

A correlation found between gold concentration in blood and patch test reactions in patients with coronary stents

SUSANNE EKQVIST¹, CECILIA SVEDMAN¹, THOMAS LUNDH², HALVON MÖLLER¹, JONAS BJÖRK³ AND MAGNUS BRUZE¹

¹Department of Occupational and Environmental Dermatology, Lund University, Malmö University Hospital, Malmö, ²Department of Occupational and Environmental Medicine, Lund University Hospital, Lund,

³Competence Centre for Clinical Research, Lund University Hospital, Lund, Sweden

Background: Patients with dental gold restorations are known to have a higher level of gold concentration in blood (B-Au).

Objectives: To further investigate, in a study on patients with intracoronary stents and contact allergy to metals, the gold and nickel release from stainless steel stent with (Au stent) and without (Ni stent) gold plating.

Method: A total of 460 patients treated with stenting underwent patch testing with metals, and information on gold and nickel exposure and blood samples were collected. About 200 blood samples were randomly selected and the analysis of B-Au and nickel concentration in blood (B-Ni) was made using inductively coupled plasma mass spectrometry.

Results: There was a correlation between the intensity of Au patch test reaction and B-Au ($P < 0.001$). This correlation could not be seen between Ni patch test reaction and B-Ni. A Au stent gave a fivefold higher B-Au than a Ni stent.

Conclusions: Gold is released from the Au stent and patients with a Au stent have a fivefold higher B-Au than patients with an Ni stent. The patch test reactions for gold were correlated with B-Au.

Key words: B-Au; B-Ni; contact allergy; metals; patch test reaction; stent. © Blackwell Munksgaard, 2008.

Accepted for publication 13 March 2008

Gold (1, 2) and nickel are metals that may cause contact allergy in a substantial number of individuals exposed to the metals. Contact allergy to these metals was shown to be correlated to female sex, wearing of jewellery and ear piercing (3, 4). Presence of dental gold has also been shown to be correlated to contact allergy to gold (5). Previous studies on dental restorations and gold concentration in blood (B-Au) have shown that B-Au is not only related to dental gold and the number of dental restorations (6) but also to contact allergy to gold (7). We have recently reported our findings regarding contact allergy to gold, nickel and other metals in 484 patients who had received a stainless steel stent (bare metal) with or without gold plating (Au stent and Ni stent, respectively) (8). Even if we could not prove

induction of contact allergy because of the stents, the result strongly suggested induction of contact allergy because of the Au stents. Furthermore, the result indicates that the Ni stent should not be ruled out as a risk factor for induction of contact allergy to this metal. The purpose of the present study was to investigate if the stents in patients with Au and Ni stent, respectively, release gold and nickel to the circulatory system and if there is any differences in B-Au and nickel concentration in blood (B-Ni) between the two groups.

Materials and Methods

Study sample

A total of 484 patients [female (F): 103; male (M): 381] participated in the study (8). All patients had

been treated with percutaneous transluminal coronary angioplasty (PTCA) and stenting. It was possible to obtain a venous blood sample before patch testing in 460 patients. Twenty-four patients had received both Au and Ni stents and their blood samples were therefore excluded. From 436 blood samples, we randomly selected 100 samples from patients with a Au stent (F: 30; M: 70) and 100 samples from patients with a Ni stent (F: 30; M: 70). The distribution between males and females in each group was chosen to be equivalent to the distribution in the entire patient material.

Questionnaire and medical history

A questionnaire was sent out together with the invitation to participate in the study. The questionnaire covered areas regarding piercing, nicotine habits, dental gold restorations and medical and occupational exposure to gold. A short standardized medical history was taken at the baseline visit. Information about risk factors for atherosclerotic disease, medication and skin disease was collected. The dermatologist who questioned the patient was unaware of whether the patient had been stented with a Au or a Ni stent.

Stents

Each patient received one of the two types of stents manufactured from the same stainless steel alloy, 316L, but differed in the aspect that one type (Au stent) was electroplated with 99.9% pure gold, whereas the other type (Ni stent) was not. Gold plating is mainly used to improve stent visibility under fluoroscopy. Stainless steel 316L is an alloy containing known sensitizing metals such as nickel, chromium and molybdenum and is commonly used by several manufacturers of stents. No clinical parameters directed the choice between stents during PTCA and stenting.

Patch testing

The patch testing procedure has been described in detail elsewhere (8). All patients underwent patch testing with the European baseline series (9) supplemented with test preparations representing

metals, preservatives, plastics and corticosteroids. The patch tests were removed after 2D and readings were performed according to International Contact Dermatitis Research Group (ICDRG) guidelines (10) on 3D and 7D. The tests were read in a blinded way by a dermatologist unaware of the responses to questionnaires and B-Au and B-Ni. The patients were not informed of the test result until testing and readings were finished. Gold sodium thiosulfate (GSTS) was patch tested in 2.0% w/w petrolatum. If the test reaction on 3D was doubtful to gold or nickel, the patient was retested 3D with the/these metals (Table 1). The retests were read on 7D and 10D.

Ethical approval for this study was given by the Ethics Committee of the Faculty of Medicine, Lund University.

Blood sampling and storage

Venous whole blood was drawn at the baseline visit before the patch testing. The test tubes used were Venoject II Lithium – Heparin 10 ml (Terumo Europe N.V., Leuven, Belgium) and two tubes for each patient were collected. The blood was stored in a freezer at -20°C until analysis.

Gold and nickel determination

Blood analyses were conducted by the Department of Occupational and Environmental Medicine at Lund University Hospital, Lund, Sweden.

The concentration of Au and Ni in blood was determined by inductively coupled plasma mass spectrometry (ICP-MS) (Thermo X7; Thermo Elemental, Winsford, UK) equipped with a conical glass nebulizer (Glass Expansion, Melbourne, Australia) with 1 ml/min uptake and a peltier chilled, conical impact bead spray chamber (Thermo Elemental). The gas flows were 13 l/min for the cooling gas, 1.1 l/min for the auxiliary gas and 0.93 ml/min for nebulizer gas. The blood samples were diluted 10 times with an alkaline solution according to Barany et al. (11). Using the dilute solution as a carrier/rinsing fluid, the samples were introduced in a segment flow mode. The samples were analysed in peak jumping mode, 100 sweeps and 1 point per peak, 50 ms dwell time for 197Au

Table 1. Gold and nickel salt test preparations tested in the stented patients

Test preparations	Concentration	Vehicle	Concentration at retest	Vehicle
Gold sodium thiosulfate (28)*	2.0% w/w	pet.	5.0% w/w†	pet.
Nickel sulfate hexahydrate (16)*	5.0% w/w	pet.	30.0%, 15.0% w/v (29, 30)†	aq.

aq., water; pet., petrolatum; w, weight; v, volume.

*Purchased from Chemotechnique Diagnostics, Vellinge, Sweden.

†Prepared at the Department of Occupational and Environmental Dermatology, Malmö, Sweden.

and ^{60}Ni , 10 ms dwell time for indium (^{197}In) and thallium (^{205}Tl) used as internal standards. The detection limit, calculated as three times the standard deviation (SD) of the blank was for Au $0.001\text{ }\mu\text{g/l}$ and Ni $0.47\text{ }\mu\text{g/l}$, respectively.

For Ni, the analytical accuracy was checked against a commercial reference material (trace elements whole blood; batch MR4206; SERO AS, Billingstad, Norway). The result obtained for Ni was 1.2 ± 0.22 (mean $\pm$ SD) versus the recommended $1.0\text{--}2.2\text{ }\mu\text{g/l}$.

As no certified reference sample for B-Au is available, outdated blood from blood donors spiked with $0.10\text{ }\mu\text{g Au/l}$ was used for the assessment of the analysis method. A measurement of 0.093 ± 0.008 (mean $\pm$ SD; $n = 19$) was obtained.

Statistical analyses

The statistical analyses were conducted using SPSS release 12.0.1 (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered to be statistically significant. Fisher's exact test was used to calculate the difference in stent types with concentration levels under the detection limit. Differences in B-Au and B-Ni between patients with stents with or without gold plating were tested using Mann–Whitney non-parametric test. Differences in B-Au because of the metal used in the stent were investigated further using a multivariate regression model, controlling for dental gold, age, ear piercing and sex. The dependent variable, B-Au, was positively skewed and the regression model was therefore established for the natural logarithm of B-Au. Spearman's correlation was used to investigate the correlation between B-Au and the intensity of the patch test reactions.

Results

The questionnaire and medical history

There were no marked/important differences in baseline characteristics between patients with Ni and Au stents (Table 2).

Gold and nickel concentration in blood

There was a correlation between the intensity of Au test reaction and B-Au ($P < 0.001$) (Fig. 1). This correlation could not be found between Ni test reaction and B-Ni. The comparison of B-Ni and B-Au between variables investigated is shown in Table 3. Patients with a Au stent had a statistically significantly higher B-Au than those with a Ni stent ($P < 0.001$). B-Au below the detection limit was observed in 30 (15%) blood samples, and in all from patients with Ni stent (Fisher's

Table 2. Baseline patient characteristics from questionnaire, medical history and patch testing

	Patients with Au stent		Patients with Ni stent	
Age, years (mean $\pm$ SD)	65.8 ± 9.5		65.6 ± 9.5	
Female:male, patients	30:70		30:70	
	%	n	%	n
Dental gold*	61.7	58/94	65.7	65/99
Ear piercing*	21.0	21/100	19.2	19/99
Contact allergy to gold	39.0	39/100	34.0	34/100
Contact allergy to nickel	9.0	9/100	15.0	15/100
Smoking*	15.3	15/98	15.2	15/99
Symptoms from oral mucosa*	12.4	12/97	10.8	10/93
Joint or muscle pain*	50.5	47/93	43.5	40/92
Any skin disease†	34.7	33/95	22.4	22/98

Au, gold; Ni, nickel; SD, standard deviation; n, patients with the condition out of patient answers or tested.

*Questionnaire sent out with invitation letter.

†Medical history at baseline visit.

exact test; $P < 0.001$). Patients with a contact allergy to gold had a statistically significantly higher B-Au than patients without such allergy ($P < 0.001$). There was statistically significant correlation between B-Au and age (Spearman's correlations; $P = 0.008$), the higher the age the higher the B-Au. There was no statistically significant correlation between the combined stent length and B-Au in patients with Au stent ($P > 0.3$).

A multivariate regression model, where known factors of significance (risk factors) for high B-Au

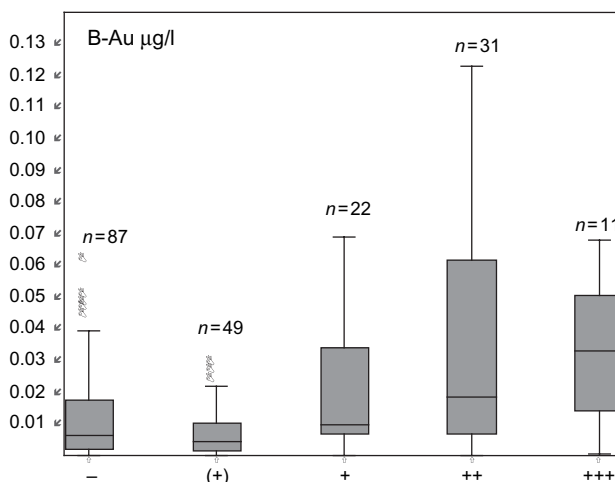


Fig. 1. The correlation between patch test reactions for gold sodium thiosulfate 2.0% in petrolatum and gold concentration in blood (B-Au); the higher the B-Au value, the stronger the patch test reaction ($P < 0.001$, Spearman's correlation). The length of the box is the interquartile range (IQR), 25–75 quartiles. The vertical line in the box is the median. Values more than three IQRs from the end of a box are labelled as extreme (extreme values are not shown). Values more than 1.5 IQRs but less than 3 IQRs from the end of the box are labelled as outliers. *outliers; n, number of patients.

Table 3. Comparison of B-Au and B-Ni in µg/l between variables investigated

Variables	B-Au (median)	Quartile (25–75)	P value	n	B-Ni (median)	Quartile (25–75)	P value
Ni stent	0.003	0.001–0.016	<0.001	100	0.669	0.431–0.970	>0.3
Au stent	0.011	0.004–0.034		100	1.009	0.421–1.218	
All stents	0.008	0.002–0.023		200	0.627	0.427–1.028	
No gold allergy	0.006	0.002–0.017	<0.001	127	0.719	0.454–1.179	0.01
Gold allergy	0.013	0.006–0.044		73	0.524	0.387–0.826	
No nickel allergy	0.009	0.002–0.025	0.09	176	0.598	0.426–1.025	0.14
Nickel allergy	0.005	0.001–0.013		24	0.862	0.440–1.382	
No dental gold	0.003	0.000–0.007	<0.001	70	0.574	0.351–0.957	0.21
Dental gold	0.014	0.006–0.023		123	0.660	0.434–1.088	
No joint or muscle pain	0.006	0.002–0.022	0.05	98	0.569	0.429–1.021	>0.3
Joint or muscle pain	0.009	0.004–0.029		87	0.705	0.419–0.977	
No skin disease	0.008	0.002–0.022	0.29	138	0.634	0.428–0.989	>0.3
Any skin disease	0.009	0.003–0.029		55	0.595	0.419–1.179	
No piercing	0.009	0.002–0.025	>0.3	159	0.610	0.426–1.025	>0.3
Piercing	0.006	0.002–0.015		40	0.642	0.408–1.123	
Female gender	0.009	0.003–0.024	>0.3	60	0.729	0.458–1.123	0.15
Male gender	0.007	0.002–0.022		140	0.602	0.402–0.969	
No oral mucosa problem	0.008	0.002–0.024	>0.3	168	0.607	0.425–1.025	>0.3
Oral mucosa problem	0.009	0.003–0.023		22	0.584	0.402–1.058	
No present smoking	0.008	0.002–0.023	>0.3	167	0.598	0.429–1.024	>0.3
Present smoking	0.006	0.002–0.031		30	0.806	0.432–1.225	
No restenosis	0.008	0.002–0.025	>0.3	166	0.634	0.434–1.027	>0.3
Restenosis	0.017	0.003–0.023		34	0.597	0.346–1.102	

B-Au, gold concentration in blood; B-Ni, nickel concentration in blood.

were considered, showed that a Au stent gave a fivefold higher concentration of B-Au than an Ni stent (Table 4).

Discussion

We found a statistically significantly higher B-Au in patients with a Au stent than in patients with a Ni stent (Tables 3 and 4). Possible routes for gold absorption are directly from circulating blood and through the coronary vessel wall. For this to occur, ionization of the metallic gold in the gold-plated stent is required. Our results strongly indicate that gold is released from gold-plated stents.

The high rate of contact allergy to gold in the whole study population suggests previous sensitization (Table 1). This result and the possibility of sensitization through the Au stent are discussed elsewhere (8).

Table 4. Multivariate model for the association between stent type and B-Au

Dependent variable: B-Au	CR*	P value	95% CR
Au stent versus Ni stent	5.1	<0.000	3.2 8.0
Dental gold	4.7	<0.000	2.9 7.6
Gold allergy	1.6	0.048	1.0 2.6
Age	1.026	0.042	1.0 1.7
Smoking	1.6	0.154	0.8 3.1

B-Au, gold concentration in blood; CR, concentration ratio.

*CR is the relative difference in B-Au between patients with and without the condition. For age, CR is the relative difference in B-Au between patients that differ 1 year in age.

B-Au was higher in patients with contact allergy to gold compared with patients without such allergy. The result became weaker but still statistically significant in our multivariate model because contact allergy to gold is strongly correlated to dental gold (Table 4). Recent results in the present project show that patients with a Au allergy and a Au stent have a threefold increased risk of developing restenosis compared with patients without these conditions (12). Smoking has been shown to be a risk factor for a high gold concentration in the red blood cells (RBC) of rheumatoid arthritis (RA) patients receiving gold therapy (13, 14). Our analytical method used was in whole blood and we could not see any association between smoking habits and B-Au. Joint and/or muscle pain seemed to be correlated with high B-Au, but the multivariate analysis showed no association because the symptoms were strongly correlated with age and dental gold. In the multivariate model, this variable could, therefore, be removed without any influence on other variables. Dental gold has been shown to be a risk factor for high B-Au (6, 15). Our results confirm these previous findings with high significance (Table 3).

Our findings regarding the patch test reaction intensity for gold and the correlation to B-Au is highly interesting. The result points towards the patch test reaction for gold being correlated to the level of B-Au, i.e., the higher the B-Au the stronger the patch test reaction (Fig. 1). This correlation could not be seen in B-Ni and nickel patch test reactions.

B-Ni did not differ between Ni- and Au-stented patients (Table 3). Both stents were manufactured from the stainless steel alloy 316L but differed in the aspect that one was gold coated. When the Au stent is expanded and the surface partly broken both stainless steel and gold will then be exposed to body fluids and a galvanic couple will be formed (16). In this case, the rate of corrosion and ion release may be stronger than it would be in the same stainless steel without gold plating. However, we could not see any result pointing towards B-Ni being higher in patients with Au-stent.

B-Au levels

In a study by Ahnslide et al. (6) on 80 dermatitis patients (43 of these with dental gold restorations), there was a correlation between B-Au and the number of dental gold restorations; the median B-Au was <0.04 , range <0.04 – 0.20 $\mu\text{g/l}$ in the entire material. Only about 50% of the B-Au levels in the entire material were above the detection limit of 0.04 $\mu\text{g/l}$. The analytic method used was ICP-MS. B-Au, obtained by use of neutron activation analysis, in a general population was reported by Minoia et al. (17) with a mean of 0.045 ± 0.0007 $\mu\text{g/l}$ ($n = 35$; range 0.002 – 0.06 $\mu\text{g/l}$). A higher B-Au, a mean of 0.22 $\mu\text{g/l}$, range 0.131 – 0.41 $\mu\text{g/l}$, obtained by sector field ICP-MS, was reported by Begerow et al. (18) in seven individuals with no known exposure to precious metals. In our patients with Au-stent, the median B-Au was 0.011 $\mu\text{g/l}$ (quartiles 0.004 – 0.034). In a previous study at our department, B-Au in 20 patients with a Au stent only were analysed (7). The median B-Au in these 20 patients was 0.007 $\mu\text{g/l}$ (quartiles 0.005 – 0.045) obtained by ICP-MS. These B-Au levels are in reasonable agreement with our present results.

B-Ni levels

Tentative reference values for B-Ni obtained from healthy populations were reported in a review article by Templeton et al. (19). In four studies, they found a mean value from the lowest 0.34 ± 0.28 $\mu\text{g/l}$, range >0.05 – 1.05 $\mu\text{g/l}$, to the highest mean 2.3 ± 0.16 $\mu\text{g/l}$, range 0.6 – 3.8 $\mu\text{g/l}$, all obtained by use of neutron activation analysis. We found a median value of 0.627 $\mu\text{g/l}$ (quartiles 0.427 – 1.028) in the entire study population.

What might be the clinical relevance of a high B-Au?

The fact that the dose of a sensitizer is significant for the allergic response is well known for both topical and systemic exposure to the allergen.

With regard to topical exposure, the decisive factors for the contact allergic response have been considered to be the individual degree of reactivity and the dose, that is, the number of molecules given per unit area of skin. However, the results of this study indicate that also the concentration level in blood of a contact sensitizer, at least concerning gold, is significant for the skin reactivity. If these results are confirmed in scientifically conducted and controlled prospective provocation tests, this means a fundamental change in our preventive approach towards allergic contact dermatitis as not only the topical exposure but also the systemic exposure have to be decreased to prevent allergic contact dermatitis. Indeed, systemic exposure to a sensitizer alone may cause systemic allergic dermatitis but systemic exposure has never, to the best of our knowledge, been suggested as a factor that influences the skin reactivity on topical exposure.

In patients treated with a gold medication, the frequency of side-effects varies between 30% and 60% in different investigations (20). In a study on cutaneous drug reactions, the risk seemed to be highest for gold compounds (21). The development of a localized reaction under gold jewellery from the first dose of gold therapy in RA patients has been described; a contact allergy to gold was, however, not verified (22, 23). In a study on RA patients with gold dermatitis and gold sodium thiomalate (GSTM) therapy by Rasanen et al. (20), one gold-allergic patient reacted at the first dose of gold therapy not only with vesicular eczematous reactions under her gold jewellery but also with widespread erythema and fever. This reaction resembles those described in a provocation study by Möller et al. (24), where an intramuscular challenge of GSTM was given to gold-allergic patients. Only the patients in the gold-allergic group reacted as previously described. Also, a flare-up reaction at contact allergy sites in a gold-treated rheumatic patient has been described in a case report by Möller et al. (25). The B-Au values in RA patients with gold therapy are obviously much higher than the B-Au values in the present study.

In another study on the prevalence of contact allergy to gold in RA patients previously treated with gold compared with RA patients intended for such treatment, the result indicated a decrease of contact allergy to gold after gold treatment (26).

There are other interesting investigations to take into consideration when thinking of the clinical relevance of a high B-Au. Graham et al. (13) studied RA patients on GSTM therapy and found that the gold concentration in RBC was considerably higher in smokers than in non-smokers.

Smoking increases the uptake of gold into RBC. In the same study, the incidence of side-effects was similar in smokers and non-smokers. However, the time of onset of side-effects was significantly shorter in smokers than in non-smokers. One possible explanation of this might be the smokers' higher B-Au in the RBC. Another study reported that dermal side-effects after long-term gold therapy occurred in patients with the highest concentration of gold in RBC (27). Altogether, this information seems to be important when we consider the clinical relevance of high B-Au.

Gold plated stents, as far as we know, are no longer in use but gold exists in several other implants like dental, eyelid gold weight, and middle ear implants as well as drug delivery chips.

Conclusions

Gold is released from the Au stent and patients with a Au stent have a fivefold increased B-Au concentration compared with patients with a Ni stent. Other factors of significance for a higher B-Au were dental gold, gold allergy and high age. There was a correlation between B-Au and the patch test reaction to gold, the higher B-Au the stronger the patch test reaction. The same correlation could not be found between B-Ni and nickel patch test reaction.

References

1. Björkner B, Bruze M, Möller H. High frequency of contact allergy to gold sodium thiosulfate. An indication of gold allergy? *Contact Dermatitis* 1994; 30: 144–151.
2. Fowler J Jr, Taylor J, Storrs F et al. Gold allergy in North America. *Am J Contact Dermat* 2001; 12: 3–5.
3. Nakada T, Iijima M, Nakayama H, Maibach H I. Role of ear piercing in metal allergic contact dermatitis. *Contact Dermatitis* 1997; 36: 233–236.
4. Sabroe R A, Sharp L A, Peachey R D. Contact allergy to gold sodium thiosulfate. *Contact Dermatitis* 1996; 34: 345–348.
5. Ahlgren C, Ahnlied I, Björkner B, Bruze M, Liedholm R, Möller H, Nilner K. Contact allergy to gold is correlated to dental gold. *Acta Derm Venereol* 2002; 82: 41–44.
6. Ahnlied I, Ahlgren C, Björkner B, Bruze M, Lundh T, Möller H, Nilner K, Schutz A. Gold concentration in blood in relation to the number of gold restorations and contact allergy to gold. *Acta Odontol Scand* 2002; 60: 301–305.
7. Svedman C, Lundh T, Tillman C, Moller H, Gustavsson C G, Bruze M. Gold concentration in blood in patients with gold-plated stents. *Contact Dermatitis* 2006; 54: 221–222.
8. Ekqvist S, Svedman C, Möller H et al. High frequency of contact allergy to gold in patients with endovascular coronary stents. *Br J Dermatol* 2007; 157: 730–738.
9. Bruze M, Goossens A, Gruvberger B. Recommendation to include methylidibromo glutaronitrile in the European standard patch test series. *Contact Dermatitis* 2005; 52: 24–28.
10. Wilkinson D S, Fregert S, Magnusson B et al. Terminology of contact dermatitis. *Acta Derm Venereol* 1970; 50: 287–292.
11. Barany E, Bergdahl I-A, Schutz A, Skerfving S, Oskarsson A. Inductively coupled plasma mass spectrometry for direct multi-element analysis of diluted human blood and serum. *J Anal At Spectrom* 1997; 1005–1009.
12. Svedman C, Ekqvist S, Möller H et al. A correlation found between contact allergy to stent material and restenosis of the coronary arteries (submitted).
13. Graham G G, Haavisto T M, McNaught P J, Browne C D, Champion G D. The effect of smoking on the distribution of gold in blood. *J Rheumatol* 1982; 9: 527–531.
14. James D W, Ludvigsen N W, Cleland L G, Milazzo S C. The influence of cigarette smoking on blood gold distribution during chrysotherapy. *J Rheumatol* 1982; 9: 532–535.
15. Drasch G, Muss C, Roeder G. Gold and palladium burden from dental restoration materials. *J Trace Elem Med Biol* 2000; 14: 71–75.
16. Gotman I. Characteristics of metals used in implants. *J Endourol* 1997; 11: 383–389.
17. Minoia C, Sabbioni E, Apostoli P et al. Trace element reference values in tissues from inhabitants of the European community. I. A study of 46 elements in urine, blood and serum of Italian subjects. *Sci Total Environ* 1990; 95: 89–105.
18. Begerow J, Turfeld M, Dunemann L. Determination of physiological palladium, platinum, iridium and gold levels in human blood using double focusing magnetic sector field inductively coupled plasma mass spectrometry. *JAAS* 1997; 12: 1095–1098.
19. Templeton D M, Sunderman F W Jr, Herber R F. Tentative reference values for nickel concentrations in human serum, plasma, blood, and urine: evaluation according to the TRACY protocol. *Sci Total Environ* 1994; 148: 243–251.
20. Rasanen L, Kaipainen-Seppanen O, Myllykangas-Luosjarvi R, Kasanen T, Pollari P, Saloranta P, Horsmanheimo M. Hypersensitivity to gold in gold sodium thiomalate-induced dermatosis. *Br J Dermatol* 1999; 141: 683–688.
21. Swanbeck G, Dahlberg E. Cutaneous drug reactions. An attempt to quantitative estimation. *Arch Dermatol Res* 1992; 284: 215–218.
22. Fulton R A, Sturrock R D, Capell H. Another hazard of gold therapy? *Ann Rheum Dis* 1982; 41: 100–101.
23. Rennie J. Local gold toxicity. *Br Med J* 1977; 1: 446–447.
24. Möller H, Ohlsson K, Linder C, Björkner B, Bruze M. The flare-up reactions after systemic provocation in contact allergy to nickel and gold. *Contact Dermatitis* 1999; 40: 200–204.
25. Möller H, Larsson A, Björkner B, Bruze M, Hagstam A. Flare-up at contact allergy sites in a gold-treated rheumatic patient. *Acta Derm Venereol* 1996; 76: 55–58.
26. Möller H, Svensson A, Björkner B, Bruze M, Lindroth Y, Manthorpe R, Theander J. Contact allergy to gold and gold therapy in patients with rheumatoid arthritis. *Acta Derm Venereol* 1997; 77: 370–373.
27. Pedersen S M, Graabæk P M. Gold in erythrocytes, whole blood, and plasma during long-term chrysotherapy. *Ann Rheum Dis* 1980; 39: 576–579.
28. Bruze M, Björkner B, Möller H. Patch testing with gold sodium thiosulfate. In: *Jadassohn Centenary Congress*, London, UK, 9–12 October 1996 (Abstract no. 49, p. 14).
29. Bruze M. Patch testing. In: *Practical Contact Dermatitis. A handbook for the practitioner*, Guin J (ed): McGraw-Hill, Inc., New York, 1995: 41–62.
30. Dooms-Goossens A, Naert C, Chrispeels M T et al. Is a 5% nickel sulphate patch test concentration adequate? *Contact Dermatitis* 1980; 6: 232.

Address:

Susanne Ekqvist
 Department of Occupational and Environmental Dermatology
 Malmö University Hospital
 Ing 73 plan 5
 SE-205 02 Malmö
 Sweden
 Tel: +46 40-337863
 Fax: +46 40-331192
 e-mail: susanne.ekqvist@med.lu.se