Histologic, Biochemical, and Ion Analysis of Tissue and Fluids Retrieved During Total Hip Arthroplasty

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Large amounts of metal and polyethylene debris and high ion readings are found in capsule and fibrous membranes of both loose titanium and cobalt–chromium stems. Prostaglandin E_2, interleukin-1, and collagenase levels are elevated when compared to control values with collagenase having the highest and most consistent elevations. Synovial fluid and blood ion readings were elevated in loose cemented and cementless stems made from both materials. Blood ion readings were not elevated in fixed stems. Fixed stems had much less particulate debris in soft tissues. The data showed that failure of most metal hip stems was initially due to a mechanical cause, with high debris and ion counts occurring secondarily in capsule and fibrous membranes. Particulate debris and high ion readings are primarily a focal problem contained by the periprosthetic fibrous connective-tissue encapsulation within the femoral canal and joint capsules. No systemic problems were manifest in any of the patients examined and followed in this study.

Cemented implants have been shown to subside or sink into the fragmented cement column and slowly migrate into the host bone.[9,21] The fragmentation of the cement mantle results in the formation of a large amount of debris in the femoral canal and hip joint.[14,18,20] Cement debris has been implicated in loosening and osteolysis of the cemented hip prosthesis and has been termed "cement disease."[15-17,20] One hope for cementless femoral stems was that in the absence of methylmethacrylate, osteolysis or cement disease would be avoided. Unfortunately, roentgenographic data of failed cementless hip prostheses have demonstrated the osteolytic process in bone. A loose cementless stem will rapidly migrate into the lateral cortex as ambulatory loads shift the stem into a varus position. Harris[10] has termed osteolysis with cementless hip prostheses as "cementless disease." These observations stimulated the question of whether implant particulate debris was the cause of the osteolysis, and if so, whether one metal was at a greater risk for this complication.

Further concern with cementless hip prostheses has been the issue of ion release because of the increased surface area of metal in the porous-coated designs. Agins *et al.*[1] found high ion readings in capsular and fibrous membranes of loose cemented titanium hip prostheses. Those authors suggested that the titanium-bearing surface as well as abrasive corrosion from the loose stem caused high ion readings. The study by Agins *et al.* raised concerns about ion levels in hip arthroplasty (THA) patients and the possible effect ions might have both locally and systemically.

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TABLE 1. Patient Distribution for Ion Study

	Implant	
Fixation Method	*Titanium*	*CoCr*
Fixed Cemented	2	2
Loose Cemented	3	11
Fixed Cementless	5	1
Loose Cementless	19	3

The present study was conducted to grade the amount of particulate debris and determine the ion readings found in tissues surrounding hip prostheses, both cemented and cementless. Periprosthetic tissues surrounding titanium and cobalt-chromium (CoCr) metals were evaluated. A group of patients' tissue was measured for biochemical factors, which are reported to stimulate bone resorption.[8] These findings were correlated to determine the contribution of debris and ions in failed cementless hip prostheses to systemic ion levels recorded in these patients.

MATERIALS AND METHODS

Forty-six patients who had THAs and required a revision were studied. Patient groups were divided by metal type and fixation status of the prosthesis (Table 1). Ten patients who had primary THAs and did not have a medical history of any metal in their bodies were used to establish control values of synovial fluid and hip capsule. International standards of ion levels for blood were used as blood control values.[2,4,24,26] Because biochemistry enzyme levels were done only in the last one-half of the study, a separate group of 12 patients who had primary THA were used as controls for synovial fluid and hip capsule levels of prostaglandin E_2 (PGE_2), interleukin-1 (IL-1), and collagenase. The ion readings were also done in these patients to confirm earlier control values. In addition, serum and blood control values were measured in these 12 patients. All 22 controls had either osteoarthrosis or osteonecrosis of the hip.

Histologic grading for all patients was done on capsular and fibrous membranes using a modification of Mirra *et al.*'s method.[22,23] Grades 0–3 were

TABLE 2. Modified Histologic Grading*

Microscopic Subject	*Grade*	*Definition*
Metal particles at high power (×400)	0	No particulate observed
	1+	1–25 particles
	2+	25–100 metal particles
	3+	101 or more metal particles
Giant cells (multimediated histiocyte) at medium power (×200)	0	No cells
	1+	1–4 cells
	2+	5–10 cells
	3+	11 or more cells
Acute inflammatory cells (polymorphonuclear leukocytes) and mononuclear histocytes at high power (×400)	0	Absent
	1+	1–10 cells
	2+	11–60 cells
	3+	60 or more cells
Polyethylene particles at high power (×400)	0	Absent
	1+	1–15 extracellular particles and/or 1–5 histocytes containing one or more fibers per cell
	2+	16–25 extracellular particles and/or 16–25 histocytes containing one or more fibers per cell
	3+	26 or more extracellular particles and/or 26 or more histocytes containing one or more particles per cell

* Mirra *et al.*[22,23]

assigned to metal, polyethylene, giant cells, and macrophages (AIC) according to the number of particles or cells per high-power field (Table 2).

Independent analysis was done for each area of review and included collecting samples, roentgenographic review, histologic grading, preparation of tissue for ion analysis, and biochemical tissue analysis. Only at the completion of the study were data collated and conclusions determined.

Roentgenograms were evaluated to determine if the stem or cup or both were loose. In addition, the presence or absence of osteolysis was determined. Osteolysis was classified as migratory if it resulted from migration of the stem of 2 mm or more (Figs. 1 and 2), or classified as focal if only a focal area of osteolysis was present with a fixed stem.

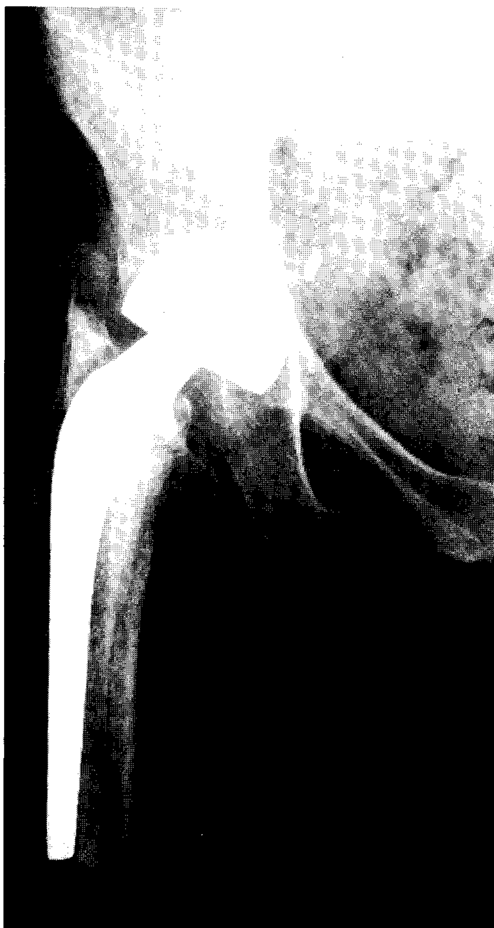


FIG. 1. Roentgenogram shows failed cemented CoCr alloy stem. Varus migration stem with severe osteolysis of lateral cortex.

Migratory osteolysis of the femur almost always occurred in the lateral cortex (from varus tilt of the stem) and anteriorly on the lateral roentgenogram (from posterior rotation of the stem). Focal osteolysis was predominantly lateral near the tip of the stem and posterior in the distal one-half of the stem.

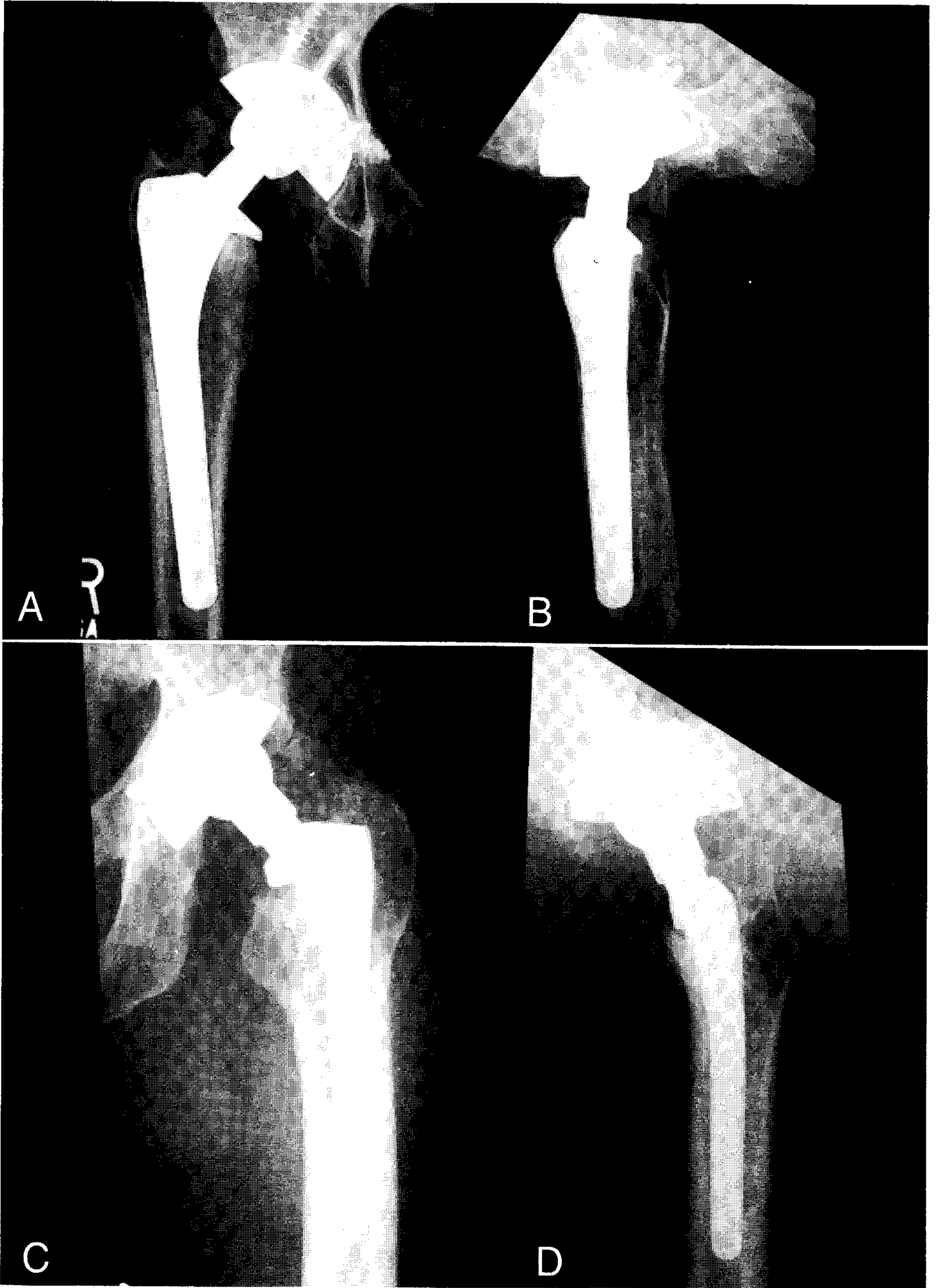
The fixed cemented titanium stems used in the study were Anatomic Porous Replacements (APR; Intermedics Orthopedics, Austin, Texas) and the fixed cemented CoCr stems were HD-2s (Howmedica, Rutherford, New Jersey). The loose cemented titanium stems were two STHs and one Triad (Johnson and Johnson, Braintree, Massachusetts). Loose CoCr stems included one Anatomic Medullary Locking (AML; Depuy, Warsaw, Indiana), two Osteonics (Osteonics, Allandale, New Jersey), and eight Charnley–Müllers (Zimmer, Warsaw, Indiana). Fixed cementless titanium stems were four APR and one Harris–Galante (Zimmer). The fixed cementless CoCr stem was an AML. Loose cementless titanium stems were 13 custom Intermedics designs that were developmental APR stems, and six APR stems. Loose cementless CoCr stems included one AML, one PCA (Howmedica), and one Aufranc–Turner (Howmedica) long stem, which had been used as a press-fit stem.

HISTOLOGIC REVIEW

Capsular and periprosthetic tissues (fibrous membrane) were evaluated for histiocytic cells, giant cells, metal, and polyethylene. Tissue for histologic evaluation was placed in a 10% buffered formalin, stained with hematoxylin and eosin, and viewed by light and polarized microscopy.[13] The complete tissue section was reviewed at ×200 magnification to determine regions of high cellular and debris concentrations. The maximal concentrations were counted using a grid ocular (10 × 10 grid) to improve counting accuracy. Counts were averaged over five fields per section and graded using the modified Mirra *et al.*[22,23] semiquantitative technique (Table 2).

ION READINGS

Trace-element analysis for ion readings was done using a Perkins–Elmer 5100 Heated Graphite Analyzer (Norwalk, Connecticut) atomic absorption spectrophotometer. This device was a Zeeman graphite option and background corrector with autosampler, hollow cathode lamp using Argon purge gas, and pyrolytically coated graphite tubes. Tissue digestion was carried out in a mixture of 77% nitric acids. The acids were certified



FIGS. 2A–2D. Four-year postoperative roentgenograms of cementless titanium alloy stem with migratory osteolysis. (A) Anteroposterior view. (B) Lateral view. Five-year postoperative roentgenograms of cementless titanium alloy stem with focal osteolysis. (C) Anteroposterior view. (D) Lateral view.

Baker Nitric-Acid Ultrix II (Phillipsburg, New Jersey) acids with certified metal ion contents. Acid blanks were run in conjunction with the digestion to isolate contaminants attributable to the acid or digestion vessels.

Ultratrace metal determination was done using stabilized temperature platform furnace technology. A pyrolytically coated graphite tube is placed in the instrument and is conditioned prior to analyzing a sample. This conditioning increases the life of the tube and also removes extraneous material that could affect the accuracy of the first several readings. The instrument was calibrated prior to each run. The calibration curves were generated and reestablished for each run. The calibration may be generated by the instrument by autodilutions of a freshly mixed standard or mixed manually with several standards made immediately prior to a run. No curve contained less than two points, whereas most curves contained four or five points. The mathematic model used to generate the curve was the multipoint or nonlinear model.

The protocol for each sample was as follows. The instrument would automatically zero at the beginning of the run. The first sample to be run was the control blank. If the blank was out of range, the run was interrupted and adjustments were made. Standard reference materials (SRM) were digested and run in tandem with the tissue samples; otherwise, internal quality controls (QC) such as Co, Cr, molybdenum, nickel, aluminum, or vanadium were used. A titanium standard using nitric acid was made for calibration. If the SRM or QC did not fall within an accepted range, the run was stopped, the instrument parameters and standard dilutions were verified, and a new calibration was conducted. This process continued until the QC or the SRM was within an accepted range.

The chromium and nickel determinations used a linear range of calibration, which was prepared fresh for each run. A four-point calibration curve was generated and samples were read directly in their respective units of concentration. Nickel standards were made from certified nickel reference solution. Cr standards were made from certified Cr reference solution. The conversion from micrograms per liter to micrograms per gram was made based on volume of digested sample in milliliters and weight in grams. In each case, the QC consisted of a standard reference material that is found in fish or internal QCs. The nickel samples required special handling because of easy contamination. This procedure involved using acid-leached disposable cups, a special (dedicated pair) set of contact rings, dedicated glassware, and pyrolytic tubes.

Each sample was analyzed twice and the results were evaluated to assure that carryover was not causing the second high results. If two sequential samples had very high values, they were separated and reanalyzed to assure that carryover was not causing the second high result. After analyzing the samples, the results were averaged. If the relative standard deviation between the results was greater than 15%, the sample was evaluated again.

Biochemistry

Tissue specimens obtained at the time of surgery were immersed in Ringer's solution. The specimens were rinsed in saline and homogenized with Hank's buffered salt solution. The homogenate was stored in eppendorf tubes at −70°. Synovial fluid samples were centrifuged and smears were made from the pellet. The rest of the fluid was stored at −70° for eventual measurement of IL-1, PGE_2, collagenase, and enzyme-linked immunosorbent assay (ELISA).

The technique for the assays was as follows. PGE_2 was assayed based on the competition between free PGE_2 and the enzyme-linked PGE_2 tracer for limited specific antibody binding sites. This anti-PGE_2 was linked with the enzyme acetylcholinesterase (AChe). The microwells were coated with mouse monoclonal antirabbit IgG. Fifty microliters of each homogenized sample was added to the coated wells together with the AChe tracer and anti-PGE_2, and covered and incubated at 4° overnight. The next day, the wells were washed and developed with Ellman's reagent (Cayman Chemical, Ann Arbor, Michigan). A yellow substance was formed. The density of the color was measured photometrically on an ELISA reader at 412 nm. A standard curve was plotted and the optical density (OD) readings of the samples were converted to give concentrations of PGE_2 that were present in the sample. Total activity of the tracer, nonspecific binding, and maximum binding were also determined. All samples were run in duplicate. Control wells had buffer in them.

IL-1 was assayed using an ELISA method by the dual antibody immunometric sandwich method. The microliter plate was coated with mouse monoclonal antibody specific for human IL-1 (Endogn, Boston, Massachusetts). This is an alkaline phosphatase conjugated antibody method. In the final step, the wells were incubated with paranitrophenyl phosphate to develop color. The plate was

read at six 15-minute intervals on a standard ELISA reader at 405 nm. Standards were run similarly and a graph was plotted. The OD readings from the samples were read from this standard curve. All controls, standards, and samples were run in duplicate. Control wells had buffer in them.

The collagenase levels were measured by an ELISA method. Microliter plates were coated with sheep anticollagenase antibody (the binding site) at a concentration of 5 μg/ml in 0.1 M sodium bicarbonate, pH 9.6. Standards were prepared from collagenase Type 1A (Sigma, St. Louis, Missouri). Samples reacted similarly to the above two techniques. For development of the color reaction, antisheep IgG alkaline phosphatase conjugate was applied at a dilution of 1:1000 in phosphate-buffered saline-Tween buffer. The plate was read in a standard ELISA reader at 405 nm. A standard curve was plotted and OD readings from the samples were read from this graph and converted to milligrams per milliliter. All standards, controls, and samples were run in duplicate. Control wells had buffer in them.

RESULTS

Roentgenograms were evaluated for fixation and osteolysis. Results of fixation are listed in Table 1. Of the loose CoCr cemented stems, five had migratory osteolysis (Fig. 1). Six of the loose cementless titanium stems had migratory osteolysis, all of which were primary THAs (Fig. 2). The migratory osteolysis in all six was secondary to poor distal fill of the stem in the anteroposterior or lateral roentgenogram or both. Distal toggle occurs with poor fill, and the mechanical instability induces osteolysis by movement and migration of the stem. There were six of the fixed cementless titanium stems. Three were revised for chronic dislocation, one for disassembly of the modular polyethylene, one for a loose cemented cup, and one for pain from a leg lengthening at the time of surgery. Three additional fixed titanium stems had focal osteolysis. Two of these three demonstrated excessive wear of polyethylene secondary to the titanium femoral head. One fixed CoCr stem was revised for pain (Fig. 3). Loose cemented CoCr stems had a range of one to 12 years to failure, whereas loose cemented and cementless titanium stems had a range of one to five years.

Histologic Analysis

The histologic analysis showed that patients with fixed cemented CoCr and titanium alloy implants had metal debris present in their capsules averaging Grade 2+ for CoCr implants and Grade 1+ for titanium. Patient tissues in this classification rarely showed the presence of polyethylene debris. The cell response for both groups was similar (AIC = Grade 1+ and giant cell = 0).

In contrast, the retrieval tissue from loose cemented stems averaged Grade 2+ for all categories (metal, polyethylene, and cells) for CoCr tissues and Grade 1+ for all categories of the titanium tissues. A careful review of the ion levels in these patients did not suggest any correlation between ion readings and histology grade for metal or polyethylene particulate.

The fixed cementless stems of both material types showed that the titanium alloy implants had readings that were one grade lower (Grade 1+ metal and Grade 0 polyethylene) when compared to the exposed CoCr tissue (Grade 2+ metal and Grade 1+ polyethylene). Although no clear trend was established, the ion readings for the tissue from fixed cementless stems were higher than those for fixed cemented stems for both materials.

The tissue analyzed in loose cementless stems showed the presence of higher levels of metal debris for both metal types. Polyethylene wear particulate was seen more commonly in the CoCr tissues, which may have been a result of their longer implantation time. CoCr tissues averaged two grades higher than titanium tissues for the presence of polyethylene debris. Histologic grade levels for metal were similar although the titanium tended to have one grade higher for

metal particulate. Overall, the presence of giant cells and mononuclear histiocytes was seen in all tissues surrounding loose implants at Grade 2+ in capsular and Grade 3+ in fibrous membrane.

The only observable difference in the tissues retrieved in migratory and focal osteolysis was the higher grades for all categories. It was common for the tissues to have Grade 3+ for all three categories (metal, polyethylene, and cells). The polyethylene particulate remains insignificant when compared to the amount of metal debris present in these tissues.

Metal and polyethylene particulate could be seen within the cytoplasmic matrix of the mononuclear histocytes and giant cells. The metal debris within cells ranged in size from 0.5 to 11 μm in maximum length. Intracellular polyethylene particles ranged in particle size from 1 to 30 μm in maximum length, with particulate over 10 μm seen mostly in multinucleated giant cells. Although particles of metal ranging up to 50 μm in length and 100–550 μm in length were observed, these particles appeared entangled and captured in the periprosthetic fibrous connective-tissue network.

In all categories, the capsular tissue had an average of one or more grades less than the femoral membrane when present. A similar observation held true for ion analysis. The ion readings were significantly higher in the femoral membrane ($p \leq 0.05$) than in the capsular tissues. This is in agreement with Brien *et al.*[3]

Ion Readings

The results of ion readings were tabulated according to the groups listed in Table 1. Only one fixed CoCr stem was studied and this is shown in Figure 3. The other groups are listed in Tables 3, 4, and 5. Statistical significance ($p < 0.05$) is shown against control values. Control values are listed for titanium alloy in Table 6 and for CoCr alloy in Table 7.

Loose cementless titanium alloy stems had statistical elevation of aluminum, titanium, and vanadium ions in capsular tissue and titanium and vanadium in synovial fluid. In blood, only titanium was statistically increased compared to control values. If stems with migratory osteolysis were isolated, all three ions were statistically increased in synovial fluid, only titanium and vanadium in capsular tissue, and none in blood. Focal osteolysis had statistical elevation only in capsular tissue and this was of all three titanium alloy ions. In fixed titanium cementless stems, aluminum and titanium were increased in synovial fluid and capsule. No blood ion elevation was found in either cementless or cemented fixed stems. Ion readings were not correlated with the percentage of metal (titanium 90%, aluminum 6%, and vanadium 4%) in titanium alloy. These results suggest that particulate debris and high

TABLE 3. Titanium Cementless Fixed Implants

	Implants (μg/l)		
Ion Readings	*Ti*	*Al*	*Va*
SF	556 ± 882*	654 ± 743*	62 ± 95
CAP	1540 ± 1238*	2053 ± 1064*	288 ± 133
FM	20813 ± 26467	10581 ± 9764	1027 ± 702
Blood	67 ± 62	218 ± 233	23 ± 31

Ti, titanium; Al, aluminum; Va, vanadium; SF, synovial fluid; CAP, capsule; FM, fibrous membrane.
* Statistical significance as compared to control values.

TABLE 4. Titanium Alloy Implants With Osteolysis

	Implant		
Ion Readings	*Ti*	*Al*	*Va*
Focal Osteolysis			
SF	49 ± 36	53 ± 34	7 ± 2
CAP	7693 ± 7431*	2450 ± 2084*	746 ± 1033*
FM	4880 ± 4482	3338 ± 1716	93498 ± 129861
Blood	38 ± 4	68 ± 60	8 ± 4
Migratory Osteolysis			
SF	86 ± 35*	256 ± 271*	25 ± 19*
CAP	19173 ± 24536*	1277 ± 997	1514 ± 1784*
FM	53158 ± 92380	2576 ± 3116	1240 ± 1306
Blood	602 ± 927	237 ± 307	55 ± 63

Ti, titanium; Al, aluminum; Va, vanadium; SF, synovial fluid; CAP, capsule; FM, fibrous membrane.
* Statistical significance as compared to control values.

ion readings in cementless titanium stems are primarily a local problem of the tissue surrounding the implants.

Only one fixed cementless CoCr alloy stem was studied (Fig. 3). Loose cementless CoCr stems had an elevation of Co, Cr, molybdenum, and nickel in synovial fluid, only nickel in capsular tissue, and only Cr in blood. In loose cemented CoCr stems, statistical blood increases were seen for all ions except molybdenum. Synovial fluid had only statistical elevation of nickel whereas capsular ion increase was Cr, Co, and molybdenum.

A summary of the results from ion readings indicated that statistical increases occurred locally in the hip synovial fluid and capsular tissue with fixed implants, but no systemic increases were seen by measurement of blood levels. The potential for systemic contamination by elevated ion readings in blood was seen only with loose implants.

TABLE 5. Loose Cemented and Cementless CoCr Alloy Implants

	Implant			
Ion Readings	*Co*	*Cr*	*Mo*	*Ni*
Cemented				
SF	76 ± 123	128 ± 219	12 ± 10	12 ± 8*
CAP	1203 ± 2768*	651 ± 814*	109 ± 99*	2317 ± 2344
FM	872 ± 1579	657 ± 977	121 ± 150	2805 ± 2303
Blood	2 ± 1*	16 ± 14*	12 ± 9	9 ± 9*
Cementless				
SF	588 ± 427	385 ± 232*	58 ± 53*	32 ± 16*
CAP	821 ± 451	3329 ± 2890	447 ± 247	5789 ± 2535
FM	2229 ± 1583	12554 ± 8055	1524 ± 1399	13234 ± 10074
Blood	20 ± 25	110 ± 150*	10 ± 4	29 ± 29

Mo, molybdenum; Ni, nickel, SF, synovial fluid; CAP, capsule; FM, fibrous membrane.
* Statistical significance as compared to control values.

TABLE 6. Control Titanium Ion Readings

	Implant		
Ion Readings	*Ti*	*Al*	*Va*
SF	13 ± 22	109 ± 158	5 ± 1
CAP	723 ± 1217	951 ± 586	122 ± 123
Blood*	17 ± 60	12.5 ± 4	5.8 ± 4

Ti, titanium; Al, aluminum; Va, vanadium; SF, synovial fluid; CAP, capsule.
* Blood values are national standards.

Biochemistry

The levels of biochemical factors were reported by the same groups as in Table 1 with one difference. Patients with loose titanium stems were divided into those who had a loose stem after a revision THA and those with migratory osteolysis, all of whom had had a primary THA. The results for PGE_2, IL-1, and collagenase in fibrous membranes are found in Figure 4.

For synovial fluid, PGE_2 in the 12 controls averaged 19 ± 3 pg/ml, three loose cementless titanium revised stems averaged 29 ± 3 pg/ml, two titanium migratory osteolytic stems were 31 ± 0 pg/ml, one fixed cementless titanium stem was 35 ± 0 pg/ml, four loose cemented CoCr stems were 31 ± 6 pg/ml, one loose cementless CoCr stem was 34 ± 0 pg/ml, and one fixed cementless CoCr stem was 23 ± 0 pg/ml.

IL-1 in 12 controls averaged 28 ± 8 pg/ml, three loose cementless titanium revised stems were 35 ± 1 pg/ml, two titanium migratory osteolytic stems were 37 ± 1 pg/ml, one fixed titanium focal osteolytic stem was 40 ± 0 pg/ml, one fixed cementless titanium stem was 32 ± 0 pg/ml, four loose cemented CoCr stems were 34 ± 6 pg/ml, one loose cementless CoCr stem was 34 pg/ml, and one fixed CoCr cementless stem was 32 pg/ml.

Collagenase in 12 controls averaged 71 ± 147 μg/ml, three loose cementless titanium revised stems averaged 196 ± 250 μg/ml, two loose cementless titanium migratory osteolytic stems averaged 37 ± 11 μg/ml, one fixed cementless titanium focal osteolytic stem was 550 μg/ml, one fixed cementless titanium stem was 18 μg/ml, four loose cemented CoCr stems were 145 ± 234 μg/ml, one loose cementless CoCr stem was 550 μg/ml and one fixed cementless CoCr stem was 1 μg/ml.

There was a significant difference between membranes from revision THA and the con-

TABLE 7. Control CoCr Ion Readings

	Implant			
Ion Readings	*Co*	*Cr*	*Mo*	*Ni*
SF	5 ± 3	3 ± 4	21 ± 8	5 ± 2
CAP	25 ± 16	133 ± 63	17 ± 8	3996 ± 6237
Blood*	0.1 − 1.2	2 − 6	0.5 − 1.8	2.9 − 7.0

Mo, molybdenum; Ni, nickel; SF, synovial fluid; CAP, capsule.
* Blood values are from national standards.

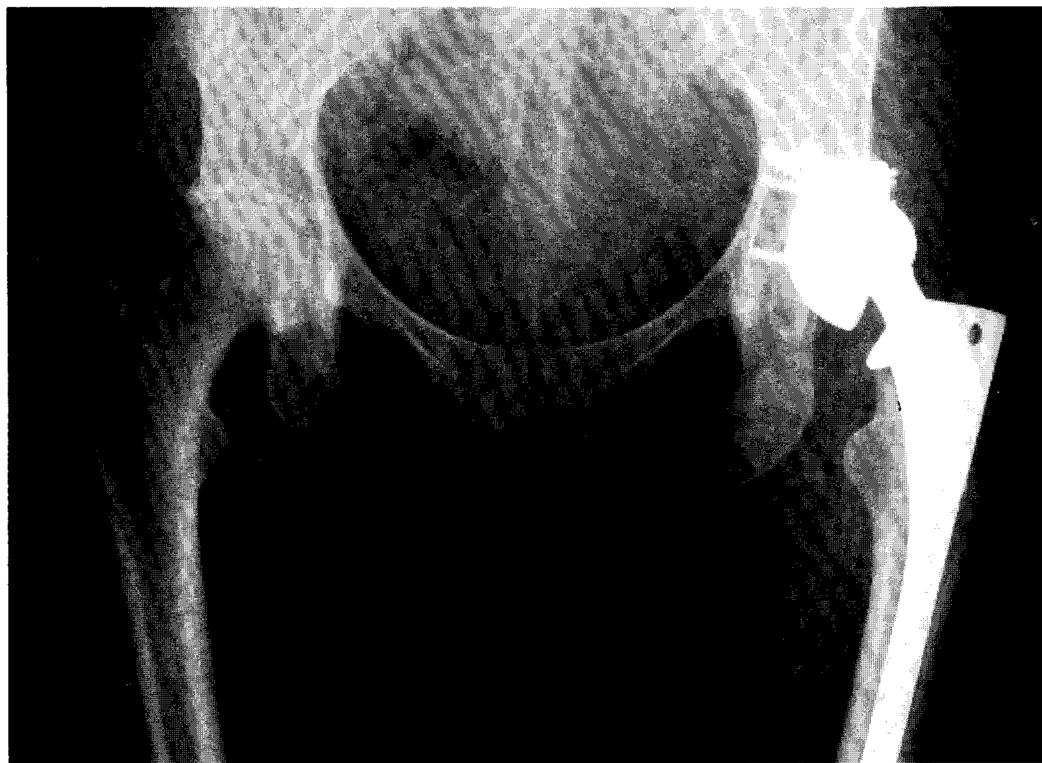
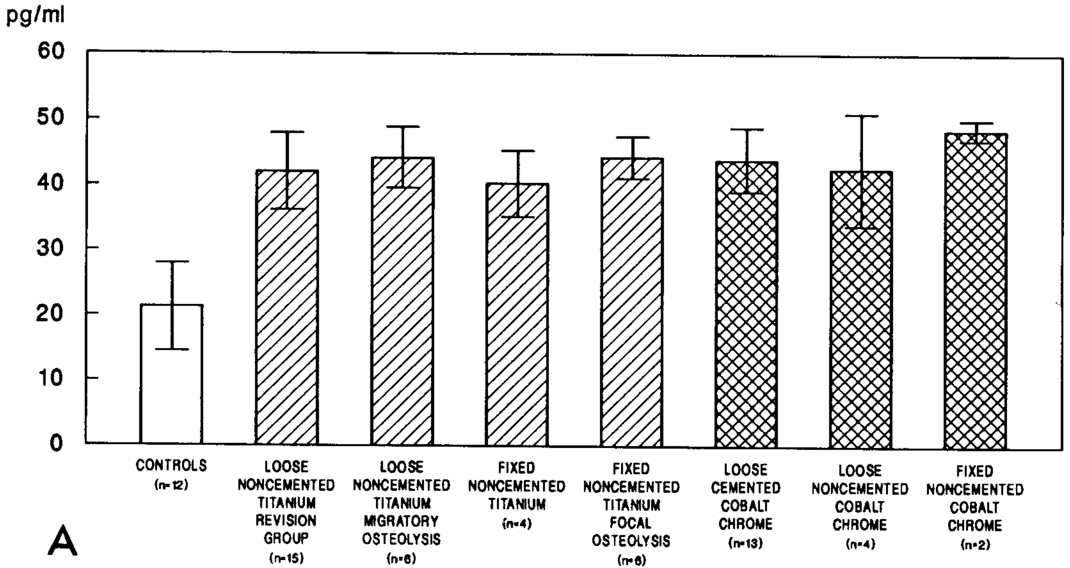


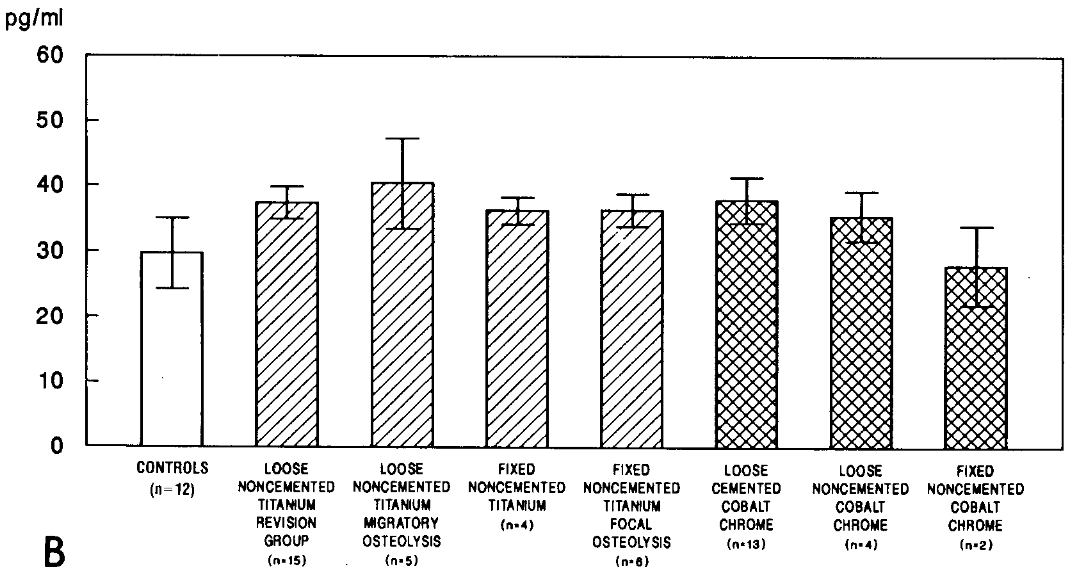
FIG. 3. Roentgenogram shows fixed cementless CoCr stem that had histologic metal Grade 2+ in capsular tissue and 3+ in fibrous membrane with no significant increase of ion readings in blood.

trols in all groups (analysis of variance). There were no differences between CoCr and titanium prostheses. Capsular and fibrous membrane measurements of PGE_2, IL-1, and collagenase were not significantly different. They were combined for graphic presentation and fixation group statistical analysis. The PGE_2, IL-1, and collagenase results are illustrated by Figures 4A–4C, where *n* represents the total number of membranes in each fixation group. The increase in IL-1 in migratory osteolysis was significant when compared with other fixation groups. Collagenase levels showed significant variation when compared to controls and between fixed stems and loose stems, regardless of whether they were titanium or CoCr.

DISCUSSION

This is the first study that correlates the histologic grades, biochemical analysis, and ion readings from clinically retrieved capsular tissue, periprosthetic tissues, and body fluids in fixed and nonfixed THA patients. The results of this study showed that loose total hip prostheses, cemented or cementless, have a large volume of particulate debris in local hip tissues. The data from this study echo the histologic results of Mirra *et al.*[22,23] for tissue retrieved from patients with loose cemented total joint prostheses. Histologic grades of metal and polyethylene and cellular reaction of macrophages (histiocyte) and giant cells in capsule averaged 2+, whereas in fibrous membrane, the grade averaged 3+ for loose





FIGS. 4A–4C. Measures of (A) PGE_2, (B) IL-1, and (C) collagenase compared to controls with standard error bars. Statistical difference was found in all groups measured against controls ($p < 0.05$). The number of membranes in each fixation group is represented by n.

cementless stems. The observations of higher debris and particulate in the periprosthetic femoral membrane suggest that cementless femoral stems rubbing against the endosteal surface will also generate particulate debris independent of the articulating metal head and polyethylene acetabular insert.

The histologic data in this study do not support that CoCr alloy implants are likely to cause less metal debris formation than tita-

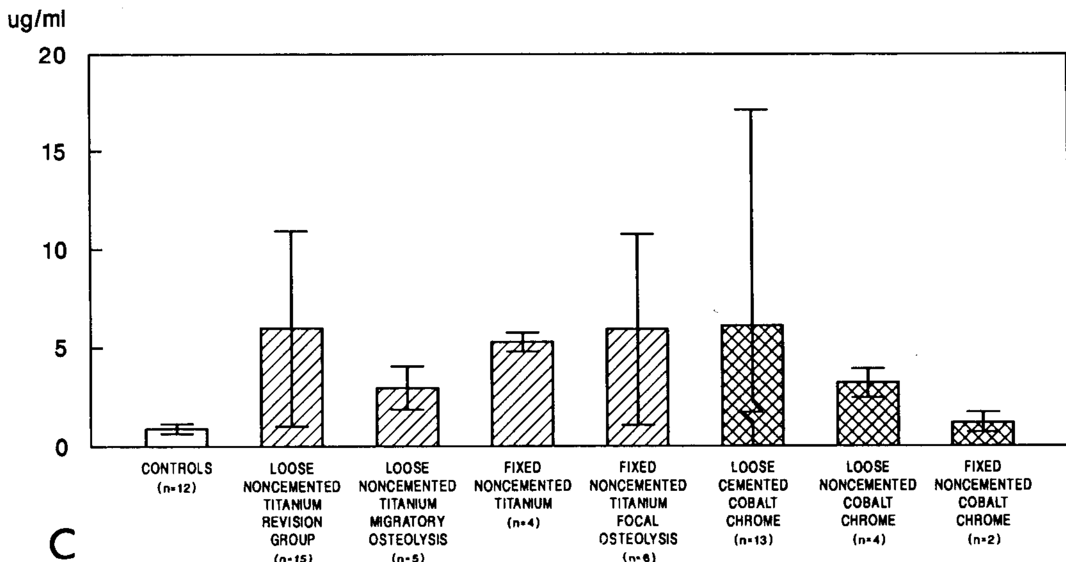


FIG. 4 (*Continued*).

nium in a mechanically loose stem. The metallosis (black-stained tissue) seen periodically in loose titanium implants has been attributed to titanium oxide formation. Although CoCr debris does not create an observable oxide response, the results in this study clearly show that metal debris is present in the patient's tissue when CoCr devices are clinically loose.

The high ion readings seen in capsular and femoral membranes were unlikely to be representative of free ion levels present in the retrieved tissue. With the exception of a few fixed implants in which the ion levels were comparable to control tissues, the remaining tissues examined contained metal and polyethylene particulate when examined histologically. It is certain that some of this particulate contaminate is bound in the cells and tissues that were being analyzed for ion levels. Ion readings are high in capsular and fibrous membranes because of the high ion liberation resulting from particle ion release caused by the heat treatment necessary for measurement. Because of these factors, it is doubtful if future studies could ever determine ion levels in capsular or periprosthetic tissues surrounding metal implants. Therefore, careful monitoring of ion levels in a patient's blood and serum may be clinically significant and should continue to be studied.

Synovial fluid analysis showed statistical elevation (compared to controls) of ions in loose and fixed cemented and cementless stems. Brien *et al.*[3] found elevation of titanium ions in synovial fluids of loose cemented hips. Synovial fluid elevation was not correlated with blood ion elevation so free exchange between blood and synovial fluid was not present. This suggests that ions are locally bound.

Elevation of ion readings in blood was found only with loose stems. With loose cementless titanium stems, titanium was statistically increased; with loose cementless CoCr stems, Cr was increased; and with loose cemented CoCr stems, Co, Cr, and nickel were all statistically elevated. No fixed stems had blood elevation that was statistically different from control.

These results suggest that particulate debris and high ion readings are primarily a local problem of the tissue surrounding the implants. Systemic elevation of blood ion readings occurred only with loose stems. This was interpreted to mean that fixed prostheses pose little threat to the patient from the material products used. To diminish the potential increase in systemic ionic levels with loose hip prostheses, early revision of loose implants is recommended. What remains to be determined is whether ion levels are reduced in patients with elevated blood and serum ion levels after stable implant fixation is obtained after revision THA.

Biochemistry results show elevation above controls for PGE_2, IL-1, and collagenase in all patients whether the implants were loose or fixed. These findings were confusing since previous studies by Goldring *et al.*[8] implicated biochemical factors, especially elevated PGE_2, as potential causes of osteolysis in THA. Recent reports have shown that the effects of PGE_2 are varied and that PGE_2 can actually stimulate bone formation.[12,19] Therefore, the data in this study suggest that the role of PGE_2 in bone resorption and osteolysis in THA remains undefined.

Elevation of the biochemical factors in capsular tissue, synovial fluid, and membranes from well-fixed cementless prostheses without osteolysis suggest that perhaps these biochemical factors are not as significant for osteolysis as mechanical factors. PGE_2 and IL-1 are present as a result of wear debris. Macrophage response to wear debris will result in secretory activity at the cellular level to facilitate encapsulation of debris. The lack of increased biochemical levels in tissues from loose stems in the face of histologic debris Grades 2+ to 3+ indicates that these biochemical factors do not increase with increasing volumes of debris. Therefore, if these factors are primarily responsible for osteolysis, why do all fixed stems not demonstrate this phenomenon? Perhaps of more importance than biochemical factors is a regional accelerating phenomenon, described by Frost,[6,7] that causes osteolysis in bone irritated by mechanical factors.

In summary, these results must be kept in perspective to overall results with THA. Harris and Mulroy[11] reported a 3% incidence of revision of cemented THA at 11 years and Engh[5] reported that 4% of cementless bone ingrowth hips at ten years needed revisions. Ruthjen *et al.*[25] had two of 68 proximally fixed CoCr bone-ingrowth prostheses revised at six years, and this study had four of 250 proximally fixed bone ingrowth titanium prostheses revised for loosening. Clearly, THA is a successful operation with a low incidence of loose implants. One can therefore anticipate that only 3%–5% of prostheses are at a significant risk for systemic ion elevation, and this most likely only while the loose implant remains in place. The clinical significance of systemic blood ion elevations, and the duration for which these ion levels must remain elevated to be clinically significant, is a subject for continued observation and study. The potential consequences of elevated systemic ions for the 3%–5% of patients at risk should be followed and reported. In the meantime, particulate and debris production can be reduced by early revision.

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