

METAL SENSITIVITY AS A CAUSE OF BONE NECROSIS AND LOOSENING OF THE PROSTHESIS IN TOTAL JOINT REPLACEMENT

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Loosening of the prosthesis, an important cause of clinical failure following total joint replacement, may be due to faulty implantation of the prosthesis, to trauma, or to infection in the tissues adjacent to the implant. Cases of loosening exist, however, in which the technique of implantation appears to have been satisfactory, in which there is no history of injury and in which there is no evidence by conventional criteria of the presence of infection. It will be argued in this paper that at least some of these cases may be due to sensitivity of the tissues to one of the metals in the alloy of which the prosthesis is composed.

With one exception, all the patients described had prostheses implanted in which both components were composed of cobalt-chrome alloy. We believe that the problem of metal sensitivity is likely to be most important with implants of this kind but that it may also occur when an alloy articulates with bone. In contrast, we believe that the problem is least important when either cobalt-chrome alloy or stainless steel is articulated with high density polyethylene.

In summary the argument to be presented is as follows. Laboratory and clinical studies have shown that when two cobalt-chrome alloy surfaces are rubbed against each other cobalt and chromium are released into the local tissues, pass into the blood stream to be presented to all body tissues, and finally appear in the urine. It is known that skin sensitivity can develop in response to certain metals implanted in the body, and that cobalt and chromium can produce skin sensitivity. We suggest that in certain patients the release of metal from a prosthesis may result in tissue sensitisation and that this can be detected clinically by a skin patch test in which a soluble salt of the metal (for example cobalt chloride) is used as the test object. We believe that the release of metal from prostheses in metal-sensitive patients causes obliterative changes in the blood vessels supplying the bone into which the prosthesis is implanted and leads to the death of this bone. We suggest that when the bone dies the integrity of the bone-prosthesis bond is prejudiced (probably as a consequence of fibrous replacement of, and fatigue failure in, the dead bone), and that the prosthesis then becomes loose.

We now report the following three groups of observations relevant to this argument: 1) a study of the amount of metal in the tissues adjacent to prostheses; 2) a study of metal sensitivity in patients with prostheses; and 3) a study of the histopathology in the tissues adjacent to prostheses in metal-sensitive patients.

RELEASE OF IONIC METAL FROM METAL ALLOYS USED AS BEARING SURFACES IN TOTAL JOINT REPLACEMENT PROSTHESES

Throughout this paper it will be helpful to bear in mind the composition in weight per cent of the cast cobalt-chrome alloys used for prostheses (BS 3531:1968). This is chromium 27 to 30; molybdenum 5 to 7; nickel 0 to 2.5; tungsten nil; carbon 0.2 to 0.35; silicon 0 to 1; manganese 0 to 1; cobalt—balance. At least one of the alloys used commercially for prostheses contains no nickel. Others may contain up to 2.5 per cent.

Coleman, Herrington and Scales (1973) found that in nine patients with prostheses composed of cobalt-chrome articulating with cobalt-chrome both blood and urinary cobalt and chromium levels were persistently raised. In contrast, they were unable to detect a significant elevation of blood or urinary cobalt and chromium in three patients with cobalt-chrome

prostheses articulating with high density polyethylene. This clinical observation supports the findings of Swanson, Freeman and Heath (1973) who showed that in laboratory simulators prostheses in which both components were composed of cobalt-chrome alloy released both cobalt and chromium into the solution bathing them during a wear test. The release of metal could not be demonstrated by these workers when cobalt-chrome was articulated against high density polyethylene nor when stainless steel was articulated against high density polyethylene. So far as we are aware, no observations have been made upon blood or urinary cobalt and chromium levels in patients with cobalt-chrome prostheses articulating against bone.

The concentration of metal in living tissues adjacent to implanted metals was studied experimentally by Ferguson, Laing and Hodge (1960). These workers found that the metallic constituents of cobalt-chrome (and of stainless steel) were detectable in the surrounding tissues four to six months after implantation of small cylinders of the alloy.

A STUDY OF THE LEVELS OF METAL IN THE TISSUES ADJACENT TO PROSTHESES

With these facts in mind we have studied the release of metal from various joint prostheses by measuring the amount of metal in the adjacent soft tissues.

Material—We have estimated the concentrations of cobalt and chromium (and in some cases of nickel) in the tissues adjacent to eleven implanted prostheses and in the joint tissues of two patients in whom no prosthesis had been inserted.

Methods—Tissue was taken at re-operation or at necropsy. The metal concentration was estimated by neutron activation analysis in ten specimens and by atomic absorption spectrophotometry in three specimens. Joint tissues from two patients having synovectomy operations and from one unrelated necropsy specimen were used as controls.

Results—We found that in the five specimens (specimens 1, 2, 3, 4, 5) with all-cobalt-chrome prostheses both cobalt and chromium levels were considerably elevated in the tissues adjacent to the prosthesis as compared with control tissue taken from three patients in whom no prosthesis had been inserted (Table I).

In the two specimens (7 and 8) taken from patients who originally had had a cobalt-chrome prosthesis articulating against bone but who later received implants of cobalt-chrome articulating against polyethylene, the tissue levels were elevated as compared with the controls but were lower than those seen in patients with all-cobalt-chrome prostheses. Similarly, intermediate levels (especially of chromium) were found in the one specimen in which cobalt-chrome articulated with bone (specimen 6), but lower levels, approaching those found in controls, were found in the three specimens (9, 10, 11) in which cobalt-chrome articulated with polyethylene.

Conclusion—Both laboratory and clinical studies show that prostheses in which both components are composed of cobalt-chrome release both cobalt and chromium into the tissues adjacent to the prosthesis and that these metals are carried in the blood-stream to be presented to the tissues of the body as a whole. (Nickel is probably also released in very small amounts.) There is some evidence that cobalt-chrome articulating with bone also results in the release of cobalt and chromium and that cobalt-chrome articulating with polyethylene results in the release of little or no metal.

THE DEVELOPMENT OF SKIN SENSITIVITY TO BURIED METAL

It is well known that the skin may become sensitive to certain metals and that such sensitivity can be demonstrated by epicutaneous patch tests in which a positive response is denoted by an eczematous reaction in the skin occurring when a solution of the relevant metal is placed on it. Although epicutaneous tests are conventionally used to demonstrate sensitivity they may in fact give falsely negative results, and intracutaneous tests are possibly more reliable, particularly in the case of trivalent chromium (Fregert and Rorsman 1966a).

TABLE I
CONCENTRATION OF COBALT AND CHROMIUM IN TISSUES ADJACENT TO JOINT PROSTHESES

| Specimen number | Joint | Articulating surfaces of prosthesis | Duration of implantation of prosthesis | Parts per million in tissue | |
|---------------------|-----------------------------|-------------------------------------|--|-----------------------------|----------|
| | | | | Cobalt | Chromium |
| 1* (from Case 9) | Hip | Cobalt-chrome on cobalt-chrome | 2 years | 23.0 | 88.0 |
| 2* (from Case 1) | Hip (right) Hip (left) | Cobalt-chrome on cobalt-chrome | 20 months | 26.0 | 32.0 |
| 3* (from Case 1) | | Cobalt-chrome on cobalt-chrome | 13 months | 24.0 | 12.0 |
| 4 | Knee | Cobalt-chrome on cobalt-chrome | 4 years | 24.0 | 103.0 |
| 5 | Knee | Cobalt-chrome on cobalt-chrome | 1 year | 14.0 | 39.0 |
| 6 | Hip | Cobalt-chrome on bone | 14 years | 1.4 | 8.8 |
| 7 | Knee | Cobalt-chrome on polyethylene† | 18 months† | 4.8 | 4.0 |
| 8* (from Case 4) | Knee | Cobalt-chrome on polyethylene‡ | 2 years‡ | 7.1 | 9.0 |
| 9 | Knee | Cobalt-chrome on polyethylene | 15 months | 2.2 | 2.0 |
| 10 } | Knee (right) Knee (left) | Cobalt-chrome on polyethylene | 18 months | 0.6 | 0.7 |
| 11 } | | Cobalt-chrome on polyethylene | 2 months | 0.08 | 0.4 |
| Control 1 | — | — | — | 0.004 | 0.1 |
| Control 2 | — | — | — | 0.05 | 0.4 |

* Positive skin sensitivity to cobalt.

† Previous cobalt-chrome on bone prosthesis for three years.

‡ Previous cobalt-chrome on bone prosthesis for four years.

Specimens 4–11 were analysed by neutron activation analysis.

Specimens 1–3 were analysed by atomic absorption spectrophotometry.

Cobalt, chromium and nickel are capable of exciting skin sensitivity. For all three elements the readiness with which sensitivity can be induced and demonstrated depends upon the solubility of the element in the form presented to the tissue, and thus upon the nature of the anion when the element is presented as a salt or upon the nature of the alloy when it is presented as the metal (Fregert and Rorsman 1966*a, b*). In the case of chromium, the valency is also relevant (Fregert and Rorsman 1964).

The incidence of skin sensibility to cobalt, chromium and nickel in the general population is unknown, but Fregert and Rorsman 1966*b*, studying a group of 5,416 patients suspected of having contact dermatitis, found an incidence of epicutaneous sensitivity in women to nickel of 2.5 per cent, to cobalt of 1.7 per cent and to chromium of 0.8 per cent. In contrast, men displayed an incidence of sensitivity to chromium of 3.8 per cent, to cobalt of 1.6 per cent and to nickel of 0.9 per cent. This difference is probably due to occupational exposure to more chromium than nickel in males.

We can find no mention in the literature of sensitivity reactions to metals occurring in deep tissues, but skin sensitivity provoked by a deep metal implant has been recognised. Thus Laugier and Fousseureau (1966) described four cases in which dermatitis had developed in patients who had had stainless steel plates or pins inserted. Brendlinger and Tarsitano (1970) reported a case of dermatitis due to sensitivity to a cobalt-chrome denture, and McKenzie, Aitken and Risdill-Smith (1967) a case of urticaria following the insertion of a cobalt-chrome nail for a femoral fracture.

A CLINICAL STUDY OF METAL SENSITIVITY IN PATIENTS WITH COBALT-CHROME PROSTHESES

In the light of the facts that 1) cobalt and chromium appear to be released when cobalt-chrome alloy is rubbed against itself, and 2) that tissue sensitivity to cobalt and chromium is

recognised in other contexts, it seemed to us reasonable to seek cobalt or chromium tissue sensitivity in patients in whom an appropriate prosthetic combination was in use.

Material and methods—Since June 1972 we have performed epicutaneous skin sensitivity tests to cobalt, chromium and, with three exceptions, to nickel upon every patient known to us having a loose uninfected prosthesis composed in part or entirely of cobalt-chrome. We have performed similar tests upon patients attending for routine follow-up appointments two or more years after hip replacement with McKee-Farrar prosthesis in whom the prosthesis was not loose. Studies upon patients having stainless steel prostheses are in progress but are too few in number to be reported here.

Skin sensitivity tests—Solutions of 2 per cent cobalt chloride, 2 per cent chromium sulphate and 2 per cent nickel sulphate are applied to the skin for forty-eight hours. The results are read at forty-eight hours, an eczematous reaction being regarded as a positive result, and an eczematous reaction with induration being regarded as a strongly positive result. It is important to appreciate that by this method sensitivity is sought to the metal in a soluble form, not in its insoluble form as the parent alloy.

Results—The patients examined fell into five groups as follows: 1) Seven patients (eight hips) with loose McKee-Farrar prostheses (cobalt-chrome on cobalt-chrome). 2) One patient with a loose Dee elbow prosthesis (cobalt-chrome on cobalt-chrome). 3) One patient both of whose knees had been unsuccessfully replaced with cobalt-chrome MacIntosh and later Freeman-Swanson prostheses. In these nine patients sensitivity tests were positive—seven to cobalt, one to cobalt and nickel and one to chromium. 4) Five further patients with loose McKee-Farrar or Ring prostheses (cobalt-chrome on cobalt-chrome). Of these five patients, loosening in one with a McKee-Farrar prosthesis was attributed to coincident Paget's disease combined with a possible fault in the stem of the prosthesis. In one patient with an uncemented Ring prosthesis and in three patients with cemented McKee-Farrar prostheses there was no apparent reason for loosening. (The patient with a Ring prosthesis had already been reported upon in a different context (Miller 1972).) 5) Twenty-four patients with normally functioning, securely fixed McKee-Farrar prostheses inserted two years or more previously. In these twenty-nine patients all sensitivity tests were negative.

TABLE II
RESULTS OF SKIN SENSITIVITY TESTS TO COBALT-CHROME AND NICKEL IN THIRTY-NINE PATIENTS WITH UNINFECTED COBALT-CHROME PROSTHESES

| | | Skin | |
|------------|-----------------|-------------------|-------------|
| | | Sensitive | Insensitive |
| Prosthesis | Loose . . . | 9 (11 prostheses) | 5 |
| | Not loose . . . | 0 | 24 |

In those cases in which the prostheses were loose (Groups 1–4) there was no evidence of sepsis, no history of trauma, and no reason to suspect technical failure.

These findings are summarised in Tables II and III. Five typical case histories from Groups 1–3 are as follows.

CASE REPORTS

Case 1—A woman aged fifty-three was first seen in 1970 with osteoarthritis of both hips. In March 1971 the right hip and in June 1971 the left hip were replaced by McKee-Farrar prostheses (Fig. 1). She did well until December 1971 when she complained of pain in the right hip. Radiographs did not show any abnormality at that time, but in April 1972 she complained of severe pain in the left thigh and radiographs revealed that the left acetabular component was loose and that there was thinning and fragmentation of the acetabular wall (Fig. 2).

TABLE III
A SUMMARY OF THE CLINICAL FEATURES FOR THE NINE METAL SENSITIVE PATIENTS REPORTED IN THE STUDY

| Case number | Sex | Age | Diagnosis | Type of prosthesis* | Date prosthesis implanted | Date of onset of pain or loosening | Skin sensitive to cobalt-chrome-nickel | Date of sensitivity test | Date prosthesis removed |
|-------------|--------|-----|----------------------|--------------------------------------|---------------------------|-------------------------------------|--|--------------------------|-------------------------|
| 1 (right) | Female | 53 | Osteoarthritis | McKee-Farrar | 3/71 | 9/72 | Cobalt | 7/72 | 11/72 |
| 1 (left) | Female | 53 | Osteoarthritis | McKee-Farrar | 6/71 | 4/72 | Cobalt | 7/72 | 7/72 |
| 2 | Male | 68 | Rheumatoid arthritis | Dee | 1/72 | 10/72 | Cobalt | 12/72 | 10/72 |
| 3 | Female | 75 | Osteoarthritis | McKee-Farrar | 4/69 | 3/70 | Nickel, cobalt | 1/73 | 6/70 |
| 4 (right) | Female | 70 | Rheumatoid arthritis | (1) MacIntosh (2) Freeman-Swanson | (1) 8/66 (2) 6/70 | (1) 1/70 (2) 11/70 | Cobalt | 6/72 | 11/72 |
| 4 (left) | Female | 70 | Rheumatoid arthritis | (1) MacIntosh (2) Freeman-Swanson | (1) 2/67 (2) 11/70 | (1) 1/70 (2) Approximately 11/71 | Cobalt | 6/72 | Not removed |
| 5 | Female | 25 | Still's disease | McKee-Farrar | 3/70 | 4/72 | Cobalt | 1/73 | 5/72 |
| 6 | Female | 76 | Osteoarthritis | McKee-Farrar | 9/70 | 11/71 | Cobalt | 1/73 | 11/71 |
| 7 | Female | 73 | Osteoarthritis | McKee-Farrar | 6/70 | 10/70 | Cobalt | 5/73 | 8/72 |
| 8 | Female | 63 | Rheumatoid arthritis | McKee-Farrar | 9/68 | 3/70 | Chrome | 10/72 | 10/72 |
| 9 | Female | 71 | Osteoarthritis | McKee-Farrar | 2/71 | 3/73 | Cobalt | 3/73 | 4/73 |

*McKee-Farrar and Dee prostheses are composed of cobalt-chrome articulating with cobalt-chrome, the MacIntosh prosthesis of cobalt-chrome articulating with bone, and the Freeman-Swanson prosthesis of cobalt-chrome articulating with polyethylene.



FIG. 1

Case 1—After bilateral total hip replacement for osteoarthritis (March and June 1971).



FIG. 2



FIG. 3

Case 1. Figure 2—The appearance in July 1972. The left acetabular wall is thin and fragmented and the cup is loose. Figure 3—The left arm forty-eight hours after the application of a solution of cobalt chloride in strengths of 1, 2 and 5 per cent. There was no reaction to solutions of chromium sulphate or nickel chloride nor to the two components of the cement used for fixation.

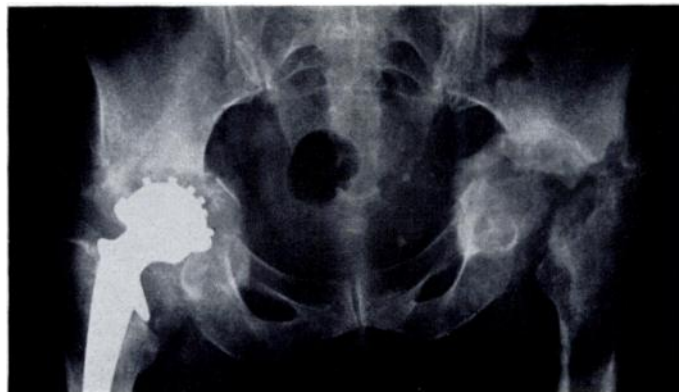


FIG. 4

Case 1—November 1972. The right hip shows changes similar to those previously observed in the left. The acetabular wall of the left hip is beginning to reform.

The acetabular appearance did not improve with bed rest and traction and in June 1972 skin sensitivity tests were carried out to cobalt, chromium and nickel. She was found to be insensitive to chromium and nickel but strongly sensitive to cobalt on two occasions (Fig. 3).

In July 1972 the prosthesis was removed from the left hip. At operation the joint was found to contain thin straw-coloured fluid under tension and large quantities of grey pultaceous material which was sterile on culture. The acetabular component was loose at the bone-cement junction and the acetabular wall was paper thin, consisting only of scar and granulation tissue containing a few flakes of necrotic bone; the chemical analysis of the material removed is shown in Table I.

By September 1972 pain in the right thigh had become severe and radiographs showed a fracture of the acetabulum. By November, multiple fractures had developed with some protrusion, the appearances being very similar to those noted previously on the left side (Fig. 4). Further patch tests confirmed a strong sensitivity to cobalt with negative reactions to chromium and nickel. In November 1972 the prosthesis was removed from the right hip and the findings and chemical analysis were exactly similar to those found in the left. Culture was again sterile, and since operation there has been no discharge or other manifestation of infection in either hip. In early February 1973 patch tests were repeated and cobalt sensitivity was again demonstrated.



FIG. 5



FIG. 6

Case 2. Figure 5—Dee elbow prosthesis immediately after insertion. Figure 6—The elbow ten months later. Bone loss and fracture have resulted in loosening of the prosthesis and disorganisation of the arthroplasty.

Case 2—A man aged sixty-eight presented in June 1971 with rheumatoid arthritis affecting the left elbow. In January 1972 total replacement of the elbow with a Dee prosthesis was carried out (Fig. 5). The initial clinical result was satisfactory, but by October 1972 the prosthesis had become loose and painful and had to be removed. Radiographs at that time showed fragmentation of bone and separation of the prosthesis (Fig. 6). At operation the synovium was found to be thickened and velvety and the joint space was occupied by pultaceous material. Both components of the prosthesis were loose and the ulnar component had eroded through the full thickness of the anterior cortex of the ulna. In December 1972 patch tests were carried out to cobalt and chromium, and he was found to be sensitive to cobalt.

Case 3—A woman aged seventy-five underwent right total hip replacement for osteoarthritis in April 1969, a McKee-Farrar prosthesis being used. She remained well until March 1970, when pain recurred and radiographs showed acetabular fractures with loosening of the acetabular component (Fig. 7). In June 1970 the prosthesis was removed and at operation it was noted that the floor of the acetabulum was in four separate fragments and was paper thin. Culture of the wound was sterile and the post-operative course was uneventful, there being no evidence of infection. In January 1973 patch tests were carried out and she was found to be slightly sensitive to chromium but strongly sensitive to cobalt and nickel. A history of allergies taken at this time revealed that five years previously she had had to stop using a watch strap, the composition of which was unknown, because of a rash.

Case 4—A woman aged seventy was first diagnosed as having rheumatoid arthritis in 1943. In 1966 a MacIntosh arthroplasty using cobalt-chrome prostheses was carried out on the right knee (Fig. 8) with a similar operation on the left knee in 1967. By January 1970 both knees had become so unstable and painful that the patient was unable to walk. Radiographs showed gross bony collapse of the femoral condyles in both knees with dislocation of the prostheses (Fig. 9), and although no evidence of this was sought at this time, it is now suggested that this was due to cobalt sensitivity.

In June 1970 the implant in the right knee was replaced by a Freeman-Swanson total knee prosthesis, in which a cobalt-chrome femoral component articulates with high density polyethylene (Fig. 10). The early functional result was satisfactory, and a similar operation was performed on the left side in November 1970. Over the following two years progressive osteolysis occurred at the distal

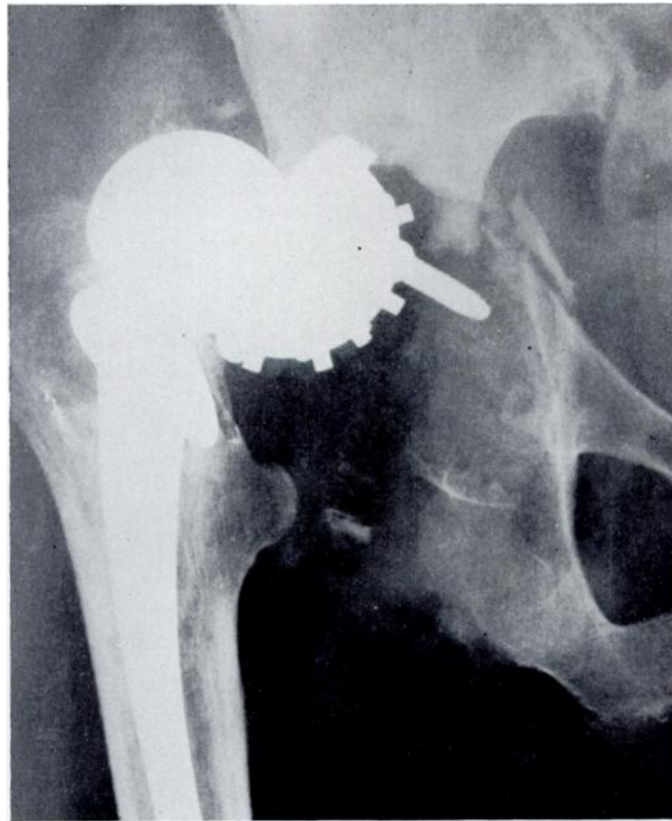


FIG. 7

Case 3—Eleven months after the insertion of a McKee-Farrar prosthesis for osteoarthritis. The acetabular wall is thin and fragmented and the cup has separated. One of the metal screws used for cement fixation is lying in the joint.

end of both femora and both femoral prostheses became loose (Fig. 11). In June 1972 a sterile fistula developed on the right side and was found to extend to one of the two cobalt-chrome staples at that time used to secure the tibial prosthesis; the staples were removed and the wound resutured, and at this stage patch tests to cobalt and chromium were carried out; the patient was found to be sensitive to cobalt. The fistula recurred and in November 1972 the prosthesis was removed from the right knee. It was found to be enclosed in a dense fibrous capsule containing an effusion under tension. Culture was again sterile.

Following this procedure the patient consented to the subcutaneous injection of: 1) cobalt aluminate (a moderately insoluble cobalt salt) suspended in 1.0 per cent carboxymethyl-cellulose, 2) cobalt-chrome wear particles (obtained in the laboratory by running an all-cobalt-chrome prosthesis in a joint simulator) suspended in 1 per cent carboxymethyl-cellulose, and 3) carboxymethyl-cellulose alone. The three injections were made into separate sites and the tissues at the site of injection were removed for histological study twelve weeks after injection.

Case 5—A woman aged seventy-seven had a total hip replacement for osteoarthritis using a McKee-Farrar prosthesis, in February 1972 (Fig. 12). She remained free from pain with a flexion range of 80 degrees, until March 1973 when she developed pain on weight-bearing which rapidly became severe, and in April radiographs showed fragmentation, thinning, and central protrusion of the acetabulum

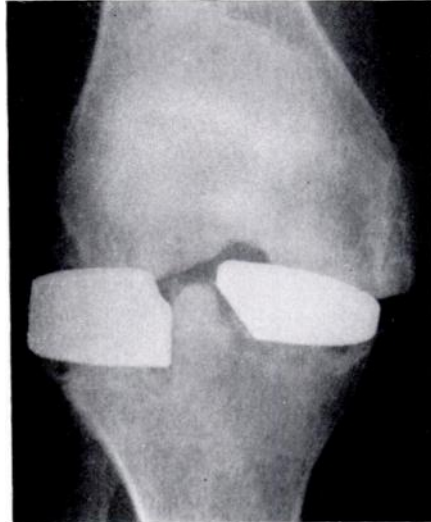


FIG. 8

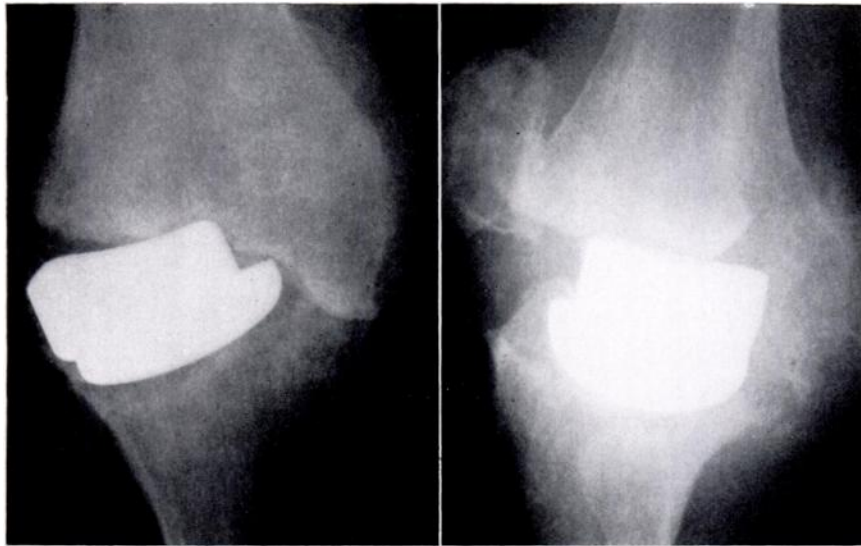


FIG. 9

Case 4. Figure 8—The right knee ten months after MacIntosh arthroplasty using cobalt-chrome-nickel prostheses. There is a suggestion of osteolysis in the tibia adjacent to the prostheses. Figure 9—The right knee four years after MacIntosh arthroplasty. The gross disorganisation of the knee suggests in retrospect that the patient may by this time have been cobalt-sensitive.

(Fig. 13). On patch testing she was found to be insensitive to chromium and nickel, but strongly sensitive to cobalt.

At operation in April 1973 the joint was found to contain grey pultaceous material sterile on culture, and the acetabular floor was fragmented and paper-thin. The material removed from the hip joint contained twenty-three parts per million of cobalt and eighty-eight parts per million of chromium.

Conclusion—Although these findings cannot usefully be analysed statistically, they strongly suggest that cobalt, chromium and nickel can produce skin sensitivity if the element reaches the skin through the bloodstream from an implanted prosthesis, just as it can when applied

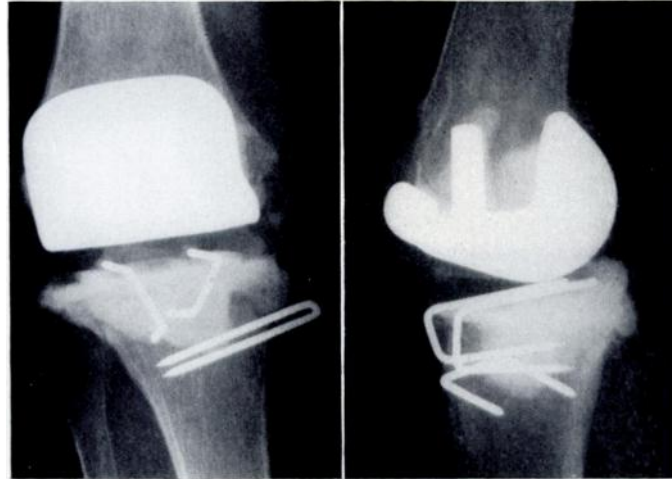


FIG. 10

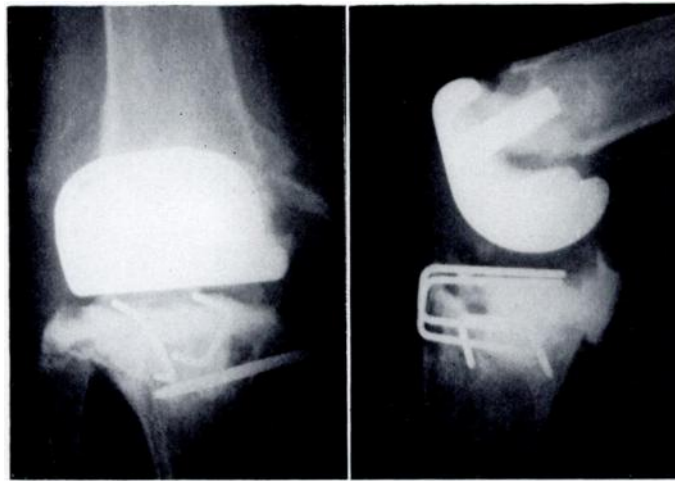


FIG. 11

Case 4. Figure 10—The right knee four months after conversion to Freeman-Swanson arthroplasty. Figure 11—The right knee two years after Freeman-Swanson arthroplasty. Osteolysis has occurred in the distal femur resulting in loosening of the cobalt-chrome-nickel femoral prosthesis and around the cobalt-chrome-nickel staples that at this time were used to secure the tibial prosthesis and to tighten the medial collateral ligament.

directly to the skin. Our findings also suggest a strong association between metal sensitivity and loosening of prostheses composed entirely of cobalt-chrome alloy.

The one case of loosening in a prosthesis composed of cobalt-chrome alloy articulating with polyethylene is hard to interpret since there exists the possibility that the patient had previously been sensitised by a cobalt-chrome prosthesis articulating with bone.

THE HISTOPATHOLOGY OF TISSUES FROM METAL-SENSITIVE PATIENTS

Material—Bone and soft tissue adjacent to prostheses were available from seven patients exhibiting skin sensitivity to cobalt. The histopathological findings are summarised in Table IV.

Results—In three cases (1, 2, 9) no viable material was available for examination, and the tissue examined comprised only soft pultaceous material consisting of infarcted connective tissues, abundant amorphous debris, cellular debris, fibrin and fragments of necrotic bone (Fig. 14). However, it was possible to make an assessment of the vascular changes in the necrotic connective tissues in these cases using phase-contrast microscopy.

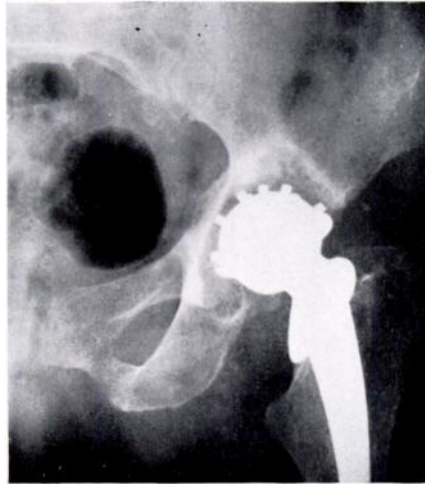


FIG. 12

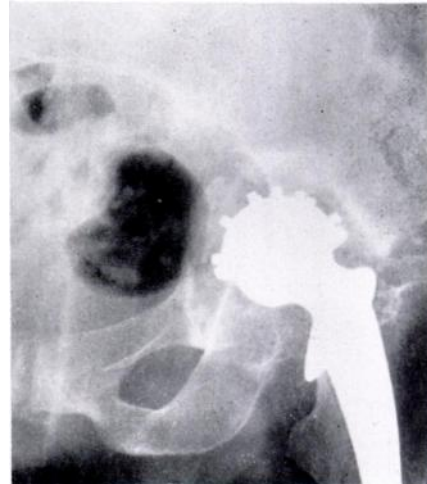


FIG. 13

Case 5. Figure 12—In February 1971, after the insertion of a McKee-Farrar prosthesis for osteoarthritis. Figure 13—In March 1973 the patient developed pain in the left hip and radiographs in April showed protrusion of the acetabulum with fragmentation and thinning of the acetabular wall.

In the four cases (3, 4, 7, 10) in which some viable tissue was available for examination, the tissues lining the joint cavity were composed of either areas of granulation tissue merging with surface fibrinoid material or infarcted soft tissues merging with amorphous debris containing fragments of dead bone. In the connective tissues underlying the surface layer, and within marrow spaces of trabecular bone around the stem of the prosthesis in some cases, were large and small sheets of macrophages and multinucleate cells (Fig. 15) containing abundant rod-shaped bodies up to 3 μm in length which exhibited strong positive birefringence when viewed between crossed polaroids with a first-order red compensator in position. Similar birefringent material was present in small quantities within the soft pultaceous material lying within the joint cavity in all cases, in the fibrinoid material lying on the joint lining, and within the thin film of fibrin which usually covered the articulating surfaces of the prosthesis. There was a variable degree of necrosis of the soft tissue and bone which appeared to be directly related to the severity and extent of obliterative changes in the vessels supplying these tissues. In all cases, some degree of fibrous intimal proliferation, fibrinoid necrosis, and thrombosis of arterioles was observed within and at the margins of infarcted tissues (Figs. 16 and 17). In places, bone adjacent to the components of the prosthesis was dead or was undergoing replacement by granulation tissue and mature fibrous tissue. In no case was there any evidence of infection of bone or connective tissue.

The patient in Case 4 had been injected subcutaneously with 1) cobalt aluminate suspended in 1 per cent carboxymethyl-cellulose; 2) cobalt-chrome wear particles (obtained in the

TABLE IV
SUMMARY OF HISTOPATHOLOGICAL FINDINGS IN BONE AND SOFT TISSUE ADJOINING COBALT-CHROME PROSTHESES
IN PATIENTS SHOWING SKIN SENSITIVITY TO COBALT

| Case number | Tissue necrosis | | Arteriolar changes | | | Tissue reaction | |
|-------------|-----------------|-------------|-------------------------------|--------------------|------------|-----------------------------|-----------------------|
| | Bone | Soft tissue | Fibrous intimal proliferation | Fibrinoid necrosis | Thrombosis | Macrophages and giant cells | Birefringent material |
| 1 | ++++ | ++++ | ++ | + | + | * | ++ |
| 2 | ++ | ++++ | ++++ | ++ | +++ | * | +++ |
| 3 | ++++ | ++++ | ++++ | + | +++ | +++ | ++++ |
| 4 | ++ | +++ | ++++ | ++++ | +++ | ++ | ++ |
| 7 | +++ | ++++ | ++++ | +++ | +++ | +++ | ++ |
| 10 | +++ | +++ | +++ | + | + | ++++ | ++++ |

+ = very small amount. ++ = small amount. +++ = moderate amount. ++++ = great amount.
* Assessment not possible owing to tissue necrosis.

laboratory by running an all-cobalt-chrome prosthesis in a joint simulator) suspended in 1 per cent carboxymethyl-cellulose; and 3) 1 per cent carboxymethyl-cellulose alone. The three separate injection sites were biopsied twelve weeks after injection. No histological reaction was seen at the sites of injection of cobalt-chrome particles or the suspending medium, 1 per cent carboxymethyl-cellulose. However, at the site where cobalt aluminate had been injected there was a prominent granulomatous collection of cells consisting of macrophages and multinucleate giant cells, with a surrounding zone of lymphocytes and occasional plasma cells (Fig. 18). Some of the macrophages and giant cells contained rod-shaped birefringent material (Fig. 19) which was identical in appearance to that seen in the joint material in all the cases in this study. An adjacent blood vessel had a surrounding aggregate of lymphocytes and macrophages (Fig. 18) and some of these macrophages also contained birefringent material. **Conclusion**—The histological findings in the tissues adjacent to the prostheses indicated that necrosis of bone and soft tissue had taken place following obliterative changes in their vascular supply. The proliferation of macrophages and multinucleate cells containing birefringent material suggested a tissue reaction to the shedding of metal from the surfaces of the prosthesis; and this view is supported by our findings of high concentrations of cobalt and chrome in these tissues (Table I), and the presence of a similar tissue reaction to injected cobalt in the skin of one of the patients (Case 4).

We conclude that the release from a prosthesis of metal ions to which the tissues are sensitive may produce changes in local blood vessels leading to interruption of the blood supply and subsequent necrosis of bone and soft tissues. The dead bone appears to undergo fibrous replacement and possibly fatigue fracture so that a combination of osteolysis and fracture formation is seen radiologically in these patients.

It is of interest that we have hitherto been unable to find evidence of fibrinoid necrosis of arterioles in the tissues around the prostheses removed from patients not exhibiting skin sensitivity to any of the metallic constituents, despite histological evidence of necrosis of bone and soft tissue in some of these cases.

DISCUSSION

The observations reported in this paper suggest that the following series of events may occur after the replacement of a joint with a metal prosthesis. If cobalt-chrome alloy is rubbed against itself under load in the body, the metal elements of which the alloy is composed are

released into the surrounding tissues. (Fragmentary findings, reported here or in preparation, suggest that smaller, but possibly significant, quantities of metal are also released when cobalt-chrome or stainless steel are rubbed against bone, or against polyethylene.)

The clinical findings show that certain patients are sensitive to cobalt, and less frequently to chromium or nickel, after the implantation of a prosthesis in which cobalt-chrome articulates with cobalt-chrome. Our findings do not permit us to distinguish between the possibilities



FIG. 14

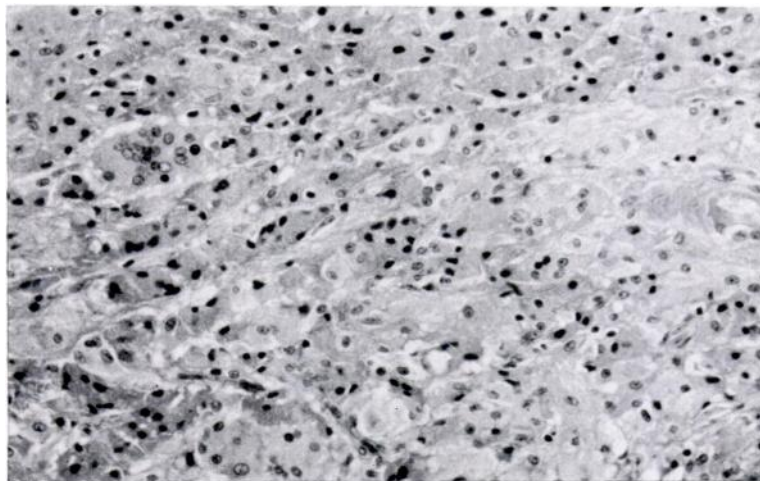


FIG. 15

Case 5. Figure 14—Debris from joint cavity comprising dead tissue, fibrin and large and small fragments of dead bone. (Haematoxylin and eosin, $\times 120$.)
Figure 15—Sheet of macrophages and multinucleate giant cells in marrow space adjacent to stem of prosthesis. (Haematoxylin and eosin, $\times 300$.)

1) that the patients were metal-sensitive before implantation of the prosthesis, or 2) that they became sensitive after implantation; or that one or other sequence of events was common to all cases. The findings in Case 4 suggest that similar sensitivity may exist after the implantation of a prosthesis in which cobalt-chrome articulates with bone, or conceivably with high density polyethylene. We have not yet sought nickel and chromium sensitivity in patients with prostheses composed of stainless steel articulating with bone or polyethylene but clearly this should be done.

Out of the fourteen patients tested in this study with sixteen loose prostheses, eight were found to be sensitive to cobalt, one to chromium and one to nickel.

The incidence of positive sensitivity tests might have been higher if intracutaneous rather than epicutaneous sensitivity tests had been used throughout, but the latter are more acceptable and more convenient. In contrast, of twenty-four patients whose prostheses were not loose,

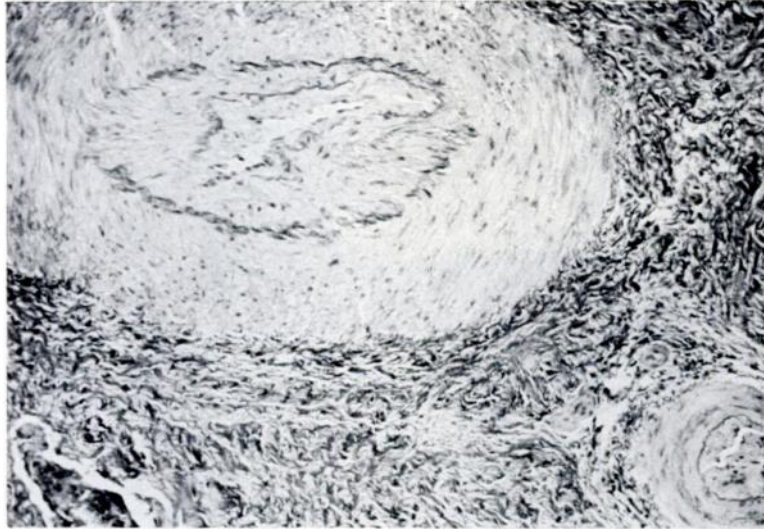


FIG. 16

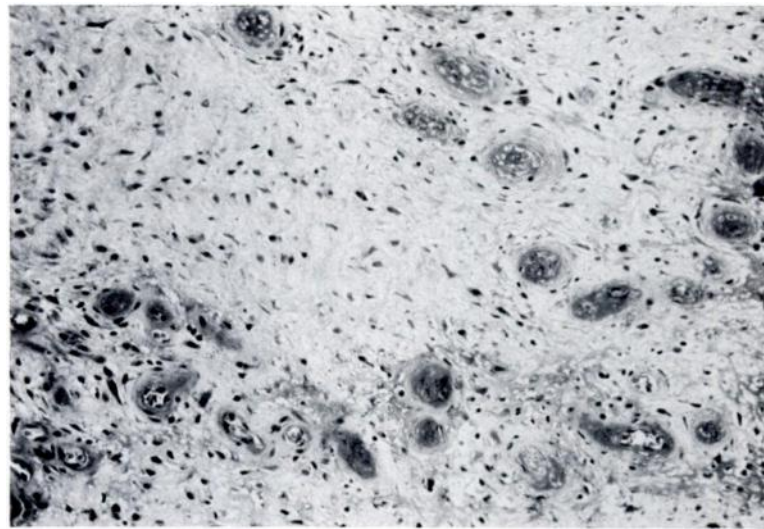


FIG. 17

Case 5. Figure 16—Connective tissue showing obliteration of the lumen of large and small arteries by marked fibrous intimal proliferation. (Elastic-van Gieson, $\times 120$.) Figure 17—Connective tissues showing fibrinoid necrosis of arterioles. (Haematoxylin and eosin, $\times 120$.)

none was sensitive. Since this series is a selected one (we have skin-tested all our recent patients with unexplained loosening of the prosthesis but only some of those without loosening), we can form no estimate of the significance to be attached to this apparent association between metal sensitivity and prosthetic loosening. Nevertheless, the combination of the overall incidence of sensitivity, the fact that every metal-sensitive patient had a loose prosthesis, and

the pathological findings, suggest to us that there exists a significant and causal association between metal sensitivity and loosening.

Pathologically, it appears that if elemental metal continues to be released into the tissues of a patient sensitised to that metal the small vessels in the tissues adjacent to the prosthesis

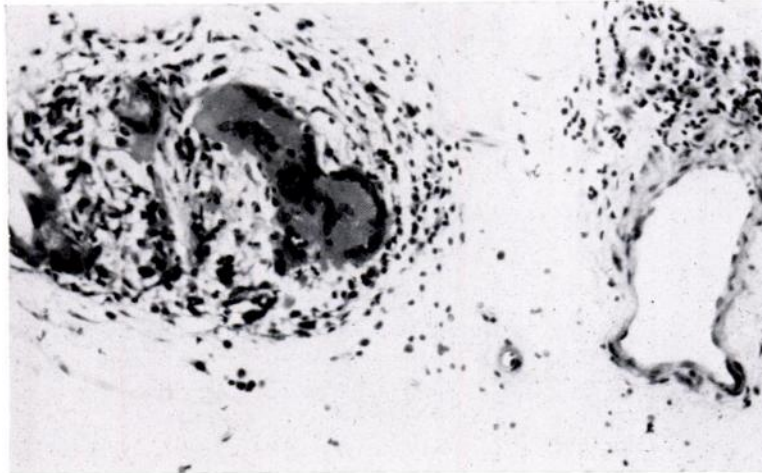


FIG. 18

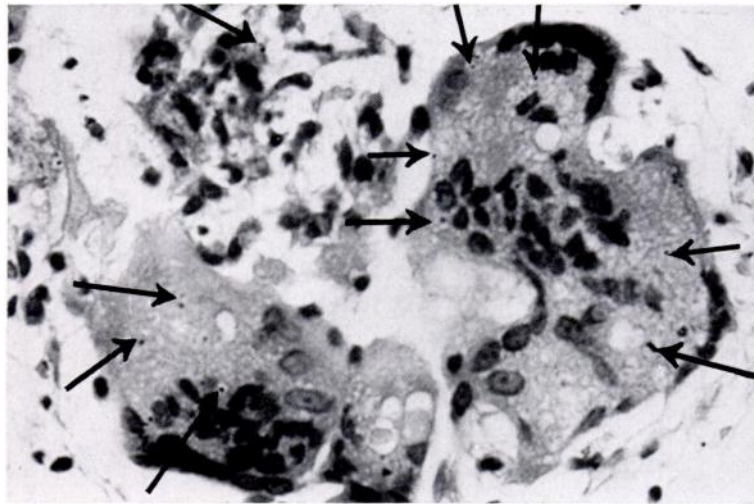


FIG. 19

Case 4. Figure 18—Epithelioid and giant-cell granuloma in subcutaneous tissue from site of injection of cobalt aluminate. Adjacent vessel has an aggregate of lymphocytes and macrophages. (Haematoxylin and eosin, $\times 120$.) Figure 19—Higher magnification of section of granuloma shown in Figure 18 shows particles (arrowed) which are birefringent when viewed by polarised light. (Haematoxylin and eosin, $\times 800$.)

become occluded and the bone dies. The infarcted bone may be replaced by fibrous tissue or may suffer fatigue fracture, and the inevitable result is loosening of the prosthesis.

Once the bond between the acrylic and the bone has failed, the acrylic must move relative to the bone and it seems reasonable to suppose that in so doing the acrylic becomes abraded. It is known from clinical experience with the acrylic Judet prosthesis that abrasion particles of acrylic produce a semi-fluid necrotic mass similar to that seen around the loose, but sterile, cemented total joint replacement prostheses reported in this paper and that this necrotic mass

may infiltrate through the tissues until a sinus forms. We believe that this mechanism, combined with tissue necrosis, was responsible for the production of the pultaceous material seen in our patients.

In summary we believe that some patients become sensitive (or are already sensitive) to one or more of the metals of which a joint prosthesis may be composed and that such sensitivity results in histologically and radiologically demonstrable local bone death and hence prosthetic loosening with the local production of necrotic but initially sterile debris.

PRACTICAL IMPLICATIONS

If we are right in believing that prostheses may become loose following bone necrosis in patients who become sensitive, or who are already sensitive, to one of the metals in the implanted alloy, certain practical implications follow.

First, since the rate of release of cobalt and chromium is much higher from prostheses in which cobalt-chrome alloy articulates with itself, it would be better to use a metal-to-polyethylene combination wherever possible. The use of a metal-to-metal implant is also contra-indicated in view of the fact that the wear particles which it produces have been shown to be carcinogenic in the rat (Heath, Freeman and Swanson 1971). Though we reject cobalt-chrome alloy articulating against itself, no general conclusions can be drawn as to the suitability of this alloy in isolation; there are as yet no grounds for preferring a combination of stainless steel and high density polyethylene to a combination of cobalt-chrome and high density polyethylene. Indeed, the rate of liberation of chromium and nickel from the former appears to be slightly higher in clinical use than the rate of liberation of chromium from the latter (work in progress) and we have reported here one case of chromium sensitivity associated with loosening. Both chromium and nickel are present in stainless steel.

Second, since patients in the general population may be sensitive to nickel, cobalt or chromium, it seems sensible to patch test all patients to these metals before the implantation of an alloy containing any one of these elements. If a patient proves to be sensitive to cobalt the joint should be replaced with stainless steel articulating with polyethylene. A patient sensitive to nickel should have a cobalt-chrome prosthesis composed of one of the cobalt-chrome alloys not containing nickel. Sensitivity to chromium would pose a difficult problem since both cobalt-chrome and stainless steel contain these elements. A practical consideration in this connection is that all prostheses should be manufactured both in stainless steel and cobalt-chrome alloy.

Third, all patients in whom a prosthesis becomes loose, or who develop bone "collapse" adjacent to an implant replacing only one component of a natural joint (such as a femoral head replacement in the hip or tibial condyle replacement in the knee) should be patch tested to the relevant metals. If they are found to be sensitive, the condition can be expected to be progressive and removal of the prosthesis is indicated. Subsequent conversion to total replacement should only be carried out if the tissues are not sensitive to the relevant metals.

Fourth, since in many publications prosthetic loosening with the production of necrotic pultaceous debris around the prosthesis is regarded as being due to infection even though no pathogenic organism is cultured, and since we now suggest that some of these cases may in fact be due to metal sensitivity, the figures now in the literature for the incidence of infection following total joint replacement may have to be revised. It seems possible that necrotic metal-sensitive debris may become secondarily infected so that even in some infected joints the failure may primarily be due to metal sensitivity.

SUMMARY

1. Evidence is presented which suggests that after total joint replacement bone necrosis and consequent loosening of the prosthesis may be due to the development of sensitivity to the metals used.

2. Nine patients, from a total of fourteen with loose prostheses, were found to be metal sensitive by skin-patch testing. In twenty-four patients with intact prostheses no sensitivity was demonstrated.
3. In material from the joints of sensitive patients the metal content was raised.
4. Examination of this material showed necrosis of bone and soft tissue following obliterative changes in the vascular supply.
5. Similar reactions were found following the injection of cobalt into a sensitive patient.
6. The release of metal around a prosthesis is greatest where metal rubs against itself.
7. We conclude that prostheses in which metal articulates with polyethylene should be preferred; that any patient in whom loosening or fragmentation occurs should be patch tested; and that if sensitivity is found the implant should be removed.

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