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HER MAJESTY THE QUEEN

Since 1948 The Journal of Bone and Joint Surgery has presented the hopes and achievements of orthopaedic surgeons throughout the Commonwealth as well as in the United States of America, with the intention of "recording scientific progress and publishing new discoveries by all English-speaking peoples for the welfare of mankind"—a task for which his Majesty King George VI sent us his best wishes in his message to the first British number.

We are deeply conscious of the continuing interest of The Royal Family in this progress and, with our humble duty, would offer loyal greetings to Her Majesty The Queen on the occasion of her Silver Jubilee. Her reign has already seen advances in our work that would have been almost beyond the imagination of the original British Editorial Board. May we combine our expression of allegiance with the promise to spare no effort in spreading these advances "wider still and wider".

EDITORIALS AND ANNOTATIONS

ANTIBIOTICS IN CEMENT

The dramatic success of most total hip replacements aggravates the disappointment for patient and surgeon alike when the operation fails because of sepsis. Concern about such failures and how to prevent them has perhaps dominated the practical techniques of total hip replacement in a way not seen with any other major surgical procedure. It has given us on the one hand the clean-air advocates, whose objective is total exclusion of micro-organisms from the wound at operation, and on the other those who interpret late infections as evidence of blood-borne invasion and have understandably placed their faith in antibiotic depots added to the cement, available on site to deal with late microbial invaders. Two papers in this issue continue the debate.

Bacteriologists in touch with the older literature on post-operative wound infection will tend to look critically at any claim that for an orthopaedic operation with an expected infection rate of, say, 1 or 2 per cent (Public Health Laboratory Service 1960; Waring and Aufranc 1971) further reduction in the incidence of infection can be confidently ascribed to the procedures used. The Public Health Laboratory Service (1960) study of post-operative wound infection, and the later analysis of their material by Lidwell (1961), showed that substantial differences in the post-operative infection rates in different hospitals were almost entirely accounted for by such factors as the age and sex of the patients, the type and duration of the operation, and the length of the incision—in other words by factors other than measures to reduce the incidence of infection. Lidwell (1963) stressed the dilemma that with progressive lowering of sepsis rates the statistical requirements for ascribing significance to further reductions in the incidence become more exacting. Other difficulties also complicate this assessment. It may well be, for instance, that those patients whose operations come to grief through sepsis have an inherently lower resistance to infection, but this we are unable to measure. Again, with so many variable factors, only a random allocation of patients to one or other procedure for the control of infection is likely to permit confident judgments on the superiority of one approach over another. This has not yet been done in the major centres engaged in total hip replacement.

The evidence cited by the pioneers of total hip
replacement in support of the procedures that they advocate is not without loopholes. Charnley and Eftekhar (1969) claimed that reduction in their incidence of infection after total hip replacement was due to progressive increase in the number of air changes per hour achieved in the enclosed system within which they operated. Their own paper makes it clear, however, that other material changes in procedure were introduced at relevant times during the eight-year period in question. Moreover, such sketchy bacteriological information as they gave is difficult to reconcile with their main conclusion. Perhaps the laborious comparative trials now in progress will in due course permit a firmer evaluation of the importance of ventilation, but total exclusion of micro-organisms from the operation wound is probably an unattainable ideal.

The antibiotic approach of Buchholz and his colleagues stemmed from the view that infections occurring after the immediate post-operative period were due to a blood-borne invasion of the joint from some other part of the body. This led them to explore the idea that an appropriate antibiotic incorporated in the cement and diffusing into surrounding tissues might have a protective effect against late bacterial complications. Using various antibiotics, but especially gentamicin, they have claimed a remarkable fall in sepsis rates. Thus Buchholz and Engelbrecht (1970) reported that between January 1969 and April 1970 their unit had performed 1,115 operations using Palacos cement with an added antibiotic, with only a single infection (0-09 per cent), and even in that one patient the infected prosthesis had been successfully exchanged. During the same period they had done 271 total hip replacements without antibiotics, with a sepsis rate of 1.2 per cent, a figure almost identical with that of Charnley and Eftekhar’s (1969) fourth and best phase. Equally impressive was the report by Buchholz and Gartmann (1972) on the high success rate of second operations on septic total hip replacements when gentamicin or a combination of gentamicin with another antibiotic was incorporated in the cement used for the salvage operation.

Dramatic though these German findings may be, the papers cited do still raise some doubts. One difficulty is the elusiveness of statistical information that one would expect to find more readily. Some essential tabulations in the paper by Buchholz and Gartmann (1972), for instance, are missing from the published text, although available from the publishers. Again, it is not always easy to find in these papers a clear answer to obvious queries; for instance on whether the information given refers to findings immediately after the operation or to later assessments of the success of the operations in question. It seems clear, nevertheless, that a prima facie case for incorporating antibiotics into acrylic cement for total hip replacement has been made. However, a number of issues still need clarifying before the findings of Buchholz’s group stampede surgeons into relying on antibiotics embedded in cement as the sole sheet anchor in ensuring the success of total hip replacement. The abundant evidence of many years testifies to antibiotics being two-edged weapons with great advantages but serious drawbacks. This makes it important to evaluate critically the quite new concept of incorporating them within a more or less permanent depot in the body.

Statistical evidence apart, surgeons anxious to establish a rational basis for adding antibiotics to acrylic cements will want answers to a number of theoretical and practical questions—the appropriate antibiotic to use, the kinetics of its liberation from the cement into the patient’s tissues, the source and nature of the micro-organisms it is expected to deal with, and its possible disadvantages. A number of workers, including the two groups whose papers are published in this issue, have added various antibiotics to different proprietary brands of cement and used simple model systems to estimate the quantity of antibiotics leached from the test objects and the length of time over which the liberation of antibiotic took place. In the work described in this issue, Hill, Klenerman, Trustey and Blowers immersed discs of Simplex cement containing fucidin, gentamicin or clindamycin in peptone water maintained at 37 degrees Celsius, and tested the inhibitory effect of the leached antibiotic in preventing the multiplication of a fairly heavy inoculum of sensitive bacterial species added to the peptone water at the beginning of the experiment. After three days the discs were retrieved from the peptone water, washed to remove antibiotic from their surface, and then placed in fresh peptone waters which were inoculated once again with the same range of test organisms. In these experiments, fucidin had a particularly transient effect; clindomycin was the most long-lasting, but its spectrum is of course narrow. Gentamicin inhibited Staphylococcus aureus for twenty-two days and E. coli for eleven days. Elson and his colleagues, also reporting in this issue, tested a number of different cements and confirmed the findings of Buchholz’s group and of a number of other workers (Marks, Nelson and Lautenschlager 1976) that for some unexplained reason more antibiotic is liberated from Palacos than from various other brands of cement. Their test method differed from that of Hill et al. in that antibiotic-containing discs were washed daily in distilled water, which was then assayed for antibiotic content by a standard method using assay plates and an indicator organism. Their findings are in broad agreement with those of Hill et al. in showing that the liberation of antibiotic falls rapidly, over a period of a week or two, to very low levels. They also report however that antibiotic-loaded acrylic cement removed from one of their patients after being in situ for two and a quarter years still retained a highly bactericidal effect on its broken surface.

The time scale of gentamicin liberation from cement in vitro tallies with in vivo findings of Wahlig and Buchholz (1972) both in experimental animals and in man.
following total hip replacement. Wahlig and Buchholz could detect gentamicin in the blood for only three or four days, and in the urine for about three weeks. From this they argued that, in the absence of detectable antibiotic in the body, hypersensitivity to it was unlikely to occur in the recipient. They also suggested that in the presence of only minute quantities of an antibiotic—well below the minimal inhibitory concentration for sensitive organisms—the emergence of antibiotic resistant bacteria could be discounted and thus another theoretical disadvantage of antibiotic-loaded cement did not apply. Both points are referred to again below.

Discussing their experimental findings, Hill et al. argue that an anti-bacterial drug designed to prevent infection after a hip operation might be required to work in two ways: first by achieving a broad-spectrum bactericidal concentration in the exposed tissues during the operation so that contaminating organisms are killed immediately, and secondly by maintaining a bactericidal concentration for a longer period to deal with blood-borne microbes that might later colonise devitalised tissues around the implant. For the first objective they dismiss antibiotic incorporated in cement because of inevitable initial delay in its diffusion into the tissues. Instead they advocate topical application or intravenous injection. For longer protection they consider the incorporation of gentamicin in cement as carrying a risk of hypersensitivity, but they are in any case sceptical about the occurrence of blood-borne infection.

These arguments call for further discussion. As Hill et al. maintain, the fact that antibiotic-containing cement is used only towards the end of the operation certainly makes it inconceivable that the immediate effect of antibiotic released from the cement can match that of antibiotics given intravenously or topically before and during the operation. Once the wound has been closed, however, and diffusion of the antibiotic from the cement has begun, other factors may need to be taken into account. First, there is the uncertainty whether bacteria causing late infection have been implanted at the operation site during the operation or have later been carried there by the bloodstream. Anecdotal evidence but also a few published reports (Artz et al. 1975; Burton and Schurman 1975) make it fairly certain that blood-borne invasion from another focus in the body can occur, but how often is unknown. If on the other hand the organisms have been lying dormant in the joint tissues the question arises whether they have been present as proplasts or spheroplasts or as bacterial “persisters” (Bigger 1944; McDermott 1958; Greenwood 1972). Secondly, total hip replacement involves considerable trauma to the femoral shaft, and in these circumstances the access of antibiotics to bacteria that have lodged near the bone may be impaired by lack of an adequate blood supply. Given this, diffusion of antibiotic from the cement and through adjacent bone could perhaps compete in effectiveness with systemic administration.

Thirdly, a number of uncertainties arise in relation to the effectiveness of antibiotics against a given microorganism. Here several variables come to mind. Which antibiotic or combination of antibiotics is most likely to deal with the range of bacteria causing wound sepsis, a range that includes not only the major pathogens but organisms such as Staphylococcus albus? How is the effectiveness of antibiotics at the site of the prosthesis influenced by local conditions such as bone necrosis or anaerobiosis? Is it possible that an antibiotic can be present in cement in concentrations low enough to avoid the risk of promoting hypersensitivity but high enough to have some residual antibacterial effect? Here a technical point that might be worth exploring arises from the fact that minimal inhibitory concentrations are expressed in terms of microgrammes per millilitre. It is possible that tiny quantities of antibiotic dissolved in sufficiently small volumes of tissue fluid could still give locally adequate bactericidal concentrations at vulnerable points near the prosthesis where micro-organisms had lodged.

The risk of hypersensitivity cannot be entirely discounted by the argument of Wahlig and Buchholz (1972) nor by their failure to demonstrate it in an admittedly long series of patients. As Holm and Vejlsgaard (1976) have pointed out, industrial workers can be exposed to particular chemicals for a long time before becoming allergic to them. Moreover, the reliability of the reporting of hypersensitivity is doubtful on several counts. Allergic manifestations following the later administration of, say, therapeutic doses of gentamicin by another clinician are unlikely to come to the notice of the orthopaedic surgeon concerned in the initial operation. Again, in the novel context of incorporating antibiotics in cement, hypersensitivity might well take an unfamiliar form, perhaps even a loosening of the prosthesis, if an immune complex phenomenon occurred at the cement surface. In the event of hypersensitivity developing and being correctly diagnosed, total removal of the offending antibiotic might well present formidable problems, as Chapman and Hadley (1976) have pointed out.

Surgeons who hesitate to use antibiotics in cement as a routine may consider it rational to use one or more appropriate antibiotics in this way in repair operations following deep infection of an earlier total hip replacement. Even here, an alternative is available in a long-term antibiotic regime such as that used by Fremont-Smith (1974).

Of the other hypothetical risks that have been considered, the emergence of antibiotic-resistant bacteria is, in the writer’s view, not likely to be a problem when antibiotic is incorporated in cement. After the first few weeks the level of circulating antibiotic will be too low to exercise a selection pressure favouring resistant organisms in other parts of the patient’s body. At the site of the prosthesis itself, bacterial multiplication to an extent likely to encourage the emergence of resistant
organisms would probably result in a deep infection of the wound.

Perhaps the greatest contribution of the Charnley school has been its insistence on meticulous asepsis at the time of operation. Final evaluation of the role of antibiotics in total hip replacement must await further clinical and experimental study.

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REFERENCES


