<tr>
<td>not infected</td>
<td>60</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>55</td>
</tr>
</tbody>
</table>
REVIEW OF DURATIONS OF PERIODS IN THE CASE HISTORIES 1962-1977

Period | Osteomyel. | Inf. prosth. | Inf. soft tissues | Not inf. | Total
| (115) | (41) | (34) | (9) | (199)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>b. manifest inf.</td>
<td>85</td>
<td>6</td>
<td>1</td>
<td>38</td>
<td>9</td>
</tr>
<tr>
<td>c. surgical treatment</td>
<td>109</td>
<td>52</td>
<td>11</td>
<td>37</td>
<td>8</td>
</tr>
<tr>
<td>d. postoperative healing</td>
<td>113</td>
<td>19</td>
<td>0</td>
<td>40</td>
<td>4</td>
</tr>
<tr>
<td>e. recurrence-free</td>
<td>87</td>
<td>7</td>
<td>2</td>
<td>32</td>
<td>2</td>
</tr>
<tr>
<td>a+b anamnesis</td>
<td>89</td>
<td>35</td>
<td>24</td>
<td>31</td>
<td>42</td>
</tr>
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<td>14</td>
<td>37</td>
<td>19</td>
</tr>
<tr>
<td>c+d treatment of infection</td>
<td>81</td>
<td>62</td>
<td>30</td>
<td>29</td>
<td>15</td>
</tr>
<tr>
<td>d+e follow-up</td>
<td>87</td>
<td>29</td>
<td>9</td>
<td>31</td>
<td>6</td>
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<td>87</td>
<td>43</td>
<td>33</td>
<td>32</td>
<td>43</td>
</tr>
<tr>
<td>Osteomyel.</td>
<td>(115)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N Mean Med.</td>
<td>114</td>
<td>9</td>
<td>6</td>
<td>39</td>
<td>7</td>
</tr>
<tr>
<td>Inf. prosth.</td>
<td>(41)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N Mean Med.</td>
<td>108</td>
<td>4</td>
<td>0</td>
<td>37</td>
<td>8</td>
</tr>
<tr>
<td>Inf. soft tissues</td>
<td>(34)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N Mean Med.</td>
<td>110</td>
<td>13</td>
<td>6</td>
<td>37</td>
<td>15</td>
</tr>
<tr>
<td>Not inf.</td>
<td>(9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N Mean Med.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>(199)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N Mean Med.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 8.9 Survey of the durations of periods of the case histories of 198 patients with 199 treated localizations, from the period 1962 to 1977. The lengths of time have always been rounded off downwards to whole months. The table shows what numbers of durations were known and what were the mean and median values.

SURVEY OF THE DURATIONS OF INTRAMURAL CARE 1962-1977

Stay in hospital | Stay in nursing home | Total duration intramural care
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteomyel.</td>
<td>(115)</td>
<td>Inf. prosth.</td>
</tr>
<tr>
<td>stay in hospital</td>
<td>114</td>
<td>9</td>
</tr>
<tr>
<td>stay in nursing home</td>
<td>108</td>
<td>4</td>
</tr>
<tr>
<td>total duration intramural care</td>
<td>110</td>
<td>13</td>
</tr>
</tbody>
</table>

Table 8.10 Survey of the total duration of intramural care of the patients classified by diagnostic category. The lengths of time have been rounded off downwards to whole months. The total duration of intramural care is subdivided into periods of hospitalization and periods in the nursing home.

RESULTS OF TREATMENT

<table>
<thead>
<tr>
<th>Result</th>
<th>Total</th>
<th>Infection exclusively</th>
<th>Osteom. Prosth.</th>
<th>Soft tissues</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>cured</td>
<td>144</td>
<td>72</td>
<td>76</td>
<td>72</td>
</tr>
<tr>
<td>not cured</td>
<td>19</td>
<td>10</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>amputation</td>
<td>8</td>
<td>4</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>uncertain</td>
<td>19</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>deceased</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>no infection</td>
<td>9</td>
<td>5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>199</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 8.11 Results of the treatments of the period 1962 to 1977. The durations of the follow-up (mean and median) are listed in Table 8.9, which also shows the recurrence-free periods.

RESULTS OF TREATMENT

<table>
<thead>
<tr>
<th>Result</th>
<th>Total</th>
<th>Infection exclusively</th>
<th>Osteom. Prosth.</th>
<th>Soft tissues</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
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<td>cured</td>
<td>75</td>
<td>81</td>
<td>89</td>
<td>92</td>
</tr>
<tr>
<td>not cured</td>
<td>4</td>
<td>4</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>amputation</td>
<td>1</td>
<td>1</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>uncertain</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>deceased</td>
<td>2</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>no infection</td>
<td>9</td>
<td>10</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>93</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 9.11 Results of the treatments of the period 1977 to 1981. The durations of the follow up (mean and median) are listed in Table 9.9, which also shows the recurrence-free periods.
### Table 9.9
Survey of the durations of periods of the case histories of 90 patients with 93 treated localizations, from the period 1977 to 1981. The lengths of time have always been rounded off downwards to whole months. The table shows what numbers of durations were known and what were the mean and median values.

<table>
<thead>
<tr>
<th>Period</th>
<th>Osteomyel. (39)</th>
<th>Inf. prosth. (41)</th>
<th>Inf. soft tissues (4)</th>
<th>Not inf. (9)</th>
<th>Total (93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>b. manifest inf.</td>
<td>35  13  2</td>
<td>41  22  5</td>
<td>4  0  0</td>
<td>8  23  8</td>
<td>88  17  2</td>
</tr>
<tr>
<td>c. surgical treatment</td>
<td>38  19  5</td>
<td>41  17  18</td>
<td>4  1  0</td>
<td>8  7  6</td>
<td>91  17  7</td>
</tr>
<tr>
<td>d. postoperative healing</td>
<td>38  10  0</td>
<td>40  3  0</td>
<td>4  0  0</td>
<td>9  0  0</td>
<td>91  6  0</td>
</tr>
<tr>
<td>e. recurrence-free</td>
<td>36  1  1</td>
<td>36  0  0</td>
<td>4  4  1</td>
<td>8  0  0</td>
<td>84  1  0</td>
</tr>
<tr>
<td>a+b anamnesis</td>
<td>37  14  12</td>
<td>37  15  12</td>
<td>3  14  13</td>
<td>8  11  10</td>
<td>85  14  12</td>
</tr>
<tr>
<td>b+c+d total infection</td>
<td>35  34  12</td>
<td>41  39  30</td>
<td>4  1  1</td>
<td>8  31  14</td>
<td>88  35  21</td>
</tr>
<tr>
<td>c+d treatment of infection</td>
<td>35  31  15</td>
<td>36  23  22</td>
<td>4  5  3</td>
<td>7  8  7</td>
<td>82  24  14</td>
</tr>
<tr>
<td>d+e follow-up</td>
<td>36  11  3</td>
<td>36  4  0</td>
<td>4  4  1</td>
<td>8  0  0</td>
<td>84  7  1</td>
</tr>
<tr>
<td>a+b+c+d total infection</td>
<td>36  16  14</td>
<td>36  16  12</td>
<td>3  15  14</td>
<td>8  11  10</td>
<td>94  16  13</td>
</tr>
</tbody>
</table>

### Table 9.10
Survey of the total duration of intramural care of the patients classified by diagnostic category. The lengths of time have been rounded off downwards to whole months. The total duration of intramural care is subdivided into periods of hospitalization and periods in the nursing home.

<table>
<thead>
<tr>
<th>Osteomyel. (39)</th>
<th>Inf. prosth. (41)</th>
<th>Inf. soft tissues (4)</th>
<th>Not inf. (9)</th>
<th>Total (119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>38  7  5</td>
<td>40  8  5</td>
<td>4  5  5</td>
<td>9  4  4</td>
<td>91  7  5</td>
</tr>
<tr>
<td>37  1  0</td>
<td>38  6  6</td>
<td>4  0  0</td>
<td>9  5  5</td>
<td>88  4  0</td>
</tr>
<tr>
<td>38  8  5</td>
<td>39  15  11</td>
<td>4  5  5</td>
<td>9  9  9</td>
<td>90  11  9</td>
</tr>
</tbody>
</table>

### Table 8.12
Number of operations that were required for the treatment of the infections of one localization in the period 1962 to 1977.

<table>
<thead>
<tr>
<th>Number of operations per localization treated</th>
<th>Number of localizations</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>123</td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>199</td>
<td>100</td>
</tr>
</tbody>
</table>

### Table 9.12
Number of operations that were required for the treatment of the infections of one localization in the period 1977 to 1981.

<table>
<thead>
<tr>
<th>Number of operations per localization treated</th>
<th>Number of localizations</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>58</td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>93</td>
<td>100</td>
</tr>
</tbody>
</table>
Table 8.13  Review of the progress of the treatment of 34 deep infections of a total hip prosthesis treated during the period 1962 to 1977.


Figure 8.2  Distribution of the localizations that have been treated in 198 patients (199 localizations). These are subdivided into infected and non-infected endoprostheses (left) and osteomyelitis or infection of soft tissues (right). The number of soft-tissue infections also includes infections of soft tissues in an osteomyelitis or infected endoprosthesis, usually abscesses or sinuses.
IRRIGATION SYSTEM

- Total number of irrigation systems used: 101
- Of which with antibiotics: 98
- Without antibiotics: 3
- Duration in situ of irrigation system in weeks:
  - 0 week: 1
  - 1 week: 12
  - 2 weeks: 12
  - 3 weeks: 29
  - 4 weeks: 11
  - ≥5 weeks: 10
- Superinfection after:
  - 1 week: 8
  - 2 weeks: 37
  - 3 weeks: 6
  - 4 weeks: 1
  - Unknown: 9
  - Total: 75
- Leaking drains: 39
- Clogged drains: 31
- Reoperation: 4
- No remarks: 27
- None: 65

Table 8.14 Review of the data concerning the suction drainage treatments performed during the period 1962 to 1981. Eighty-seven treatments were carried out before 1977, 14 treatments during the period after 1977. The data presented comprise the duration of the treatment, the reason of termination, the recorded drain problems and the superinfections.

LOOSENING OF ENDOPROSTHESIS

- Septic
- Aseptic

GENTAMICIN-PMMA-BEADS

- Total number of times implanted at operation: 116
- Removed manually without anaesthesia: 7
- Not removed (deceased): 2
- Removed at a second operation: 107
- Numbers of beads implanted
  - Duration in situ in weeks
    - 5-30: 27
    - 45-60: 19
    - 75-90: 24
    - 100-150: 25
    - 180-360: 20
    - 0-1 week: 2
    - 1-2 weeks: 20
    - 2-3 weeks: 69
    - 3-4 weeks: 16
    - ≥4 weeks: 6
    - Unknown: 1

Table 9.14 Review of the treatments with gentamicin-PMMA beads during the period after 1977. Data presented comprise the techniques of removal, the numbers of beads inserted and how long they were left in situ.

OSTEOMYELITIS

SOFT TISSUE INFECTION

Figure 9.1 Distribution of the localizations that were treated in 90 patients (93 localizations). These have been subdivided into infected c.q. non-infected endoprostheses (left) and osteomyelitis or soft-tissue infection (right). The numbers of infections of soft tissues include the infections of soft tissues in osteomyelitis or infected endoprostheses, which were mostly abscesses or sinuses.
Chapter 9. Treatment after 1977 of 90 patients with gentamicin-PMMA beads

9.1. Introduction

At the Department of Orthopaedics of the Sint Radboud Hospital (R.C. University) of Nijmegen, gentamicin-PMMA beads have been used in the treatment of infections since 1977. During the first 1 1/2 years, the gentamicin-PMMA beads were used side by side with the suction drainage system, from 1979 suction drainage was no longer used in the treatment of infections.

For patients with osteomyelitis, infected endoprostheses and infections of soft parts in whom gentamicin-PMMA beads were used, the surgical procedure did not differ significantly from that described in Chapter 8. Complete debridement remains essential, and the same holds true of complete removal of bone cement in infected endoprostheses. Infections of soft parts have only been treated with gentamicin-PMMA beads in an early postoperative phase or in case of pronounced extension of the infection.

Greater uniformity of the treatment was possible than prior to 1977, and in particular, more attention could be given to a complete, correct bacteriological diagnosis, owing to the prospective nature of this part of the investigation.

9.2. Use of gentamicin-PMMA beads

Following nettoyage of the focus of infection, chains of gentamicin-PMMA beads are implanted in the residual cavity, care being taken to place beads wherever in the entire region infection is assumed to exist.

As experience grew with the passage of time, emphasis was progressively placed on complete packing of the entire infected cavity, using as many beads as possible. This was done to achieve a maximal concentration of gentamicin in the entire wound.

Wounds are drained by suction for a few hours, and subsequently by syphoning. In larger cavities, good compression with a pressure bandage is important to limit the volume of the haematoma, thereby keeping the local gentamicin concentration high. It is especially after removal of total hip prostheses that very large haematomas with considerable blood loss may occur. If at all possible, the wound is closed. However, an open wound does not in itself constitute a contraindication to the treatment. In that case, a dry bandage is applied. While replacing bandages, strict asepsis is observed, and patients with open wounds are isolated, to prevent development of resistant bacteria in the hospital. Sealing the wound with plastic foil proved ineffective. The foil always came unstuck and the moist environment caused pronounced maceration of the skin. A few attempts to seal wound defects with synthetic skin (Epigard®, Parke-Davis; Coldex®, Temca) gave good results. Removal of chains protruding from the skin was carried out without anaesthesia in the first few patients. This method of removal proved laborious, often painful and sometimes impossible without severing adhesions in the subcutaneous layer or fascial sheath. After a few such experiences, the chains were placed in the wound in their entirety, and removed under anaesthesia. It is only in the case of an open treatment or of favourable local circumstances and a cooperative patient that occasionally, the chains are still removed without anaesthesia.

If at surgical removal doubt arises whether the infection is cured, another nettoyage may be performed and gentamicin-PMMA beads implanted a second time. However, there are only few reliable criteria by which to judge healing. The impression has been gained that an all-or-nothing reaction must be postulated: in case of failure of the treatment, hardly any granulation tissue develops and a purulent secretion persists.

If the treatment is successful, a markedly proliferating granulation tissue develops after as little as a few days, and pus is absent. In case of open treatment, the gentamicin-PMMA beads are then covered rapidly by granulation tissue.

This assessment is more difficult to make in the treatment of infections of endoprostheses, especially hip prostheses. In the usually large cavity left by the removed prosthesis, a haematoma forms which undergoes liquefaction and assumes a light-brown colour. The granulation tissue remains mucous for a long time and at removal of the beads after two or three weeks is still soft, with a reddish-brown colour. It is only after three to six weeks that the granulation tissue grows firmer and becomes organised, and by then, the connective tissue firmly encases the beads even in large cavities.

It was only in the few earliest cases of the group of patients described here that the beads were left in situ for long periods, of up to eight weeks. In these cases this was done because it was expected that at a second operation the entire wound would have to be explored, for instance for cancellous bone grafting or reimplantation of a prosthesis. Subsequently, the gentamicin-PMMA beads were always left in situ for periods of approximately two weeks, even when a cancellous bone grafting was performed immediately. Removal of these gentamicin-PMMA beads, two weeks after the first operation, was combined increasingly often with immediate reimplantation of a new prosthesis, without waiting for six months to one year as used to be the custom.

9.3. Therapeutic complications

In the course of the use of gentamicin-PMMA beads, the following complications proved to be more or less specific of this method of treatment:

1. In large cavities, a large haematoma may develop, especially after removal of a hip prosthesis. The haematoma may be combated by application of a
pressure bandage or by simultaneous implantation of gauzes (Klemm, 1981). The latter method has not been used by us.

2. The last gentamicin-PMMA bead may slip off the chain; this usually occurs when the chains are removed too late. In one patient, the removal was delayed because of a myocardial infarction. In another patient, a bead slipped off during intramedullary introduction of two chains with the insertion implement. Whether a bead has slipped off, as sometimes happens during removal, may be checked by inspecting the end of the chain.

3. Cutaneous necrosis may develop after attempts to close the skin hermetically in spite of tightness. In one woman, a gentamicin-PMMA bead was placed in the subcutaneous tissue on the tibia, following which the pressure caused necrosis of the overlying skin.

4. No allergic reactions to the gentamicin-PMMA beads have been observed by us.

5. Renal dysfunction during the treatment occurred in two patients. In neither case was it caused by the treatment with gentamicin-PMMA beads. In the first patient, sepsis had been present prior to the first operation and this had led to a disorder of renal function. In the second case, the renal dysfunction developed in the course of the treatment with gentamicin-PMMA beads. However, thorough examination failed to reveal any connection with the treatment; the findings suggested that the renal dysfunction was due to a periartritic nodosa. These two patients are described in Chapter 15, stating the frequently determined serum gentamicin levels.

6. Two patients have died. In both, severe sepsis constituted the indication for operation. In one, a woman, severe cardiac decompensation and renal dysfunction developed (see above). The other patient suffered from hepatic dysfunction as well and briefly after operation a septic shock occurred which could not be attributed to the gentamicin-PMMA treatment.

9.4. The study

9.4.1. Introduction
The study of the clinical efficacy of gentamicin-PMMA beads has a prospective character, unlike the study of the patients described in Chapter 8. From mid-1977, the treatments were followed personally by the author. The treatments were performed as uniformly as possible, by the method described in par. 9.2. Growing insight prompted a few adjustments of the treatment, which are described in the same paragraph.

The patients' medical files have been analysed in the same way as for the retrospective study of the patients described in Chapter 8 (Table 8.0). Patients whose treatment had already been completed were invited for the follow-up examination or, occasionally, interviewed by telephone.

9.4.2. Material
From July 1977 up to and including April 1981, 90 patients were treated with gentamicin-PMMA beads, three of them in two different localizations. Table 9.1 lists these patients' data (sex, origin) (Table 9.1).

These 90 patients were divided into four main groups on the basis of the diagnosis (as in par. 8.4.2). There were four infections of soft parts not associated with osteomyelitis or an infected endoprosthesis. In addition, a large number of soft-part infections (mostly sinuses) did occur in combination with osteomyelitis or an infected endoprosthesis (Table 9.2 and Fig. 9.1). Each main diagnostic category has been divided into sub-groups as shown in Table 9.3. In these 90 patients, 93 localizations were treated by 147 operations. In addition to these 147 operations, all of them performed for an existing or postulated infection, a number of after-treatments were carried out. The numbers of operations required for treatment of the infection are also shown in Table 9.3, classified by main diagnostic groups and diagnostic sub-groups.

At each of the 147 operations, several interventions were carried out. These interventions are listed in Table 9.4, with the percentages of the total of 147 operations at which they were carried out. The numbers of after-treatments are listed in the same table. This table shows that gentamicin-PMMA beads were implanted at 116 of the 147 operations. Most of the 31 operations at which no beads were implanted, were carried out prior to subsequent implantation of gentamicin-PMMA beads. These operations without gentamicin-PMMA beads have nevertheless been included in the coding, in order to gain a complete insight into the case histories.

Table 9.5 lists the causative agents cultured at the 147 operations. The several bacteria encountered in mixed infections have been listed separately. The number of anaerobic causative agents is larger than in Table 8.5 because from mid-1977, anaerobic cultures were always included. The larger proportion of sterile cultures when antibiotics were used (8% against 1%) is explained by the fact that culture material was collected at removal of the gentamicin-PMMA beads. Even in case of an unsuccessful treatment with gentamicin-PMMA beads, the culture is nevertheless often negative, possibly owing to the locally high concentration of antibiotic.

The fact that the proportion of unreliable or incomplete data was much smaller than in the retrospective study (1% against 19%) is explained by the prospective character of this part of the study. The numbers of monomicrobial and mixed infections are shown separately in Table 9.6.

Table 9.8 shows the median age in years at the time of the first operation.

Table 9.9 surveys the durations of the various periods in the evolution of the disease in the 90 patients in whom 93 localizations were treated. The durations have been rounded off downwards to whole months. They have been distilled from the case histories according to the scheme shown in Table 9.7. Just as Table 8.9, Table 9.9 states what phases of the evolution were known and what were the mean and median durations for the main diagnostic category in question.

Table 9.10 gives a survey of the duration of intramural care of the patients, subdivided by diagnostic groups. This duration has been calculated per patient by adding up the durations of the various stays, in the hospital and in the nursing home, which are listed separately.
9.5. Results

The results of the treatment with gentamicin-PMMA beads in 90 patients, three of them treated for two different localizations, are shown in Table 9.11. These figures have been corrected by omitting the results of the treatment in the nine patients in whom no infection could be demonstrated: the patients with a painful loose prosthesis in whom infection could be excluded on the basis of the peroperative cultures. Of the remaining patients, after a median follow-up of 13 months, 89% proved free from recurrence for a median period of 12 months. The cure rate in the osteomyelitis group (92%) was higher than that of the group with infected endoprostheses (85%). All four patients with an infection of soft parts were cured.

In 44% of the infections, more than one treatment was necessary (Table 9.12). When a treatment failed, this was always found to be due to inadequate debridement. If nettoyage and sequestrectomy had been over-cautious or a cement rest was left in situ, reoperation was always necessary. The results of the treatment of infected total hip prostheses are shown in Table 9.13. In the group of 24 patients in whom a total hip prosthesis was removed, immediate reimplantation was carried out ten times. One of these reimplantations was performed after removal of just a loose femoral component of the total prosthesis. This second exchange of the femoral component proved once more unsuccessful, and a Girdlestone resection was carried out (patient 4 in Chapter 15). In nine patients, reimplantation with use of antibiotic-loaded cement was successful.

In the patients with an infected endoprosthesis of the knee, arthrodesis of the knee was carried out after removal of the prosthesis and treatment of the infection. Consolidation was not always easy to achieve, especially in patients with Guepar prostheses. Also, in two of these patients the infection could not be controlled, and in one of these, a thigh amputation was ultimately necessary and revealed the presence of cement up to high in the femur.

9.6. Discussion

In considering the data in this chapter, it should be kept in mind that out of the 147 operations performed on the 90 patients, 31 were carried out without use of gentamicin-PMMA beads. In 21 cases, the subsequent operations were carried out with implantation of gentamicin-PMMA beads. These operations have been included in the coding in order to obtain a complete survey of the case history. Ten times, after earlier use of gentamicin-PMMA beads was followed by a recurrence, a different method of treatment, without beads, was opted for. In two patients, the method of treatment was even changed twice: alternatingly, gentamicin-PMMA beads and suction drainage.

In other words, the results as shown in Table 9.11 are not to be attributed exclusively to treatment with gentamicin-PMMA beads. A detailed analysis of the effect of one type of operation is presented in Chapter 10.

The prospective nature of this part of the study may affect the results. Observance of a protocol for the treatment of infections guarantees increased attention for the treatment of infections. This is confirmed by a smaller number of unusual culture results and a larger number of anaerobic causative agents detected, compared with the study of the period prior to 1977.

Table 9.5, listing the causative agents encountered shows a persistently important part of Staphylococcus aureus (see also Table 8.5 and Tables 2.1 and 3.9). There has been no major shift in the range of causative agents of the infection compared with the period prior to mid-1977. In particular, the group of Pseudomonas and Proteus shows no pronounced increase. On the other hand, a decrease can be observed of the proportion of penicillin-sensitive strains of Staphylococcus aureus. Further, there is a slight increase of Staphylococcus albus and enterobacteriaceae. The higher frequency with which anaerobic bacteria were demonstrated in our material (over 7%), should be attributed to the systematic anaerobic culturing from mid-1977.

The fact that thorough culturing, including anaerobic and multiple culturing, provides more data and frequently surprises as well is illustrated by Fig. 9.2. Among the 58
cases of infected total hip prostheses described in Chapters 8 and 9, there were ten in which different culture results were obtained from the different localizations. The combination of sterile cultures and Staphylococcus albus was seen frequently, and also that of Klebsiella and anaerobic bacteria. It is clear that if only material for a single culture had been collected, the erroneous conclusion that no infection was present, might have been drawn in nine of these ten cases. In these ten patients, there was other evidence suggestive of an infection, as well, so that contamination as the cause of a positive culture side by side with sterile cultures can be excluded.

Table 9.14 lists the data of the 116 treatments with gentamicin-PMMA beads. Removal of the beads without anaesthesia was carried out only seven times. Mostly the beads were left in situ for two to three weeks.

Table 9.15 allows a comparison of the results of our treatment with the results as reported in the literature.

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Follow-up</th>
<th>Prim. + Sec. healed</th>
<th>Recid.</th>
<th>Doubtful</th>
<th>Not healed</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>In Contzen 1977:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klemm '77</td>
<td>69</td>
<td>-4 years</td>
<td>67%</td>
<td>14%</td>
<td>19%</td>
<td>osteomyelitis</td>
<td></td>
</tr>
<tr>
<td>Übelhör et al. '77</td>
<td>78</td>
<td>-2 years</td>
<td>79%</td>
<td></td>
<td>21%</td>
<td>osteosynth. inf.</td>
<td></td>
</tr>
<tr>
<td>Jenny '77</td>
<td>40</td>
<td>-1 years</td>
<td>85%</td>
<td></td>
<td>15%</td>
<td>osteomyelitis</td>
<td></td>
</tr>
<tr>
<td>Vecsei '77</td>
<td>18</td>
<td>1/4-2 years</td>
<td>67%</td>
<td>28%</td>
<td>5%</td>
<td>17 osteomyelitis, 3 total hip</td>
<td></td>
</tr>
<tr>
<td>Winkelman et al. '77</td>
<td>20</td>
<td>-10 months</td>
<td>70%</td>
<td></td>
<td>30%</td>
<td>osteomyelitis</td>
<td></td>
</tr>
<tr>
<td>In Burri + Rüter 1979:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klemm '79</td>
<td>147</td>
<td>3-6 years</td>
<td>86%</td>
<td>6%</td>
<td>7.5%</td>
<td>osteom., prosth. ST</td>
<td></td>
</tr>
<tr>
<td>Müller et al. '79</td>
<td>171</td>
<td>1-3 years</td>
<td>85%</td>
<td></td>
<td>15%</td>
<td>osteom., prosth.</td>
<td></td>
</tr>
<tr>
<td>Vecsei '79</td>
<td>75</td>
<td>1-4 1/2 years</td>
<td>92%</td>
<td></td>
<td>3%</td>
<td>osteomyelitis</td>
<td></td>
</tr>
<tr>
<td>Schulte et al. '79</td>
<td>40</td>
<td>1/2-2 1/2 years</td>
<td>80%</td>
<td></td>
<td>20%</td>
<td>osteom., prosth. ST</td>
<td></td>
</tr>
<tr>
<td>Lambiris et al. '79</td>
<td>88</td>
<td>1 year</td>
<td>80%</td>
<td>8%</td>
<td>4.5%</td>
<td>osteom., prosth. ST</td>
<td></td>
</tr>
<tr>
<td>Jenny et al. '79</td>
<td>134</td>
<td>1/2-4 1/2 years</td>
<td>70%</td>
<td>10%</td>
<td>20%</td>
<td>osteom., soft tiss.</td>
<td></td>
</tr>
<tr>
<td>Probst et al. '79</td>
<td>205</td>
<td>1/2-4 years</td>
<td>89%</td>
<td></td>
<td>11%</td>
<td>osteomyelitis</td>
<td></td>
</tr>
<tr>
<td>in v. Rens + Kayser 1981:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klemm '81</td>
<td>101</td>
<td>3 years</td>
<td>86%</td>
<td>6%</td>
<td>8%</td>
<td>osteom., stable</td>
<td></td>
</tr>
<tr>
<td>Groote et al. '81</td>
<td>27</td>
<td>3 years</td>
<td>82%</td>
<td>7%</td>
<td>11%</td>
<td>osteom., unstable</td>
<td></td>
</tr>
<tr>
<td>Vecsei '81</td>
<td>44</td>
<td>1/2-3 years</td>
<td>73%</td>
<td></td>
<td>27%</td>
<td>osteom., prosth.</td>
<td></td>
</tr>
<tr>
<td>Härlé et al. '81</td>
<td>118</td>
<td>1-6 years</td>
<td>96%</td>
<td></td>
<td>4%</td>
<td>osteomyelitis</td>
<td></td>
</tr>
<tr>
<td>Härlé '81</td>
<td>47</td>
<td>1/4 years</td>
<td>55%</td>
<td></td>
<td></td>
<td>haemat. osteomyelitis</td>
<td></td>
</tr>
<tr>
<td>Weise et al. '81</td>
<td>44</td>
<td>1/2-3 1/2 years</td>
<td>82%</td>
<td>0%</td>
<td>5%</td>
<td>osteom., soft tiss.</td>
<td></td>
</tr>
<tr>
<td>Jenny et al. '81</td>
<td>34</td>
<td>9-45 months</td>
<td>71%</td>
<td>5%</td>
<td>5%</td>
<td>chron. osteomyelitis</td>
<td></td>
</tr>
<tr>
<td>Probst et al. '81</td>
<td>31</td>
<td>8-34 months</td>
<td>58%</td>
<td>6%</td>
<td>3%</td>
<td>inf. pseudarthr.</td>
<td></td>
</tr>
<tr>
<td>Eberle '81</td>
<td>68</td>
<td>1-3 years</td>
<td>75%</td>
<td>8%</td>
<td></td>
<td>osteomyelitis, arthritis</td>
<td></td>
</tr>
<tr>
<td>in several journals:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ackermann '80</td>
<td>31</td>
<td>2-28 months</td>
<td>65%</td>
<td></td>
<td>35%</td>
<td>many indications</td>
<td></td>
</tr>
<tr>
<td>Asche '78</td>
<td>38</td>
<td>3 1/2 years</td>
<td>82%</td>
<td></td>
<td>18%</td>
<td>hand inf.</td>
<td></td>
</tr>
<tr>
<td>Goudarzi '81</td>
<td>40</td>
<td>3-24 months</td>
<td>82%</td>
<td>8%</td>
<td>10%</td>
<td>osteomyelitis</td>
<td></td>
</tr>
<tr>
<td>Graeber '80</td>
<td>12</td>
<td>3-24 months</td>
<td>64%</td>
<td>11%</td>
<td>25%</td>
<td>inf. pseudarthrosis</td>
<td></td>
</tr>
<tr>
<td>Härlé '78</td>
<td>296</td>
<td>2-5 1/2 years</td>
<td>79%</td>
<td></td>
<td>21%</td>
<td>osteomyelitis</td>
<td></td>
</tr>
<tr>
<td>Hedström et al. '80</td>
<td>35</td>
<td>?</td>
<td>94%</td>
<td></td>
<td>6%</td>
<td>osteomyelitis</td>
<td></td>
</tr>
<tr>
<td>Jenny</td>
<td>48</td>
<td>?-2 years</td>
<td>73%</td>
<td>2%</td>
<td>2%</td>
<td>osteomyelitis, arthritis</td>
<td></td>
</tr>
<tr>
<td>Kantor '78</td>
<td>24</td>
<td>9-39 months</td>
<td>92%</td>
<td>8%</td>
<td></td>
<td>osteomyelitis, arthritis</td>
<td></td>
</tr>
<tr>
<td>Mehdi et al. '80</td>
<td>51</td>
<td>1-36 months</td>
<td>80%</td>
<td></td>
<td>20%</td>
<td>osteomyelitis</td>
<td></td>
</tr>
<tr>
<td>Vecsei et al. '81</td>
<td>60</td>
<td>1 year</td>
<td>92%</td>
<td></td>
<td>8%</td>
<td>osteomyelitis</td>
<td></td>
</tr>
<tr>
<td>Vecsei et al. '81</td>
<td>25</td>
<td>3-5 years</td>
<td>88%</td>
<td></td>
<td>12%</td>
<td>osteomyelitis</td>
<td></td>
</tr>
</tbody>
</table>

Table 9.15 Review of the literature on the results of the treatment of osteomyelitis with gentamicin-PMMA beads; where necessary, percentages have been calculated. 1) ST: soft tissue infection)
9.7. Comparison of the results of the treatments with suction drainage and with gentamicin-PMMA beads

A prospective comparison of the two methods of treatment of infection has been carried out in our patients in 1977 and 1978. In these years, two groups of patients (with osteomyelitis or with an infected total hip prosthesis) were divided at random into two groups, of which one was treated with gentamicin-PMMA beads and the other with suction drainage. In all, 27 patients were treated in 1½ years. The therapeutic results of treatment with gentamicin-PMMA beads seemed better (Table 9.16). However, statistical analysis showed that there was no significant difference between the two treatment groups in regard to the proportions of cured and non-cured patients (Fisher exact test, \( p = 0.50 \)). The number of patients proved too small to allow a statistically significant conclusion. Since the results were not demonstrably worse, either, it was decided, on the basis of the 'clinical' impression, always to use gentamicin-PMMA beads from 1979. This decision was largely based on the many practical advantages of this treatment: patients' comfort, nurses' workload and bacteriological superiority.

```
Results 1977-1978

<table>
<thead>
<tr>
<th></th>
<th>Suction drainage</th>
<th>Gentamicin-PMMA beads</th>
</tr>
</thead>
<tbody>
<tr>
<td>prim. cured</td>
<td>N 7, %50</td>
<td>N 8, %61</td>
</tr>
<tr>
<td>sec. cured</td>
<td>-</td>
<td>1, %8</td>
</tr>
<tr>
<td>not cured</td>
<td>6, %43</td>
<td>3, %23</td>
</tr>
<tr>
<td>not certain</td>
<td>1, %7</td>
<td>1, %8</td>
</tr>
<tr>
<td>Total</td>
<td>14, 100</td>
<td>13, 100</td>
</tr>
</tbody>
</table>

Table 9.16 Comparison of the results of a prospective study of treatment with suction drainage or with gentamicin-PMMA beads, with at-random allotment of treatments. There is no statistically significant difference (Fisher exact text, \( p = 0.50 \)).
```

Since further prospective comparison of the two methods of treatment was no longer possible, the results were compared with the retrospectively studied group described in Chapter 8. The diagnostic distribution of this group was similar to that of the group of patients who had been treated with gentamicin-PMMA beads. The earlier group had been treated in the same clinical department by a team of orthopaedic surgeons which, in spite of some coming and going, nevertheless displayed a high degree of continuity and uniformity of treatment. In spite of the difference between the two groups of patients where moment of treatment and investigation technique are concerned, there is a good deal of similarity.

Comparison of the cure rates in the two groups leads to the conclusion that 'cure' was on the whole achieved more often in the group treated after 1977: 89% as against 76% in the group treated prior to 1977. This difference is more pronounced if only the osteomyelitis cases are considered: 92% and 72%, respectively (see Tables 9.11 and 8.11).
the number of infections cured by that number of operations (Fig. 9.3). We then find that in patients treated with gentamicin-PMMA beads (84 infections) the cure rate of 89% was achieved after a maximum of three operations in one patient. In the 190 infections treated by a different method, a success rate of 76% required a larger number of operations. This difference between the two treatment groups in the number of operations required to achieve the ultimate result is even larger if we include the operations that had been performed elsewhere. In the group of patients treated with gentamicin-PMMA beads, namely, the proportion of referred patients amounts to 46%, as against 65% in the other group (see Tables 8.1 and 9.1).

That cure is obtained faster with the gentamicin-PMMA-bead treatment is also confirmed by the different durations of the 'periods of post-operative healing', which (according to the medical files) was less than one month with the gentamicin-PMMA beads (Table 9.9) as against two months with other methods of treatment (Table 8.9).

Comparing results of two methods of treatment, as done here, is a precarious business. It should be kept in mind that 'cured' means 'still free from recurrence'. It is only incompletely possible to take into account differences in indication, age structure, sex, follow-up, etc. To account for these factors, statistical analyses have to be carried out. These statistical calculations are presented in Chapter 10. For this purpose, use has been made of the analysis of the case history and of the findings at operation as stored in the computer (Tables 8.0 and 8.7).

Apart from the results of treatments, we also have to consider the discomfort to the patient caused by these treatments. Accordingly, in Chapters 8 and 9, we have discussed the numbers of operations that are required, and any additional treatment that may be necessary, such as systemic antibiotics. The number of complications, including superinfection via the irrigation system, also plays a part in this comparison. This comparison, in as far as relevant, has already been described in Chapters 8 and 9. To facilitate the figures concerning the two groups of patients, the tables have been drawn up uniformly and are presented side by side.
Chapter 10. Comparative statistical analysis of treatment with suction drainage and with gentamicin-PMMA beads

10.1. Introduction

When a new method of treatment is being used, and ultimately a choice will have to be made between it and existing methods that have already proven their value, comparison of the therapeutic results is the main element. Other aspects of the treatment, such as technique, costs, patient stress and nursing workload, are important but secondary: the final result is paramount. When results are compared in a non-statistical manner, as done in Chapter 9, the possible influence of a number of factors such as age distribution, differences in diagnosis, duration of follow-up

TOTAL NUMBER OF OPERATIONS 1962-1981

infection of soft parts

not infected 62

ostomyelitis

infected prosthesis 430

Intermediate operations: 194

incomplete data: 19

deceased: 2

number of operations: 236

incomplete data: 15

amputation: 9

analysed intermediate operations: 175

analysed final operations: 210

genta beads 25

irrigation system 36

‘others’ 114

genta beads 67

irrigation system 51

‘others’ 92

Recurrence function (par. 10.4 + 5)

Duration of healing function (par. 10.4 + 6)

chance of T > 0 duration of T

chance of G = 0 duration of G

(par. 10.5.2) (par. 10.5.3)

(par. 10.6.2) (par. 10.6.3)

Table 10.1 Review of the operations analysed statistically in Chapter 10, indicating the distribution of operations of various types, and the paragraphs in which these operations are discussed.

Table 10.2 Review of the total number of localizations treated, numbers of operations performed and the main diagnoses.

<table>
<thead>
<tr>
<th>Main diagnosis</th>
<th>Number of localizations with 1, 2, 3, 4, 5 or 6 operations</th>
<th>Numbers of localizations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 2 3 4 5 6</td>
<td></td>
</tr>
<tr>
<td>osteomyelitis infected prosthesis</td>
<td>77 33 23 12 6 3</td>
<td>154</td>
</tr>
<tr>
<td>infection of soft tissues</td>
<td>52 24 3 2 1 0</td>
<td>82</td>
</tr>
<tr>
<td>not infected</td>
<td>34 2 2 0 0 0</td>
<td>38</td>
</tr>
<tr>
<td>Total</td>
<td>181 59 28 14 7 3</td>
<td>292</td>
</tr>
</tbody>
</table>

Table 10.1 Review of the total number of localizations treated, numbers of operations performed and the main diagnoses.

etc. cannot be included in the analysis. Comparison of the two groups of patients requires the application of statistical methods in which the differences between the groups of patients are taken into account.

10.2. Material

Only those operations have been used in the statistical analysis in which the main diagnosis was osteomyelitis or infected endoprosthesis and concerning which all data could be collected that were necessary for an explanatory analysis of the surgical results. Table 10.1 and 10.2 presents a survey of the total number of localizations treated (bilateral in four patients) that have been included in the material. Subdivisions have been made on the basis of the number of operations performed per localization and on the basis of the main diagnosis. The total number of infections treated amounts to 274; in addition, 18 non-infected endoprostheses have been treated. In 236 localizations (81%), the main diagnosis was either osteomyelitis or infected
The total number of operations performed in these cases is 430 (see also Tables 8.3 and 9.3).

The 430 operations are divided into two groups (see table 10.1):

a. Intermediate operations: these operations were followed by other operations because of a recurrence of the inflammation.

b. Final operations: these operations were not followed by others. Accordingly, they are either the last operation of a series of treatments, or, in the case of patients whose first operation they were, their only operation.

The intermediate operations numbered 194, the final operations 236.

At two final operations, the patients died and at nine final operations, amputation proved necessary; these 11 final operations have not been taken into account.

Therefore, the numbers of intermediate operations and final operations in principle to be considered for statistical analysis are 194 and 225, respectively.

However, the data required for statistical analysis were not always present in the medical files. For 6% of the intermediate operations, the duration of the period free from recurrence is unknown. The duration of the postoperative healing period is unknown for 4% of the final operations. For 175 intermediate operations and 210 final operations, we know only the duration of the period free from recurrence and of the postoperative healing period, but also all values of a number of background variables. It was decided to base the analysis on 175 of the 194 intermediate operations (90%) and 210 of the 225 final operations (93%) (Table 10.1).

Of the intermediate operations, none of the gentamicin-PMMA-bead operations had to be excluded for lack of data; 10% of the intermediate operations with suction drainage and 12% of those treated by other methods had to be excluded for this reason. Of the final operations, the percentages for the three methods of treatment (gentamicin-PMMA beads, suction drainage and 'other' treatments) that had to be excluded amounted to 1%, 6% and 11%, respectively.

For this reason, in interpreting the results of the explanatory and comparative analyses in the paragraphs below, the possibility should be taken into account that owing to selective dropping-out of the suction drainage operations and 'other' treatments, the picture that emerges is slightly distorted. This distortion has to be attributed to the fact that the operations with gentamicin-PMMA beads were studied prospectively, and the other methods of treatment retrospectively.

10.3. Statistical methods

For this study, methods are applied that are used to study the survival time data. In many studies of the duration of survival, the cardinal element is the duration of the interval between a marking point and the occurrence of a particular critical event. In the present study, such a marking point is the moment of operation, while the critical event is the presence of a recurrence after an intermediary operation or the statement that the infection was cured at a final operation.

The function most often used to describe durations of survival is the survival function \( S(t) \); this is defined as: \( \text{probability to survive at least for a period of time } t \). In the context of this investigation, the concepts 'survival time' and 'survival function' have to be adjusted to the critical events as defined for intermediate operations and final operations, respectively. The following definitions are used to describe durations of recurrence and durations of postoperative healing in 'survival time' terminology.

For intermediate operations: survival time is: the duration of the period free from recurrence

For final operations: survival time is: the duration of postoperative healing.

So, the meaning of 'survival time' in regard to intermediate operations and final operations is different and to some extent even contradictory. Also, in the analysis of final operations, we face the problem of the incomplete follow-up, i.e. for a number of operations, the moment at which the infection can be declared cured falls outside the follow-up period. All that is known about these operations is that the duration of postoperative healing exceeds the observation period. This eventuality is called a censored observation.

Accordingly, in the statistical analysis of the final operations, this problem of incomplete follow-up has to be taken into consideration. In this connection it should be postulated, however, that the censoring takes place according to a mechanism that is independent of the mechanism that determines the duration of postoperative healing.

In describing and comparing the therapeutic results of gentamicin-PMMA-bead treatments, suction-drainage treatments and treatments by other methods, use is made of 'recurrence functions' and 'healing time functions'. The definitions of these functions correspond to the definitions of survival functions in studies of survival times:

\[ R(t) = \text{probability of a recurrence-free period of at least } t \text{ months} \]

\[ G(t) = \text{probability of a duration of healing of at least } t \text{ months} \]

In addition to a description and comparison of surgical results with the aid of recurrence functions and duration of healing functions, regression models are applied for a comparative analysis of the three surgical techniques. As mentioned above, in comparing methods of treatment it is important also to take into account background variables that—in a statistical sense—may influence the surgical result\(^{1}\). The regression models applied in the paragraphs below meet this purpose.

10.4. First review of therapeutic results of intermediate operations and final operations

For the description of the surgical results, the recurrence-free periods at intermediate operations and the duration of postoperative healing at final operations are subdivided into intervals. We have opted for a subdivision based on the following moments:

- moment of operation (0), immediately after operation
- }
Table 10.3 RECURRENCE-FREE PERIODS AT 1'S INTERMEDIATE OPERATIONS SUBDIVIDED INTO GENTAMICIN-PMMA BEAD TREATMENT, IRRIGATION SYSTEM AND 'OTHER' OPERATIONS

<table>
<thead>
<tr>
<th>Interval (months)</th>
<th>Type of operation</th>
<th>Recurrence function $R(t)$</th>
<th>Cumulative percentage without recurrence at end interval $t$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gentamicin</td>
<td>Irrigation</td>
<td>Others</td>
</tr>
<tr>
<td></td>
<td>PMMA beads (25)</td>
<td>Suction drainage (36)</td>
<td>'other' treatments (114)</td>
</tr>
<tr>
<td>0 - 0+</td>
<td>25</td>
<td>36</td>
<td>114</td>
</tr>
<tr>
<td>0+ - 30</td>
<td>6</td>
<td>14</td>
<td>52</td>
</tr>
<tr>
<td>30 - 60</td>
<td>6</td>
<td>11</td>
<td>36</td>
</tr>
<tr>
<td>60 - 120</td>
<td>3</td>
<td>7</td>
<td>24</td>
</tr>
<tr>
<td>120 - 240</td>
<td>2</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>240 - 600</td>
<td>0</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>600</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

1) 0 = moment of operation  0+ = immediately after the operation  2) = end point of interval not included

(0+) and 30, 60, 120, 240 and 600 months, respectively, after operation.

The recurrence functions $R(t)$ and the duration of healing functions $G(t)$ corresponding to the three types of operation—gentamicin-PMMA beads, suction drainage and 'other methods'—are compared with the aid of the Lee-Desu statistic (SPSS computer package). In the comparative analysis of the duration of healing functions $G(t)$, the incomplete follow-up of operations is taken into account. The distorting influence of a possible difference in background variables on this comparison is studied in paragraphs 10.5 and 10.6.

**10.4.1 Intermediate operations**

Table 10.3 presents a survey of the recurrence-free periods with gentamicin-PMMA beads, suction drainage and other operations. The recurrence functions $R(t)$ of these three surgical techniques are represented graphically in Fig 10.1. This figure shows at time $t$ after operation (X-axis) the probability (Y-axis) that the recurrence will take place. The recurrence will take place because it is an intermediate operation.

No clearly significant differences between the three recurrence functions is found ($p = 0.23$). However, there is some evidence to suggest that after gentamicin-PMMA-bead operations the interval before a recurrence will be shorter, this by comparison with 'other' operations ($p = 0.10$). We find for gentamicin-PMMA-bead operations that if a recurrence takes place (in 25 of the 102 operations), this recurrence is observed immediately following the operation in 76% (19 of the 25 recurrences). However, when no recurrence takes place immediately after the operation, it takes three months before a recurrence is observed. After 'other operations', 54% show immediate recurrence. For suction drainage operations this proportion amounts to 61%.

**10.4.2 Final operations**

Table 10.4 shows a survey of the durations of postoperative healing. The duration of healing function $G(t)$ of gentamicin-PMMA beads, suction drainage and other operations, are represented in Fig 10.2. The therapeutic results of the three types of operation are clearly different ($p < 10^{-4}$).

At paired comparison, also, the functions $G(t)$ prove to differ significantly from each other (genta-suction $p < 10^{-4}$, genta-'other' $p < 10^{-6}$, suction-'other' $p = 0.05$). At 'final' operations with gentamicin-PMMA beads, 52% is immediately declared cured. Subsequently, the number of patients that is 'cured' is larger during the entire case history, with extrapolation where necessary.

For 'other' operations, the median duration of healing is three months and with the suction drainage operations, it even takes over four months after the final operation before 50% of the patients (operations) are declared cured.
Table 10-4 POSTOPERATIVE HEALING TIME AT 210 FINAL OPERATIONS SUBDIVIDED INTO GENTAMICIN-PMMA BEAD TREATMENT, IRRIGATION SYSTEM AND 'OTHER' OPERATIONS

<table>
<thead>
<tr>
<th>Interval(^1) (months)</th>
<th>Type of operation</th>
<th>Healing function (G(t))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of patients not yet cured at beginning of interval(^2)</td>
<td>Cumulative percentage not yet cured at end interval(^3)</td>
</tr>
<tr>
<td></td>
<td>Genta</td>
<td>Irrg</td>
</tr>
<tr>
<td>0-0+</td>
<td>67</td>
<td>51</td>
</tr>
<tr>
<td>0+ - 30</td>
<td>32</td>
<td>48(2)</td>
</tr>
<tr>
<td>30-60</td>
<td>13(2)</td>
<td>28(2)</td>
</tr>
<tr>
<td>60-120</td>
<td>4</td>
<td>19(1)</td>
</tr>
<tr>
<td>120-240</td>
<td>2(1)</td>
<td>16(3)</td>
</tr>
<tr>
<td>240-600</td>
<td>1(1)</td>
<td>10(4)</td>
</tr>
<tr>
<td>600</td>
<td>0</td>
<td>3(2)</td>
</tr>
</tbody>
</table>

1) 0 = moment of operation 0+ = immediately after the operation
2) ( ) = numbers of operations with a censored duration of healing during the interval in question
3) end point not included

10.4.3 Conclusion

There is some evidence to suggest that at intermediate operations the interval before a recurrence, if any, is shorter if gentamicin-PMMA-bead treatment is applied. At the final operations, it is then evident that the patient is declared healed sooner and more often. In this connection, the difference in follow-up has been taken into account. However, this comparison still fails to take into account the differences in background variables such as age at the time of the operation, sex and diagnosis. To what extent possible differences in background variables influence the results obtained here is studied in the next two paragraphs.

10.5. Analysis of intermediate operations

10.5.1 Definition of the problem and variables

At the analysis of the intermediate operations, there are two questions to be answered:

a. What variable(s) influence(s) the probability of occurrence of a period free from recurrence after the operation?\(^*\)

b. If a recurrence-free period takes place, what variables then contribute to an explanation of the duration of that period?

The variables that were considered to be of possible importance for these questions and which therefore have been included in this analysis are:

1. age at the time of the operation
2. sex
3. diagnosis
4. duration of the manifest inflammation
5. in regard to the anamnesis is it the first operation of the (own) patient or is it a patient who has been operated before, sometimes several times (own or referred)?
6. the type of (surgical) treatment

In order to find answers to questions a and b, logistic and multiple linear regression analyses have been carried out. The interpretation of the results of these analyses depends on the definitions of the variables in question. These variables are defined below. A distinction is made between

\(^*\) Influence is used in a statistical sense, i.e. no reference is made to causal relationship

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variables to be explained (dependent variables) and explanatory (independent) variables:

- variable to be explained:
  \( T = \text{duration of recurrence-free period of an intermediate operation in months} \)

- explanatory variables:
  \( z_1 = \text{age at the time of the operation in years} \)
  \( z_2 = \text{sex (0 = man, 1 = woman)} \)
  \( z_3 = \text{diagnosis (0 = osteomyelitis, 1 = infected endoprosthesis)} \)
  \( z_4 = \log (d + 1), \text{in which} \ d = \text{duration of the manifest inflammation in months}^* \)
  \( z_5 = 0 = \text{own patient and first operation}, z_1 = \text{others.} \)

To study the results of operations with gentamicin-PMMA beads and irrigation systems, use has been made of so-called ‘dummy variables’ \((z_6, z_7)\). This pair of variables describes the classification of the operations in three types as follows:

\[
\begin{align*}
z_6 = 1 & \quad z_7 = 0 : \text{gentamicin-PMMA beads} \\
z_6 = 0 & \quad z_7 = 1 : \text{irrigation system} \\
z_6 = 0 & \quad z_7 = 0 : \text{others.}
\end{align*}
\]

In addition, analyses have been carried out to study the influence of the variables \(z_1\) to \(z_7\) inclusive on the result. For these analyses, only data concerning operations with gentamicin-PMMA beads and irrigation systems have been used.

### 10.5.2. Explanatory variables of the probability of a recurrence-free period after an intermediate operation

#### 10.5.2.1. Method

In the linear logistic regression model, the chance of a recurrence-free period is explained from the values of variables \(z_1\) to \(z_7\) inclusive. The probability of a recurrence-free period \(P(T > 0)\), is expressed as a function of variables \(z_1\) to \(z_7\) inclusive by:

\[
P(T > 0) = \frac{\exp(\beta_0 + \sum_{j=1}^{7} \beta_j z_j)}{1 + \exp(\beta_0 + \sum_{j=1}^{7} \beta_j z_j)}
\]

The meaning of the regression coefficients \(\beta_1\) to \(\beta_7\) inclusive in the model may in general be described as follows:

\(\beta_1 = 0\): the corresponding variable \(z_1\) exerts no influence on the probability of occurrence of a recurrence-free period.

\(\beta_j = \text{positive: the higher the value of the corresponding explanatory variable} z_j, \text{the higher the probability of a recurrence-free period.}\)

\(\beta_j = \text{negative: the higher the value of} z_j, \text{the less} \) this probability.

For instance, if the dichotomous variable \(z_3\) has a negative regression coefficient \(\beta_3\), this means that the chance of a recurrence-free period after an intermediate operation is less for the diagnosis ‘prosthesis’ compared with the diagnosis ‘osteomyelitis’ (for equal values of the other variables included in the model).

#### 10.5.2.2. Results

For the analysis, only those intermediate operations \((175)\) have been used for which the values of all explanatory variables are known. The mean values of these variables are listed in Table 10.5.

The percentages of the intermediate operations followed by a recurrence-free period are 24% for ‘genta-bead-operations, 39% for ‘irrigation system’ operations and 46% for ‘other’ operations (see also Table 10.3 and par. 10.4.1). If a possible influence of variables \(z_1\) to \(z_7\) inclusive is discounted, no clearly significant difference between these three operations is demonstrable. At most we can say that there is an indication of a difference in probability of occurrence of a recurrence-free period (Chi-square test for a \((3 \times 2)\) table, \(p = 0.13\)).

A logistic regression analysis with simultaneous use of variables \(z_1\) to \(z_7\) inclusive and the surgical method of treatment yields the following: A significant ‘overall’ influence of these seven explanatory variables is not demonstrable \((H_0 : \beta_1 = \beta_2 = \ldots = \beta_7 = 0, \text{likelihood ratio test, } p = 0.22\).

However, an investigation of the influence of the individual explanatory variables on the probability of a recurrence-free period in which the values of the other explanatory variables are taken into account, yields an indication that at operations with gentamicin-PMMA beads the probability of a recurrence-free period is less than with ‘other’ operations \((\beta_6 = -1.02, p = 0.05)\). In this respect, no significant differences are found between irrigation-system operations and ‘other’ operations and between irrigation-system operations and gentamicin-PMMA-bead operations \((p = 0.38 \text{ and } p = 0.27, \text{respectively})\).

The joint influence of the explanatory variables \(z_1\) to \(z_5\) inclusive on the chance of a recurrence-free period \((H_0 : \beta_1 = \beta_2 = \ldots = \beta_5 = 0)\) has been studied for each of the three groups of operation types separately (genta beads, irrigation system, others). No significant influence is demonstrable (logistic regression analyses: \(p = 0.69, p = 0.30, p = 0.22\)).

#### 10.5.2.3. Conclusion

There is some evidence to suggest that if after an operation a recurrence develops, the probability of a recurrence-free period after a treatment with gentamicin-PMMA beads is relatively small as compared with suction drainage system or other treatment. In this comparison, the influence of the other explanatory variables on the result has been taken into account.

The explanation of the above-mentioned statistical findings may be sought in difference between the three types of treatment (genta beads, irrigation system, others) and possibly also in differences in the set-up of the study (genta beads and no genta beads, respectively predominantly prospective and retrospective).

In treatments with gentamicin-PMMA beads it usually became clear during the approximately two weeks of the treatment whether or not the infection was ‘under control’. If it was not, another treatment was instituted immediately: recurrence-free periods occur less often because more often, presence of a recurrence was presumed immediately after the operation.

*) The duration of the manifest inflammation \((d)\) showed a highly skew distribution. In order to obtain a more symmetrical distribution with fewer extreme values, a logarithmic transformation has been applied.

\(^{c}\log (d + 1)\)
Table 10.5 EXPLANATORY VARIABLES CONCERNING THE CHANCE OF A RECURRENT-FREE PERIOD \( P(T>0) \) AT INTERMEDIATE OPERATIONS (LOGISTIC REGRESSION ANALYSIS)

<table>
<thead>
<tr>
<th>Type of operation</th>
<th>( N )</th>
<th>( P(T&gt;0) )</th>
<th>( z_1 )</th>
<th>( z_2 )</th>
<th>( z_3 )</th>
<th>( z_4 )</th>
<th>( z_5 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>gentamicin-PMMA beads</td>
<td>25</td>
<td>24</td>
<td>44</td>
<td>44</td>
<td>48</td>
<td>2.0 (6)</td>
<td>32</td>
</tr>
<tr>
<td>suction drainage system</td>
<td>36</td>
<td>39</td>
<td>43</td>
<td>42</td>
<td>25</td>
<td>2.4 (10)</td>
<td>22</td>
</tr>
<tr>
<td>'others'</td>
<td>114</td>
<td>46</td>
<td>37</td>
<td>41</td>
<td>14</td>
<td>2.4 (10)</td>
<td>19</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>175</td>
<td>41</td>
<td>39</td>
<td>42</td>
<td>21</td>
<td>2.4 (10)</td>
<td>22</td>
</tr>
</tbody>
</table>

**INFLUENCE EXPLANATORY VARIABLES**

<table>
<thead>
<tr>
<th>Explanatory variable</th>
<th>Regression coefficient ( \beta_j )</th>
<th>Estimate</th>
<th>Value of ( \rho )</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>( z_1 ) \beta_1</td>
<td>0.01</td>
<td>0.23</td>
</tr>
<tr>
<td>sex</td>
<td>( z_2 ) \beta_2</td>
<td>-0.38</td>
<td>0.26</td>
</tr>
<tr>
<td>diagnosis</td>
<td>( z_3 ) \beta_3</td>
<td>-0.25</td>
<td>0.66</td>
</tr>
<tr>
<td>manifest duration</td>
<td>( z_4 ) \beta_4</td>
<td>0.09</td>
<td>0.44</td>
</tr>
<tr>
<td>1st operation</td>
<td>( z_5 ) \beta_5</td>
<td>-0.52</td>
<td>0.20</td>
</tr>
<tr>
<td>gentamicin operation</td>
<td>( z_6 ) \beta_6</td>
<td>-1.02</td>
<td>0.05*</td>
</tr>
<tr>
<td>suction drainage op.</td>
<td>( z_7 ) \beta_7</td>
<td>-0.35</td>
<td>0.38</td>
</tr>
</tbody>
</table>

1) \( d = \) duration of the manifest inflammation in months
* significant

With other methods of treatment, it is usually much less clear whether or not there is response to the therapy: the diagnosis of 'recurrence' is made later. One possible explanation is that the use of systemic antibiotics (in 70%, against 29% with genta-bead operations) masks a recurrence for a greater length of time.

This higher degree of certainty in the treatment combined with a fixed two-week schedule is one of the advantages of the gentamicin-PMMA-bead treatment, as others have emphasized as well (Müller, 1978). 

Table 10.6 EXTREME LENGTHS OF THE DURATION OF RECURRENCE-FREE PERIODS (T>0) OBSERVED AFTER INTERMEDIATE OPERATIONS

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>( T ) Months</th>
<th>Operation</th>
<th>( z_1 )</th>
<th>( z_2 )</th>
<th>( z_3 )</th>
<th>( z_4 ) (( d ))^1</th>
<th>( z_5 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>2146</td>
<td>379</td>
<td>others</td>
<td>10 yr</td>
<td>M</td>
<td>osteom.</td>
<td>1.8 (5)</td>
<td>no</td>
</tr>
<tr>
<td>2146</td>
<td>30</td>
<td>others</td>
<td>46 yr</td>
<td>M</td>
<td>osteom.</td>
<td>6.1 (437)</td>
<td>no</td>
</tr>
<tr>
<td>2146</td>
<td>49</td>
<td>irrigation</td>
<td>49 yr</td>
<td>M</td>
<td>osteom.</td>
<td>6.2 (468)</td>
<td>no</td>
</tr>
<tr>
<td>2026</td>
<td>72</td>
<td>others</td>
<td>13 yr</td>
<td>M</td>
<td>osteom.</td>
<td>3.6 (35)</td>
<td>no</td>
</tr>
<tr>
<td>2147</td>
<td>69</td>
<td>others</td>
<td>6 yr</td>
<td>F</td>
<td>osteom.</td>
<td>2.9 (18)</td>
<td>no</td>
</tr>
<tr>
<td>2123</td>
<td>68</td>
<td>others</td>
<td>29 yr</td>
<td>F</td>
<td>osteom.</td>
<td>5.0 (147)</td>
<td>no</td>
</tr>
<tr>
<td>2067</td>
<td>62</td>
<td>others</td>
<td>27 yr</td>
<td>F</td>
<td>osteom.</td>
<td>1.1 (2)</td>
<td>no</td>
</tr>
</tbody>
</table>

1) \( d = \) duration of the manifest inflammation in months \( z_4 = \log (d + 1) \)
presents a survey of these extreme values. The diagnosis was osteomyelitis in all cases, and haematogenous osteomyelitis in five of the seven operations. One patient (nr 2146) underwent three 'intermediate operations' followed by very long recurrence-free periods. The seven extreme cases, listed in Table 10.6, have been discounted in the analysis below.

### Table 10.7 REVIEW OF DURATIONS OF RECURRENT-FREE PERIODS T (MONTHS) AFTER EXCLUSION OF EXTREME VALUES

<table>
<thead>
<tr>
<th>Type of operation</th>
<th>N</th>
<th>Tmean</th>
<th>S.D.</th>
<th>Tmin</th>
<th>Tmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>gentamicin-PMMA beads</td>
<td>6</td>
<td>9.2</td>
<td>6.5</td>
<td>3</td>
<td>19</td>
</tr>
<tr>
<td>suction drainage</td>
<td>13</td>
<td>5.2</td>
<td>3.2</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>'other'</td>
<td>46</td>
<td>5.5</td>
<td>4.3</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>65</td>
<td>5.8</td>
<td>4.4</td>
<td>1</td>
<td>19</td>
</tr>
</tbody>
</table>

If the values of the explanatory variables $z_1$ to $z_5$ inclusive are not taken into account, a direct comparison of the mean T-values ($T_{mean} = 9.2, 5.2$ or $5.5$ months, see Table 10.7) reveals no clearly significant difference (analysis of variance one-way classification $F^2_{62} = 2.06, p = 0.14$).

### Table 10.8 EXPLANATORY VARIABLES CONCERNING THE DURATION OF RECURRENT-FREE PERIODS (T>0) OBSERVED AFTER INTERMEDIATE OPERATIONS (MULTIPLE LINEAR ANALYSIS). THE FIGURES STATED REFER TO A MEAN VALUE OR A PERCENTAGE

<table>
<thead>
<tr>
<th>Type of operation</th>
<th>N</th>
<th>Tmean (months)</th>
<th>$z_1$ Age (yrs)</th>
<th>$z_2$ Woman %</th>
<th>$z_3$ Prosthesis %</th>
<th>$z_4 (d)^{1)}$ Manifest duration (mean)</th>
<th>$z_5$ 1st operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>gentamicin-PMMA beads</td>
<td>6</td>
<td>9.2</td>
<td>39</td>
<td>50</td>
<td>50</td>
<td>2.2(8)</td>
<td>17</td>
</tr>
<tr>
<td>suction drainage</td>
<td>13</td>
<td>5.2</td>
<td>39</td>
<td>31</td>
<td>15</td>
<td>2.4(10)</td>
<td>38</td>
</tr>
<tr>
<td>'other'</td>
<td>46</td>
<td>5.5</td>
<td>44</td>
<td>35</td>
<td>20</td>
<td>2.4(10)</td>
<td>26</td>
</tr>
<tr>
<td>Total</td>
<td>65</td>
<td>5.8</td>
<td>42</td>
<td>35</td>
<td>22</td>
<td>2.4(10)</td>
<td>28</td>
</tr>
</tbody>
</table>

### INFLUENCE OF EXPLANATORY VARIABLES

<table>
<thead>
<tr>
<th>Explanatory variables</th>
<th>Regression coefficient $\hat{\beta}_j$</th>
<th>Value of $p$</th>
<th>$z_4$ Manifest inflammation in months $= \log (d + 1)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>$z_1$  $\hat{\beta}_1$</td>
<td>0.96</td>
<td>$z_4 = \log (d + 1)$</td>
</tr>
<tr>
<td>sex</td>
<td>$z_2$  $\hat{\beta}_2$</td>
<td>0.08 (*)</td>
<td></td>
</tr>
<tr>
<td>diagnosis</td>
<td>$z_3$  $\hat{\beta}_3$</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>manifest duration</td>
<td>$z_4$  $\hat{\beta}_4$</td>
<td>0.05 (*)</td>
<td></td>
</tr>
<tr>
<td>1st operation</td>
<td>$z_5$  $\hat{\beta}_5$</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>genta beads</td>
<td>$z_6$  $\hat{\beta}_6$</td>
<td>0.11 (*)</td>
<td></td>
</tr>
<tr>
<td>irrigation system</td>
<td>$z_7$  $\hat{\beta}_7$</td>
<td>0.83</td>
<td></td>
</tr>
</tbody>
</table>

$1)^d = \text{duration of the manifest inflammation in months}$

* significant

Table 10.8 presents a survey of the values of variables $z_1$ to $z_7$, inclusive, and the estimated regression coefficients $\hat{\beta}_j (j = 1, \ldots, 7)$ with the corresponding levels of significance (results of tests of the seven $H_0$-hypotheses $\hat{\beta}_j = 0, j = 1, \ldots, 7$). There is some evidence to suggest that the explanatory variables exert some (slight) influence on the duration of the recurrence-free period ($H_0$-hypotheses $\beta_1 = \beta_2 = \ldots = \beta_7 = 0, F^2_{7} = 1.88, p = 0.09$).

In particular, some influence is demonstrable of the variables sex ($z_2$), manifest duration ($z_4$) and genta beads ($z_6$). The mean duration of the recurrence-free period ($T_{mean} = 9.2, 5.2$ or $5.5$ months, see Table 10.7) reveals no clearly significant difference (analysis of variance one-way classification $F^2_{62} = 2.06, p = 0.14$).

Influence of explanatory variables

manifest inflammation and after genta-bead operations. However, the influence of these three explanatory variables is of little importance for the prognosis of the duration of the recurrence-free period. A possible influence of the sex cannot be explained adequately.

Nor is it simple to explain the influence of a long duration of the manifest inflammation. The assumption was that an infection of long duration would be difficult to treat and consequently would lead to bad results, in other words, faster recurrence. In regard to the duration of the recurrence, the inverse may apply, however.

The longer interval between genta-bead operations and recurrences is in agreement with the finding that the
probability of a recurrence-free period is smaller and the recurrence more often develops immediately. When gentamicin-PMMA beads are used, namely, a subsequent recurrence-free period whenever a recurrence has not been diagnosed immediately postoperatively (see also par. 10.5.2.3).

10.6. Analysis of final operations

10.6.1. Definition of the problems, variables and models

This analysis is concerned with the surgical results of those operations that were not followed by any more operations during the follow-up period stated. In other words, the analysis concerns the 'first and only' operation (of a patient of our own department) or a 'last' operation. The question here is: what variables influence the duration of postoperative healing (G)? The following classification is used:

G = 0: patient has been declared cured immediately after operation and is free from recurrence during the follow-up period;

G = g: patient has been declared cured g months after the final operation (in the course of the follow-up period);

G > g: patient has not yet been declared cured during the follow-up period of g months (censored observation).

The set of explanatory variables for the duration of postoperative healing comprises the same variables as used for the explanation of the duration of the recurrence-free period (the variables z1 to z5 inclusive and the dummy variables z6 and z7, see par. 10.5).

Just as in par. 10.5, the main question is divided into two subquestions:

a. what variables influence the probability of immediate cure (p(G = 0))?

b. what variables contribute to an explanation of the duration of postoperative healing if the patient is not cured immediately?

To answer question a, logistic regression analyses have been carried out once more (see also par. 10.5.2). To answer question b, use has been made of the 'proportional hazards model' of Cox. In this model, 'hazard rate' function λ(t) occupies a central position (theory of the analysis of survival time data). In the present study, the following meaning is ascribed to λ(t): λ(t) ∆t = the chance that a patient who has not yet been declared cured t months after operation will yet be classified as such during the subsequent period ∆t.

In the proportional hazards (PH) model, λ(t) is defined as a function of a number of explanatory variables. In the present study, these are the variables z1 to z7 inclusive: (defined in par. 10.5.1)

\[ \lambda (t) = \lambda_0 (t) \exp (\beta_1 z_1 + \beta_2 z_2 + \ldots + \beta_7 z_7). \]

The term 'proportional hazards model' derives from the assumption that of two groups, both of them individually

10.6.2. Results of logistic regression analysis

Only those final operations have been used for the analysis of which the values of all explanatory variables (z1 to z7 inclusive) are known: 210 operations.

A review of the values of these variables is shown in Table 10.9. The percentages of the final operations at which the patients were immediately declared cured, are clearly different for the three types of operation (chi-square test, (3 x 2) table, p < 10^4). In the group of gentamicin bead operations, 52% of the patients were declared cured immediately after the 'final' operation. This proportion is considerably larger than those seen after the 'final' operations with irrigation systems or other methods of treatment (6% and 15%, respectively).

In the comparison of the three types of operation, the possible influences of the explanatory variables z1 to z7 inclusive should also be considered. To this purpose, the following logistic regression model has been used:

\[ P (G = 0) = \frac{\exp (\beta_0 + \sum_{j=1}^{7} \beta_j z_j)}{1 + \exp (\beta_0 + \sum_{j=1}^{7} \beta_j z_j)}. \]

A positive (negative) sign of the regression coefficient \( \beta_j \) indicates influence of the variable in question, \( z_j (j = 1, \ldots, 7) \).

The general rule is once more that with a positive regression coefficient, the higher the value of the corresponding explanatory variable, the higher the probability of cure immediately after the operation. In case of a negative regression coefficient, this chance grows smaller and \( \beta_j = 0 \) means that no influence of the variable in question is demonstrable.

The results of the logistic regression analysis are listed in Table 10.9 and show clearly that the diagnosis (osteomyelitis or prosthesis), the manifest duration and the
Table 10.9  EXPLANATORY VARIABLES CONCERNING THE CHANCE OF CURE IMMEDIATELY AFTER THE LAST OPERATION (PG=0)

<table>
<thead>
<tr>
<th>Type of operation</th>
<th>N</th>
<th>P(G=0) %</th>
<th>z1 Age (yrs)</th>
<th>z2 Woman %</th>
<th>z3 Prosthesis %</th>
<th>z4(d) Manifest duration (mean)</th>
<th>z5 First operation %</th>
</tr>
</thead>
<tbody>
<tr>
<td>gentamicin-PMMA beads</td>
<td>67</td>
<td>52</td>
<td>48</td>
<td>48</td>
<td>48</td>
<td>2.6(12)</td>
<td>25</td>
</tr>
<tr>
<td>suction drainage system</td>
<td>51</td>
<td>6</td>
<td>48</td>
<td>47</td>
<td>41</td>
<td>2.9(17)</td>
<td>10</td>
</tr>
<tr>
<td>'other'</td>
<td>92</td>
<td>15</td>
<td>42</td>
<td>40</td>
<td>23</td>
<td>3.0(19)</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>210</td>
<td>25</td>
<td>45</td>
<td>44</td>
<td>35</td>
<td>2.9(17)</td>
<td>19</td>
</tr>
</tbody>
</table>

INFLUENCE OF EXPLANATORY VARIABLES

<table>
<thead>
<tr>
<th>Explanatory variables</th>
<th>Regression coefficient</th>
<th>Estimate value of βj</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>age z1</td>
<td>β1</td>
<td>-0.0006</td>
<td>0.65</td>
</tr>
<tr>
<td>sex z2</td>
<td>β2</td>
<td>0.536</td>
<td>0.20</td>
</tr>
<tr>
<td>diagnosis z3</td>
<td>β3</td>
<td>1.523</td>
<td>0.005(*)</td>
</tr>
<tr>
<td>manifest duration z4</td>
<td>β4</td>
<td>0.331</td>
<td>0.03(*)</td>
</tr>
<tr>
<td>first operation z5</td>
<td>β5</td>
<td>-0.015</td>
<td>0.95</td>
</tr>
<tr>
<td>genta beads z6</td>
<td>β6</td>
<td>1.693</td>
<td>0.000(*)</td>
</tr>
<tr>
<td>irrigation system z7</td>
<td>β7</td>
<td>-1.481</td>
<td>0.02(*)</td>
</tr>
</tbody>
</table>

1) d = duration of the manifest inflammation in months
z4 = log (d + 1)
(*) significant

At 67 gentamicin-PMMA-bead operations, 52% were immediately declared cured. In regard to this number, a differentiation should be made on the basis of diagnosis and duration of manifest infection. There are clear indications that at operations with use of gentamicin-PMMA beads the probability of a direct cure is greater if the diagnosis had read 'infected prosthesis' and the duration of the manifest infection has been relatively long (longer than 12 months).

At operation with irrigation systems or 'other' methods of treatment only three and 14 patients, respective-
Table 10.11 DURATIONS OF POSTOPERATIVE HEALING AFTER 67 GENTAMICIN-PMMA BEAD TREATMENT OPERATIONS, SUBDIVIDED ACCORDING TO THE DIAGNOSES OF PROSTHESIS AND OSTEO-MYELITIS

<table>
<thead>
<tr>
<th>Interval(^1) (months)</th>
<th>Operations</th>
<th>Healing function G(t)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prosthesis</td>
<td>Osteom.</td>
</tr>
<tr>
<td>0 - 0(^+)</td>
<td>32</td>
<td>35</td>
</tr>
<tr>
<td>0(^+) - 3.0</td>
<td>10</td>
<td>22</td>
</tr>
<tr>
<td>3.0 - 6.0</td>
<td>3</td>
<td>10(2)</td>
</tr>
<tr>
<td>6.0 - 12.0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>12.0 - 24.0</td>
<td>1(1)</td>
<td>1</td>
</tr>
<tr>
<td>24.0 - 60.0</td>
<td>1(1)</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) 0 = moment of operation  \(0^+\) = immediately after the operation

\(^2\) (J) = number of operations with a censured duration of healing during the interval in question

\(^3\) end point not included

Table 10.12 EXPLANATORY VARIABLES CONCERNING THE POSTOPERATIVE DURATION OF HEALING G(G > 0)\(^1\). THE FIGURES REFER TO A MEAN OR A PERCENTAGE

<table>
<thead>
<tr>
<th>Type of operation</th>
<th>N</th>
<th>cens. %</th>
<th>G or F mean (months)</th>
<th>(z_1) Age (yrs)</th>
<th>(z_2) Woman %</th>
<th>(z_3) Prosthes- sis (%)</th>
<th>(z_4) Mean manifest duration</th>
<th>(z_5) First operation %</th>
</tr>
</thead>
<tbody>
<tr>
<td>gentamicin-PMMA beads</td>
<td>32</td>
<td>12</td>
<td>3.9</td>
<td>42</td>
<td>44</td>
<td>31</td>
<td>2.3(9)</td>
<td>28</td>
</tr>
<tr>
<td>suction drainage</td>
<td>48</td>
<td>29</td>
<td>13.7</td>
<td>46</td>
<td>46</td>
<td>38</td>
<td>2.9(17)</td>
<td>10</td>
</tr>
<tr>
<td>'other'</td>
<td>78</td>
<td>24</td>
<td>11.7</td>
<td>41</td>
<td>33</td>
<td>19</td>
<td>3.0(19)</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>158</td>
<td>23</td>
<td>10.7</td>
<td>43</td>
<td>39</td>
<td>27</td>
<td>2.8(15)</td>
<td>16</td>
</tr>
</tbody>
</table>

INFLUENCE EXPLANATORY VARIABLES PH-MODEL

<table>
<thead>
<tr>
<th>Explanatory variable</th>
<th>Regression coefficient (\beta)</th>
<th>Estimate Value of (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>(z_1) (\beta_1)</td>
<td>-0.008 0.16</td>
</tr>
<tr>
<td>sex</td>
<td>(z_2) (\beta_2)</td>
<td>0.03 0.89</td>
</tr>
<tr>
<td>diagnosis</td>
<td>(z_3) (\beta_3)</td>
<td>0.13 0.66</td>
</tr>
<tr>
<td>manifest duration</td>
<td>(z_4) (\beta_4)</td>
<td>-0.13 0.12</td>
</tr>
<tr>
<td>1st operation</td>
<td>(z_5) (\beta_5)</td>
<td>-0.29 0.27</td>
</tr>
<tr>
<td>genta beads</td>
<td>(z_6) (\beta_6)</td>
<td>0.39 0.09(*)</td>
</tr>
<tr>
<td>suction drainage system</td>
<td>(z_7) (\beta_7)</td>
<td>-0.16 0.48</td>
</tr>
</tbody>
</table>

\(^1\) In the censuring of the duration of postoperative healing G, the duration of the follow-up period F has been used for the calculation of 'mean' in the column 'G or F.'

\(^2\) \(d = \) duration of the manifest inflammation in months

\(^3\) \(z_4 = \log (d + 1)\)

(*) significant

Figure 10.3 Graphic representation of the function of healing time G(t) in a treatment with gentamicin-PMMA beads of osteomyelitis (35 operations) or an infected endoprosthesis (32 operations). Just as in Fig. 10.2, at moment t, the probability that the patient will be declared cured after the time is \(Y\)%.
immediately been declared cured (Table 10 9 ) These operations have been analysed by means of the proportional hazard (PH) model In this model, censored observations are taken into account After 36 operations (23 % of 158), the patient has not been declared cured during the follow-up period The mean value of the duration of healing (G) or follow-up period (F) at a censored observation was 11 months This mean value, therefore, constitutes an underestimation of the actual mean duration of healing A review of the frequencies of censored observations per type of operation is given in Table 10 12 This table also describes the influence of the explanatory variables on the duration of postoperative healing

The $H_0$-hypothesis that variables $\zeta_1$ to $\zeta_7$ inclusive do not contribute to an explanation of the duration of postoperative healing (G) is rejected ($H_0 \beta_1 = \beta_2 = \ldots = \beta_7 = 0, p = 0.04$) The type of operation is the principal explanatory variable for G There exists a clear indication that the duration of postoperative healing after final operations with gentamicin-PMMA beads is shorter than after 'other' operations ($\beta = 0.39, p = 0.09$) No significant difference is demonstrable between operations with suction drainage and 'other' operations ($\beta = -0.16, p = 0.48$)

A distinct difference is observed between the suction-drainage system and the treatment with gentamicin-PMMA beads ($p < 0.05$, normal approximation) Some weak indications are found of a possible influence of the age and the manifest duration of the inflammation on the duration of postoperative healing As expected, advanced age and a long manifest duration of the inflammation seem not contributory to a short duration of postoperative healing if the patient cannot be declared cured immediately after an operation

10.6.4 Conclusion

After operations with use of the gentamicin-PMMA beads, the duration of postoperative healing is distinctly shorter, and the frequency of immediate cure higher than after operations with use of an irrigation system or other methods In this comparison, incomplete follow-up and differences in background variables (age at the time of the operation, sex, diagnosis, duration of the manifest inflammation and the patient's anamnesis) have been taken into account However, since in this analysis there has been a selective dropping-out of irrigation-system and 'other' operations (6 % and 11 %, respectively), the results of the comparison may be distorted

The healing time functions of gentamicin-PMMA bead operations for the diagnoses of infected endoprosthesis and osteomyelitis, respectively, are different (overall comparison, without adjustment for differences in background variables) The duration of postoperative healing is shorter for the diagnosis of infected endoprosthesis There are indications of an influence of the manifest duration of the inflammation on the duration of postoperative healing
11.1 Introduction

β2-Microglobulin is a natural body protein with a molecular weight of 11,800 dalton.

After glomerular filtration 99.9% of it is reabsorbed in the proximal tubular cell where subsequently it is metabolized completely. No reabsorption to the plasma occurs. Out of the 340 mg that are filtered per day, only 370 µg (0.1%) is excreted with the urine (Sbardijn et al., 1979). If the urine has a pH value lower than 6.5, a pseudohydrolysis takes place as the result of which the concentration of β2-microglobulin in acid urine decreases (Evrin and Wibell, 1972; Wibell, 1974). This hydrolysis appears to be caused by a natural body component that is activated by the low pH (Hiesche, 1981). An increase of the excretion of β2-microglobulin may be brought about by increased production, and consequently, increased supply of β2-microglobulin while the glomerular filtration rate (GFR) remains unchanged. If the supply of β2-microglobulin and the glomerular filtration remain unchanged, an increased urinary excretion of β2-microglobulin may result from a diminished reabsorption in the proximal tubulus. Accordingly, determination of β2-microglobulin in the urine may afford insight into the function of the proximal tubular cell (Fermin et al., 1974; Wibell, 1974; Sbardijn et al., 1979; Uthmann et al., 1981) (Fig. 11.1).

During treatment with gentamicin, the renal excretion of β2-microglobulin rises (Schentag et al., 1978).

Determination of β2-microglobulin in the urine renders it possible for the nephrotoxicity that may be caused by aminoglycosides to be demonstrated sooner and more sensitively than by other methods such as determination of enzymes, demonstration of cylindruria or ultimately also the determination of the serum creatinine level (Schentag et al., 1979). The plasma creatinine level, namely, is influenced only after a reduction of renal function to 30% of the normal level (Bricker et al., 1960).

The nephrotoxicity which may occur during treatment with gentamicin changes the function of the kidney and consequently, the renal excretion of gentamicin and synthesis

Figure 11.1 β2-Microglobulin after synthesis in the body cells and release into the blood circulation is filtered completely in the renal glomerulus. In the proximal tubulus, it is reabsorbed and a small proportion is excreted with the urine (a). If the tubular reabsorption of the β2-microglobulin is decreased and the supply remains unchanged, the excretion with the urine increases (b). (See also Fig. 12.8).
endogenous substances such as β2-microglobulin. The renal clearances of these substances constitute the most direct parameters of the glomerular and tubular functions, more direct than determination of serum or urine levels.

A direct measurement of the renal function is a continuous determination of the renal clearances of creatinine, β2-microglobulin and enzymes that may be released due to damage to tubular cells. The best way to accomplish this is by determination of the clearance of a specific substance in all spontaneously voided volumes of urine, the collection times of the volumes being kept as short as possible.

The renal clearance (ml/min) is the ratio of the renal excretion rate and the plasma concentration of a substance. The renal clearance constant varies in the course of the 24-hour period and depends on a number of factors such as the urinary pH, urine flow, GFR and interaction in tubular transport. The degree of deterioration of the renal clearance is dependent for every individual substance on the partial influences of the mechanisms of the secretion.

The purpose of this experiment was to determine to what extent the renal excretion and clearance of creatinine and of β2-microglobulin change under the influence of gentamicin, and to gain at least some degree of insight into the mechanism of the changes of the renal clearance and of the excretion of β2-microglobulin observed in the course of gentamicin treatment.

11.2 Material and methods

11.2.1 The test subjects

Three healthy male test subjects (26, 33, 36 years) were subjected to a total of five experiments (Table 11.1). Every experiment lasted three days. During these three days, the urine was kept alkaline (pH 7.5 - 8.5) by ingestion of approx. 10 g sodium bicarbonate daily. The first day served as the blank period, to record the excretion rate of β2-microglobulin. On the second day, gentamicin was administered intravenously in doses of 20, 60, 80 or 120 mg. In two experiments, a second dose was given: in test subject H.D., the injection of 20 mg was repeated after four hours, in test subject G.W., the injection of 60 mg was repeated after four hours. Test subject G.W. underwent three experiments: one injection of 80 mg, two injections of 60 mg and one injection of 120 mg. The intervals between the three experiments in this test subject were one year and six months, respectively. Throughout the experiments, the subjects used no alcohol, nor any drugs apart from the bicarbonate.

11.2.2 Blood samples

The blood samples were collected by intravenous puncture.

<table>
<thead>
<tr>
<th>Subject</th>
<th>M/F</th>
<th>Age</th>
<th>Height</th>
<th>Weight</th>
<th>Gentamicin I.V.</th>
</tr>
</thead>
<tbody>
<tr>
<td>P.E.</td>
<td>m</td>
<td>36</td>
<td>1.79 m</td>
<td>72 kg</td>
<td>80 mg</td>
</tr>
<tr>
<td>H.D.</td>
<td>m</td>
<td>26</td>
<td>1.92 m</td>
<td>80 kg</td>
<td>2 × 20 mg</td>
</tr>
<tr>
<td>G.W.</td>
<td>m</td>
<td>33</td>
<td>1.93 m</td>
<td>90 kg</td>
<td>80 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 × 60 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>120 mg</td>
</tr>
</tbody>
</table>

Table 11.1 Data concerning the test subjects and the dosage of gentamicin in the experiments (five in all).

The collection of undiluted venous blood necessitated the removal of the contents of the intravenous catheter and of the three-way cock (approx. 1½ ml). After the collection of the blood, physiological saline with heparin was injected into the catheter to prevent the formation of thrombi in the system. Each blood sample had a volume of approx. 2 ml. On the first (blank) day, two or three samples were taken. After the injection of gentamicin into the right-sided median cubital vein, blood samples were collected every 15 minutes for three hours and thereafter, every 30 minutes for five hours. Subsequently, some five to eight blood samples more were taken until the 36th hour after the injection of gentamicin.

11.2.3 Urine samples

Throughout the experiments, all amounts of urine were collected after spontaneous micturition, their volumes were measured and one sample of approx. 8 ml per voiding was kept. After the injection of gentamicin, urine samples were collected at the same intervals as the blood samples. Moderate water loading, of approx. 500 ml water per hour during the first few hours after the injection ensured production of enough urine to allow frequent, spontaneous micturition. During the experiment, the urinary pH was checked by means of a Copenhagen radiometer (PMH61).

11.2.4 Determinations

In all samples of blood and urine, in this study of test subjects totalling approx. 350 samples, the concentrations of creatinine and of β2-microglobulin were determined. From
the moment the gentamicin was injected, the gentamicin level as determined as well. The creatinine level was determined by an automated Jaffé method. The concentration of β2-microglobulin was determined by radioimmunoassay (Phadebas® β2-microtest: made available by Pharmacia, Zoetermeer, the Netherlands, and Uppsala, Sweden). The gentamicin concentration was determined by radioimmunoassay (made available by Merck, Amsterdam, the Netherlands, and Darmstadt, GFR). All analyses were carried out by the ABL Central Medical Laboratory of Assen, the Netherlands.

For every portion of urine, the clearances were calculated for β2-microglobulin, creatinine and gentamicin according to the equation:

\[
\text{renal clearance} = \frac{\text{renal excretion rate}}{\text{plasma concentration}}
\]

or

\[
C_r = \frac{dQ/dt}{C_a} \text{ (ml/min)},
\]

in which Q and C_a are exposed in μg (gentamicin), μmol (creatinine) and ng (β2-microglobulin), respectively.

11.3 Results

In Figs 11.3 to 11.6 inclusive the plasma levels of gentamicin (G) and the renal excretion rate of gentamicin (G), creatinine (creat.) and β2-microglobulin (β2-M) are plotted against the time. The period from -25 to 0 hours constitutes the blank period (day 1); this shows the mean renal excretion rate of the volunteer.

At t = 0 hours, an intravenous injection of gentamicin was administered: of 20, 60, 80 or 120 mg (Figs 11.3, 11.4, 11.5 and 11.6, respectively). At t = 4 hours, test subjects H.D. and G.W. were given second injections of gentamicin, of 20 and 60 mg, respectively (Figs 11.3 and 11.4). In the figures, the immediate renal excretion of gentamicin with the urine is visible; this excretion runs parallel to the falling plasma level. After 35 hours, 93.3 to 100% of the dose of gentamicin injected has been excreted.

The plasma level of gentamicin shows a biphasic course, as visible most clearly in Figs 11.4, 11.6 and 11.7. During the first phase, the distribution of gentamicin over the body is superimposed on the renal excretion. Fig. 11.7 shows that this phase runs an oscillating course. The plasma levels of creatinine and β2-microglobulin, which are not shown, remained constant throughout all the experiments (Table 11.2). Since the renal excretion rate and plasma level of creatinine did not change, the renal clearance of creatinine also remained constant during this experiment.

The renal excretion rate of β2-microglobulin responds to the gentamicin injection with a rise. This rise, which is visible in all the experiments shown, proves dose-dependent (Fig. 11.8) and disappeared again within a few hours. A second injection after four hours possibly results in a rise that slightly exceeds the rise seen after the first injection (Figs 11.3 and 11.4).

**Figure 11.3** Plasma concentration-time curve of gentamicin (G) and the renal excretion rate-time curves of gentamicin (G), β2-microglobulin (β2-M) and creatinine (creat.) in a test subject after two intravenous injections of 20 mg gentamicin. Gentamicin does not perceptibly influence the renal excretion rate of β2-microglobulin.
Fig. 11.4  Plasma concentration-time curve of gentamicin (G) and the renal excretion rate-time curves of gentamicin (G), β2-microglobulin (β2-M) and creatinine (creat.) in a test subject after two intravenous injections of 60 mg gentamicin. There is a slight possibility of influence of gentamicine on the renal excretion rate of β2-microglobulin, the reaction being slightly stronger after the second dose.

Figure 11.5  Plasma concentration-time curve of gentamicin (G) and the renal excretion rate-time curve of gentamicin (G), β2-microglobulin (β2-M) and creatinine (creat.) in a test subject after a single intravenous injection of 80 mg gentamicin. The renal excretion rate of β2-microglobulin is distinctly influenced by the gentamicin injection.
Figure 11.6 Plasma concentration-time curve of gentamicin (G) and the renal excretion rate-time curves of gentamicin (G), β2-microglobulin (β2-M) and creatinine (creat) in a test subject after a single intravenous injection of 120 mg gentamicin. The rise of the renal excretion rate of β2-microglobulin is more pronounced than after injection of a smaller dose of gentamicin.

Figure 11.7 Detail of Fig. 11.6, showing the first 14 hours after injection of 120 mg gentamicin. After 14 hours, 100% of the gentamicin injected has been excreted with the urine. The plasma concentration-time curve of gentamicin shows a biphasic, oscillating course.

Figure 11.8 Renal excretion rate of β2-microglobulin plotted against the time after the injection. The maximal excretion rate of β2-microglobulin depends on the dose of gentamicin that is injected at time $t = 0$. The normal range of the renal excretion rate of β2-microglobulin is shaded ($100 \pm 60$ ng/minute). Starting at a dose of approx. 70 mg gentamicin, the rate of excretion of β2-microglobulin rises above the normal value. Normalization is accomplished after approx. 7 hours.
Table 11.2 Kinetic parameters of gentamicin, creatinine and β2-microglobulin. Data obtained in five experiments and three test subjects. The values obtained during the blank period and those obtained during the period after the gentamicin injection are shown separately.

<table>
<thead>
<tr>
<th>Subj. dose</th>
<th>Flow ml/min</th>
<th>Plasma conc. β2-M µg/ml</th>
<th>Plasma conc. creatinine µmol/l</th>
<th>Cl. β2-M ml/min</th>
<th>Cl. creatinine ml/min</th>
<th>Genta r½ h</th>
<th>Excr. gentam. ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>P.E. blank</td>
<td>7.27±0.32</td>
<td>1.63±0.84</td>
<td>1.335±0.11</td>
<td>85.2 ±1.1</td>
<td>0.047±0.011</td>
<td>145.63±28.40</td>
<td>-</td>
</tr>
<tr>
<td>80 mg</td>
<td>7.72±0.30</td>
<td>1.96±0.51</td>
<td>86.40±6.14</td>
<td>143.73±27.16</td>
<td>2 h</td>
<td>92.2%</td>
<td>82.88±29.01</td>
</tr>
<tr>
<td>H.D. blank</td>
<td>8.78±0.97</td>
<td>1.35±0.39</td>
<td>101 ±9.85</td>
<td>117.20±15.89</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2×20 mg</td>
<td>8.73±0.58</td>
<td>2.59±1.89</td>
<td>94.1 ±8.11</td>
<td>119.57±26.00</td>
<td>2 h</td>
<td>93.3%</td>
<td>117.26±34.33</td>
</tr>
<tr>
<td>G.W. blank</td>
<td>6.26±0.56</td>
<td>0.95±0.73</td>
<td>84.60±5.20</td>
<td>162.30±25.09</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>80 mg</td>
<td>7.67±0.77</td>
<td>4.98±4.27</td>
<td>84.24±5.52</td>
<td>148.88±12.98</td>
<td>2 h</td>
<td>94.5%</td>
<td>84.31±11.55</td>
</tr>
<tr>
<td>G.W. blank</td>
<td>7.50±0.23</td>
<td>1.04±0.36</td>
<td>108 ±5.29</td>
<td>107.74±7.10</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2×60 mg</td>
<td>7.60±0.30</td>
<td>4.55±3.55</td>
<td>99.8 ±8.13</td>
<td>118.66±14.20</td>
<td>2 h</td>
<td>95.7%</td>
<td>71.21±21.30</td>
</tr>
<tr>
<td>G.W. blank</td>
<td>7.62±0.93</td>
<td>3.84±2.52</td>
<td>89.00±8.00</td>
<td>94.65±19.10</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>120 mg</td>
<td>7.95±0.25</td>
<td>6.37±2.84</td>
<td>89.30±5.84</td>
<td>109.17±31.64</td>
<td>2 h</td>
<td>100%</td>
<td>103.11±28.68</td>
</tr>
</tbody>
</table>

Figs 11.9 and 11.10 represent the relationship between the renal excretion rates of β2-microglobulin and of gentamicin (both expressed in µg/min.). In Fig. 11.9, an exponential relationship appears to be present. When the renal excretion rate of gentamicin is plotted against the logarithm of the excretion rate of β2-microglobulin, a linear relationship is indeed found. In Fig. 11.10, just as in Fig. 11.8, the range of the normal value is shown: 100 ng/min ± 60 ng/min. It is only when the renal excretion rate of gentamicin rises above approx. 150 ng/min, that the renal excretion rate of β2-microglobulin increases to above the normal value. This dose-dependent effect of the rise of the excretion rate of β2-microglobulin is also represented in Fig. 11.8. Here, after an injection of 60 mg gentamicin, an excretion rate of β2-microglobulin is reached that exceeds the normal value only minimally.

After injection of 80 and 120 mg, a more pronounced effect is visible. The normal value of the renal excretion rate of β2-microglobulin (100 ± 60 ng/min) was calculated from the blank periods: the period before the injection of gentamicin and the period after normalization of the excretion of β2-microglobulin (with the urinary pH alkaline).

Fig. 11.11 shows that the renal clearance of gentamicin is independent of the urine flow, provided this flow is adequate, over approx. 1 ml/min.

11.4 Discussion

Approaching the kinetics of β2-microglobulin as a drug or foreign substance, by means of the renal clearance concept is a fairly new procedure. By regarding the natural body compound, β2-microglobulin as a drug and by approaching it pharmacokinetically, we obtain more data than are supplied by the usual measurements of concentrations in serum or urine, a fortiori if for the urine assay, the 24-hour
The renal excretion rate of gentamicin plotted against the logarithm of the renal excretion rate of ß2-microglobulin. The interrelationship is linear. At a renal excretion rate of gentamicin in excess of approx. 150 µg/minute, the renal excretion rate of ß2-microglobulin rises above the normal value of 100 ± 60 ng/minute, based on determinations in three test subjects given seven injections of gentamicin.

The renal clearance of gentamicin plotted against the urine flow in one test subject after injection of 80 or of 120 mg gentamicin. At a flow rate in excess of 1 mg/minute, the gentamicin clearance is independent of the urine flow (see also Fig. 11.3).

Just et al. found that gentamicin and polypeptides are absorbed in the same way in the proximal tubule binding to the surface of the tubular cell in the brush border membrane. There is competition for the binding to the brush border membrane in which the number of amino groups per molecule proved to be a particularly important element (Just et al., 1977, Just and Habermann, 1977).
12.1 Introduction

ß2-Microglobulin is produced by nearly all cells in the human body. Lymphocytes and tumour cells produce much ß2-microglobulin. If the GFR (glomerular filtration rate) remains unchanged, a rising serum level of ß2-microglobulin is always due to an increased synthesis. This phenomenon occurs in patients with tumours, with leukaemia and with chronic diseases such as rheumatoid arthritis, SLE and Crohn's disease (Revillard, 1979). Wide and Thoren observed an increased clearance of ß2-microglobulin after operations or injuries. The same influence is exerted on insulin, albumin and luteinizing hormone (LH).

Just as ß2-microglobulin, these substances undergo complete glomerular filtration, and the major portion is reabsorbed in the proximal tubulus. For one to three days after an operation, these substances show an increased urinary clearance while the creatinine clearance remains unchanged (Wide and Thoren, 1972).

Davey determined the renal excretion of ß2-microglobulin and alanine aminopeptidase (AAP) in patients after an operation or injury with infections, or with hypotension after an infarction. He also studied the influence of a treatment with aminoglycosides. He used 24-hour urine samples over periods of five days. He observed that the excretion of ß2-microglobulin was maximal within four days after the operation or the injury, or the onset of the hypotension or the infection, while that of AAP was maximal after five to six days. The excretion of ß2-microglobulin returned to normal faster than that of the AAP.

With his measuring techniques, there appeared to be an insufficient difference between patients and a control group where the excretion of ß2-microglobulin was concerned (Davey, 1979).

In Chapter 11, the importance was emphasized of a study of the effect of gentamicin on renal function if low serum levels are present constantly for long periods of time.

The growing use of gentamicin-PMMA beads in the treatment by orthopaedic surgery of bone infections rendered it desirable to study the influence of gentamicin on the kidney after implantation of gentamicin-PMMA beads. Chapter 11 describes the influence of gentamicin on the proximal tubulus as determined with the aid of ß2-microglobulin. However, use of the clearance of renal excretion rate of ß2-microglobulin to study the influence of gentamicin during and after an operation, requires thorough familiarity with the intrinsic effect of the operation on these parameters.

The studies described below were intended to gain insight into the changes of the clearance and the renal excretion of ß2-microglobulin during and after an operation.

12.2 Material and method

12.2.1 Patients and their operations

Of four patients, each was subjected to one operation. Data on the patients and the type of operations are shown in Table 12.1. Samples of blood and urine were collected for three days. The patients were willing to take sodium bicarbonate, approx. 10 g daily. During the operation, acidification of the urine was prevented by moderate hyperventilation, and as long as oral nutrition was not possible, 125 ml bicarbonate 4.2% were administered via the infusion system every six hours.

Patients 1, 2 and 3 were subjected because of a discopathy to anterior spondylodesis in the lumbar spine between the vertebral bodies of L5 and S1. Patient 3 also underwent a spondylodesis between the bodies of L4 and L5. In patient 4, release of the right-sided median nerve was performed because of a carpal tunnel syndrome.

For anterior lumbar spondylodesis, the L5-S1 disc is exposed extraperitoneally by means of an incision to the left of the median line. The disc is situated at the level of the bifurcation of the aorta and the vena cava. The L4-L5 disc is reached by preparing the aorta and inferior vena cava to the right of the spinal column, usually after ligation of one or several venous rami. The disc is excised and the covering plates of the two adjoining vertebral bodies are chiselled away, resulting in a square defect. Two corticocancellous grafts, taken from the iliac crest, are wedged into the defect. Nearly all the blood loss during the operation occurs from the period of chiselling away the covering plates and taking the grafts from the iliac crest. Most of the blood loss is from the cancellous bone. Sometimes, there may be considerable blood loss from the venous plexus of the spinal canal, as well. Once the grafts are wedged in, further blood loss is slight. In patients 1, 2 and 3 this operation took approx. four to five hours in all, and the peroperative blood loss varied from 1200 to 1800 ml (Table 13.5). All three operations were carried out under general anaesthesia, with supplementary epidural anaesthesia (marcain, level L1-L2) in patient 3.

The release of the median nerve in patient 4 was performed under Bier's anaesthesia. The arm was exsanguinated by bandaging and injected intravenously with 50 ml of a

### Table 12.1

<table>
<thead>
<tr>
<th>Patient</th>
<th>M/F</th>
<th>Age</th>
<th>Height</th>
<th>Weight</th>
<th>Operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>f</td>
<td>23</td>
<td>1.75 m</td>
<td>54 kg</td>
<td>ant. spondylodesis L5-S1</td>
</tr>
<tr>
<td>2</td>
<td>m</td>
<td>25</td>
<td>1.71 m</td>
<td>64 kg</td>
<td>ant. spondylodesis L5-S1</td>
</tr>
<tr>
<td>3</td>
<td>m</td>
<td>39</td>
<td>1.89 m</td>
<td>94 kg</td>
<td>ant. spondylodesis L4-L5-S1</td>
</tr>
<tr>
<td>4</td>
<td>f</td>
<td>53</td>
<td>1.61 m</td>
<td>73 kg</td>
<td>release median nerve</td>
</tr>
</tbody>
</table>

Data concerning the four patients and the operations performed on them.
was then made over the wrist, after which the transverse carpal ligament could be identified and severed. The operation field and avoids blood loss. A volar incision marccain solution. The exsangumation improves the view of the operation field and avoids blood loss. Popcastically, the patients were kept under observation in the recovery room for two to three hours and then returned to the wards. The drugs administered to the patients are listed in Table 12.2.

### Medication

<table>
<thead>
<tr>
<th></th>
<th>1 SJ</th>
<th>2 KL</th>
<th>3 Bo</th>
<th>4 P-B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nocturnal medication (oral)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diazepam</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>nitrazepam</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td><strong>Premedication (i m)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diazepam</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>droperidol</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>fentanyl + droperidol (ml)</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>piritramide</td>
<td></td>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td><strong>Peroperative (i v)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>atropine</td>
<td>½</td>
<td>½</td>
<td>½</td>
<td>½</td>
</tr>
<tr>
<td>bupivacaine (ml)</td>
<td>20**</td>
<td>50*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>calcium gluconate</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
</tr>
<tr>
<td>diazepam</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>droperidol</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>fentanyl</td>
<td>0,35</td>
<td>0,20</td>
<td>0,20</td>
<td>0,20</td>
</tr>
<tr>
<td>furosemide</td>
<td>7,5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>gallamine</td>
<td>15</td>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>metaraminol</td>
<td>¾</td>
<td></td>
<td></td>
<td>¾</td>
</tr>
<tr>
<td>piritramide</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>piritramide</td>
<td>7</td>
<td></td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>pancuronium</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>prothypendyl</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>succinyl choline</td>
<td>130</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>thiopental</td>
<td>250</td>
<td>500</td>
<td>500</td>
<td>500</td>
</tr>
<tr>
<td><strong>Infusion (ml)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>glucose 3.3%/NaCl 0.25% sol</td>
<td>1500</td>
<td>1000</td>
<td>2000</td>
<td>500</td>
</tr>
<tr>
<td>Haemaccel 3.5% solution</td>
<td>500</td>
<td>500</td>
<td>1000</td>
<td>1000</td>
</tr>
<tr>
<td>NaCl 0.9% solution</td>
<td>625</td>
<td>2000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na-bicarbonate 4.2% solution</td>
<td>100</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ringer's solution</td>
<td>2500</td>
<td>2500</td>
<td>1000</td>
<td>1000</td>
</tr>
<tr>
<td>whole blood</td>
<td>1000</td>
<td>500</td>
<td>1000</td>
<td>500</td>
</tr>
<tr>
<td>packed cells</td>
<td>1000</td>
<td>1000</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Per- and postoperative (i v)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ampicillin 4 dd</td>
<td>1000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fluocoxacin 4 dd</td>
<td>1000</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 0.25% Bier's anaesthesia
** Epidural anaesthesia

Doses of all drugs stated in mg, unless otherwise stated.

Table 12.2 Data concerning the drugs, anaesthetic gases and infusion fluids that have been administered to the patients before, during and after the operation.

### 12.2.2 Blood and urine samples

For three days, of every urination, the volume and the moment of voiding were recorded and a sample was kept. In the course of the operations of patients 1, 2 and 3 an amount of urine could be collected every half hour, because a urinary catheter is introduced for this operation. Postoperatively, the interval between collection of urine samples was increased gradually to four hours. Urine of patient 4 was only obtained by spontaneous micturition. Blood was collected by venipuncture, three to four times both on the day before and on the day after the operation. Peroperatively, and in the recovery room, blood could be collected via an intra-arterial line, inserted for the anaesthesia. In the absence of an intra-arterial line, blood was collected by means of a three-way cock system connected to the infusion.

Blood and urine were kept in a refrigerator (4°C) for some time, and then, after pipetting off the serum, stored in a freezer (-25°C) until the time of laboratory assay.

### 12.2.3 Determinations

The plasma levels of creatinine, β2-microglobulin and creatinine (μmol/l) and ß2-microglobulin (ng/ml) are also plotted. The plasma levels of creatinine and β2-microglobulin are not affected by the operation. Fluctuation within the limits of normal can be observed during the periods of frequent sample-collecting (during operation and in the recovery room) (Table 12.3).

The variability of the urine flow is physiological, and also visible during the preoperative 'blank' period. A noticeable element here is a pronounced decrease of the urine flow in patients 1 and 4, occurring early in the morning, just before the operation. The same decrease is observed in patient 2, shortly before the beginning of the anaesthesia, and in patient 3, of longer duration, for several hours during the operation. The decrease of the urine flow was associated with a decrease of the renal excretion of creatinine and β2-microglobulin. Normalization of the flow is associated with a relative, short-lasting polyuria, probably a sort of compensation effect. This can be observed in patients 1 and 4 but not in patients 2 and 3.

The renal excretion rate of creatinine is not affected by the operation in patients 1, 2 and 3. In patient 4, there is a brief increase of the renal excretion. Especially in patients 1, 2 and 3, the renal excretion rate of β2-microglobulin shows a pronounced rise after normalization of the urine flow during the operation. In a very short time, a maximum is reached that is always more than 15,000 ng/min in patients 1, 2 and 3. Even almost reached 100,000 ng/min when

A normalization of this renal excretion rate of β2-microglobulin occurs in patient 1 in 40 hours, with a "half-life" of four hours. In patients 2 and 3, the decrease is much less fast and appears to run a biphasic course.

The renal excretion rates of β2-microglobulin and creatinine in patient 4 paralleled the urine flow from the time of the operation.
Figure 12.1 Plasma concentration-time curve of $\beta_2$-microglobulin ($\beta_2$-M) and creatinine (creat), the renal excretion rate-time curves of $\beta_2$-microglobulin and creatinine and the variations of the urine flow with the passage of time in patient 1 ($S_1$). At time $t=0$, an anterior spondylodesis L5-S1 was performed.

Figure 12.2 Plasma concentration-time curve of $\beta_2$-microglobulin ($\beta_2$-M) and creatinine (creat), the renal excretion rate-time curves of $\beta_2$-microglobulin and creatinine and the variations of the urine flow with the passage of time in patient 2 ($K$). At time $t=0$, an anterior spondylodesis L5-S1 was performed.
<table>
<thead>
<tr>
<th>Subj. or surgery</th>
<th>Blank</th>
<th>pH</th>
<th>Flow ml/min</th>
<th>Plasm conc. β₂-M μg/ml</th>
<th>Plasm conc. creat. μmol/L</th>
<th>Cl. β₂-M ml/min</th>
<th>Cl. creat. ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Sj</td>
<td>blank</td>
<td>6.97±0.77</td>
<td>0.87±0.56</td>
<td>1.32±0.11</td>
<td>66.2±7.3</td>
<td>0.039±0.016</td>
<td>68.70±14.28</td>
</tr>
<tr>
<td></td>
<td>surgery</td>
<td>6.87±0.53</td>
<td>1.97±1.43</td>
<td>1.30±0.28</td>
<td>69.3±4.8</td>
<td>variable</td>
<td>65.90±32.10</td>
</tr>
<tr>
<td>2. K.</td>
<td>blank</td>
<td>8.06±0.65</td>
<td>1.08±0.83</td>
<td>1.87±0.12</td>
<td>88.67±9.56</td>
<td>0.055±0.040</td>
<td>84.13±29.58</td>
</tr>
<tr>
<td></td>
<td>surgery</td>
<td>7.22±1.22</td>
<td>1.58±1.10</td>
<td>1.76±0.24</td>
<td>84.40±7.74</td>
<td>6.145±4.716</td>
<td>92.75±46.08</td>
</tr>
<tr>
<td>3. Bo.</td>
<td>blank</td>
<td>7.90±0.70</td>
<td>2.62±2.75</td>
<td>1.40±0.082</td>
<td>123.25±29.76</td>
<td>0.101±0.075</td>
<td>96.38±36.46</td>
</tr>
<tr>
<td></td>
<td>surgery</td>
<td>5.54±0.48</td>
<td>0.95±0.53</td>
<td>1.43±0.18</td>
<td>110.25±15.41</td>
<td>variable</td>
<td>97.00±56.63</td>
</tr>
<tr>
<td>4. P-B.</td>
<td>blank</td>
<td>8.69±0.66</td>
<td>1.17±0.51</td>
<td>1.64±0.13</td>
<td>75.00±4.64</td>
<td>0.029±0.007</td>
<td>41.94±14.68</td>
</tr>
<tr>
<td></td>
<td>surgery</td>
<td>7.75±0.93</td>
<td>1.49±1.99</td>
<td>1.62±0.13</td>
<td>69.40±7.42</td>
<td>0.063±0.051</td>
<td>95.37±73.60</td>
</tr>
</tbody>
</table>

Table 12.3 Kinetic parameters of β₂-microglobulin and creatinine in four patients who underwent an operation. The data are subdivided into those obtained in the course of the blank period and those obtained since the operation.

Figure 12.3 Renal excretion rate-time curve of β₂-microglobulin and creatinine, and the variations of the urine flow with the passage of time in patient 3 (Bo). At time t = 0, an anterior spondylodesis was carried out at levels L4-5 and L5-S1. The plasma levels of creatinine and β₂-microglobulin are not shown, but were constant (Table 12.3).

There is a direct proportionality between the renal excretion rates and clearances of creatinine and β₂-microglobulin in patient 4 (Fig. 12.5). Both clearances show a similar correlation with the urine flow (Fig. 12.6). In these figures, the urine flow on the day of the operation varied between almost 0 and almost 6 ml/min.
Figure 12.5 Correlation of the clearances of β2-microglobulin and of creatinine in patient 4. The fluctuating urine flow brought about a variable creatinine clearance. The renal clearances of creatinine and β2-microglobulin show a linear interrelationship. It is indicated when the samples are collected: during operation or in the blank period.

Figure 12.6 Correlation of the renal clearances of creatinine and of β2-microglobulin, respectively, with the urine flow in patient 4 (P-B). The flow varied from 0 to almost 6 ml/minute. The clearances of creatinine and β2-microglobulin are influenced by the urine flow. Just as in Fig. 12.5, this figure indicates what samples were collected at operation.
Figure 12.7 Correlation of the renal clearances of creatinine and of β₂-microglobulin, respectively, with the urine flow in patient 1 (Sj). The figure shows at what stage of the treatment the samples have been collected. Furosemide exerts influence on the creatinine clearance but not on the clearance of β₂-microglobulin.

For patient 1 (Sj), the correlation of the clearances of creatinine and β₂-microglobulin and the urine flow are shown in Fig. 12.7. The stages at which the samples have been collected are shown. The relationship between the creatinine clearance and the urine flow is clearly influenced by Lasix®; while the creatinine clearance remains constant, the urine flow increases. The clearance of β₂-microglobulin shows no correlation with the urine flow during the first hour of the operation, nor in the three samples of urine collected at operation. Then follows a period of pronounced rise of the excretion of β₂-microglobulin, during the stay in the recovery room. This correlation with the flow was not present at operation, nor after return to the ward. Furosemide does not affect the renal excretion rate of β₂-microglobulin.

12.4 Discussion

The operation exerts a distinct influence on the renal excretion rate and the apparent renal clearance of β₂-microglobulin.

12.4.1. Influence of the urine flow

At the operation of patient 4 (P-B), brief and not very traumatic, there is a decrease of the apparent renal clearance, probably resulting from a decrease of the urine flow and running parallel to the change of the creatinine clearance.

It is a known fact that whether renal function is normal or disturbed, the renal creatinine clearance depends not only on the diet, body surface, activity, sex and age but also on the urine flow (Vree et al., 1981b).

The same holds true of the gentamicin clearance in renal dysfunction (Walenkamp and Vree, 1981). The decrease of the urine flow in the hours just before operation may be a normal diurnal fluctuation, possibly enhanced by dehydration because the patient had to be kept fasting for the operation.

12.4.2. Influence of the surgical trauma

In patients 1, 2 and 3, also, the decrease of the urine flow was accompanied by a decrease of the renal excretion of β₂-microglobulin. The marked rise of this excretion could here not be attributed solely to an increase of the urine flow, however, although of course the latter played its part.

An important observation is that the plasma level of β₂-microglobulin is not increased by the operation. Tissue damage at operation might lead to a depletion of β₂-microglobulin from the damaged cells. The fact that nevertheless, the plasma level of β₂-microglobulin does not rise after an operation (Table 12.3) might be explained by the complete and direct filtration of β₂-microglobulin in the glomerulus. In that case, the rise of the renal excretion rate of β₂-microglobulin might be caused by a limited capacity of the proximal tubulus to reabsorb β₂-microglobulin.

Another explanation of the raised renal excretion of β₂-microglobulin is that when tissue is damaged, substances other than β₂-microglobulin are released which competitively inhibit the reabsorption of β₂-microglobulin.
Presumably, these substances are aminoacids or compounds with aminoacid groups.

In that case, the observed effect of the operation is analogous to the influence of gentamicin since this antibiotic, also, causes a raised renal excretion of β2-microglobulin. Gentamicin, also, enters into competition for the binding to the brush border membrane and consequently for the adsorption by pinocytosis (Just et al., 1977; Just and Habermann, 1977; Mogenson and Sølling, 1977; Whelton et al., 1978; De Broe, 1982).

Furthermore, the temporarily decreased reabsorption of β2-microglobulin in the proximal tubulus might be caused by a transient relative ischaemia of the kidney due to the operation. This effect might be brought about by the administration of drugs and by loss of blood. However, the frequent checks of the blood pressure and pulse rate during the operations never revealed a decrease of blood pressure or pulse rate as a manifestation of underfilling of the vascular system. For patients 1 and 2 (Sj and K), the blood loss, duration of the operation and type of operation, as well as the maximal renal excretion of β2-microglobulin were identical. However, in patient 1 the return to normal values was faster. In patient 3, the operation involved two levels of the spinal column, so that it lasted longer and blood loss was larger. The maximal renal excretion rate of β2-microglobulin in this patient amounted to almost 100,000 ng/min, very much more than in patients 1 and 2. Within the measuring period, hardly any decrease of the renal excretion rate occurred.

In patient 4, who underwent a short-lasting operation with only slight trauma, the renal excretion rate of β2-microglobulin showed hardly any increase.

### 12.5 Conclusion

The renal excretion rate of β2-microglobulin is raised by an operation. There appears to exist a correlation between the severity of the surgical trauma and the maximal renal excretion rate of β2-microglobulin. This raised renal excretion rate and the raised apparent β2-microglobulin clearance may be due to an increased supply of β2-microglobulin from the damaged cells, or to competition of β2-microglobulin with some other-unspecified-substance with amino acid groups. A limited absorption mechanism in the brush border of the proximal tubular cell leads to this competition, or to an excessive supply of β2-microglobulin to be reabsorbed and consequently to a raised renal excretion rate of β2-microglobulin (Fig. 12.8).

The fact that Davey (1979) observed too little difference in renal excretion rates of β2-microglobulin between patients and a control group becomes understandable if we realise that when measurements are carried out only in 24-hour portions of urine, all minor fluctuations in excretion rates of β2-microglobulin are missed. Good insight into the effect on this excretion rate exerted by gentamicin (Chapter 11), by an operation (this chapter) or by gentamicin-PMMA beads (Chapter 13), can only be gained by studying the clearance in frequently collected samples.

![Diagram](image_url)
Chapter 13. The influence of gentamicin and of the operation on the function of the proximal tubular cell of patients with implanted gentamicin-PMMA beads

13.1 Introduction

The value of ß2-microglobulin as a sensitive parameter of effect on the function of the proximal tubulus had to be investigated first, in order to render it possible to study the question whether treatment with gentamicin-PMMA beads might have a transient or permanent influence on renal function (Chapters 11 and 12).

So far it has been maintained that a toxic side effect of treatment with gentamicin-PMMA beads is improbable because the plasma gentamicin levels are virtually always below the level of demonstrability (Dingeldein and Wahlig, 1977; Wahlig et al., 1978; Wahlig, 1979, 1981).

Bergmann and Dingeldein carried out experiments in animals and found no influence of gentamicin-PMMA beads on, among other factors, serum creatinine and the serum urea level (Bergmann and Dingeldein, 1978). No more direct measurement of the influence of gentamicin-PMMA beads on the kidney has been carried out.

Extensive use of gentamicin in the form of gentamicin-PMMA beads on 'non-vital' indications justifies a more thorough study of the influence of gentamicin on the kidney during treatment with these gentamicin-PMMA beads, which treatment is sometimes protracted. It is especially in at-risk patients such as young children, the elderly, patients with renal dysfunction and patients treated with other possibly nephrotoxic drugs, that more certainty is to be desired than has been obtained from studies in otherwise healthy laboratory animals or humans as performed by the above-named authors.

The nephrotoxicity of gentamicin has been studied mostly during intermittent administration of this drug. The effects of continuous administration of gentamicin have been studied only sporadically.

Reiner et al. (1978) subjected dogs for ten successive days to a continuous infusion or one large daily dose of gentamicin. Continuous infusion brought about a greater decrease of renal function as measured with the aid of the creatinine clearance.

Serum creatinine is an insensitive and very late-responding parameter of nephrotoxic effects of aminoglycosides. A rise of the serum gentamicin level, also, is far too late a warning to permit timely adjustment of the treatment (Schenig et al., 1979); when it occurs, namely, the glomerular filtration is already diminished.

As mentioned before (Chapter 11), the renal excretion of ß2-microglobulin responds very sensitively even to a single injection of gentamicin. Also, the reaction is dose-dependent. The effect, a rise of the renal excretion rate of ß2-microglobulin, is limited to one to two hours after the intravenous injection. The influence of the operation on the renal excretion rate has also been described: in addition to the influence of the urine flow on the renal excretion rate of ß2-microglobulin, of creatinine and of gentamicin, the operation itself also affects the excretion of ß2-microglobulin (Chapter 12).

<table>
<thead>
<tr>
<th>Patient</th>
<th>M/F</th>
<th>Age</th>
<th>Height</th>
<th>Weight</th>
<th>Diagnosis</th>
</tr>
</thead>
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<tr>
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<td>f</td>
<td>28</td>
<td>1.67 m</td>
<td>88 kg</td>
<td>osteomyelitis tibia</td>
</tr>
<tr>
<td>6. Ta</td>
<td>m</td>
<td>25</td>
<td>1.86 m</td>
<td>76 kg</td>
<td>osteomyelitis femur</td>
</tr>
<tr>
<td>7. vdB</td>
<td>m</td>
<td>33</td>
<td>1.86 m</td>
<td>82 kg</td>
<td>osteomyelitis tibia</td>
</tr>
<tr>
<td>8. Go</td>
<td>m</td>
<td>21</td>
<td>1.94 m</td>
<td>68 kg</td>
<td>osteomyelitis femur</td>
</tr>
<tr>
<td>9. dG</td>
<td>m</td>
<td>67</td>
<td>1.68 m</td>
<td>57 kg</td>
<td>painful total hip loosening</td>
</tr>
</tbody>
</table>

Table 13.1 Data concerning five patients in whom gentamicin-PMMA beads were implanted, stating the diagnoses.

13.2 Material and method

13.2.1 Patients and operations

Five patients underwent a total of ten operations. The data on these patients are shown in Table 13.1: sex, age, height and weight and indication for operation. Patient 5 (AL-B) suffered from a recurrent posttraumatic osteomyelitis with formation of infiltrates in the covering soft tissues of the distal left tibia. Patient 6 (Ta) had a recurrence of an infection of the distal left femur, of traumatic origin. Patient 7 (vdB) had a recurrent posttraumatic osteomyelitis of the entire right tibia dating from a complicated removal of an intramedullary nail. Patient 8 (Go) had a postoperative infection after a supracondylar osteotomy in the left femur. The osteotomy had been performed to correct an abnormal posture in an area where an osteomyelitis had been treated previously. Patient 9 (dG) suffered from a painful loose total hip prosthesis on the right.

Each patient underwent two operations. In all cases, the first operation involved nettoyage of the inflammation followed by implantation of gentamicin-PMMA beads. In patient 7, the nettoyage comprised intramedullary drilling-out of the entire tibia. In patient 8, a condylar plate and eight screws were removed and in patient 9, a total hip prosthesis with bone cement was taken out. In these five patients, 40 to 360 gentamicin-PMMA beads were implanted into the bone and as a rule, a few beads were placed in the soft tissues as well. In patients 8 and 9, most of the gentamicin-PMMA beads...
<table>
<thead>
<tr>
<th>Medication</th>
<th>Patient 5 Al-B OK1 OK2</th>
<th>Patient 6 Ta. OK1 OK2</th>
<th>Patient 7 vdB. OK1 OK2</th>
<th>Patient 8 Go. OK1 OK2</th>
<th>Patient 9 dG. OK1 OK2</th>
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</tr>
<tr>
<td>diazepam</td>
<td>10</td>
<td>10</td>
<td>10</td>
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<td>15</td>
<td>15</td>
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<tr>
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</tr>
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</tr>
<tr>
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<td>x</td>
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<td>15</td>
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</tr>
<tr>
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<td>18</td>
<td>17</td>
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<tr>
<td>glucose 3.3 %/NaCl 0.25 %</td>
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<td>1000</td>
<td>1000</td>
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<tr>
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</tr>
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<td>NaCl 0.9 % sol.</td>
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<td>100</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Na-bicarbonate 4.2 %</td>
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<td>450</td>
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<td>Ringer's sol.</td>
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</tbody>
</table>

**doses of all drugs stated in mg, unless otherwise stated**

Table 13 2 Data concerning the drugs, anaesthetic gases and infusion fluids that were administered to five patients before, during and after the operation Each patient underwent two operations

beads were imbedded in soft tissues. At the second operations, after nine to 14 days, the gentamicin-PMMA beads were removed and in patient 9, a new total hip prosthesis was reimplanted as well.

In none of these patients had the orienting preoperative blood testing revealed any abnormalities of renal or hepatic function. There were no concurrent diseases, apart from status after cataract operation in patient 9. The durations, and the peroperative blood losses of the various operations are listed in Table 13.5. In Table 13.2, the drugs administered on the day before operation, or during and directly after the operation are listed in alphabetical order. Patients 7 (vdB) and 9 (dG) on the day of the operation were given 4 x 1 g cefalotin at six-hour intervals.

Epidural anaesthesia (marcain and/or scandicain) was administered to patients 6 (Ta) and 7 (vdB).

Since the measurements had to be carried out during the entire period of treatment, all patients had to take sodium bicarbonate throughout the treatment to maintain alkalinity of the urine.

Patient 5 (Al-B) took five tablets of 0.5 g every three hours but was unable to keep this up from approx the eighth day after operation, because of vague symptoms attributed to the bicarbonate. Therefore, the other patients took one tablet every hour, plus four to five tablets of 0.5 g at night before going to sleep. A few days after the first operation, dosage was changed to one tablet every other
hour pH checks showed whether the urine remained sufficiently alkaline. On this regimen, there were no complaints and the urine remained sufficiently alkaline (pH > 7.5). No attempts were made to reduce the dosage of sodium bicarbonate further.

During the operations, just as in the patients described in Chapter 12, it was attempted to maintain moderate hyperventilation and if postoperatively nothing could be taken orally, 125 ml sodium bicarbonate 4.2% in physiological saline was administered every six hours.

13.2.2 Blood and urine samples

In all, approx 215 samples of blood and 485 of urine were collected from these five patients. Collection and storage procedures were the same as described in Chapters 11 and 12. During and shortly after operation, blood samples could be collected frequently, every 30 minutes, usually from the infusion system. The urine samples were always obtained by spontaneous voiding, except in patient 9 (dG) during the first operation because at that time he was wearing a bladder catheter. The period of the measurements lasted from one day before the first operation to three or four days after the second operation, in all 350 to 450 hours in each patient.

13.2.3 Determinations

In all samples of blood and urine, the concentrations of creatinine and β2-microglobulin were determined, and from the first operation (OK-1) the gentamicin concentration, also. The determinations were carried out as described previously (Chapters 11 and 12).

Furthermore, in the urine samples of all patients the concentration of alanine aminopeptidase (AAP) was determined. This enzyme was determined by an Emit method which had a lower limit of demonstrability of 6 mU/ml.

The renal excretion rates of β2-microglobulin, gentamicin, creatinine and AAP were calculated, and expressed in ng/min, μg/min, μmol/min and mU/min, respectively.

13.3 Results

Figs 13.1 to 13.5 inclusive show the renal excretion rate-time profiles of β2-microglobulin and gentamicin. Fig 13.5 also shows the renal excretion rate-time profiles of creatinine and alanine aminopeptidase and the plasma levels of gentamicin and β2-microglobulin with the passage of time. The moments of operation are always indicated by OK-1 and OK-2.

The renal excretion rate of β2-microglobulin shows a preoperative decrease in nearly all patients. This decrease corresponds to a decrease of the urine flow. In patient 5, the urine flow decreased, not before but during the OK-2 operation. At the first operation (OK-1), all patients show a marked rise of the renal excretion of β2-microglobulin. The excretion peaks reached vary in patient 5 (Al-B) approx 1500 ng/min, in patient 6 even 110,000 ng/min. In patients 5 (Al-B) and 9 (dG), this peak value was only reached after about two days.

Normalization of this raised excretion rate occurs within 50 to 100 hours in patients 5 to 8 inclusive. In patient 9 (dG), on the other hand, the renal excretion rate remained constant at the peak level of 60,000 ng/min for almost 200 hours, to fall below the upper limit of normal during the next 150 hours, just before the second operation is scheduled. This decrease in this patient occurs in two phases, each with a 't½' of 15 hours. In the other patients, the renal excretion once normalized showed a fluctuation within the normal range of 100 ± 60 ng/min.

It was only in patient 5 (Al-B) that from the eighth...
Figure 13.2 Renal excretion rate-time curves of gentamicin and ß2-microglobulin in patient 6 (Ta). ß2-Microglobulin shows a marked rise of the renal excretion rate as the consequence of OK-1 but not as the consequence of OK-2. The constant excretion rate of gentamicin amounts to approx. 3 µg/minute. In this patient, 90 gentamicin-PMMA beads were implanted.

postoperative day the excretion of ß2-microglobulin showed a highly irregular pattern with decreases that sometimes dipped far below the normal values. This pronounced fluctuation corresponds to the periods during which the patient took the bicarbonate very irregularly and insufficiently, so that the pH of the urine fell too low and hydrolysis of the ß2-microglobulin became possible.

The second operation (OK-2) causes no rise of the excretion of ß2-microglobulin in patient 5 to 8 inclusive. The renal excretion did show a rise in patient 9 (dG). This second operation involved only a minor trauma in patients 5 to 8 inclusive, since it consisted exclusively in removal of the gentamicin-PMMA beads. In patient 9, however, not only were the gentamicin-PMMA beads removed but a new total hip prosthesis was also implanted. In patients 6 to 9 inclusive, it was attempted at these second operations to administer identical anaesthetics, just as at OK-1. Patients 6 (Ta) and 7 (vdB) were subjected to epidural anaesthesia at OK-1 and at OK-2.

Figure 13.3 Renal excretion rate-time curves of gentamicin and ß2-microglobulin in patient 7 (vdB). Drilling out the medullary cavity of the tibia caused a very marked rise of the renal excretion rate of ß2-microglobulin, many times higher than occurs after less drastic interventions, as shown in Figs. 13.1 and 13.2. Implantation of 49 gentamicin-PMMA beads results in a renal excretion rate of gentamicin of approx. 4 µg/minute. The removal of the gentamicin (OK-2) was not followed by a reaction of the renal excretion rate of ß2-microglobulin.
Figure 13.4 Renal excretion rate-time curves of gentamicin and β₂-microglobulin in patient 8 (Go). Ninety gentamicin-PMMA beads were implanted along the femur and beneath the m. vastus lateralis (OK-1). Removal of the beads did cause some rise of the β₂-microglobulin in this patient. The excretion rate of gentamicin in the course of the treatment remained fairly constant in this patient, as well, at approx. 10 μg/minute.

The renal excretion rate of gentamicin remained constant throughout the treatment with gentamicin-PMMA beads (Table 13.3). In patient 5 (Al-B) there was a brief rise after the implantation, to a maximum of 10 μg/min, but a fall occurred within two days. Patient 9 (dG) showed a maximal excretion of gentamicin of 120 μg/min after approx. 48 hours. In this patient, the excretion of gentamicin fell after approx. five days to a plateau level of approx. 40 μg/min. In the other three patients, the excretion of gentamicin remained constant throughout, with plateau levels of approx. 3 μg/min (just as in patient 5) or of 10 μg/min (patient 8). After the bead treatment, of 9 to 14 days' duration, approx. 20 to 30% of the total amount of gentamicin implanted had been excreted. In patient 9, however, this proportion amounted to 69.6%. In this patient (dG), the effect of implantation of a hip prosthesis with the aid of gentamicin-containing cement at OK-2, was demonstrable in the plasma and urine: a rapid rise, to 1.3

Table 13.3 Kinetic parameters of gentamicin, β₂-microglobulin and creatinine in the five patients in whom gentamicin-PMMA beads were implanted. The data are subdivided in those that were obtained during the blank period and those obtained after the first or the second operation.
Figure 13.5  Patient 9 (dG) This figure shows the plasma concentration-time curves of gentamicin and β2-microglobulin (β2-M), and the renal excretion rate-time curves of β2-microglobulin, gentamicin-creatinine and alanine aminopeptidase. At time t = 0, a total hip prosthesis is removed and 360 gentamicin-PMMA beads are implanted (OK-1). At the time of the removal of the gentamicin-PMMA beads (OK-2), a new total hip prosthesis is implanted, with the aid of gentamicin-containing bone cement. In this patient, the plasma-gentamicin concentration was constantly measurable throughout the treatment (as a rule below 1 μg/ml) and the rate of urinary excretion of gentamicin was relatively high. This was also the only patient in whom the rate of excretion of alanine aminopeptidase was measurable. This excretion rate rises slightly in the course of the treatment. The renal excretion rate of β2-microglobulin in this patient, just as in patient 7 (Fig 13.3) rises to very high values.

μg/ml and 96 μg/min was followed by a rapid decrease.

The serum level of gentamicin in patients 5 to 8 inclusive always remained below the detection limit (RIA method, 0.15 μg/ml), apart from a few determinations immediately after implantation. Given a renal clearance of 100 ml/min, it can be calculated from the renal excretion rate that the serum level of gentamicin amounted to 0.03 μg/ml when 48 to 90 gentamicin-PMMA beads were in situ. In patient 9 (dG), 360 gentamicin-PMMA beads were implanted, and the renal clearance for gentamicin was 88 ± 37 ml/min and that for creatinine, 79 ± 43 ml/min. The serum level in this 67-year-old patient remained above the detection limit throughout the treatment, and reached a peak of 1.8 μg/ml and a plateau value of 0.4 μg/ml.

These plasma concentrations of gentamicin are in accordance with values found in another patient in whom also 360 gentamicin-PMMA beads were implanted after
The plasma level of $\beta_2$-microglobulin was not affected by the operation in any of the patients, and remained constant in all patients throughout the treatment with gentamicin-PMMA beads (Table 13.3). It was only in patient 9 that a very slight rise of the plasma level was observed in the course of the measuring period of over 400 hours.

### 13.4 Discussion

In general, the nephro- and ototoxicity in the treatment with aminoglycosides is regarded as a dose-related problem (Barza and Lauermann, 1978). Dahlgren observed no nephrotoxic side effects in patients when the minimal value of the serum gentamicin level during intermittent administration was lower than 2 $\mu$g/ml. As the criterion for nephrotoxicity he regarded a rise of the serum creatinine level (Dahlgren et al., 1975).

Others regard a rise of the minimal gentamicin level as an indication of developing nephrotoxicity. This rise is a manifestation of this nephrotoxicity, rather than a cause of it (Holm et al., 1979).

After a single injection of radioactively labelled gentamicin it is found that uptake of gentamicin occurs exclusively in the proximal tubulus. In this part of the tubulus, the uptake into the tubular cell increases in the farther distal tracts; a correlation appears to exist with the concentration gradient of the urine (Morin et al., 1979, 1980). In the cell, gentamicin is concentrated in the lysosomes (Morin et al., 1979, 1980; De Broe et al., 1981).

However, when gentamicin is administered for longer periods of time, it is found that after an initial uptake in the lysosomes only, after seven days the gentamicin is distributed over all subcellular fractions (Kohlehepp et al., 1979).

Although the effect on lysosomes (Morin et al., 1979, 1980) and on brush border enzymes such as AAP (Mondorf et al., 1978a) has an incompletely understood relationship with the nephrotoxicity, it is nevertheless regarded as an early and valuable indication of a toxic effect on the kidney during treatment with aminoglycosides. $\beta_2$-microglobulin is a sensitive parameter which responds faster than, for instance, AAP (Schentag et al., 1979a, Sethi et al., 1981).

Studies in volunteers have shown that assay of $\beta_2$-microglobulin provides a reproducible and sensitive parameter for the dose-dependent effect of gentamicin on the proximal tubulus (Chapter 11). Since the effect of the operation on the renal excretion of $\beta_2$-microglobulin is known (Chapter 12), the $\beta_2$-microglobulin might be used to investigate the influence of the very slight but continuous presence of gentamicin in the kidney after implantation of gentamicin-PMMA beads (this chapter).

As mentioned in the paragraph above, during treatment of patients with gentamicin-PMMA beads, the serum level of gentamicin is very low, and as a rule below the detection limit. Personal findings in eight patients (patients 5 to 9 inclusive and patients 1 and 2, described in Chapter 15) are in agreement with literature data on this topic (Dingeldein and Wahlig, 1977; Jenny et al., 1977; Wahlig et al., 1978; Wahlig, 1979, 1981).

The urinary concentration of gentamicin is of little importance since it is affected strongly by the urine flow. All literature on the gentamicin-PMMA beads state that this urinary concentration remains low, mostly lower than 10 $\mu$g/ml (Jenny et al., 1977; Wahlig, 1981). However, in a patient described elsewhere, in whom 360 gentamicin-PMMA beads were implanted, urinary gentamicin levels above 20 $\mu$g/ml were found until the 10th day (see Chapter 15, patient 3). In patient 9, the maximal urinary concentration even rose to as much as 200 $\mu$g/ml, 12 hours after implantation of the beads.

As regards the renal excretion rate of gentamicin after implantation of gentamicin-PMMA beads, values ranging from 4 to 12 $\mu$g/ml were observed after implantation in four patients of 48 to 90 gentamicin-PMMA beads in the bone and soft tissues (Table 13.3). However, in patient 9, after implantation of 360 gentamicin-PMMA beads, this rate amounted to approx. 95 $\mu$g/min. These observations do not permit any simple conclusions concerning the influence of the types of tissue around the gentamicin-PMMA beads on the amount of gentamicin excreted by the kidneys.

In patient 8, the gentamicin-PMMA beads were localized along the femur, covered by the m. vastus lateralis. In patient 9, the 360 gentamicin-PMMA beads were situated partly in the proximal femur, partly at the site of the removed hip joint, surrounded by the periarticular musculature (Fig. 13.6). In the other three patients, the gentamicin-PMMA beads were situated mostly in more or less sclerotic bone.

After removal of the gentamicin-PMMA beads, the remaining gentamicin (present in the wound and in the kidney) is excreted slowly with the urine. After nine to 14 days' treatment with gentamicin-PMMA beads, 20 to 40% of the total amount of gentamicin implanted had been excreted in patients 5 to 8 inclusive. In patient 9, 70% had been excreted. It is this total proportion of gentamicin that is excreted, rather than the value of the renal excretion rate of gentamicin that constitutes a manifestation of the capacity of the tissues around the gentamicin-PMMA beads to collect gentamicin from the beads via the wound, to distribute it in the body and subsequently to excrete it through the kidneys (Table 13.3).

Some impression of the pharmacokinetic properties of gentamicin from gentamicin-PMMA beads may be gained by postulating that the amount of gentamicin that is released from the beads via the wound into the blood circulation and into the rest of the body equals the amount of gentamicin that is excreted by the kidneys. This holds true during the period in which the renal excretion rate remains at a plateau level (see Figs. 13.1 to 13.5 inclusive).

This implies the assumption that the amount of gentamicin lost by drainage of the wound is nil. In regard to patients 5 to 8 inclusive, this assumption was correct: the wound was hermetically closed. In patient 9, approx. 200 ml exudate was lost through the wound drains on the first postoperative day. On the assumption that there is no extra-renal excretion of gentamicin and that where gentamicin is concerned, the body may be regarded as a single compartment or distribution space, it may be stated that the supply of gentamicin equals its elimination. As an equation: $D.K_c = C.K_e$ in which $D$ is the total amount of gentamicin that is excreted during the treatment, $K_e$ is the diffusion constant from the beads via the wound to the body, $C$ is the amount of gentamicin that is present in the wound.
Figure 13.6  X-ray films of patient 9 (dG): after extraction of the total hip prosthesis with the bone cement, 360 gentamicin-PMMA beads are implanted (a). Two weeks later, the gentamicin-PMMA beads are extracted and a new total hip prosthesis is reimplanted immediately (b). Example of a shortened two-stage reimplantation as the treatment of an infected total hip prosthesis.

plasma level of the gentamicin and $K_0$ is the renal clearance of gentamicin. Then,

$$K_0 = \frac{C \times K_d}{D} = \frac{\text{renal excretion rate}}{\text{dose}}.$$

If the plasma level $C$ of gentamicin is not known (in patients 5 to 8 inclusive), it is calculated from the renal excretion rate and the gentamicin clearance (postulating that the gentamicin clearance equals the creatinine clearance):

$$C = \frac{\text{renal excretion rate}}{\text{gentamicin clearance}}.$$

From the diffusion constant $K_d$ (expressed in 1/hr), a 'half-life' of gentamicine can be calculated (expressed in days). This 'half-life' is the length of time required for 50% of the amount of gentamicin to be released from the beads via the wound to the body and to reach the kidney for excretion. The 'half-life' follows from:

$$t_{1/2} = \frac{\ln 2}{K_d} = 0.693 \frac{K_0}{K_0}.$$

The half-life values for release of gentamicin from gentamicin-PMMA beads in vivo are shown in Table 13.4.

These values differ considerably from the in-vitro values calculated by Wahlig: 3.3 days (Wahlig, 1979). This difference has a simple explanation in the entirely different circumstances, the main one of which is the difference in the bathing fluid and the replacement of this fluid. There does appear, now, to exist an influence of the localization of the beads and of its environment: in patient 6 ($t_{1/2} = 10$ days), three chains were lying rolled up in the medullary cavity of the femur. In patient 8 ($t_{1/2} = 6.0$ days), three chains were lying in the soft tissues along the femur, covered by muscle tissue.

The renal excretion rate of $\beta_2$-microglobulin is influenced by the operation but is not influenced by the continuous presence of gentamicin. If the slight but protracted and continuous excretion of gentamicin by the kidney were to exert an adverse effect on the kidney, it might be expected that the excretion rate of $\beta_2$-microglobulin would rise gradually, especially with prolongation of the treatment with gentamicin to 10 to 14 days. This expectation is based on the reasoning that a continuous presence of gentamicin in the tubulus may bring about a continuous uptake and consequently, a toxic action in the cell. In the excretion of gentamicin, namely, there is a slow phase of over 100 hours (Schentag et al., 1977, 1978a).
However, the amount of gentamicin that is constantly present in the tubulus during treatment with gentamicin-PMMA beads does not demonstrably influence the rate of excretion of β2-microglobulin. In all cases, the excretion rate falls to normal levels after a shorter (patients 6, 7 and 8) or longer (patients 5 and 9) interval. A transient effect of the implantation of a new hip prosthesis.

Removal of gentamicin-PMMA beads from the lower leg is a minor operation involving very little trauma (patients 5 and 7). Removal of beads from along the femur, from beneath the m. vastus lateralis, is somewhat more traumatizing and the removal of gentamicin-PMMA beads from the hip is the most traumatizing of all second operations (OK-2), a fortiori when it is combined with implantation of a new hip prosthesis.

Table 13.4 Data concerning the numbers of gentamicin-PMMA beads, their position and the duration of the treatment in five patients. The table also shows the calculated half-life required for uptake from the wound and excretion with the urine.

<table>
<thead>
<tr>
<th>Patient</th>
<th>N beads</th>
<th>Mg. genta</th>
<th>In tissue</th>
<th>Way of implantation</th>
<th>Duration of therapy</th>
<th>T0, beads</th>
</tr>
</thead>
<tbody>
<tr>
<td>5. Al-B.</td>
<td>48 b</td>
<td>216 mg</td>
<td>bone</td>
<td>in heaps</td>
<td>14 d</td>
<td>7.3 d</td>
</tr>
<tr>
<td>6. Ta.</td>
<td>90 b</td>
<td>405 mg</td>
<td>bone</td>
<td>in heaps</td>
<td>14 d</td>
<td>10.6 d</td>
</tr>
<tr>
<td>7. vd B.</td>
<td>49 b</td>
<td>220.5 mg</td>
<td>bone</td>
<td>stretched</td>
<td>10 d</td>
<td>7.7 d</td>
</tr>
<tr>
<td>8. Go.</td>
<td>90 b</td>
<td>405 mg</td>
<td>soft tissue</td>
<td>stretched</td>
<td>9 d</td>
<td>6.0 d</td>
</tr>
<tr>
<td>9. d G.</td>
<td>360 b</td>
<td>1620 mg</td>
<td>bone + soft tissue</td>
<td>in heaps</td>
<td>14 d</td>
<td>5.7 d</td>
</tr>
</tbody>
</table>

The effect of the operation on the renal excretion of β2-microglobulin (Chapter 12) has been confirmed once more at these ten operations and may now be defined more precisely.

At these 10 operations, also, the extent of the rise of the renal excretion of β2-microglobulin depends on the severity of the operation. The maximal value of this renal excretion rate is determined not so much by the duration of the operation or the blood loss involved but by the trauma sustained by the patient's tissues. Drilling out a tibia (patient 7, vdB) or removing a hip prosthesis with bone cement (patient 9, dG) are major, severely traumatizing operations, comparable to an anterior spondylodesis at two levels (patient 3, Bo). It should be noted that the operation of patient 7 lasted less long and led to less loss of blood than the operations of these other two patients (Table 13.5).

Exact quantification of the degree of tissue trauma at an operation is not possible. However, when it was estimated by five orthopaedic surgeons, there was a remarkable degree of agreement (Table 13.5).

This factor, to be called the 'clinical trauma score' can be plotted in a graph against the maximal excretion of β2-microglobulin. This means combining exact objective data with subjective clinical assessments, but a relationship nevertheless emerges. The peak level of the excretion rate of β2-microglobulin increases rapidly once the clinical trauma score reaches a certain liminal value, approximately at 50%. For this purpose, the trauma score of the most

<table>
<thead>
<tr>
<th>Patient</th>
<th>Blood loss</th>
<th>Operation time</th>
<th>Clinical trauma score (%)</th>
<th>Mean tr. score (%)</th>
<th>Max. excr. β2-microglob.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.</td>
<td>2.</td>
<td>3.</td>
</tr>
<tr>
<td>1. Sj.</td>
<td>1200 cc</td>
<td>4 h</td>
<td>65</td>
<td>60</td>
<td>65</td>
</tr>
<tr>
<td>2. K.</td>
<td>1300 cc</td>
<td>4 h</td>
<td>65</td>
<td>60</td>
<td>65</td>
</tr>
<tr>
<td>3. Bo.</td>
<td>1800 cc</td>
<td>5 h</td>
<td>80</td>
<td>85</td>
<td>80</td>
</tr>
<tr>
<td>4. P-B</td>
<td>0 cc</td>
<td>15'</td>
<td>5</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>5. Al-B.</td>
<td>150 cc</td>
<td>1.15'</td>
<td>45</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>10 cc</td>
<td>15'</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>6. Ta.</td>
<td>600 cc</td>
<td>1.30'</td>
<td>60</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>7. vd B.</td>
<td>200 cc</td>
<td>2.30'</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>20 cc</td>
<td>30'</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>8. Go.</td>
<td>400 cc</td>
<td>1.30'</td>
<td>40</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td>9. d G.</td>
<td>1000 cc</td>
<td>2.30'</td>
<td>80</td>
<td>80</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>1700 cc</td>
<td>3 h</td>
<td>60</td>
<td>65</td>
<td>70</td>
</tr>
</tbody>
</table>

Table 13.5 Data concerning the blood loss and operation time of 14 operations in nine patients. These are the patients described in Chapters 12 and 13. The table lists the clinical trauma scores as estimated by six orthopaedic surgeons. It also shows the maximal renal excretion rate of β2-microglobulin of the patient in question at that operation (see also Fig. 13.7).
Figure 13.7 Maximal renal excretion rate of β2-microglobulin plotted against the clinical trauma score of 14 operations in nine patients. A score of 100 corresponds to the clinical trauma score of the most traumatizing of these 14 operations in these nine patients. Once a trauma score of approx. 50 percent is exceeded, the renal excretion rate of β2-microglobulin rises markedly.

Figure 13.8 The renal excretion rate of alanine aminopeptidase plotted against the renal excretion rate of creatinine in patient 9 (dG). There is a linear relationship.

Figure 13.9 The renal clearances of gentamicin and creatinine plotted against each other in patient 9 (dG). There is an increasing correlation with decreasing renal function, represented by the divergent dotted lines.
The renal clearances of creatinine and gentamicin plotted against the urine flow in patient 9 (dG). The two clearances each show their own correlation with the urine flow.

The clearance of gentamicin and creatinine in patient 9 is plotted in Fig. 13.9. The clearances of the two substances are directly proportional, but the correlation grows less pronounced as the clearance of the two compounds increases. The correlation is more pronounced when renal function is decreased. This correlation between the clearances of gentamicin and creatinine is a known phenomenon (Detti, 1976; Lode, 1979) and has been described earlier in a woman with very severe renal dysfunction during treatment with gentamicin-PMMA beads (Walenkamp and Vree, 1981; Chapter 15, patient 1).

In patient 9, a correlation of the clearances of creatinine and gentamicin with the urine flow could also be demonstrated (Fig. 13.10). This correlation, also, has been described elsewhere (Vree et al., 1981b), and it has been demonstrated in the patient mentioned above with very slight urine flow, from 0.1 to 0.2 ml/min (Walenkamp and Vree, 1981; Chapter 15, patient 1).

### 13.5 Conclusion

Investigation of the influence of gentamicin and of an operation on the renal excretion rate of β2-microglobulin during treatment with gentamicin-PMMA beads shows the known effect of an operation. Data collected at four earlier operations have been confirmed once more by the 10 operations on these five patients. An operation causes a pronounced rise of the renal excretion rate of β2-microglobulin if the traumatic effect of the operation exceeds a critical limit. The treatment with gentamicin causes no measurable influence on the reabsorption of β2-microglobulin in the proximal tubular cell the renal excretion rate of β2-microglobulin, namely, is not perceptibly raised by gentamicin. From this we conclude that at any rate this reabsorption mechanism in the proximal tubulus is not adversely affected by the treatment with gentamicin-PMMA beads.

The glomerular filtration, as revealed by the creatinine clearance and the corresponding filtration of β2-microglobulin proved not to be affected by the gentamicin treatment, either. On the basis of this finding, also, we consider the conclusion justified that gentamicin-PMMA beads were not nephrotoxic in the patients we have studied.
Chapter 14. Study of patients treated with gentamicin-PMMA beads for ototoxic side effects

14.1 Introduction

Gentamicin may bring about loss of hearing and disturbances of the equilibrium (see par. 6.4.3). Some relevant factors are the total dose of gentamicin per kg body weight, earlier use of ototoxic drugs and the renal function (Igarashi et al., 1971; Jackson and Ancieri, 1971; Fee et al., 1978).

The loss of hearing comprises in the first place a loss of high tones, while the disturbance of the balance manifests itself with dizziness and nausea (Lode, 1979; Carrière, 1980). Allegedly, when ototoxicity is present, the balance is affected in two-thirds and the hearing in one-third of the cases (Jackson and Ancieri, 1971). It is believed in that most studies, too little attention is paid to the vestibular function (Bailey, 1981), possibly because subjective symptoms often fail to occur, owing to compensation, mostly by visual and proprioceptive functions. According to some, the ototoxicity, unlike the nephrotoxicity, is irreversible (Waitz, 1978; Igarashi et al., 1971; Jackson and Ancieri, 1971). It is known from the literature on ototoxic side effects that the toxic effect of aminoglycosides is due to a disturbance of the integrity of the ciliated cells. It is therefore an obvious assumption that in vestibular toxicity, the function of the ciliated cells is also involved.

The function of the cochlear ciliated cells can be examined simply and accurately by means of a tone threshold audiogram.

Of the vestibular neuroepithelium, only the horizontal semi-circular duct is accessible to examination in clinical practice. Flow of endolymph inside this canal constitutes the physiological stimulus for the ciliated cells situated in the ampullar crest. The endolymph can be made to flow either by rotatory stimulation or by caloric stimulation. In the latter case, a convection current in the endolymph is induced by changing the local temperature (by irrigation of the external acoustic meatus). Caloric stimulation was opted for because unlike rotatory stimulation it is suitable for application in bedridden patients.

14.2 Material and method

14.2.1 The patients

The measurements were carried out in the same patients in whom the renal functions were measured (patients 5 to 9 inclusive of Chapter 13).

No vestibular examination could be carried out in patients A-B) and 7 (vdB).

Prior to the operation, all patients were examined by an ORL specialist. There were no abnormalities of ear, nose or throat. If necessary, cerumen was removed before the audiometric examination was carried out.

14.2.2 Cochlear examination

In all five patients, hearing acuity was determined one day before the first operation (blank test), two or three days after the first operation and one day before removal of the gentamicin-PMMA beads (the eighth to 13th day post-operatively). The measurement was performed by means of a tone audiogram (Peeters audiometer, type AP6). The air conduction threshold was determined in all cases. Bone conduction was investigated only if it was necessary for audiometric reasons. An additional audiogram was made if in the meantime patients complained of tinnitus or if the tone threshold deteriorated.

14.2.3 Vestibular examination

The equilibrium was examined in three patients: one day before the operation (blank) and one day before removal of the gentamicin-PMMA beads. The vestibular examination is based on the vestibulo-ocular reflex (VOR). Every (apparent) rotatory movement of the head evokes a compensatory ocular movement, intended to stabilize the image of the environment on the retina. The principal parameter of the VOR is the angular velocity of the slow phase of the nystagmic movement, which is found by computerized analysis of the electronystagmogram (ENG) (Huygen, 1979).

At every vestibular examination, it was first checked in various positions of the patient whether spontaneous nystagmus was present and whether the reflex movements of the eyes were intact. Before every irrigation of the external meatus, a calibration signal was recorded: alternatingly with the glance aimed 10° to the right and 10° to the left.

With the head in 30° anteflexion, which places the horizontal semi-circular duct in a vertical position, the external meatus was irrigated for 20 seconds with water of 30° or of 44° C (Nijhuis and Huygen, 1980).

Both ears were irrigated with cold as well as with warm water, at five-minute intervals. The nystagmus was recorded in complete darkness, with the eyes open.

After every irrigation, the average velocity (degrees/second) of the slow phase of a number of nystagmic movements was determined during the culmination phase (single response value). The total response per labyrinth (total response value) is then the sum of the single response values for cold and warm irrigation of that ear.

The caloric sensitivity, always expressed as the velocity of the slow nystagmic phase in degrees per second, may be defined for each labyrinth separately (total response value per labyrinth) or for both labyrinths together (total response value per subject).

The fluctuations of the caloric sensitivity were calculated by means of the equation:

\[
\frac{B - A}{B + A} \times 100 \%
\]

in which A is the preoperative caloric sensitivity and B the postoperative sensitivity. Equations of this type are
habitually used in caloric studies, in which A and B in that case represent the simultaneous total response value per labyrinth. In practice, differences in caloric sensitivity are regarded as significant if they exceed approx. 20%.

### 14.2.4. Ototoxicity criteria

In the literature on ototoxicity, various quantitative criteria are used for both vestibular and cochlear toxicity. We shall return to this in the discussion.

### 14.3 Results

The results of the audiometric tests are shown in Table 14.1 and those of the vestibular measurements in Table 14.2. The findings obtained in the individual patients are discussed below.

In patient 5 (Al-B), examination revealed no ORL abnormalities. The preoperative audiograms were normal and no significant changes of the tone threshold occurred after operation.

The preoperative vestibular examination showed no abnormalities. Postoperative repetition of the vestibular examination was not possible in this patient.

Patient 6 (Ta) showed no abnormalities at ORL examination. A slight subjective hypacusis disappeared after removal of inspissated cerumen from both external meatuses.

The preoperative audiograms revealed a mild perceptive loss for high tones on the left (4 and 8 kcps).

After operation, the tone threshold showed no significant changes.

### Table 14.2 Results of the vestibular examination by means of electronystagmography in three patients before and after the treatment with gentamicin-PMMA beads

<table>
<thead>
<tr>
<th>Patient</th>
<th>Postop. I</th>
<th>Postop. II</th>
<th>Postop. III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 6</td>
<td>10</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Patient 7</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Patient 8</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>

* Calculated according to the equation: \( \frac{B-A}{B+A} \times 100\% \)

### Table 14.1 The results of audiometric examination of five patients before, during and after treatment with gentamicin-PMMA beads

<table>
<thead>
<tr>
<th>Patient 6 (Ta)</th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>postop. (A)</td>
<td>32</td>
<td>63</td>
</tr>
<tr>
<td>postop. (B)</td>
<td>25</td>
<td>54</td>
</tr>
<tr>
<td>change*</td>
<td>-12%</td>
<td>-8%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient 8 (Go)</th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>preop. (A)</td>
<td>49</td>
<td>97</td>
</tr>
<tr>
<td>postop. (B)</td>
<td>45</td>
<td>91</td>
</tr>
<tr>
<td>change*</td>
<td>-4%</td>
<td>-3%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient 9 (dG)</th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>preop. (A)</td>
<td>51</td>
<td>113</td>
</tr>
<tr>
<td>postop. (B)</td>
<td>55</td>
<td>112</td>
</tr>
<tr>
<td>change*</td>
<td>+4%</td>
<td>-0%</td>
</tr>
</tbody>
</table>

f: higher than 120, 'dropped out'

*: extra determination because of tinnitus

**: extra determination because of deterioration, two weeks after OK-2
The preoperative vestibular examination showed no abnormalities. Postoperatively, the vestibular labyrinth showed slightly less caloric irritability than before operation (total 8% less, 12% on the right and 3% on the left).

Patient 7 (vdB) preoperatively had no ORL abnormalities either. This patient had a history of several episodes of otitis media on the right, and there was mild subjective hypacusis in that ear.

Preoperative audiometry revealed no abnormalities on the left but on the right there was a marked perceptive loss of high tones (at 4 and especially at 8 kcps). This loss may have been due to acoustic trauma although in his case the right-left asymmetry was difficult to explain. Postoperatively, no significant changes of the tone threshold were observed, and this also holds true of an interim determination performed because of complaints of tinnitus. No vestibular examinations were performed in this patient.

In patient 8 (Go) there were no ORL abnormalities.

The preoperative audiogram showed a considerable elevation of the tone threshold, amounting to approx. 30 dB at 4 kcps for the left ear, for which there was no anamnestic explanation.

Postoperatively, there were no significant changes of the tone threshold on the left. On the right there was only a slight change at 8 kcps while postoperatively, values of 15 and 10 dB were found instead of the preoperative 0 dB.

The vestibular examination preoperatively showed no abnormalities and postoperatively, the response was virtually unchanged.

Patient 9 (dG) at ORL examination showed no abnormalities of ear, nose or throat. Ophthalmologically, there was bilateral status post cataract operation and bad central vision after retinal haemorrhages. The preoperative audiogram revealed considerable presbyacusis: a perceptive loss for high tones at advanced age.

The first postoperative audiogram (I) revealed deteriorations of 15 and 20 dB at 2 and 4 kcps, respectively, on the right while at 8 kcps the threshold was unchanged. The second postoperative audiogram (II) revealed a systematic deterioration of 10 to 15 dB over the low-tone range in both ears, whereas on the right, the high tones now showed a slight improvement of the tone threshold. A follow-up audiogram (III) showed bilateral improvement of the threshold for low tones. The improvement of the loss of high tones had already been observed at the second postoperative determination, although this was performed at a time when the gentamicin treatment had reached its maximal duration (13 days).

At vestibular examination before operation, a normal response was observed which postoperatively remained unchanged.

14.4 Discussion

Impairment of the hearing and balance is said to occur in 10% of the patients and to be symptomatic in 2% (Barza and Lauermann, 1978). Allegedly, sensitive test methods and prospective studies reveal three to five times that incidence (Jackson, 1977). Unfortunately, most studies did not include vestibular examination. The ototoxicity of gentamicin is said to be vestibular in two-thirds and cochlear in one-third of the cases (Jackson and Arcieri, 1971).

According to Lode (1979), adverse effects on hearing and equilibrium occur only after protracted treatment and high dosage. However, at this time it is not yet possible to identify maximal or minimal thresholds at which ototoxicity occurs (Barza and Lauermann, 1978). It is probably the reason why the vague concept of 'individual sensitivity' has been introduced for ototoxicity. In spite of meticulous posology, there are always a few patients who sustain ototoxic damage (Sack et al., 1978). Most authors recommend control tests of the renal function during treatment with gentamicin because ototoxicity occurs more often in renal dysfunction (Jackson, 1977; Barza and Lauermann, 1978; Bailey, 1981).

Control of the hearing by means of audiometry is also recommended. However obvious its desirability, a pre-treatment audiogram to determine the initial value is not always made. This is sometimes understandable, in view of the patients' bad condition, since parenteral gentamicin treatment is mostly given for severe infections. However, in audiological practice, it has become clear that severe illness need not preclude audiometric examinations. Since audiometry is a psychophysical determination, deterioration of the general condition in severe illness or after major surgery does affect the findings. Bad general condition raises the tone threshold for all frequencies, whereas gentamicin toxicity affects the registration of the high tones alone (Carrière, 1980; Winkel et al., 1978).

The sense of balance may be difficult to investigate in severely ill patients. The caloric test, however, is usually feasible in bedridden patients.

The existing uncertainty about the threshold of the serum gentamicin level at which ototoxicity occurs, enhances the desirability of investigation of possible otological side effects during treatment with gentamicin-PMMA beads. Since such an investigation implies that the serum gentamicin levels have to be known, this study has been restricted to the five patients described in Chapter 13.

Audiometric examination could be carried out in all five patients. In four of the five patients, the preoperative audiograms showed abnormalities, and these were pronounced in patient 7 (vdB). In the course of the treatment, there were no significant changes of the tone threshold in four patients. In this respect it should be noted that in audiometry, the measuring inaccuracy is approx. 5 to 10 dB. In patient 9 (dG), the tone threshold was raised for a number of frequencies. Winkel et al. (1978) regard 10 dB as the limit for cochlear toxicity. In view of the inaccuracy of the determination, we consider this a rather strict standard. Others use different criteria, e.g. Fee et al. (1978, at least 20 dB) and Tjernström et al. (1973, 30 dB). If such criteria are applied, the slight shift of the tone threshold observed in our patients cannot be attributed to ototoxicity (Table 14.1).

Vestibular examination could be performed in only three patients, owing to circumstances. These examinations revealed no important abnormalities. Patient 6 (Ta) was the only one in whom a slight difference to the disadvantage of the right labyrinth was observed: 12% calculated according to the equation in par. 14.2.3. Calculation according to Fee et al. (1978) shows that this corresponds to a decrease of 22% which is still far below the threshold of 33% which these authors apply as the criterion of vestibular toxicity in a similar study of caloric responses during treatment with gentamicin. The criterion for vestibular toxicity applied by
Tjernström et al. (1973) in our opinion is hardly usable. These authors' criterion is 'reduced caloric irritability' which amounts to complete non-irritability during irrigation with water of 30 or 40°C.

Although no distinct safety margin for the ototoxicity during treatment with gentamicin can be deduced from the literature, the serum gentamicin levels in these studies have always been considerably higher than those in our patients. We determined a serum gentamicin level that amounted to approx. 0.03 μg/ml (Chapter 13).

Although the group of our own patients in whom this study was carried out was too small to justify statistical conclusions, we may nevertheless say that the findings in regard to possible adverse effects on hearing or balance were reassuring.

14.5 Conclusion

In spite of the above, certain patients have to be regarded as being at risk where ototoxicity is concerned. These are in the first place:

- patients with renal dysfunction
- patients who have been treated with an aminoglycoside before
- patients subjected to simultaneous parenteral treatment with aminoglycosides.

Such at-risk patients should be regularly examined for ototoxicity during every treatment with an aminoglycoside. Unlike an adverse effect on the balance, namely, bilateral impairment of the hearing cannot be compensated.

Patients without an increased risk do not require such control examinations during treatment with gentamicin-PMMA beads.

Examination for ototoxicity is best performed by means of audiometry alone. It is a simple, reliable determination that is easy to perform, at any rate by qualified personnel.

Finally, it should be kept in mind that even in the so-called at-risk patients, deterioration of the hearing will probably only become demonstrable when the gentamicin in the wound has had ample time to do its work. Therefore, if audiometric abnormalities are observed, the treatment with the gentamicin-PMMA beads may be discontinued.
The ten case histories recorded below serve to illustrate what possibilities exist and what problems arise in the treatment of infections with gentamicin-PMMA beads.

In the first three patients, we were able to collect several samples of serum, urine and/or wound exudate. In each of these three patients, an unforeseen situation was involved, in which as many samples as possible were collected which, however, could not be processed as the samples in Chapter 13 were. The first two patients were treated with gentamicin-PMMA beads in the presence of severe renal dysfunction. In the third patient, just as in patient nr 9 of Chapter 13 (dG), 360 beads were implanted.

1. Patient R.W., female, born 1907

1955 Implantation of a Judet prosthesis in both hips with bilateral trochanteric osteotomy and fixation on both sides with a metal nail (Fig. 15.1a).

1964-1965 On the right, the prosthesis was removed because of painful acetabular protrusion, following which a subtrochanteric femoral osteotomy was carried out. Postoperatively, an infection developed which healed after removal of the osteosynthesis material.

Figure 15.1
Figure 15.2 The plasma concentration of gentamicin, the renal excretion rate of creatinine and gentamicin, and the concentration of gentamicin in the wound exudate plotted against the time in a patient who postoperatively developed severe renal dysfunction. The figure shows the moments at which the patient was dialysed (days 6 and 9). In spite of severe renal dysfunction and inadequate haemodialysis, the concentration of the gentamicin remains constant at a level of 3 to 4 μg/ml (also due to 2 x 80 mg gentamicin i.v.).

Figure 15.3 The renal clearance of gentamicin plotted against the urine flow (a) and against the renal clearance of creatinine (b). The renal clearance of gentamicin is linearly dependent on the urine flow if the latter amounts to less than approx. 1 ml/minute (see also Fig. 11.11). There is a linear interdependence of the clearances of gentamicin and creatinine.
1965–1966

On the left, the prosthesis had to be removed because of a deep, fistulizing inflammation. Subsequently, the patient was mobilized with two Girdlestone hips (Fig. 15.1b).

March 1980

After 14 years' freedom of symptoms, pain developed in the left hip, with fever and later, sepsis. An abscess in the left hip was evacuated, the metal nail was removed and 150 gentamicin-PMMA beads were implanted (Fig. 15.1c). Progressive renal failure (1 ml/min) necessitated dialysis. Progressive circulatory insufficiency led to death from cardiac decompensation ten days after the operation.

From the first postoperative day, serum, urine and wound exudate could be examined in this case. We found that in spite of severe renal dysfunction, the serum gentamicin level reached a plateau at approx. 3 µg/ml, or 2 µg/ml after dialysis. The level of this plateau was determined not only by gentamicin-PMMA beads but also by two intravenous injections of 80 mg gentamicin administered before operation (Fig. 15.2).

With this method of administration of gentamicin,
Figure 15.5 Plasma concentration-time curve of gentamicin, \(\beta_2\)-microglobulin and creatinine in a woman with severe renal dysfunction. This patient was treated with implantation of first 75, than 45 and subsequently 30 gentamicin-PMMA beads. In spite of a renal creatinine clearance of approx. 4 to approx. 7 ml/minute, the gentamicin level of the plasma decreased gradually in the course of this treatment to below the level of demonstrability (0.15 \(\mu g/\text{ml}\)).

Figure 15.6 The plasma concentrations of creatinine and \(\beta_2\)-microglobulin, respectively, plotted against each other during the treatment with gentamicin-PMMA beads in patient J-V. During the period of deteriorated renal function, there is a linear interrelationship. The blank values derive from data of test subjects and patients described in Chapters 11, 12 and 13.

also, the low renal clearance of gentamicin and creatinine and the small urine flow showed an interrelationship, represented in Fig. 15.3ab. This patient has been reported earlier (Walenkamp and Vree, 1981).

2. Patient J.-V., female, born 1905

1974 A Shiers prosthesis was implanted in the right knee because of gonarthrosis (Fig. 15.4a).

1975 Because of painful loosening, the prosthesis was removed with its cement after which arthrodesis of the right knee was performed by means of external fixation. An infected pseudarthrosis developed.

1976 After removal of some remaining cement, re-arthrodesis was performed by means of external fixation (Fig. 15.4a). Consolidation and good wound healing ensued.

1979 In an accident, the patient sustained a fracture through the arthrodesis of the right knee. This was treated by external fixation (Fig. 15.4a).

1980 Consolidation remained insufficient in spite of electrostimulation.

1981 Rearthrodesis was carried out with a long intramedullary nail and cancellous bone grafting (Fig. 15.4a). Postoperative wound infection occurred. After abscess drainage, implantation of 75 gentamicin-PMMA beads. Because of insufficient healing, the beads were removed and replaced by 45 new ones.
Another exchange was carried out two weeks later, then combined with sequestrectomy (30 gentamicin-PMMA beads) (Fig. 15.4). Once again the infection failed to heal: the intramedullary nail had to be removed. After sequestrectomy, an irrigation system was introduced. The system did not function well and was withdrawn after 10 days. The wound healed by second intention and six months later, spontaneous abscess development was seen in the right hip, as well. This, also healed by second intention.

During the first treatment with gentamicin-PMMA beads, the patient had been temporarily discharged. After readmission for the second operation, renal function was found to have deteriorated (serum creatinine 408 mol/l,
serum urea level 18.3 mol/l. In view of the renal dysfunction, plasma samples were collected frequently from the second operation, for four weeks. During this period, the renal creatinine clearance rose from approx. 4 to approx. 17 ml/min. As Fig. 15.5 shows, the serum creatinine level and the serum β2-microglobulin excretion rate increased slightly during these four weeks. In spite of repeated reimplantation of gentamicin-PMMA beads, the serum gentamicin level within three weeks fell to below the detection limit (RIA method 0.15 μg/ml).

In this case the raised plasma creatinine and β2-microglobulin levels were directly proportional (Fig. 15.6). Renal failure was due to a necrotizing vasculitis, possibly the consequence of periarteritis nodosa. This diagnosis was based on a cutaneous and a renal biopsy. The renal failure was treated with cyclophosphamide, on which renal function improved. Follow-up examination eight months later showed consolidation of the arthrodesis; signs of infection had by then been absent for two months.

3. Patient K.-B., female, born 1916

1975 Bilateral implantation of total hip prostheses because of coxarthrosis. Postoperatively, a wound infection developed in the left hip; it was treated by six weeks’ oral administration of antibiotics. In spite of this, the hip remained painful for four years and the BSR remained raised (Fig. 15.7 a+b).

January 1980 An infiltrate in the left thigh was treated with antibiotics by the family doctor. An abscess developed.

March 1980 Removal of the hip prosthesis on the left with all cement because of a deep infection. 360 Gentamicin-PMMA beads were implanted, instead of the more usual 120-250 beads (Fig. 15.7 c).

The beads were removed after two weeks. This patient will probably not be considered for reimplantation. She was free from symptoms after mobilization on the Girdlestone hip.

In view of the large number of gentamicin-PMMA beads implanted, the gentamicin levels of serum, urine and wound exudate were determined. The findings are listed in Table 15.1 and represented graphically in Fig. 15.8. This patient has been described previously (Walenkamp, 1981).

360 gentamicin PMMA beads

**Table 15.1** The gentamicin concentrations in serum, urine and wound exudate in a woman aged 64 years. On day 0, 360 gentamicin-PMMA beads were implanted. The serum concentration was measured by the RIA technique, the concentrations in urine and wound exudate by means of the agar diffusion method (see Fig. 15.8).

<table>
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<tr>
<th>Day postop.</th>
<th>A.M./P.M.</th>
<th>Serum</th>
<th>Urine</th>
<th>Exudate</th>
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<td>-</td>
<td>275</td>
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<td>p.m.</td>
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<td>9.0</td>
<td>215</td>
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<td>12.8</td>
<td>155</td>
</tr>
<tr>
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<td>-</td>
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<td>13.3</td>
<td>155</td>
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<tr>
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<td>-</td>
<td>-</td>
</tr>
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<td>-</td>
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<td>-</td>
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<td>-</td>
<td>-</td>
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<td>14</td>
<td>a.m.</td>
<td>neg.</td>
<td>6.2</td>
<td>-</td>
</tr>
</tbody>
</table>

4. Patient P.J., male, born 1925

March 1971 Total hip prosthesis on the right because of necrosis of the femoral head after a fracture of the femoral neck (Fig. 15.9 a).

October 1971 A revision was carried out because of a loose head-neck prosthesis. This component was remplemented (Fig. 15.9 b).

Material collected at operation on culture proved to contain Staphylococcus albus which was considered to have contaminated the wound at operation. Postoperatively, signs of loosening gradually reappeared, combined with pain (Fig. 15.9 c).

Revision because of loose acetabular prosthesis. The entire prosthesis was removed with the cement, and a total hip prosthesis with a long femoral stem was implanted with the aid of con-
ventional cement (Fig. 15.9). The peroperative culture once again revealed Staphylococcus albus. Ampicillin and lincomycin were administered for two weeks.

January 1974

The right knee was painful. The BSR was normal. The hip scan showed no abnormalities.

May 1974

Sinus in the right hip from which Staphylococcus aureus could be
April 1979
Reoperation was performed after all: extraction of the hip prosthesis with all cement. All along the femur there were countless sinuses. Deep culture: Staphylococcus aureus. 360 Gentamicin-PMMA beads were implanted and left in situ for two weeks; no additional systemic antibiotics were given (Fig. 15.9e). A third reimplantation was refrained from. The patient was mobilized on a Girdlestone hip. Two and a half years later, the patient was free from symptoms and showed no signs of infection (Fig. 15.9f).

5. Patient E.H., female, born 1923
1953 Plastic correction of the left acetabulum because of congenital dysplasia of the hip. The patient developed coxarthrosis (Fig. 15.10a).
May 1979 Total hip prosthesis on the left.
September 1979 Pain in the left hip.
January 1980 The loose total hip prosthesis and all the cement were removed. The peroperative culture showed Staphylococcus albus. 210 Gentamicin-PMMA beads were implanted. The pain persisted after operation. At revision, three weeks later, a cement rest was found to be the cause of the persistent infection. After its removal, 240 gentamicin-PMMA beads were implanted (Fig. 15.10b). These were removed after two weeks, and at this same operation, a total hip prosthesis was reimplanted (Allo pro cup and Müller 'Geradschaft' = straight-stem prosthesis). One year later, the patient was free from symptoms and from signs of infection (Fig. 15.10d).

6. Patient O.W., female, born 1932
January 1979 Bilateral Guepar prostheses because of rheumatoid arthritis.
March 1979 Four weeks after implantation of the prostheses, a right-sided wound abscess had to be incised. Culture: Staphylococcus albus. Treatment: flucloxacillin and lincomycin orally for three months. The wound healed by second intention but the knee remained painful (Fig. 15.11a+b).
August 1980 The prosthesis had to be removed and a ventral window was made in the tibia. 180 Gentamicin-PMMA beads were implanted (Fig. 15.11c). Three weeks later, the beads were removed and still another abscess, along the femur, was found. At this time, 120 gentamicin-PMMA beads were implanted (Fig. 15.11d). Their removal had to be postponed for two months, because of a myocardial infarction. Removal proved difficult and one bead slipped off the chain and

Figure 15.10
remained in situ. Subsequently, an arthrodesis of the knee was performed with implantation of autologous and homologous cancellous bone. External fixation was applied (Fig. 15.11e).

Postoperatively, a pin tract inflammation developed, which healed by second intention after removal of the external fixation material. Consolidation was complete and one year after the last operation, the patient was free from signs of inflammation (Fig. 15.15f).

7. Patient T. W., male, born 1962

November 1980  Fever and violent pain developed in the left distal forearm. The family doctor administered antibiotics but the pain proved more intense and spread over the forearm. Radiological examination
January 1981

Nettoyage with removal of a sequestrum, 25 cm long, out of the involucrum of the radius. There was purulent arthritis of the wrist joint; puncture of the elbow joint revealed sterile hydrops. 90 Gentamicin-PMMA beads were implanted and left in situ for two weeks during which large doses of antibiotics were given (Fig. 15.12b). The gentamicin-PMMA beads were

Figure 15.11

‘no abnormalities’ (Fig. 15.12c and Fig. 2.6b). After approx. 10 days, surgical decompression of the left forearm was carried out, with drainage down into the deep tissues, ventrally and dorsally. The patient was treated on the diagnosis of compartment syndrome. Necrotic tissue had to be removed on several occasions. A second X-ray, made late in December 1980, revealed extensive lesions in the entire left radius, compatible with

Figure 15.12

haematogenous osteomyelitis (Fig. 15.12b).
removed after two weeks and intensive after-treatment was administered with physiotherapy and a dynamic splint for the fingers and wrist. Complete restoration of function of elbow and fingers could be achieved. The wrist remained in a slightly dislocated position which impaired its function. In the X-ray film, the radius showed reossification within the involucrum (Fig. 14.12d-e). Ten months after the treatment, the patient was free from signs of infection. The wrist gave slight trouble during heavy labour. The pronation-supination movement was possible over an arc of 70° (Fig. 14.12f).

8. Patient P. C., male, born 1957

June 1976 Due to a motorcycle accident the patient sustained a number of fractures, including a complicated tibial fracture on the left (Fig. 15.13a). It was treated by external fixation.
1976-1977 In view of delayed union, a cancellous bone graft was performed. Osteomyelitis developed. Sequestrectomy and oral antibiotics did not result in healing (Fig. 15.13b+c). February 1978 Nettoyage was performed with evacuation of pus from the medullary cavity. After sequestrectomy, 60 gentamicin-PMMA beads were implanted (Fig. 15.13d). The beads were removed eight weeks later. In view of the presence of a generalized acne pustulosa, no cancellous bone grafting was carried out. January 1979 Triple arthrodesis was carried out of the left bony tarsus for correction of talipes equinovarus. Postoperatively, undisturbed wound healing (Fig. 15.13e). October 1981 At follow-up examination, the patient was free from symptoms or signs of crural infection.


1969 In a car accident the patient among other lesions sustained a comminuted, uncomplicated crural fracture on the right. Fixation was carried out with a medullary nail (Fig. 15.14a).

1975 Removal of the medullary nail created considerable technical problems. It was only possible after splitting of the tibia over its entire length (Fig. 15.14b). Postoperatively, an osteomyelitis developed which necessitated several sequestrectomies in succession (Fig. 15.14c). Pain in the lower leg persisted, with occasional febrile episodes and progressive functional impairment. X-ray films showed sclerosis spreading over a large portion of the tibial cortex; the planigram revealed several small sequestra (Fig. 15.14d). Computed tomography was carried out to determine the thickness of the cortex over the entire circumference and the entire length of the tibia (Fig. 15.14e).
Through a window, proximally-lateral and distally-medial, the entire tibia was drilled out to a diameter of 13 mm. The operation was carried out in an exsanguinated shield, with cefalotin prophylaxis for 24 hours. Using the special insertion instrument, 49 gentamicin-PMMA beads were introduced into the medullary cavity. The skin was closed, and the gentamicin-PMMA beads were removed two weeks later. The peroperative culture was sterile at that moment.
Immediately after the drilling-out of the tibia, the patient was free from pain. Six months after the operation, the patient was still free from symptoms and from signs of infection (Fig. 14.14).


This patient has a spina bifida at the level of L1 with severe lordoscoliosis (lordosis of 123°, convex left-sided thoracolumbar scoliosis of 70°).

This patient was subjected to several osteotomies of the legs and operations on the spine (Fig. 15.15).

April 1975  Decubitus developed in the left buttock, owing to imbalance leading to excessive pressure.

September 1975  Exploration of a sinus going down to the ischium. An exostosis was removed; the wound was closed with a rotation skin flap.

January 1979  Recurrence of the decubitus.

September 1979  Osteomyelitis of the ischial tuberosity with a fracture through the superior ramus of the pubis (Fig. 15.15).  

October 1979  Sequestrectomy of the ischium was performed with implantation of 60 gentamicin-PMMA beads, the wound being left open. The wound continued to produce exudate, with hardly any formation of granulation tissue (Fig. 15.15). The genta beads were removed through the open wound without anaesthesia (Fig. 15.15). A connection between the sinus and the hip joint could be demonstrated.

January 1980  Resection of the head and neck of the left hip and of part of the ischium was carried out. 180 Gentamicin-PMMA beads were implanted and the wound was closed. The beads were removed by a reoperation two weeks later (Fig. 15.15).  

Eighteen months later, the patient was free from symptoms and showed no signs of infection (Fig. 15.15).
Chapter 16. Conclusions

In Chapter 7, five questions were formulated, based on a study of the literature. Their answers follow from the clinical study in which the results of the various methods of treatment of infections of bones and soft tissues in patients were investigated (Chapters 8, 9 and 10). Other answers were obtained from the pharmacokinetic and toxicological studies which were concerned not only with the renal excretion of gentamicin but also with the influence of gentamicin on renal function and on the organs of hearing and balance (Chapters 11-14).

These investigations provide the following answers to the questions asked earlier.

1. Is the use of gentamicin-PMMA beads in the treatment of infections successful?

Treatment of infections was followed by cure in 89% of the cases after a median follow-up of 13 months. In 39 treatments of osteomyelitis, the cure rate was 92% and the treatment of 41 infected endoprostheses resulted in healing in 85%. Four infections of soft tissues, all healed.

In answering this question it should be kept in mind that ‘healing’ is relative. The conclusions concerning the therapeutic result drawn at the time of discontinuation of the study require further corroboration by long-term follow-up of these patients.

2. Is the treatment of the infection by means of these chains of beads more successful than other methods of treatment?

This question ought to be answered in the affirmative on the basis of comparison of the cure rates in the group of patients whose treatment was completed prior to 1977 (without use of gentamicin-PMMA beads) and the group whose treatment was administered wholly or in part after 1977 (without use of gentamicin-PMMA beads). In the second group of patients, the cure rate after treatment of an infection was 89% as against 76% in the first group.

In order to minimize the influence of the follow-up and of the various background variables, a statistical analysis has been carried out. With utilization of survival time studies, case histories of patients with osteomyelitis or infected endoprostheses have been analysed. It was found that when gentamicin-PMMA beads had been used in the treatment, the cure rate after operation was higher at any moment of the case history than when suction drainage or ‘other’ methods of treatment had been used. In this comparison, differences in follow-up were taken into account. The higher cure rate after use of gentamicin-PMMA beads proved not to be attributable to the background variables.

However, this conclusion, also, should be interpreted with due reservations. The conclusion, namely, is based on comparison of data collected from a prospective study with data collected from a retrospective study.

In spite of the statistical analysis in which as many variables as possible were taken into account, such a comparative study is less conclusive than a wholly prospective study with allotment at random would have been.

3. Are there other aspects of treatment of infections, apart from the cure rate, on the basis of which the use of gentamicin-PMMA beads is or is not to be preferred? If so, what are they?

We find that one important advantage of the use of gentamicin-PMMA beads, which is also confirmed by statistical analysis, is clearer and faster insight into the effects of the treatment. After the operation, it is sooner clear whether a relapse occurs and if the patient after an operation is not immediately declared cured, the postoperative period required to accomplish healing is significantly shorter. Thus, the beads provide not only a clearer but also a shorter treatment. The two factors are particularly also of subjective benefit to the patient who not rarely has had a chronic inflammation.

Another advantage to the patient is that less systemic antibiotherapy is required. Moreover, when an irrigation system was used, leaking and clogged drains occurred in 30 to 40% of the cases, and superinfection in 27%. The patients treated with gentamicin-PMMA beads were spared these difficulties. Also, patients treated with gentamicin-PMMA beads appreciated the freedom of movement of the extremity and the primarily closed, dry wound; this held especially true of patients previously subjected to suction drainage treatment.

The number of operations necessary for the treatment of an infection before cure was achieved was also smaller when gentamicin-PMMA beads were used.

4. Do low serum levels if gentamicin affect the kidney, in other words, are nephrotoxic side effects to be expected?

In order to answer this question, three sub-problems were solved:

a. ß2-microglobulin was found to be a sensitive parameter for the influence of gentamicin on the proximal tubular cell if the ß2-microglobulin was determined in small fractions during its renal excretion. The reabsorption of ß2-microglobulin in the proximal tubular cell is influenced dose-dependently by gentamicin, probably through competition between ß2-microglobulin and gentamicin in the brush border membrane of the tubular cell.

b. The rate of excretion of ß2-microglobulin is increased not only by gentamicin but also by surgical trauma. Similarly to the dose-dependent relationship with gentamicin, more severe surgical trauma is found to cause larger rise of the maximal ß2-microglobulin excretion.

c. The low serum levels of gentamicin that occur during treatment with gentamicin-PMMA beads cause no rise of the renal excretion rate of ß2-microglobulin during that treatment. From this it is concluded that tubular function is not affected. The glomerular filtration function of the kidney is found not to be decreased during the treatment, either. On the basis of our study of these patients and of the literature, nephrotoxic side effects may be regarded as improbable.

5. Are ototoxic side effects (audiologic or vestibular) to be feared during treatment with gentamicin-PMMA beads?

It may be stated on the basis of our orienting investigation that it is highly improbable that the treatment with gentamicin-PMMA beads will cause deterioration of the hearing or of the equilibrium.
Chapter 17. Summary

17.1 Introduction

The problem of infection in orthopaedic surgery deserves special attention because its consequences are so serious. A growing number of skeletal infections is being caused by a growing number of endoprostheses implanted and increasing use of osteosynthesis material. In the treatment of these infections, the possibility of implanting gentamicin-PMMA beads has been available since 1976, as a supplement to the classical surgical measures. In the wound, these beads release a relatively large amount of gentamicin which exerts a local bactericidal action.

This study begins with a survey of the literature on the problem of osteomyelitis and the infected endoprosthesis. The properties of the antibiotic-containing cement, of gentamicin and of the gentamicin-PMMA beads are described. A report is then presented of a clinical investigation, in two parts: a retrospective study of the results of treatments before use of gentamicin-PMMA beads and a prospective study of the results of treatment with gentamicin-PMMA beads. A statistical analysis of the clinical data collected was carried out to compare the types of treatment.

The third part of this study is concerned with the possible nephrotoxic and ototoxic side effects of the gentamicin-PMMA beads.

17.2 Osteomyelitis

The pathological and clinical pictures of endogenous and exogenous osteomyelitis are concisely described. The diagnosis is discussed with special reference to its bacteriological elements. Correct collection of culturing material and adequate interpretation of culturing results are essential. It appeared suitable to combine the introduction of this new method of treatment of osteomyelitis with a survey of the history of that treatment, illustrating what elements of the new method of treatment had already been tried. As late as the 19th century, the treatment of osteomyelitis was symptomatic. Still, the generally accepted management consisted in sequestrectomy, drainage and rest. Around the turn of the last century, antiseptics were used and from World War II, antibiotics. Again and again, surgeons who expected that the infections would be cured by application of non-surgical measures exclusively, were disappointed. By themselves, antiseptics and antibiotics never brought about cure. In the course of the 20th century, it was found that in addition to stabilization of the infected area, it was especially the prevention of cavitation that was essential for the treatment of osteomyelitis.

The gentamicin-PMMA beads combine the advantages of packing of the cavities with the advantages of local antibiotic therapy. In this respect, the ‘novelty’ of the gentamicin-PMMA beads is relative.

17.3 Infected endoprostheses

In the endoprosthesis, the bone-cement interface is a source of many problems. With the passage of years after implantation of the prosthesis, loosening occurs in a growing number of patients. To the present day, part of these loosenings are erroneously regarded as a purely mechanical problem. Actually, a low-grade infection is often involved.

Therefore, after the discussion of the symptomatology of the acute, latent and haematogenous infection of the endoprosthesis, the diagnosis is discussed in greater detail. The BSR is a very important parameter, especially if it is determined frequently. In acute or in fulminating exacerbation of the latent infection of the prosthesis, making the diagnosis is usually not difficult. In the latent low-grade infection, the diagnosis is a problem, however. So far, no single method of clinical examination exists that allows reliable distinction between the aseptic loosening and the loosening due to a latent infection of the prosthesis. Such latent infections can only be diagnosed by means of peroperative collection of multiple samples for culturing, preferably from the tissue, and in every case some of these should be placed in an anaerobic transportation medium.

Treatment of an acute infection of a prosthesis is most successful if extensive nettoyage is carried out at an early stage and protracted antibiotic therapy is administered. This applies to the acute superficial but particularly also to the acute deep infection of a prosthesis.

Only occasionally can a latent low-grade infection be treated by conservative means. Definite healing can only be achieved by removal of the entire prosthesis with all the cement. Then, the choice has to be made between reimplanting a prosthesis or leaving it out (Girdlestone, arthrodesis). If reimplantation is decided upon, the best results according to the literature are obtained with antibiotic-containing cement. The reimplantation can be performed at the same surgical session as the extraction and nettoyage ‘one-stage reimplantation’. If a shorter or longer interval is allowed before reimplantation, we speak of a ‘two-stage’ procedure. This interval may be used to treat the infection. This may be done with the aid of the gentamicin-PMMA beads. For a brief period (10 to 14 days), the beads may contribute to the treatment of the infection by a local, very highly active bactercidal treatment with gentamicin.

17.4 Antibiotic-containing cement

The development of the antibiotic-containing cement was initially wholly empirical. Buchholz mixed bone cement with antibiotics to reduce the incidence of infection of the prosthesis. Various studies of several combinations of antibiotics and types of cement showed that the release of antibiotic is proportional, among other things, to the surface of the cement and the concentration of the antibiotics in the cement. The bathing fluid, also, influences the amount of antibiotic diffusing from the cement. The process involved...
is always diffusion, and therefore an aqueous environment is required.

Some antibiotics are unsuitable to be mixed in bone cement because they are not heat-stable or water-soluble. Where the clinical applicability is concerned, it is important how much of the antibiotic is released per unit of time and particularly also whether the bacteriologically active concentration is reached. If (for bacteriological reasons) gentamicin is chosen, the best cement to mix it with is palacos.

Experiments in animals have shown that antibiotic-containing cement should be expected to be active mostly during and shortly after the operation. Activity for longer than approx. six weeks after the operation could not be proved conclusively. During clinical use, therefore, a protective effect is only to be expected peroperatively (against contamination) and for a brief postoperative period (against haematogenous infection). This is illustrated sufficiently by the good results after the use at one-stage reimplantation following removal of infected endoprostheses.

17.5 Gentamicin-PMMA beads

As the surface of antibiotic-containing cement increases, relatively more antibiotic is released into the environment. Owing to the large surface of the gentamicin-PMMA beads, the gentamicin concentration around the beads is very high. In between the beads, wound secretion remains possible. In spite of a very high local concentration of gentamicin in the wound secretion, the serum level remains very low, although continuous.

Since the gentamicin levels in the wound may rise to many times the minimal inhibitory concentration (MIC) or the minimal bactericidal concentration (MBC) of the causative agents, it is necessary to exactly quantify the 'resistance' of a micro-organism by determining the MIC.

The release of the gentamicin from the beads and its activities have been demonstrated in vitro and in vivo. In clinical use, the practical advantages to the patient and the nursing staff are considerable, especially by comparison with treatment with an irrigation system. From the bacteriological and economic points of view, also, the beads offer advantages.

Published reports concern not only use in skeletal infections, but also in infections of soft tissues.

Absolute contraindications have been mentioned, but not all authors concur. However, there exist certain relative contraindications that render it necessary to weigh the advantages of the use of the beads against the disadvantages of some other method of treatment. Allegedly, the principal contraindication is pregnancy. However, in case of infection the possible adverse effects (on the foetus) of gentamicin-PMMA beads have to be weighed against the drawbacks of another treatment.

Other relative contraindications are: resistant bacteria, renal dysfunction, gentamicin allergy, an open wound, sclerotic bone and osteosynthesis material in situ. Still, in all these cases use of gentamicin-PMMA beads is possible if certain precautions are taken.

17.6 Gentamicin

The aminoglycoside, gentamicin, is a bactericidal, broad-spectrum antibiotic. Its excretion from the body takes place virtually exclusively through the kidney. In the kidney, all the gentamicin is filtered in the glomerulus and a small portion is reabsorbed in the proximal tubulus. The ciliated cells in the proximal tubulus, just as the ciliated cells in the organs of hearing and equilibrium, constitute a 'deep compartment' in which the gentamicin concentration rises markedly due to accumulation, and from which the release of gentamicin is retarded. The nephrotoxicity and the ototoxicity are due to transient or permanent damage to these ciliated cells. In the kidney, damage to the proximal tubular cell leads to increased depletion of several substances. One of these is β2-microglobulin. Ototoxic lesions manifest themselves with a raised tone threshold and with disorders of the equilibrium.

17.7 Definition of the problem

The study of the literature and experiences with practical use have prompted the following questions, answers to which have been sought:

1. What are the results of the treatment of infections with the aid of gentamicin-PMMA beads?
2. Is this treatment of the infections more successful than other methods of treatment used earlier?
3. Are there other aspects of the treatment of infections, apart from the cure rate, on the basis of which the use of gentamicin-PMMA beads is or is not to be preferred?
4. Are nephrotoxic side effects to be expected from the continuous presence for 10 to 14 days of a low serum concentration and from the continuous renal excretion of gentamicin?
5. Does treatment with gentamicin-PMMA-bead chains cause ototoxic side effects?

Clinical study

17.8 The treatment without gentamicin-PMMA beads

Between 1962 and 1977, 199 localizations in 198 patients were treated. In none of these treatments were gentamicin-PMMA beads used. The treatments are studied retrospectively. The diagnoses were divided into four main groups:

- 115 cases of osteomyelitis
- 41 infected endoprostheses
- 34 infections of soft tissues
- 9 endoprostheses which in retrospect proved not to have been infected.

In all, 345 operations were carried out. Nettoyage was performed practically always, with sequestrectomy and when necessary, removal of an endoprosthes. Seventy per cent of the operations were combined with systemic antibiotic treatment. At 87 of the 345 operations, an irrigation system was introduced as well.

After a follow-up with a median duration of three years, 76% of the patients proved to have been free from recurrence of infection for periods of a median duration of 28 months. These figures do not include the patients whom the endoprosthesis in retrospect proved not to have been infected.

Between 1962 and 1977, 34 total hip prostheses were...
treated for infections. Successful reimplantation was possible in 14 patients; after one reimplantation the result was uncertain. In 18 patients, the treatment terminated in a Girdlestone operation, in one patient in an arthrodesis. Incomplete removal of the prosthesis always (six patients) resulted in a recurrence of the inflammation.

A review of the 87 treatments with an irrigation system combined with the 14 irrigation system treatments described in Chapter 9, shows that during these 101 treatments most irrigation systems were removed after two or three weeks, often because of problems involving leaking and clogged drains. A superinfection occurred in 27 patients.

17.9 Treatment with gentamicin-PMMA beads

Between 1977 and April 1981 inclusive, 90 patients were treated with gentamicin-PMMA beads for 93 localizations:
- 39 cases of osteomyelitis
- 41 infected endoprostheses
- 4 infections of soft tissues
- 9 endoprostheses which on retrospect proved not to have been infected.

In all, 147 operations were carried out. This figure includes those operations that were performed before the introduction of gentamicin-PMMA beads, in order to gain complete insight into the case histories of the patients.

At 116 operations, gentamicin-PMMA beads were implanted. The use of systemic antibiotics in the treatment of the infection was limited to 29% of the 147 operations (in 16% of the 116 gentamicin-PMMA-bead operations).

After a follow-up of a median duration of 13 months, 89% of the patients proved to have been free from recurrence for periods of a median duration of 12 months.

Twenty-four patients were treated for a deep infection of a total hip prosthesis, which treatment ultimately resulted in nine successfully reimplanted prostheses and 15 Girdlestone hips.

A first rough comparison of the two groups of patients, without statistical analysis and without exact classification of the types of operation shows that it is especially in patients with osteomyelitis that ‘healing’ can be accomplished more often with than without gentamicin-PMMA beads (92% and 72%, respectively, free from recurrence). Where gentamicin-PMMA beads were used, the patients’ case histories show a smaller number of operations required to accomplish the healing.

17.10 Statistical analyses of the treatments of infections

A statistical analysis was made of those operations that were performed for osteomyelitis or for an infected endoprostheses. In this connection, a distinction was made between operations that were followed by at least one other operation because of a recurrence of the inflammation (intermediate operations) and operations that were the last ones in the case history (final operations). In addition, the operations were classified according to the type of treatment: gentamicin-PMMA beads, suction drainage and ‘other’ operations.

The analysis of the intermediate operations shows that the probability of a recurrence-free period after an operation with gentamicin-PMMA beads is less than after an operation at which neither gentamicin-PMMA beads nor an irrigation system was used. If a recurrence-free period occurs, there are indications that the duration of the recurrence-free period is longer in women, in cases with long duration of manifest inflammation and after gentamicin-PMMA bead operations. The fact that after intermediate operations with use of gentamicin-PMMA beads a recurrence either develops immediately or takes a longer time to develop, is explained by the more active policy in treatment with gentamicin-PMMA beads: at removal of the beads either reoperation is decided upon immediately because the lack of success of treatment is clear, or the treatment appears successful, in which case a recurrence is found to take a longer time to develop. This clarity may be attributable to the less frequent use of systemic antibiotics.

Of the final operations it may be stated that if gentamicin-PMMA beads are used, the duration of the postoperative period until the patient is healed is distinctly shorter than if suction drainage or some other method of treatment is used. This conclusion takes into account the incomplete follow-up and differences in variables. The postoperative healing time is shorter in infected endoprostheses than after treatment of an osteomyelitis.

Also, advanced age and a long manifest duration of the inflammation are not contributory to a brief postoperative healing time (if the patient is not declared cured immediately after an operation). If gentamicin-PMMA beads are used, the probability that the patient may be regarded as cured immediately after the operation is better than after treatment with an irrigation system, particularly in the treatment of an infected endoprosthesis. This holds especially true in cases with long duration of the manifest inflammation.

In general it may be stated that if gentamicin-PMMA beads are used for the treatment, the cure rate after operation is always higher than among patients treated by other methods (irrigation system or ‘other’ treatments). For this conclusion the difference in follow-up is taken into account. On more detailed analysis, this difference in cure rates is not attributable to background variables.

Pharmacokinetic and toxicological study

17.11 The effect of gentamicin on the renal excretion of β2-microglobulin

β2-Microglobulin is a highly sensitive parameter of influences on the proximal tubulus of the kidney. The intention was to use this parameter for a study of the possible renal side effects of treatment with gentamicin-PMMA beads. To this purpose, the measuring method with the aid of β2-microglobulin had to be elaborated and refined.
For this reason, a study was made first of the effect of various doses of gentamicin on the renal clearance of β2-microglobulin, during five experiments on three volunteers. A dose of 20, 60, 80 or 120 mg was administered intravenously, either once or twice. A dose-dependent influence of gentamicin on the reabsorption of β2-microglobulin in the proximal tubular cell could be demonstrated. This may be explained by competition of β2-microglobulin and gentamicin for reabsorption in the brush border membrane of the tubular cell. In the healthy volunteers, the normal value of the renal excretion of β2-microglobulin was found to amount to 100 ± 60 ng/min. It was only when the renal excretion of gentamicin rose above 150 μg/min, that an increased renal excretion of β2-microglobulin became demonstrable.

17.12 The effect of an operation on the renal excretion rate of β2-microglobulin

The effect of an operation on the renal excretion rate of β2-microglobulin was studied in four patients (three cases of anterior spondylodesis, one of carpal tunnel release). The first finding obtained was a dependence on flow the renal clearances of both β2-microglobulin and creatinine decrease when the urine flow grows less. In addition, the surgical trauma brings about a marked to very marked increase of the renal excretion rate of β2-microglobulin. This effect was confirmed once more at ten operations in the five patients described in Chapter 13.

The value of the maximal renal excretion of β2-microglobulin appeared to be correlated with the severity of the trauma. When the operations were compared with the aid of a so-called 'clinical trauma score' it was found that when the trauma score rose to above approx. 50%, the renal excretion rate of β2-microglobulin increased greatly. We measured one maximal value of 110,000 μg/min.

The increase of the excretion of β2-microglobulin under the influence of a trauma may be attributable to increased depletion from injured tissues. This presupposes a limited capacity of the proximal tubulus to reabsorb β2-microglobulin. Another possibility is that the trauma releases other substances which in the proximal tubulus enter into competition for the limited tubular reabsorption. In that case, these substances released by the trauma ought, just as gentamicin, to contain one or several amino groups.
prolonged when an infection of a prosthesis is not diagnosed correctly or if it is treated inadequately. This contrasts sharply with the briefness—confirmed by statistical analysis—of the period required to suppress infections, even infections of long standing.

From among the patients with osteomyelitis, a choice has been made of the various types of osteomyelitis: hematogenous osteomyelitis, post-traumatic osteomyelitis and one osteomyelitis resulting from decubitus.

17.16 Epilogue

Skeletal infections are still a serious problem and are often difficult to cure. They are often badly crippling and because of their chronic character they frequently bring about great mental stress as well. The treatment of infected endoprostheses, and particularly also of osteomyelitis, is often difficult and takes a long time. We believe on the basis of our investigation that in several important respects, this treatment may be improved by using antibiotic-containing cement, especially in the form of gentamicin-PMMA beads. The results of treatment with gentamicin-PMMA beads are equivalent and possibly even superior to those of other methods of treatment, such as suction drainage. The management of the patient also differs considerably from that with other methods of treatment. The patient is treated for a fixed period of two weeks. If an immediate favourable effect on the inflammation fails to occur, this period may be repeated one or more times. With gentamicin-PMMA beads, namely, it sooner becomes clear whether the treatment is successful. If it is successful, relapses occur later, if at all. Also, the local treatment is more comfortable to the patient since it takes place with the wound closed, with the possibility of adequate mobilization and as a rule without systemic administration of antibiotics.

The perusal of 288 case histories and of the literature also leads to conclusions of a more general nature.

A correct bacteriological diagnosis constitutes the key to the treatment of osteomyelitis and infected endoprostheses. Only too often, endoprostheses with loosening due to a low-grade infection are treated as a purely mechanical problem. As a result, the problem is solved only temporarily and cure is relayed and rendered more difficult. Great importance attaches to more thorough and efficient preoperative diagnostics, including better distinction between septic and aseptic loosening. Lack of diagnostic certainty is particularly embarrassing when at revision of a painful prosthesis one component is found to be loose while the other is still anchored firmly.

Treatment of osteomyelitis is mostly a step by step procedure. Occasionally, a single step suffices to cure the patient, but often several longer and shorter steps are necessary. Keeping this fact in mind will have a beneficial effect and prevent discouragement when a relapse occurs. Complete nettoyage and elimination of the causative agent may be accomplished in phases. In this stepwise approach to cure, the gentamicin-PMMA beads are expedient stepping stones.
18.1 Inleiding

De bijzondere aandacht voor het probleem van de infectie in de orthopaedische chirurgie wordt gerechtvaardigd door de ernstige consequenties ervan. Een toenemend aantal infecties van het skelet wordt veroorzaakt door een toenemend aantal geïmplanteerde endoprothesen en een toenemend gebruik van osteosynthesemateriaal. Bij de behandeling van deze infecties is het sinds 1976 mogelijk als aanvulling op de klassieke chirurgische maatregelen gentamicine-PMMA-kralen te implanteren. Deze kralen zijn een aanvulling op de klassieke chirurgische maatregelen.

In deze studie werd allereerst een overzicht van de literatuur gegeven, waarbij het probleem van de osteomyelitis en de geïnfecteerde endoprothesen werd besproken. Tevens werden besproken de eigenschappen van het antibioticum-houdend cement, van gentamicine en van de gentamicine-PMMA-kralen. Er werd vervolgens een klinisch onderzoek beschreven dat uiteen valt in een retrospectieve studie naar de resultaten van behandelingen voordat gentamicine-PMMA-kralen werden gebruikt en een prospectief uitgevoerde studie naar de resultaten van de behandeling van infecties met gentamicine-PMMA-kralen. Een statistische analyse ter vergelijking van beide behandelingsoorten werd aan de hand van dit patiëntenvoortouvoerder het derde deel van de studie richtte zich op mogelijke bijwerkingen van de gentamicine-PMMA-kralen op de nier of op het gehoor.

Literatuur

18.2 Osteomyelitis

In het kort werd ingegaan op het pathologische en klinische beeld van de endogene en exogene osteomyelitis. De diagnose werd besproken, waarbij met name werd ingegaan op de bacteriologische aspecten ervan. De afname van de kweek en een goede uitleg van de kweekuitslag is essentieel.

Bij de invoering van een nieuwe methode ter behandeling van osteomyelitis was in de geschiedenis van die therapie te bespreken, waarvoor werd geïllustreerd welke elementen van de nieuwe therapietrouw al bewijs waren. Beschreven werd hoe tot in de 19e eeuw de behandeling van osteomyelitis symptomatisch was. Toch was een diagnose te stellen, drainage en rust een algemeen gebruik.

De latente, low-grade infectie kan slechts in een uitgebreid onderzoek worden vastgesteld. Behandelen moet worden behandeld met antibiotica. Dit geldt voor de acute oppervlakkige, maar vooral ook voor de acute diepe prosthe-sixfectie.

De latente, low-grade infectie kan slechts in een beperkt aantal gevallen conservatief worden geholpen. De enige definitieve genezing kan door verwijdering van de gehele prothese met alle cement worden verkregen. Daarna moet worden gekeken voor een reimplantatie van een prothese of voor het verwijderen er van (Girdlestone, arthrode). Wordt een reimplantatie uitgevoerd, dan worden de resultaten verkregen met behulp van antibiotieemhoudend cement. De reimplantatie kan tijdens dezelfde operatie als de extractie en nettoyage worden verricht, 'one-stage' reimplantatie.

Wordt een korte of langere tijd gewacht met de reimplantatie, dan spreekt men van een 'two-stage' procedure. Deze kunnen gedurende een korte tijd (10-14 dagen) bijdragen aan de behandeling van de infectie door een lokale, zeer sterk werkzame bactercide behandeling met gentamicine.
18.4 Antibioticumhoudend cement

De ontwikkeling van het antibioticumhoudend cement was aanvankelijk geheel empirisch: Buchholz vermengde botcement met antibiotica om het infectiepercentage van de prothese te vermineren. Nader onderzoek toonde dat antibioticum door diffusie uit het botcement konden worden afgestaan. Diverse onderzoeken van verschillende combinaties van antibiotica en cementsoorten toonden dat de afgifte van antibiotica evenredig is met onder andere de oppervlakte van het cement en de concentratie van het antibioticum in het cement.

Ook de omgevende vloeistof bepaalt hoeveel antibioticum uit het cement diffundeert. Steeds betreft het een diffusie en is dus een waterig milieu vereist.

Sommige antibiotica blijken niet geschikt om in botcement te worden verwerkt doordat ze niet hittestabiel of wateroplosbaar zijn. Voor klinische toepasbaarheid is van belang hoeveel van het antibioticum per tijdseenheid wordt afgestaan, waarbij van belang is of de bacteriologisch werkzame concentratie wordt bereikt. Wordt (op bacteriologische gronden) gekozen voor gentamicine, dan is vermeniging in palacos de beste combinatie.

De werkzaamheid van antibioticumhoudend cement blijkt bij dierproeven vooral tijdens en kort na de operatie te moeten worden verwacht. Werkzaamheid langer dan ongeveer zes weken na de operatie, kon echter onvoldoende worden aangetoond. Bij klinische toepassing is daarom een beschermend effect alleen peroperatief (tegen contaminatie) en kort postoperatief (tegen haematogene infecties) te verwachten. De goede resultaten na het gebruik bij 'one-stage' reïmplantatie, na verwijdering van de afgifte van antibioticum uit het cement dilferende, afhankelijk van onder andere de concentraties (MBC) van de verwekkers, is het noodzakelijk de cumulatie sterk te vertragen, en waaruit het gentamicine vertraagd wordt afgegeven. De nefrotoxiciteit en de otoxiciteit zijn gebaseerd op een tijdelijke of blijvende beschadiging van deze haarcellen.

In de nier ontstaan door beschadiging van de proximale tubuluscel verhoogde depleties van diverse stoffen. Eén daarvan is het β2-microglobuline.

De beschadiging in het oor uit zich door een verhoogde toordrempling en door evenwichtstoornissen.

18.5 Gentamicine-PMMA-kralen


De afgifte van het gentamicine uit de kralen en de werkzaamheid ervan is 'in vitro' en 'in vivo' aangetoond. Bij toepassing in de kliniek zijn de praktische voordelen voor de patiënt en voor de verpleging van belang, vooral in vergelijking met de behandeling met een spoelsysteem. Ook in bacteriologisch en economisch opzicht zijn voordelen aanwezig.

Naast toepassingen bij infecties van het skelet zijn ook ervaringen beschreven bij weke delen infecties.


18.6 Gentamicine

Het aminoglycoside gentamicine is een bactericide, breed-spectrum antibioticum. De eliminatie in het lichaam geschiedt vrijwel geheel via de nier. In de nier wordt gentamicine volledig gefilterd in de glomerulus en voor een klein gedeelte geresorbeerd in de proximale tubulus. De haarcellen in de proximale tubulus vormen evenals de haarsnoren in het gehoor- en evenwichtsoord, een 'diep compartment', waarin de gentamicineconcentratie door accumulatie sterk stijgt, en waaruit het gentamicine vertraagd wordt afgegeven. De nefrotoxiciteit en de otoxiciteit zijn gebaseerd op een tijdelijke of blijvende beschadiging van deze haarcellen.

18.7 Probleemstelling

Op basis van de literatuurstudie en op basis van het gebruik in de praktijk, rijzen de volgende vragen, waarop een antwoord is gezocht:

1. Wat zijn de resultaten van de behandeling van infecties met behulp van gentamicine-PMMA-kralen?
2. Is deze behandeling van de infecties succesvoller dan destijds, toen gebruik werd gemaakt van andere behandelingen?
3. Zijn er andere overwegingen dan het genezingspercentage, dat van belang zijn bij de behandeling van infecties en op grond waarvan de toepassing van gentamicine-PMMA-kralen wel of niet de voorkeur verdient?
4. Zijn er nefrotoxische bijwerkingen te verwachten van de 10 tot 14 dagen continu aanwezige lage serumconcentratie en van de continue renale excretie van gentamicine?
5. Leidt de behandeling van gentamicine-PMMA-kralen in de praktijk, rijzen de volgende vragen, waarop een antwoord is gezocht:

Klinische studie

18.8 De behandeling zonder gentamicine-PMMA-kralen

De diagnoses werden in vier hoofdgroepen ingedeeld - 115 osteomyelitiden - 41 geïnfecteerde endoprothesen - 34 weke delen infecties - 9 endoprothesen, die achteraf niet geïnfecteerd bleken
In totaal werden 345 operaties uitgevoerd. Vrijwel steeds werd een nettoyage, met sequestrectomie en eventueel een verwijdering van een endoprothese uitgevoerd. In 70% van de operaties werd eveneens een systemische antibioticum-behandeling gegeven. Bij 87 van de 345 operaties werd bovendien een spoelsysteem ingebracht.

Na een follow-up van mediaan drie jaar bleek 76% van de patiënten, gedurende een periode die mediaan 28 maanden bedroeg, vrij van recidief van infectie. Daarbij zijn de patiënten geïsoleerd, waarbij achteraf bleek dat de endoprothese niet geïnfecteerd was.

Van 1962 tot 1977 werden 34 total hip prothesen behandeld voor infecties. Bij 14 patiënten was een succesvolle reimplantatie mogelijk, na een reimplantatiet was het succes onzeker. Bij 18 patiënten eindigde de behandeling met een Girdlestone operatie, bij een patiënt met een arthrodese. Incomplete verwijdering van een prothese leidde steeds (zes patiënten) tot een recidief van de ontsteking.

Bestudering van de 87 behandelingen met een spoelsysteem, een spoelsysteembehandelingen uit hoofdstuk 9, toonde dat bij deze 101 behandelingen de meeste spoelsystemen na twee a drie weken werden verwijderd, doorgaans in verband met problemen van lekkage en stoppen van de drains. Een superinfectie trad bij 27 patiënten op.

18.9 Behandeling met gentamicine-PMMA-kralen

Van 1977 tot en met april 1981 werden 90 patiënten voor 93 localisaties behandeld met gentamicine-PMMA-kralen - 39 osteomyelitiden - 41 geïnfecteerde endoprothesen - 4 weke delen infecties - 9 endoprothesen, die achteraf niet geïnfecteerd bleken te zijn
Er werden 147 operaties uitgevoerd. Daarbij zijn ook de operaties meegeteld, voordat gentamicine-PMMA-kralen werden gebruikt om een volledig overzicht van de ziektegeschiedenissen van de patienten te verkrijgen.

Bij 116 operaties werden gentamicine-PMMA-kralen geïmplanteerd. Het gebruik van systemische antibiotica bij de behandeling van de infectie bleef beperkt tot 29% van de 147 operaties (in 16% van de 116 gentamicine-PMMA-kralenoperaties)

Bij een mediane follow-up van 13 maanden bleek 89% der patiënten gedurende een periode van mediaan 12 maanden vrij van recidief

24 Patienten werden behandeld voor een diepe infectie van een totale heupprothese, uiteindelijk resulterend in negen succesvol gereimplanteerde prothesen en 15 Girdlestone-heupen.

Vergelijking van beide patiëntengroepen in eerste instantie zonder statistische analyse en zonder exacte uitslectering van de operatietypen, toont dat vooral bij patienten met een osteomyelitis met behulp van gentamicine-PMMA-kralen vaker 'genezing' kan worden bereikt dan zonder gentamicine-PMMA-kralen (92% tegen 72% recidiefvrij)

Worden gentamicine-PMMA-kralen gebruikt dan tonen de ziektegeschiedenissen van de patiënten een kleiner aantal operaties, nodig om de genezing te bereiken.

18.10 Statistische analyses van de infectiebehandelingen

In een statistische analyse zijn die operaties betrokken, die werden uitgevoerd voor een osteomyelitis of een geïnfecteerd endoprothese. Daarbij is een onderscheid gemaakt tussen de operaties die nóg door een andere operatie werden gevolgd, omdat er een recidief van de ontsteking optreedt (tussenoperaties) en operaties die de laatste vormden in de ziektegeschiedenis (eindoperaties).

Daarnaast zijn de operaties onderscheiden al naar gelang de soort behandeling gentamicine-PMMA-kralen, spoelsysteem of 'overige' operaties.

Bij analyse van de tussenoperaties blijkt dat de kans op een recidievrij periode na een operatie met gentamicine-PMMA-kralen kleiner is dan na een operatie, waarbij noch gentamicine-PMMA-kralen noch een spoelsysteem werd gebruikt. Als er een recidievrij periode optreedt zijn er aanwijzingen dat de duur van de recidievrij periode langer is bij vrouwen, bij een lange duur van de manifeste ontsteking en na gentamicine-PMMA-kralen-operaties. De verklaring voor het feit dat een recidief na tussenoperaties bij gebruik van gentamicine-PMMA-kralen of direct optreedt, of langer op zich laat wachten, wordt verklaard door de aktevere houding tijdens de behandeling met gentamicine-PMMA-kralen, bij verwijdering van de kralen wordt of direct besloten tot re-operatie omdat duidelijk is dat de behandeling geen succes had, of de behandeling lijkt succesvol en dan blijkt een recidief langer op zich te laten wachten. Deze duidelijkheid wordt wellicht verklaard door het minder frequent systemisch gebruik van antibiotica.

Voor de eindoperaties geldt dat bij gebruik van gentamicine-PMMA-kralen de tijd die postoperatief verloopt voordat de patiënt genezen is, duidelijk korter is dan wanneer een spoelsuystemen of andere behandelmethonen worden gebruikt. Hierbij is rekening gehouden met onvolledige follow-up en verschillen in variabelen. De postoperatieve genezingsduur is bij geïnfecteerde endoprothesen korter dan na behandeling van een osteomyelitis.

Een hoge leeftijd en een lange manifeste duur van de ontsteking zijn daarnaast niet bevorderlijk voor een korte postoperatieve genezingsduur (indien de patiënt na een operatie niet direct genezen is). Worden gentamicine-PMMA-kralen gebruikt, dan is met name bij behandeling van een geïnfecteerde endoprothese de kans groter dat direct na de behandeling de patiënt als genezen kan worden beschouwd dan na behandeling met een spoelsysteem. Dit vooral als de duur van de manifeste ontsteking lang is.

In het algemeen geldt dat als bij de behandeling gebruik is gemaakt van gentamicine-PMMA-kralen, dat postoperatief steeds het genezingspercentage van de patiënt hoger is dan bij patiënten die met andere methoden zijn behandeling (spoelsysteem of 'overige' behandelingen). Hierbij is rekening gehouden met het
verschil in follow-up Dit verschil in genezingsspercentage blijkt bij nadere analyse niet door de achtergrondvariabelen verklaarbaar.

Pharmacokinetisch en toxicologisch onderzoek

18.11 De invloed van gentamicine op de renale excretie van β2-microglobuline

β2-Microglobuline vormt een zeer gevoelige parameter voor beïnvloeding van de proximale tubulus in de nier. De bedoeling was deze parameter te gebruiken voor een onderzoek naar een mogelijke bijwerking op de nier van een gentamicine-PMMA-kralenbehandeling. Daarvoor moest de meetmethode met behulp van β2-microglobuline verfijnd en uitgewerkt worden.

Allereerst is daarvoor het invloed van diverse doseringen gentamicine op de renale klaring van β2-microglobuline onderzocht bij drie proefpersonen in vijf experimenten. Een dosis van 20, 60, 80 of 120 mg werd één of twee maal intravenus toegediend. Gewonden is dat de terugresorptie van β2-microglobuline in de proximale tubuluscel dosis-afhankelijk wordt beïnvloed door gentamicine. De verklaring ervaart kan worden gevonden in een competitie tussen β2-microglobuline en gentamicine voor resorptie in de ‘brush-border’-membraan van de tubuluscel. Bij de gezonde proefpersonen blijkt de normaalwaarde van de renale β2-microglobuline-excretie 100 ± 60 ng/min. Pas bij een renale excretie van gentamicine of meer dan 150 μg/min wordt een versterkte renale excretie van β2-microglobuline meetbaar.

18.12 De invloed van een operatie op de renale excretiesnelheid van β2-microglobuline

De invloed van een operatie werd nagegaan op de renale excretiesnelheid van β2-microglobuline bij vier patiënten (drie voorste spondylodesen, één carpal tunnel release). In de eerste plaats werd een flow-afhankelijkheid gevonden van de renale klaring van zowel β2-microglobuline alsook de creatinine vermindert bij een geringere urineflow. Daarnaast veroorzaakt het trauma van een operatie een sterke, tot zeer sterke stijging van de renale excretiesnelheid van β2-microglobuline. Deze beïnvloeding wordt in hoofdstuk 13 bij nog eens 10 operaties bij vijf patiënten onderzocht naast dit trauma-effect geen meetbare beïnvloeding van de β2-microglobuline-excretie vindt worden. Allereerst is daarvoor het invloed van diverse doseringen gentamicine op de renale klaring van β2-microglobuline onderzocht bij drie proefpersonen in vijf experimenten. Een dosis van 20, 60, 80 of 120 mg werd één of twee maal intravenus toegediend. Gewonden is dat de terugresorptie van β2-microglobuline in de proximale tubuluscel dosis-afhankelijk wordt beïnvloed door gentamicine. De verklaring ervan kan worden gevonden in een competitie tussen β2-microglobuline en gentamicine voor resorptie in de ‘brush-border’-membraan van de tubuluscel. Bij de gezonde proefpersonen blijkt de normaalwaarde van de renale β2-microglobuline-excretie 100 ± 60 ng/min. Pas bij een renale excretie van gentamicine of meer dan 150 μg/min wordt een versterkte renale excretie van β2-microglobuline meetbaar.

18.13 De invloed van behandeling met gentamicine-PMMA-kralen op de renale excretie van β2-microglobuline

De renale excretiesnelheid van β2-microglobuline in bij vijf patiënten was bij gemiddelde van 3,3 dagen De ‘in vivo’ halfwaardetijd wordt mogelijk geëlimineerd Deze halfwaardetijd bleek 6 tot 10 dagen te zijn, in tegenstelling tot de ‘in vitro’ halfwaardetijd van 3,3 dagen De ‘in vivo’ halfwaardetijd wordt mogelijk beïnvloed door de ligging van de kralen en door de soort weefsels er omheen.

Dit pharmacokinetisch onderzoek toonde bij alle vijf patiënten aan hoe de gentamicine-PMMA-kralen een echte ‘slow-release’ systeem vormen sedert de gehele behandeling werd een constante afgifte geregistreerd door de gentamicine. Die serumconcentratie bleef daarbij steeds onder 1 μg/ml en de urineconcentratie was doorgaans beneden 10 μg/ml. De renale excretiesnelheid van gentamicine was 4 tot 12 μg/min na implantatie van 48 tot 90 gentamicine-PMMA-kralen.

Een benadering van de halfwaardetijd van gentamicine in vivo geeft weer hoe lang het duurt voordat 50% van de hoeveelheid gentamicine vanuit de kralen via de wond aan het lichaam wordt afgenomen en in de nier geëlimineerd Deze halfwaardetijd bleek 6 tot 10 dagen te zijn, in tegenstelling tot de ‘in vitro’ benadering halfwaardetijd van 3,3 dagen. De ‘in vivo’ halfwaardetijd wordt mogelijk beïnvloed door de ligging van de kralen en door de soort weefsels er omheen.

18.14 De invloed van een behandeling met gentamicine-PMMA-kralen op het gehoor en het evenwichtsorgaan

Bij vijf patiënten werd een toondrempel-audiogram verricht vóór en tijdens de behandeling Bij drie van hen kon een nyctagmografisch onderzoek worden verricht vóór en tijdens de behandeling.

Wij vonden bij het audiometrisch onderzoek geen tekenen van ototoxiciteit en bij het vestibulair onderzoek evenmin.

Alhoewel uit deze oriënterende studie naar ototoxiciteit geruststellende resultaten worden verkregen, zou bij patiënten met een verhoogd risico voor ototoxiciteit dienen te worden gecontroleerd op beschadiging van het gehoor. Dubbelzijdige beschadiging van het gehoor is
immers anders dan beschadiging van het evenwicht, niet te compenseren. Deze controle op ototoxiciteit kan het beste gedaan worden door middel van alleen audiometrie. Patiënten zonder verhoogd risico zouden tijdens een behandeling met gentamicine-PMMA-kralen niet gecontroleerd hoeven te worden.

18.15 Casuïstiek
Aan de hand van de ziektegeschiedenissen van 10 patiënten wordt geïllustreerd welke problematiek zich in het algemeen bij de behandeling van botinfecties voordoet, en wat de plaats van de behandeling van gentamicine-PMMA-kralen in de ziektegeschiedenissen was. Steeds was deze behandeling een onderdeel van een vaak langdurige behandeling.


De patiënten met infecties van endoprothesen illustreren hoe de ziektegeschiedenis onnodig kan worden verlengd, doordat een infectie van de prothese als zodanig niet wordt erkend of onvoldoende behandeld. De korte periode die – ook bij statistische analyse – nodig blijkt om een vaak al langdurig bestaande infectie te elimineren, staat daarmee in schril contrast.

Van de patiënten met osteomyelitis is een keuze gemaakt uit de verschillende soorten osteomyelitis: haematogene en posttraumatische osteomyelitis en een osteomyelitis veroorzaakt door decubitus.

18.16 Slotbeschouwing
Infecties van het skelet blijven ernstig en vaak moeilijk te genezzen. Ze zijn vaak sterk invaliderend en door het chronisch karakter vormen ze veelal een zware psychische belasting. De behandeling van geïnfecteerde endoprothesen en vooral ook van osteomyelitis is vaak moeizaam en langduurig.

Op grond van onze studie menen wij dat deze behandeling op een aantal belangrijke punten kan verbeteren door gebruik te maken van antibioticumhoudend cement met name in de vorm van gentamicine-PMMA-kralen. De resultaten van behandeling met gentamicine-PMMA-kralen zijn gelijkwaardig, mogelijk zelfs beter dan met andere behandelmethodeen in de praktijk.


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Parts of this study have been published previously:


subj. dG  360 PMMA beads