

Metal sensitivity causing loosened joint prostheses

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SUMMARY Metal sensitivity, as measured by an in-vitro assay on peripheral blood lymphocytes, was evaluated in patients with failed joint prostheses. Lymphocyte transformation to chromium, cobalt, and nickel was measured in 24 patients having revision surgery for a painful or loose prosthesis and compared with that in 11 patients who had a successful hip prosthesis in situ for at least 2 years previously. A positive response (lymphocyte stimulation index greater than 3) to at least one of the metals was found in 71% of the revision group compared to 9% of controls ($P < 0.01$). The positive correlation between prosthesis failure and in-vitro metal sensitivity suggests that cell-mediated immunity to metals may play a role in prosthesis failure. Furthermore, this simple in-vitro test may provide the basis of a useful diagnostic test for an often difficult clinical problem.

As total joint arthroplasty is becoming an increasingly common procedure, so the complications are now being seen in greater numbers.¹ Failure of a total joint replacement may be due to a number of factors, including faulty technique, infection, and trauma.² Recently sensitivity to metal wear products has been suggested as a cause of some of these failures.³

It has been shown in vitro that metal wear products are released from prostheses⁴ and in vivo that metal can be demonstrated in the blood, urine,⁵ and tissues adjacent to the prosthesis³ in patients with total hip replacements. Metal sensitivity in patients with metal implants has been demonstrated by positive patch tests^{6,7} and also by the development of eczematous dermatitis in some patients.

Hypersensitivity to metal is considered to be due to a type IV reaction, mediated by T lymphocytes independently of antibody and complement. Such hypersensitivity can be demonstrated in vivo by patch testing, measuring the delayed skin response at 48 hours. As the in-vitro correlate of this activity is lymphocyte transformation, it would be expected that positive reactions would be easily demonstrable in such cases. Despite these theoretical considerations attempts to demonstrate this successfully have been variable in their results.⁸⁻¹⁰

In one study of patients having total joint prostheses there was a good correlation between positive

patch tests and lymphocyte transformation to nickel, but not to cobalt.¹⁰ In that study 7 of the 15 patients who were negative on skin testing had a positive nickel transformation, suggesting that lymphocyte transformation may be a more sensitive test.

Correlation between prosthesis failure and metal sensitivity as determined by patch testing has been demonstrated by a number of groups,¹¹⁻¹³ though not found by others.^{14,15} An attempt has also been made to correlate the histopathology of the tissues adjacent to the failed prosthesis with patch test results. It has been suggested that the metal sensitivity causes obliterative changes in blood vessels, leading to bone necrosis and then loosening.³

In the present study we have evaluated the lymphocyte transformation responses to the 3 metals present in the metal prosthesis, nickel, chromium, and cobalt, and correlated the results with failure of the prosthesis.

Patients and methods

In-vitro metal sensitivity testing was carried out on patients with a failed joint prosthesis and in a matched group of controls without any evidence of prosthesis failure. The test group consisted of 24 successive patients who presented to the Combined Orthopaedic Service with a failed joint prosthesis. For the purpose of this study a failed total joint prosthesis was considered to be one that required operative intervention because of pain. The control group was randomly selected from asymptomatic

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patients having a total hip replacement 24 to 30 months previously. The 2 groups were comparable in age and sex, though the failed prosthesis group had a longer duration of having the prosthesis in situ (Table 1).

All failed prosthesis patients were extensively investigated to establish the cause of failure. The final diagnosis, as shown in Table 1, was based on findings at operation, extensive bacteriological sampling, radiographs, radionuclide scans, and histopathology.

Lymphocyte transformation responses to nickel, cobalt, and chromium were measured by a routine lymphocyte transformation technique. Peripheral blood lymphocytes (PBL) were separated from heparinised blood on a Ficoll-Hypaque gradient. The PBLs were washed 3 times in phosphate buffered saline and then suspended in RPMI 1640 (Gibco) with 10% fetal calf serum (Commonwealth Serum Laboratories) at a concentration of 2×10^6 /ml. Cultures, in triplicate, consisting of 0.2 ml of lymphocyte suspension added to each well of a

flat-bottomed microtitre tray were incubated for 6 days in the presence of the metal salts $NiCl_2 \cdot 6H_2O$, $CrCl_3 \cdot 6H_2O$ and $Co(NO_3)_2 \cdot 6H_2O$ at final concentrations ranging from 10^{-3} to 10^{-6} M. $1\mu Ci$ of 3H -thymidine was added 20 hours before harvesting, and the cells were harvested on to glass fibre filter paper using a Skatron harvester. The paper discs were dried, suspended in liquid scintillant, and counted in a Packard liquid scintillation spectrometer. The stimulation index was calculated as the ratio of the median count in disintegrations per minute (dpm) for the metal concentration giving the maximum response to the median dpm of the cells in the absence of metal.

$$\text{Stimulation index} = \frac{\text{median dpm of test}}{\text{median dpm of control}}$$

A response was considered positive if the stimulation index was greater than 3. Results were considered satisfactory if the coefficient of variation for each triplicate was less than 20%. Statistical tests were performed by χ^2 with Yates's correction.

Table 1 Clinical details

	No.	Sex		Mean age (range)	Duration months (range)	Type of prosthesis	Cause of failure		
		M	F						
Failed prosthesis	24	19	5	67 (49-80)	41 (6-120)	Charnley	21	Loosening	13
						McKee	1	Infection and loosening	8
						Farrar	2	Fracture femur and loosening	1
						GSB knee	1	Fracture femoral component and loosening	1
							'Pain' alone	1	
Control	11	8	3	69 (55-78)	26 (24-30)	Charnley	11	—	—

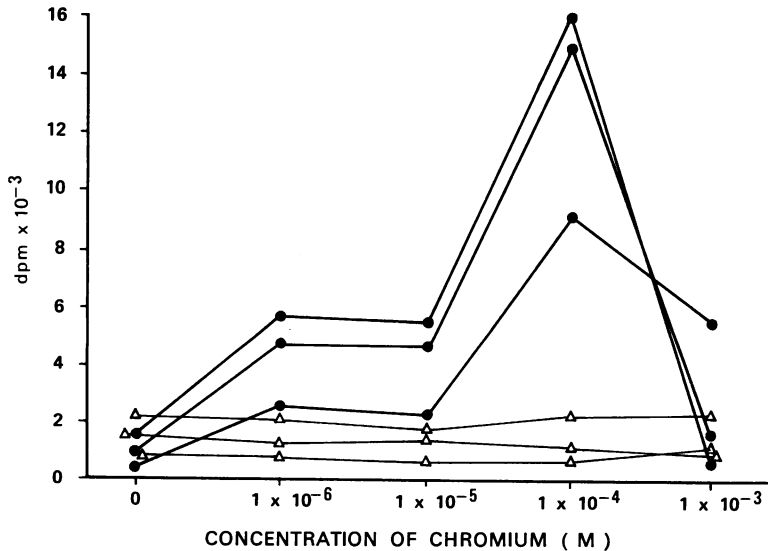


Fig. 1 Lymphocytic transformation dose response curves of some failed prosthesis patients (●) and controls (Δ) to chromium chloride

Results

In the failed prosthesis group 17 of the 24 patients (71%) showed sensitivity to one or more of the metals compared to one of the eleven controls (9%) ($\chi^2=9.17$, $P<0.01$) (Table 2).

Typical dose response curves for the 3 metal salts used are shown in Figs. 1, 2, and 3. If there was a response to chromium it usually occurred at a concentration of 1×10^{-4} M of the salt (Fig. 1). With cobalt, peak responses were more variable, although in general they occurred at lower con-

centrations (1×10^{-6} M) (Fig. 2). With the nickel salt, peak responses occurred at either 1×10^{-5} or 1×10^{-4} M (Fig. 3).

The peak lymphocyte responses (expressed as Δ

Table 2 Number of patients sensitive to each metal

	No.	Total no. positive	No. sensitive to chromium	No. sensitive to nickel	No. sensitive to cobalt
Failed group	24	17	15	7	5
Controls	11	1	1	0	0

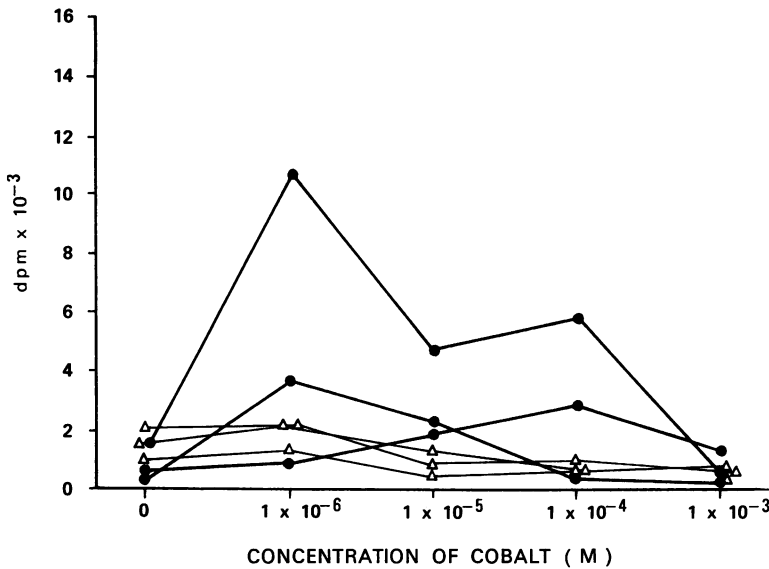


Fig. 2 Lymphocytic transformation dose response curves of some failed prosthesis patients (●) and controls (Δ) to cobalt nitrate.

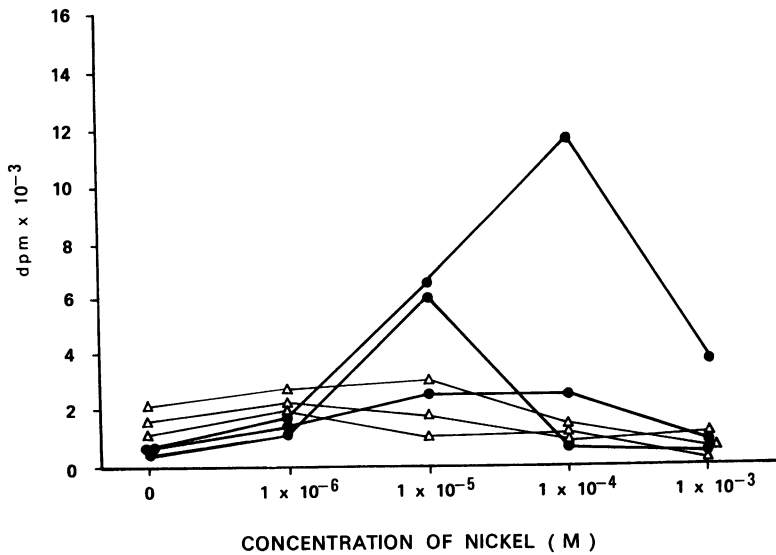


Fig. 3 Lymphocytic transformation dose response curves of some failed prosthesis patients (●) and controls (Δ) to nickel chloride.

dpm, i.e. dpm stimulated – dpm unstimulated) of the patients and controls to each metal salt is shown in Fig. 4. It can be seen that chromium was most discriminatory in showing a difference between patients with a failed prosthesis and the controls. Nickel was less, and cobalt was the least discriminatory in this regard. The unstimulated dpm were usually less than 2×10^3 .

Of the 17 patients with positive responses in the test group 3 responded to all 3 metals, 3 to chromium and nickel, 1 to chromium and cobalt, 8 to chromium alone, and 1 each to cobalt and nickel alone. The mean stimulation indices for the control group was less than 2.0 with each of the 3 metals. In contrast the mean indices were elevated in the test group, being 6.7 for chromium, 3.8 for nickel, and 2.4 for cobalt (Table 3).

The majority of the lymphocyte studies were performed on blood collected in the convalescent period after surgery. The possibility was considered that the manipulation involved in the removal of the prosthesis could lead to excess antigen release and be primarily responsible for the high indices in the surgical group. We performed studies on 3 patients before and after surgery (Table 4), and it can be seen that there was no appreciable difference between the stimulation indices at these times. The small variation between the repeat measurements indicates that the assay is reproducible. Similar reproducibility has been obtained using this assay in patients with contact dermatitis due to metal sensitivity (Zilko, unpublished).

Table 3 Mean stimulation indices

		Mean stim. index	Range
Chromium	Test group	6.2	0.5–24.2
	Controls	1.7	0.6–4.7
Nickel	Test group	3.8	0.8–25.6
	Controls	1.5	1.0–2.4
Cobalt	Test group	2.4	0.5–9.0
	Controls	1.3	0.6–2.6

Table 4 Lymphocyte stimulation tests done on the same patients on 2 different dates

Patient	Date	Peak stimulation index		
		Chromium	Cobalt	Nickel
1	20/7/78	5.10	1.16	2.71
	4/8/78	4.54	1.33	2.32
2	4/7/78	3.65	1.01	2.42
	20/7/78	7.52	2.51	2.26
	14/2/78	1.45	1.21	0.79
	20/7/78	1.04	1.27	1.11

Within the failed prosthesis group there was no difference between those with a positive or negative response in terms of clinical history, duration of prosthesis insertion, histological appearance, and the presence or absence of infection.

Discussion

The results presented above show a strong correlation between prosthesis failure and metal sensitivity as measured by an in-vitro lymphocyte

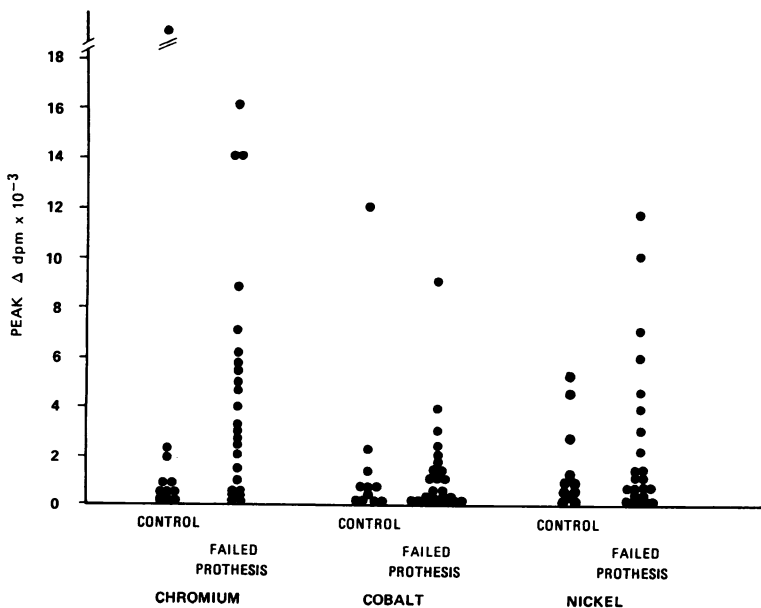


Fig. 4 Peak lymphocyte responses of patients with failed prosthesis and controls to chromium chloride, cobalt nitrate and nickel chloride.

transformation method. This corresponds to 2 studies based on patch testing,^{3 10} though both these studies were on failed metal-to-metal prosthesis. Several other studies of metal-to-metal prostheses found no correlation between positive patch tests and loosening of the prostheses.^{14 15} In all these studies the highest incidence of sensitivity was to cobalt, the metal which makes up the greatest proportion of the alloy used in this prosthesis. By contrast, our study was on failed metal-to-plastic prosthesis and the greatest incidence of sensitivity was to chromium. In these prostheses cobalt is said to be absent from the alloy, though it may be present in trace amounts.

In a lymphocyte transformation study of metal sensitivity in patients having total hip replacements without loosening, Elves found¹⁰ 46% had positive tests to nickel. By contrast, our control group contained no patients sensitive to nickel and only 1 sensitive to chromium, an antigen for which Elves did not test.

The correlation between sensitivity and prosthesis failure may imply a possible role of cell-mediated mechanisms in the pathogenesis of prosthesis failure. It has been postulated that metal sensitivity may cause obliterative changes in blood vessels supplying the bone adjacent to the failed prosthesis, with the necrosis that follows leading to a decrease in the bond between the bone and cement, eventually allowing loosening.³ The main inflammatory cell infiltrate in the adjacent tissues and blood vessel walls was mononuclear and as such is quite in keeping with a delayed type hypersensitivity response.

It could be argued that there are more metal wear particles shed by a loosened prosthesis, and that the in-vitro transformation response is a consequence of an increased antigen dose. However, since wear particles are found adjacent to non-loosened prostheses it is unlikely that these differences are only quantitative in terms of antigen exposure. This question may be answered in future studies by following patients sequentially, in which case patients with loosening should change from having a negative to a positive lymphocyte transformation response.

From a practical point of view this in-vitro test may have much to offer in the assessment of cases of loosening and the selection of prostheses for patients prior to implantation. The lymphocyte transformation test appears to be more sensitive and specific than patch tests, requires only 1 sample

of blood, and the patient needs no follow-up visit. If the metal sensitivity is detected preoperatively, it is possible to choose a prosthesis which does not have the metal as a component. If a patient has a prosthesis in situ which is loosened, a positive lymphocyte transformation test would indicate that the condition will be progressive and that removal of the prosthesis is indicated.

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