Increased chromosome translocations and aneuploidy in peripheral blood lymphocytes of patients having revision arthroplasty of the hip

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The long-term biological effects of wear debris are unknown. We have investigated whether there is any evidence of cumulative mutagenic damage in peripheral blood lymphocytes of patients undergoing revision arthroplasty of predominantly metal-on-plastic total hip replacements compared with those at primary arthroplasty.

There was a threefold increase in aneuploidy and a twofold increase in chromosomal translocations which could not be explained by the confounding variables of smoking, gender, age and diagnostic radiographs. In the patients with TiVaAl prostheses there was a fivefold increase in aneuploidy but no increase in chromosomal translocations. By contrast, in patients with cobalt-chrome prostheses there was a 2.5-fold increase in aneuploidy and a 3.5-fold increase in chromosomal translocations. In six patients with stainless-steel prostheses there was no increase in either aneuploidy or chromosomal translocations.

Our results suggest that future epidemiological studies of the putative long-term risks of joint replacement should take into account the type of alloy used in the prosthesis.

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Over the past 30 years total hip arthroplasty (THA) has been developed and refined to enhance durability and reproducibility.[1] Total joint arthroplasty, however, is being performed in an increasing number of younger patients, and orthopaedic surgeons are therefore seeking implants which will give lengthy survival. Assessment of the long-term mechanical behaviour in vivo of all biomaterials in common use in prostheses is in progress.[2] Little is known about the long-term biological effects, although many studies have addressed the role of wear debris in the local inflammatory response associated with aseptic loosening. Because of the composition of the prostheses currently in use there may be systemic exposure to chromium (Cr), cobalt (Co), nickel (Ni) and aluminium (Al) as a result of the formation of wear debris. A fivefold increase in serum chromium can be detected three years after insertion of a Co-Cr alloy prosthesis.[3] Particulate wear debris accumulates in tissue adjacent to the prosthesis and disseminates in the body to the liver, spleen, bone marrow and lymph nodes, with the highest levels being detected in local bone marrow and lymph nodes.[4,5] Some of these metals are known to be clastogens and to damage DNA.[6-8] Therefore it is important to investigate the possible long-term effect of exposure to wear debris.

Our previous work[5,9] has shown a significantly higher rate of chromosomal aberration in local bone-marrow cells adjacent to the prosthesis at revision surgery compared with bone marrow from the iliac crest from the same patient or from a primary THA. Furthermore, at revision arthroplasty, there was clonal expansion of lymphocytes in the blood from two of 21 patients in whom the implant had been in situ for more than ten years. Some epidemiological studies have suggested that prolonged exposure to metal debris after joint replacement may predispose to the development of lymphoma and leukaemia.[10-12] Similar investigations have not shown an increase in leukaemia and lymphoma, but the duration of all of these studies has been for less than 20 years.[13,14]

The chromosome painting method of fluorescent in situ hybridisation (FISH) is a well-recognised and sensitive method for identifying genetic damage.[15] Multicolour chromosome painting detects non-lethal, cumulative stable exchanges, in contrast to conventional metaphase analysis which identifies mainly unstable exchanges that lead to cell death.

It is more convenient and sensitive than conventional metaphase analysis[16] and has been shown to be a valid method for quantifying chromosomal rearrangements due to both chemical exposure[17] and radiation.[18-20] A low level of genetic damage can be seen in the general population and increases are positively correlated with age and smoking.[21-23] The FISH technique allows the detection of numerical chromosomal aberrations (aneuploidy) as well as structural chromosomal abnormality (translocations and breaks). Aneuploidy results from mutations which disrupt cell division checkpoints causing an alteration in chromosomal number, and both changes have been identified in most types of tumour.

We have investigated whether there is evidence that cumulative damage (translocations and aneuploidy) is present in the peripheral blood of patients at revision arthroplasty compared with those who have a primary procedure. We have previously shown increased asymmetrical (unstable, lethal) chromosomal damage in bone marrow with increased metal content adjacent to the prosthesis.[5] Peripheral blood obtained at revision arthroplasty has been compared with that taken at primary arthroplasty in patients with osteoarthritis and matched for gender and a history of smoking, and has been examined by FISH and high-resolution, inductively-coupled plasma mass spectrometry (ICPMS) to detect metal levels.

Patients and Methods

We studied 31 patients presenting for revision hip arthroplasty and 30 control patients having a primary THA. The mean age of those having the latter procedure was 63.9 ± 12.7 years and of those with revision arthroplasty 71 ± 13.4 years. In the revision group the prosthesis used had been a Charnley in 11, D-series in nine, Müller in two, Sheehan in two and Thompson, Ring, Cony-Müller, Long-Wagner and Ultralock-Zimmer in one each; in two the implant was unknown. Eleven prostheses were made of Co-Cr alloy, 13 of titanium-vanadium-aluminium (TiVaAl) alloy, six of stainless-steel (SS) and one of a hybrid of Ti and Co-Cr. All patients had osteoarthritis and all except two at primary arthroplasty took non-steroidal anti-inflammatory drugs (NSAIDs).

A comprehensive data sheet was obtained for each patient detailing occupational exposure, numbers of diagnostic radiographs, drugs taken, smoking, the type of prosthesis and the cause of its failure. A peripheral blood sample was obtained before operation after informed consent. A venflon cannula was inserted into a vein in the forearm and 5 ml of peripheral blood were withdrawn into a plastic syringe and discarded. A further 5 ml were placed into a 5 ml Tecklab plastic container suitable for analysis of trace metals. This was immediately frozen at -80°C and the concentration of Cr, Co and Ni in whole blood analysed by double-focusing magnetic sector high-resolution ICPMS. Another 10 ml of blood (EDTA tube) were collected and mononuclear cells were purified on a Ficoll-Paque density gradient and frozen at -70°C for isolation of DNA. A further 10 ml were collected in a lithium-heparin tube for metaphase spreads and cultures were set up within 24 hours.

Metaphase preparations. Replicate cultures (5 ml) were initiated by the addition of 5 ml of McCoys 5A (Gibco Life Technologies, Paisley, UK) supplemented with 25mM Hepes, 12.5% fetal bovine serum, penicillin (100 U/ml) and streptomycin (100 U/ml) with phytohaemaglutinin (1.25%; Glaxo-Wellcome, Ware, UK). Duplicate cultures for each patient were incubated at 37°C. Seventy hours after initiation, colchicine (Gibco) (2.2 g/ml) was added and the cultures incubated for a further 45 minutes. The cells were harvested and slides prepared in a standard assay as described by Ellard et al.[17]

Chromosome painting. Each patient was evaluated for stable chromosomal aberrations (translocations) by simultaneous painting of chromosomes 1, 2 and 3. FISH analysis was performed with commercial human chromosome paints (Cambio, Cambridge, UK). The methods for in situ hybridisation and detection are described by Ellard et al.[17]

We examined 300 metaphase spreads per patient on duplicate slides. Fluorescence microscopy was performed using an Olympus BX60 microscope equipped with a single band-pass filter (Olympus, Southall, UK) to visualise the green and red fluorochromes and a triple band-pass filter (Chromatechnology, USA) which allows simultaneous detection of DAPI, FITC and Texas Red. A Cytovision digital-imaging system (Applied Imaging Ltd, Richmond, UK) was used to capture, digitise, annotate and print multicolour images (Fig. 1).

Non-disjunction assay. Whole blood cultures were initiated as described for metaphase preparation. After incubation for 44 hours at 37°C, 6 g/ml of cytochalasin-B (Sigma, Gillingham, UK; stock solution 2 mg/ml in dimethylsulphoxide) were added. The cultures were harvested after 72 hours, and the cells were pelleted and resuspended in 1 ml of phosphate-buffered solution. The lymphocytes were separated and FISH applied for chromosomes 1 and 2 centromere specific paints (Cambio) following the protocol of Doherty et al.[24]

Statistical analysis. This was carried out using the Stata package (StataCorp, Stata Statistical Software Release 6.0, College Station, Texas). The numbers of aneuploidies and chromosomal translocations for each patient were compared by log-linear models to estimate the mean rates (%) of aneuploidy and translocation and their ratios, with robust confidence limits, using total numbers of metaphases per patient (divided by 100) as the exposure measure. Log-linear models assume that the numbers of abnormalities are not normally distributed, but that their exposure-weighted arithmetic means and their ratios are approximately log-normally distributed. The models were used to estimate the mean rates of abnormality for primary patients, revision patients and each subclass of these (Ti, Co-Cr and SS

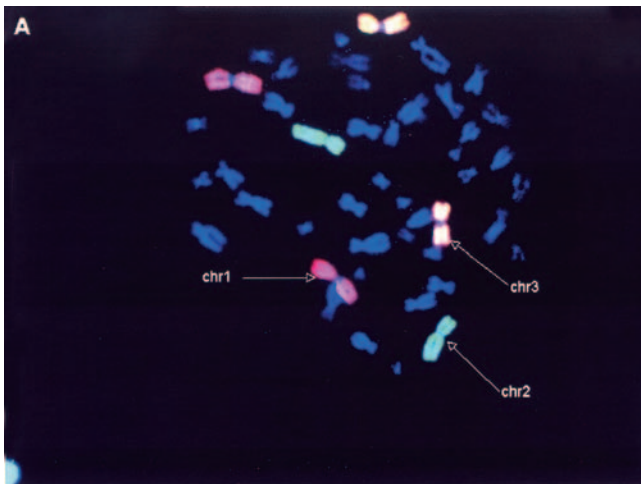

Fig. 1a

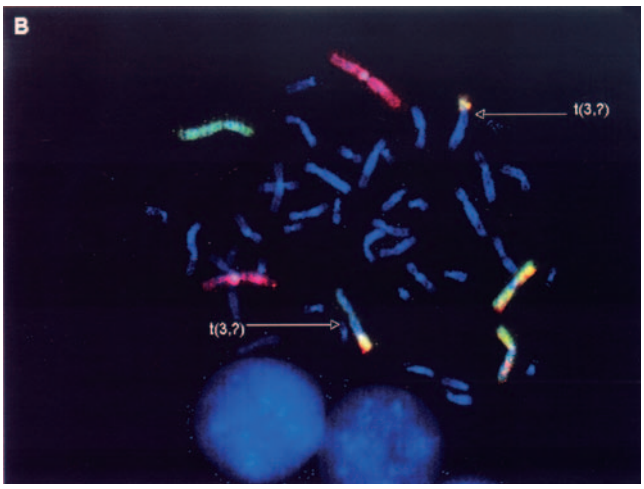

Fig. 1b

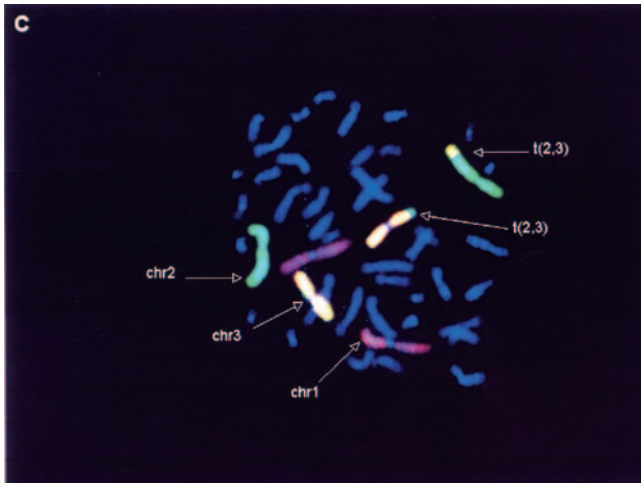

Fig. 1c

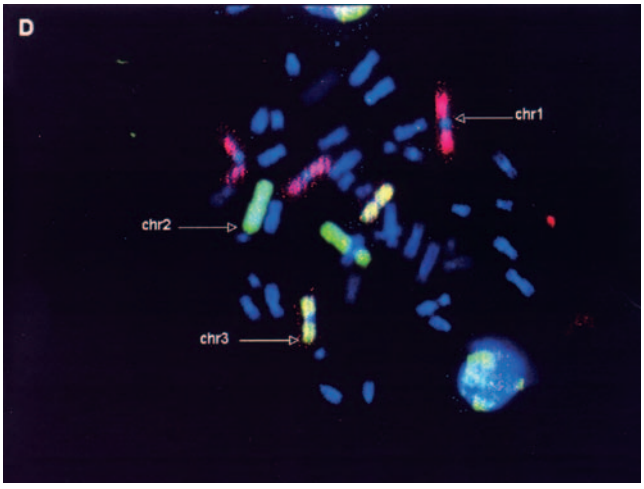

Fig. 1d

Figure 1a – A cell at metaphase painted with probes specific for chromosomes 1, 2 and 3. Chromosome 1 is directly labelled with CY3 (red), chromosome 2 is labelled with FITC (green), and chromosome 3 is labelled with a 3:2 ratio of CY3 to FITC (yellow). The cell is counter-stained with DAPI (blue). Figure 1b – A painted cell with the same probes in which a reciprocal translocation between a painted and unpainted chromosome is apparent. Figure 1c – Another painted cell with the same probes in which a reciprocal translocation between two painted chromosomes is evident. Figure 1d – A painted aneuploid cell with three copies of chromosome 1 (CY3 labelled, red; n=47).

prostheses), and then used to estimate unadjusted and mutually-adjusted rate ratios for the three types of secondary prosthesis relative to the primary patients, and also for the possible confounders of gender (male/female), smoking status (current and ex-smokers *versus* smokers), age (estimated as a multiplicative effect per decade), and numbers of radiographs in the previous eight years (estimated as a multiplicative effect per five radiographs). Adjusted rate ratios were estimated relative to a baseline incidence rate, interpreted as the incidence for a 65-year-old female non-smoker with ten radiographs in the previous eight years, receiving a primary prosthesis. The levels of Co and Cr were recorded to the detectability limit of 0.2 ppb if undetectable, and then compared between types of prosthesis by log-normal linear regression with robust confidence limits, which is equivalent to unequal-variance *t*-tests on the logs. Log-normal linear regression assumes that the data are not normally distributed, but that the sample geometrical means are log-normally distributed. The geometrical mean levels of Co and Cr were estimated for primary patients, revision patients and the three types of prosthesis and ratios of geometrical means between the revision groups and the primary group were estimated.

Results

The mean incidence of aneuploidy in peripheral blood lymphocytes was increased approximately threefold in all patients at revision arthroplasty compared with those at primary procedure (Tables I and II). The mean incidence of chromosomal aberrations was approximately doubled at revision arthroplasty compared with the primary operation.

Table I. Details of the control group of 30 patients having primary arthroplasty and of the 31 having revision arthroplasty

Case	Gender	Age (yr)	Radiograph 8*	Radiograph 1*	Smoking†	Cr (ng/g)	Co (ng/g)	Aneuploid cell index‡	Translocation index‡
Control (primary)									
1	F	46	11	11	S	2	0.5	0.72	0.36
2	F	88	5	5	GU	<RL§	<RL	0	0.82
3	F	73	5	5	S	–	–	0.33	0.33
4	F	38	14	10	GU	<RL	<RL	1.95	0.32
5	M	81	4	4	S	<RL	<RL	0.36	1.82
6	M	72	10	7	NS	–	–	0	0.65
7	F	77	10	10	N/S	1	<RL	2.22	0.37
8	F	84	4	4	N/S	–	–	0.34	0.68
9	F	42	13	8	GU	<RL	<RL	0.33	0.66
10	M	66	5	5	GU	2	0.4	1.99	0.66
11	F	69	6	6	GU	<RL	<RL	0	0.33
12	M	79	4	4	GU	–	–	0	0.65
13	F	49	12	11	N/S	<RL	<RL	0	0.62
14	M	50	4	4	GU	<RL	<RL	0.33	0.66
15	M	74	10	8	N/S	0.4	0.28	1.66	1.33
16	F	61	5	5	N/S	–	–	0.66	1.66
17	M	60	11	6	N/S	0.4	0.26	0.32	0.96
18	F	73	11	8	N/S	–	–	0.32	0.32
19	F	63	14	8	N/S	0.4	0.26	0	0.34
20	F	67	12	6	S	0.6	<RL	0	0.33
21	M	60	12	6	S	–	–	0.67	1.33
22	F	69	4	4	N/S	<RL	<RL	0.32	0.32
23	M	59	6	6	N/S	–	–	0.34	1.03
24	F	61	11	11	N/S	–	–	0.83	0.41
25	F	76	8	8	N/S	–	–	0.34	
26	F	62	7	4	N/S	0.5	<RL	1	0.33
27	F	59	8	6	N/S	1	<RL	0.34	2.72
28	M	55	14	10	GU	–	–	0	0.33
29	M	61	4	4	GU	0.6	<RL	0.66	0.33
30	F	43	9	9	N/S	<RL§	<RL	0	0.33
Revision¶									
1 (C)	F	50	7	7	N/S	1	0.98	0.34	2.76
2 (S)	M	78	13	7	GU	<RL	0.46	1.05	0.35
3 (C)	M	80	6	4	S	0.7	0.66	0.88	1.76
4 (T)	M	71	12	10	S	0.6	0.68	4.36	1.34
5 (T)	M	69	4	3	N/S	0.4	0.26	3.22	0.32
6 (C)	F	90	12	12	S	<RL	<RL	0.33	3.64
7 (C)	M	84	11	9	N/S	0.4	<RL	1.32	2.63
8 (T)	F	71	4	4	N/S	0.9	0.06	1.03	2.06
9 (C)	F	83	6	6	N/S	<RL	<RL	1.71	1.71
10 (S)	F	84	15	15	N/S	–	–	0	0.63
11 (C)	F	75	12	7	N/S	0.9	0.38	1.68	1.01
12 (T)	F	34	12	10	N/S	<RL	0.28	3.95	0.99
13 (S)	F	80	11	7	S	0.9	<RL	1.08	0.72
14 (S)	F	56	14	14	GU	0.5	<RL	0.35	0.35
15 (T)	M	79	6	2	GU	0.4	0.7	1.44	2.16
16 (T)	M	60	15	9	S	0.5	0.48	7.27	0.35
17 (T/C)	F	80	8	6	N/S	0.7	<RL	4.64	1.99
18 (T)	F	66	14	2	N/S	1	0.48	1.65	2.64
19 (T)	M	58	4	4	GU	0.8	<RL	0	0.34
20 (C)	F	71	12	8	GU	–	–	4.78	2.73
21 (C)	F	59	6	4	GU	<RL	<RL	2.62	1.97
22 (C)	M	66	12	7	S	0.9	0.76	0.32	2.57
23 (C)	F	83	10	8	N/S	2	<RL	0	4.3
24 (C)	M	77	7	7	GU	<RL	<RL	1.31	2.95
25 (S)	M	53	10	4	N/S	0.3	0.28	1.29	0.97
26 (C)	F	90	10	8	N/S	3	6	0.95	2.86
27 (T)	M	32	14	8	N/S	<RL	<RL	3.97	0.99
28 (T)	F	68	11	8	N/S	<RL	<RL	4.2	0.76
29 (T)	M	83	15	12	N/S	–	–	0.65	0.33
30 (C)	F	89	4	4	GU	<RL	0.78	0	2.57
31 (S)	M	85	15	13	N/S	<RL	<RL	0	1.24

* number of radiographs taken in last eight and one years, respectively
† S, smoker; N/S, non-smoker, GU, given up smoking
‡ of total cell number
§ below the limit of detection
¶ T, TiVaAl; C, cobalt-chrome; S, stainless-steel

Table II. Mean (arithmetic; 95% CI) aneuploidy index (%) and translocation index (%) for the 30 primary and 31 revision patients and for the type of prosthesis

	Aneuploidy index	Translocation index
Primary (30 patients)	0.53 (0.35 to 0.81)	0.72 (0.55 to 0.95)
Revision (31 patients)	1.73 (1.20 to 2.49)	1.68 (1.32 to 2.13)
Ti (11 patients)	2.88 (1.89 to 4.37)	1.11 (0.73 to 1.71)
Co-Cr (13 patients)	1.24 (0.71 to 2.17)	2.59 (2.18 to 3.08)
SS (6 patients)	0.64 (0.33 to 1.26)	0.70 (0.49 to 0.99)

Table III. Log-linear regression of aneuploidy index with respect to predictors (see text)

Rate predictor	Unadjusted analysis rate ratio (95% CI)	p value	Adjusted analysis rate ratio (95% CI)	p value
Primary (30 patients)	1.00		1.00	
Ti (13 patients)	5.43 (3.00 to 9.85)	<0.0005	5.08 (2.79 to 9.23)	<0.0005
Co-Cr (11 patients)	2.35 (1.17 to 4.72)	0.016	2.75 (1.33 to 5.68)	0.006
SS (6 patients)	1.21 (0.55 to 2.68)	0.639	1.13 (0.44 to 2.86)	0.804
Age (per decade)	0.85 (0.71 to 1.01)	0.059	0.87 (0.76 to 1.00)	0.053
Radiographs in 8 years (per 5)	1.52 (0.94 to 2.44)	0.086	1.27 (0.85 to 1.90)	0.245
Gender				
Female (ref)	1.00		1.00	
Male	1.39 (0.73 to 2.66)	0.319	0.99 (0.63 to 1.56)	0.982
Smoking status				
Non-smoker (ref)	1.00		1.00	
Current smoker	1.38 (0.53 to 3.61)	0.506	1.41 (0.80 to 2.41)	0.236
Ex-smoker	0.93 (0.45 to 1.89)	0.832	1.30 (0.63 to 2.67)	0.479
Baseline index (adjusted)			0.46 (0.27 to 0.80)	

Table IV. Log-linear regression of translocation index with respect to predictors (see text)

Rate predictor	Unadjusted analysis rate ratio (95% CI)	p value	Adjusted analysis rate ratio (95% CI)	p value
Primary (30 patients)	1.00		1.00	
Ti (13 patients)	1.54 (0.93 to 2.57)	0.094	1.55 (0.94 to 2.57)	0.088
Co-Cr (11 patients)	3.60 (2.61 to 4.97)	<0.0005	3.39 (2.49 to 4.61)	<0.005
SS (6 patients)	0.97 (0.62 to 1.51)	0.889	0.998 (0.64 to 1.50)	0.941
Age (per decade)	1.24 (1.08 to 1.43)	0.003	1.06 (0.98 to 1.14)	0.153
Radiographs in 8 years (per 5)	0.94 (0.73 to 1.20)	0.593	0.94 (0.74 to 1.19)	0.607
Gender				
Female (ref)	1.00		1.00	
Male	0.89 (0.59 to 1.33)	0.560	1.01 (0.78 to 1.29)	0.965
Smoking status				
Non-smoker (ref)	1.00		1.00	
Current smoker	1.09 (0.62 to 1.90)	0.768	0.98 (0.70 to 1.37)	0.893
Ex-smoker	0.88 (0.53 to 1.47)	0.621	0.83 (0.62 to 1.11)	0.203
Baseline index (adjusted)			0.75 (0.53 to 1.05)	

We compared the raw data for the patients with the considerable data available in the general population for the index of chromosomal translocations (but not aneuploidy). Of the patients at revision arthroplasty, 45% had an incidence of chromosomal translocations greater than two standard deviations above the mean of the general population ($p < 0.05$) and 32% had values greater than three standard deviations from this mean ($p < 0.01$).

The highest level of chromosomal translocations was found in three patients: one with a Ring Mark 3 metal-on-metal prosthesis in situ for 19 years, one with a McKee Farrar Co-Cr prosthesis in situ for 28 years, and one with an Exeter stainless stem which had been in situ for one year when it had fractured. Two of the patients in the study (1 control, 1 revision) had a history of occupational exposure in the chemical industry; one of these (control, case 27) showed an increase in translocations.

The indices of chromosomal translocations and aneu-

ploidy were different in patients with different implants. Those with metal-on-plastic prostheses made of TiVaAl alloy had an increase in aneuploidy but no significant increase in chromosomal translocations. Patients with Co-Cr replacements had an increase in chromosomal translocations but no increase in aneuploidy and those with SS prostheses had no increase in either aneuploidy or chromosomal translocations (Table II).

We reanalysed the data to take account of the confounding variables of age, the number of diagnostic radiographs in the last year or last eight years, gender and smoking status (Tables III and IV). There were minor changes in aneuploidy and chromosomal translocations in association with the individual confounding variables, but these did not reach statistical significance (Tables III and IV). There was a tendency for aneuploidy to decrease with age, to increase with the number of radiographs and to increase with smoking. Likewise, there was a tendency for chromosomal translocations to increase with age. When the data had been adjusted for these confounding variables there was still a highly significant, fivefold increase in aneuploidy in patients with Ti-alloy-based prostheses, with no significant change in chromosomal translocations. By contrast, there was a 2.5-fold increase in aneuploidy and a 3.5-fold increase in chromosomal translocations in patients with Co-Cr prostheses. There were no changes in either of these in patients with SS prostheses (Tables III and IV).

Analysis of the data in the revision group in Table I shows the difference in the induction of aneuploidy and chromosomal translocations. Apart from one patient, those with high chromosomal translocations (cases 1, 6, 7, 18, 20, 22 to 24, 26 and 30) were different from those with high aneuploidy (cases 4, 5, 12, 16, 17, 20, 21, 27 and 28). Five out of the ten patients with a high index of chromosomal translocations had blood levels of Co or Cr which were above the normal range (Co>0.5 ppb; Cr>2 ppb; Table I). Six of the eight patients with levels of Co or Cr above the normal range had high levels of chromosomal translocations (>mean+2SD of the general population data). By contrast, one of the nine with high aneuploidy had a level of Co or Cr which was outside the normal range observed.

Discussion

Our study has shown an increase in symmetrical non-lethal chromosomal translocations and of aneuploidy in the peripheral blood of patients at revision arthroplasty compared with those having a primary replacement. This was not accounted for by age, gender, smoking or taking NSAIDs. It was also not related to previous diagnostic radiographs. No relationship was seen between the levels of aneuploidy or chromosomal translocations and the number of radiographs either in the last eight years or in the last year. Nor did we see an increase of the type of chromosomal damage which was specific to exposure to x-rays such as chromosomal breaks and dicentric chromosomes. This was also not noted in our previous study.[55]

Our previous data showed an increase in asymmetrical chromosomal aberrations in bone-marrow cells adjacent to a worn prosthesis, which was similar to that in bone marrow away from the prosthesis and in bone marrow at primary arthroplasty. Furthermore, two patients had a clonal expansion of lymphocytes at the longest interval between primary and revision arthroplasty.[5,9] Therefore, we can now conclude that there are clastogenic changes in both the peripheral blood and the bone marrow of patients at revision arthroplasty and that these consist of both potentially lethal and non-lethal in type.

An unexpected finding in our study was that the form of mutagenic change appeared to depend on the metal alloy composition of the wear debris. Patients with Ti prostheses had a nearly fivefold increase in aneuploidy but no change in chromosomal translocations if account was taken of the confounding variables of gender, age and smoking. Those with Co-Cr prostheses had a 2.5-fold increase in aneuploidy and a 3.5-fold increase in chromosomal translocations. Patients with SS prostheses had no change in either aneuploidy or chromosomal translocations. It therefore appears that different metal alloys provoke a spectrum of biological changes and that these include clastogenic, inflammatory and toxic reactions.[25]

The mechanism of the changes which we have seen is not clear and our study does not prove that it is the metal in the wear debris which is responsible. The differential reaction described above, however, suggests that this is likely. It is known that certain compounds of transition metals including Cr and Ni are toxic and mutagenic.[26,27] In general, in metal genotoxicity there appears to be two predominant modes of action involving either an induction of oxidative damage or an interaction with DNA repair processes.[28] One of the mechanisms of direct damage is via the generation of active oxygen species in a fenton-like reaction. In addition, the DNA may be targeted by metal ions which enter the cell with the formation of DNA-metal adducts. It is possible that such mechanisms may account for the induction of the chromosomal translocations which we have seen in our study. Relatively less is known about the induction of aneuploidy. There has been a report, however, that Va is associated with an increase in aneuploidy of acrocentric chromosomes.[29] This may therefore explain the difference between the patients with Co-Cr and TiVaAl prostheses.

The fact that there are mutagenic changes in peripheral blood lymphocytes does not prove that there will be clinical changes in the patient in the long term. Our study does suggest, however, that the biological reaction to a worn prosthesis may depend on the composition of the alloy in it. There are some discrepancies in the epidemiological data concerning any possible long-term risks after joint replacement surgery.[30] The results of our study suggest that, in future, such investigations should compare patients with

prostheses of different alloy composition as well as of different design. Patients with high and low metal levels should also be included in these studies.

Chromosomal translocations and aneuploidy are genetic changes in normal patients which are known to accumulate with time, as a result of increasing age and other environmental factors such as smoking. Our study has shown that there is a statistically significant increase above normal background levels of non-specific translocations and aneuploidy at revision arthroplasty and that the nature of the change may depend in part on the type of prosthesis. Chromosome painting is a useful biomarker of genetic damage and coupled with measurement of metal levels may provide one way of monitoring the long-term biological effects of joint replacement surgery using different materials.

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