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Morphology of Endogenous Flare-up Reactions in Contact Allergy to Gold

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In a double-blind study, 20 patients with contact allergy to gold were given an intramuscular injection of gold sodium thiomalate or placebo, inducing a clinical and histological flare-up of healed patch test sites in the gold-injected but not in the placebo group. The test area of the placebo group showed some perivascular lymphocytic foci (UCHL-1+) and vascular endothelial ELAM-1 staining. The gold group, with flare-up, showed larger and more extensive lymphocytic foci with ELAM-1+ endothelium as well as lymphocytic epidermotropism. CD1a+ LC cells were downgraded, tryptase+ mast cells accumulated and CD68+ monocytes/macrophages markedly increased. Probably, a significant part of the tissue priming as a result of patch testing comprises memory T-cells and endothelial ELAM-1 upgrading, but blood-borne CD68+ monocytes may also be instrumental in the flare-up. ***Key words: skin; immunocytochemistry.***

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Eczematous flare-up reactions frequently occur during the course of allergic contact dermatitis. This implies a reactivation of a previous contact dermatitis, be that accidental at an earlier site of e.g. a nickel-containing buckle, or intentional at a former patch test site. Flare-up reactions are easily provoked by systemic exposure to the allergen. Pompholyx is a common clinical expression of such a flare-up, but exacerbating eczematous patches may occur anywhere on the body (1).

Contact allergy to gold sodium thiosulfate (GSTS) has recently been recorded in high frequency among patients routinely patch-tested for eczematous disease (2–4). Patients with contact allergy to GSTS also react to gold sodium thiomalate (GSTM), epicutaneously as well as intradermally (5). We have recently shown (6) that patients with contact allergy to gold regularly react with different cutaneous and general symptoms and signs when exposed parenterally to GSTM.

Although clinically important, the pathogenesis of the cutaneous flare-up in contact dermatitis has not been sufficiently clarified. In order to obtain a better understanding of the skin memory function in contact allergy, the flaring skin as well as its quiescent base have been studied in the present work by morphological methods, using contact allergy to gold as a model.

MATERIAL AND METHODS

Twenty patients patch-tested with a standard series and found positive to GSTS (0.5% pet) were invited to a double-blind provocation study. Informed consent was obtained, as well as permission from the Ethics committee of the Lund University Medical Faculty.

The patients were patch-tested with serial aqueous dilutions of GSTS (Chemotechnique Diagnostics) and GSTM (Rhône-Poulenc Rorer), stepwise by a factor of $\sqrt{10}$, starting with 5% and 36%, respectively. In preliminary (unpublished) observations these test concentrations had been shown to be non-irritant. The patients were also tested with auranofin (Ridaura ® SmithKline Beecham) 47%, the highest dispensable concentration. If the patient at the preliminary patch test had also shown a positive reaction to another standard allergen, this was now repeated. Thus, 5 subjects were in addition tested with nickel sulfate, and one each with cobalt chloride, neomycin sulfate, p-phenylenediamine base, and the preservatives Kathon CG, thimerosal, and Euxyl K 400.

The patch tests were applied for 48 h with Finn chambers ® on Scanpor®. Since patch test reactions to gold salts usually are long-lasting and often develop late (7), they were read on day 7 only.

Five weeks later, i.e. 6 weeks after the test application, the patients were examined and residual test reactions recorded. They were then given an intramuscular injection of GSTM (Myocrisin® Rhône-Poulenc Rorer) 0.5 ml of a 20 mg/ml solution or placebo. Two days after the GSTM/placebo injection the patients were examined for cutaneous or general reactions. Two-millimetre punch biopsies were taken for routine histopathology and immunohistochemistry, usually two of each type, from test reactions and/or clinical flare-ups (rashes), and transferred to formalin or fresh-frozen.

Immunohistochemistry

Biopsies were fresh-frozen in isopentane at −80°C. Six-µm frozen sections were air-dried, fixed for 10 min in acetone and washed in PBS. Endogenous peroxidase was blocked by treatment with 0.3% H_2O_2 in PBS for 30 min, followed by 1% normal rabbit serum in PBS for 30 min to block non-specific background staining. Primary monoclonal antibodies (anti CD45RO = UCHL-1, DAKO; anti HLADR: clone CR3/43, DAKO; anti human mast cell tryptase: clone AA1, Dako; anti intercellular adhesion molecule-1, ICAM-1/CD54, Immunotech; anti E-selectin = endothelial leukocyte adhesion molecule-1/ELAM-1, CD62E, Immunotech; FXIIIa, Behring; S-100, DAKO; CD1a, Immunotech; CD68, DAKO) were applied at optimal dilutions for 60 min at room temperature or overnight at 4°C. Following a PBS rinse, the sections were incubated with HRP-conjugated rabbit anti-mouse IgG (DAKO) in PBS. ELAM-1 detection was also performed with the ABC technique. Anti-tryptase incubations were preceded by trypsin treatment. Bound peroxidase was revealed with 0.01% H_2O_2 (30 min), and the sections were counterstained with Mayer's haematoxylin and mounted.

RESULTS

At 48 h after the parenteral provocation, the patch tests were reactivated in 9/10 patients after receiving the active agent GSTM but in none after placebo (Table I). These flare-ups were observed by the patients after only 4–6 h after the injection, as a strong itch on the test area of the back. At 48 h, the test sites were activated with a vigorous dermatitis of a dermal, often oedematous character (Fig. 1), in a few cases also epidermal/eczematous. In the non-reacting tests

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Table I. *Clinical reactions and 40 biopsy sites in 20 patients with contact allergy to gold given one intramuscular injection (IM) with gold (G) or placebo (P)*

Pat no.	IM	Clinical flare-up as fever and/or rash, eczema	Reactivation of GSTS test	Biopsy from rash or eczema	Skin test GSTM	GSTS	Aura	ST	ID
1	P	x			x	x			
2	P				x			x	
3	P								
4	P				x	x			
5	G	x	x		x	x			
6	G	x	x	x	x	x			
7	G	x			x	x			
8	G		x		x	x			
9	G	x	x		x		x		
10	P				x			x	
11	G	x	x	x	x				
12	P				x		x		
13	G	x	x		x				x
14	G	x	x		x		x		
15	G					x	x		
16	P				x				x
17	P					x			x
18	G	x	x		x			x	x
19	G	x	x			x		x	
20	P					x	x		

GSTS = gold sodium thiosulfate; GSTM = gold sodium thiomalate; Aura = auranofin; ST = standard allergen; ID-old intradermal gold test.

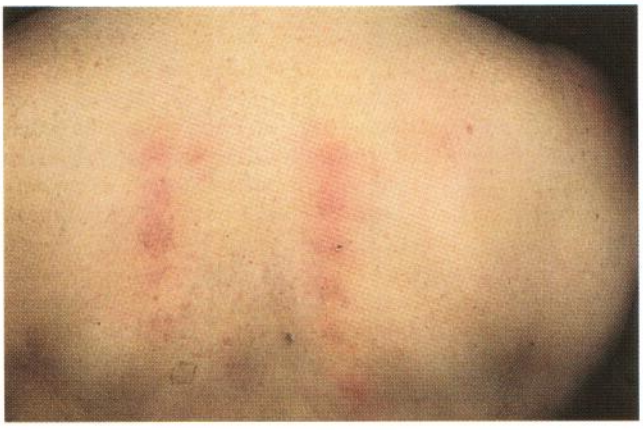


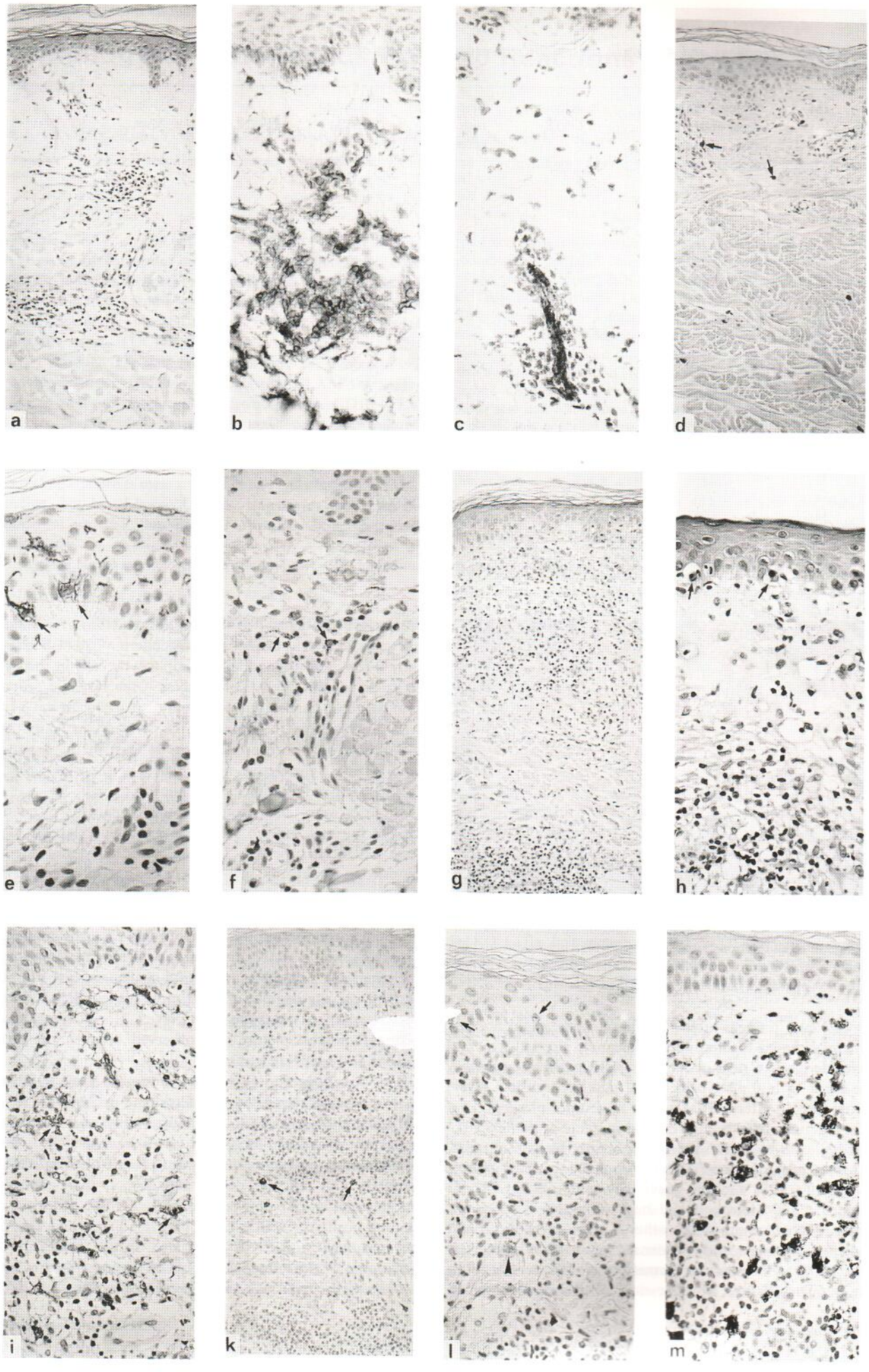
Fig. 1. Positive patch tests to gold sodium thiosulfate and gold sodium thiomalate in serial dilutions, abated since 6 weeks but reactivated by an intramuscular injection of 10 mg gold sodium thiomalate. Dermal as well as epidermal features may be observed 48 h later.

there was, even 6 weeks after application, some slight postinflammatory change facilitating identification.

A toxicoderma-like rash occurred in 7/10 patients given the active agent vs 1/10 after placebo. A high but transient fever occurred in 8/10 after GSTM but in none after placebo. The clinical reactions have been presented in detail separately (6). Forty duplicate biopsies were taken blindly from test areas and rashes according to Table I. Among 4 patients tested intradermally 9–24 months previously with GSTS, 2 had received a GSTM injection and both showed a flare-up, in contrast to no flare-up in the other 2 given placebo. These intradermal flare-ups showed dense lymphocytic infiltrates perivascularly in the reticular dermis but insignificant reaction in the papillary dermis. Routine-stained sections of biopsies from the 4 patients with patch test reactions to standard allergens, as well as the 2 with a toxicoderma-like rash, showed only a few perivasular foci of lymphocytic cells in the upper reticular/papillary dermis, regardless if the systemic provocation had been carried out with gold or placebo. In the 3 cases with test reactions to auranofin, the perivascular lymphocytic infiltration was more pronounced, at least in the 2 patients who received the active agent. These 9 biopsies were not further analysed immunocytochemically.

Biopsies were taken from 9 of the 10 patients receiving a GSTM injection, and in 8 of these 9 a clinical flare-up of the tests had been observed. In total, the GSTM test site was biopsied in 17 patients. In 6/17 there was a weak inflammation, all after placebo, and among the other 11 patients there was a single gold-challenged case, in which the clinical symtoms required corticosteroid treatment. In this case, the subsequent biopsy showed a PMN- and eosinophil-rich inflammation. In the remaining 2 placebos and 8 gold-challenged cases, biopsies showed varying degrees of focal mononuclear cell infiltrates, perivascularly at the superficial plexus. No difference in the histopathological picture was observed between the flaring GSTM and GSTS reactions.

The placebo group (Fig. 2a-f) showed a small number of focal moderately sized dermal infiltrates (Fig. 2a) of UCHL1+ (Fig. 2b) and HLADR+ lymphocytic cells, and the vascular endothelium at these foci stained with ELAM-1 (Fig. 2c). A small number of tryptase+ cells were evenly distributed in the papillary and reticular dermis but also at the lymphocytic infiltrates (Fig. 2d). In the epidermis, LC-like dendritic cells stained positively with CD1a (Fig. 2e), S-100 and HLADR but negatively with FXIII and CD68. In the dermis, only an occasional CD1a-stained cell could be demonstrated, whereas S-100-, CD68- and HLADR-stained cells were readily ob-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served, the two latter mainly in the papillary dermis (Fig. 2f). Many of the stained dermal cells were associated with the lymphocytic infiltrates.

The GSTM group showed endothelial ELAM-1 staining similar to the placebo (not illustrated) but differed from the placebo in the following way (Fig. 2g-m). Lymphocytic, UCHL1+ and HLADR+ perivascular infiltrates were larger, also with a more extensive involvement of reticular dermis (Fig. 2g). Papillary dermis showed oedema, occasionally with a few PMN, and lymphocytic epidermotropism was accompanied by ICAM-1 staining of basal epidermal cells and occasional apoptotic basal cells (Fig. 2h). Epidermal and dermal S-100+ and HLADR+ cells were present but staining seemed slightly irregular. A significant number of dendritic-shaped HLADR+ cells appeared in the papillary dermis, and S-100+ cells tended to accumulate at the papillary dermal lymphocytic infiltrates. S-100 stained nerves were invariably demonstrated within these infiltrates, also seen in the placebo group. Also, FXIII+ cells tended to accumulate at the lymphocytic infiltrates and in the oedematous papillary dermis (Fig. 2i). In the dermis, most of the tryptase+ mast cells were associated with the lymphocytic infiltrates (Fig. 2k), where some of them showed evidence of degranulation. In the epidermis, CD1a staining was weak and stained cells were unevenly distributed (Fig. 2l), with only an occasional stained cell in the dermis. The number of CD68-stained often dendritic-shaped dermal cells was increased, the majority associated with the lymphocytic foci (Fig. 2 m).

DISCUSSION

Au(I) may via its reactive intermediate metabolite Au(III) induce alterations in unidentified self-proteins, resulting in an activation, in sensitive subjects, of T-cells to cryptic self-peptides (8, 9). Such "Au(III)-specific" T-cells are likely to be involved in contact allergy to Au(I) (cf 10) as well as in adverse reactions to Au(I) drugs (8, 11). Reactivation of a memory pool of "metal-specific" T-cells should therefore be expected to occur in a contact allergic (patch test-positive) individual following a systemic administration of Au(I). Such activated T-cells are expected to express a "memory" phenotype (cf 12, 13), and in the present study, they may correspond to some of the UCHL1+ (=CD45RO=memory phenotype) T-cells found in the flare-up infiltrates. However, UCHL1-positive T-cells were also found to persist at the previous, 6-week-old patch test site of the placebo group, in which no flare-up was registered, a finding similar to previous observations on nickel (14). Also, the flare-up showed features overlapping at the tissue level with a strong contact allergy reaction to Au (cf 10). This may partly be due to the fact that "the primed tissue condition" was initially induced by the Au patch testing.

In the present study, evidence of a flare-up was noticed within hours of the parenteral injection and this test reaction was biopsied at 48 h. The rapid response suggests that gold itself is involved at a very early stage. Injected gold salt (15) shows a universal distribution and "endogenous" uptake of the injected gold may thus be a significant blood-borne "early inducing factor". Experimentally, Oliveira et al. (16) showed that Au can enhance the release of classical inflammatory mediators from mast cells. This seems to be dependent upon mast cell surface IgE. Askenase and his group (17) found that the early phase of "elicited skin contact sensitivity" in mice is mediated by serotonin via mast cells sensitized locally by IgE through their FceRI. Notably, the clinical experience is that the present flare-up reactions differ macroscopically from patch test reactions, the former exhibiting more of urticaria-like features. This would be consistent with involvement of "immediate-type" components at the early phases. In the present study, oedema was histologically found at the flare-up site as well as perivascular lymphocytic infiltrates and also a changed distribution of tryptase+ mast cells, indirectly suggesting involvement of the mast cells.

Since parenteral gold is expected to be universally distributed, including skin, additional factors must be operative for a localized flare-up to occur at the previous GSTM test site. It is possible that the flare-up phenomenon may consist of two major closely interconnected phases, the initial one being vascular, as discussed above. In the present study, the residual changes or "priming" at the previous patch test site were found to include ELAM-1 endothelial activity as well as persistence of lymphocytic cells.

ELAM-1 is not expressed in normal skin (18, 19), and we therefore conclude that patch testing to gold induces ELAM-1 to become part of the "priming", as indicated in our 6-week placebo group. It is not known if gold, similarly to nickel (20, 21), may induce endothelial gene transcription of adhesion molecules, such as ELAM-1. Alternatively, this may occur via keratinocyte-induced IL-1, known to be involved in contact sensitivity reactions (22). The induced endothelial ELAM-1 was always found to be associated with infiltrates of lymphocytes (cf 23), some of which expressed a memory phenotype (UCHL1). Of special interest is that circulating memory type T-cells have been shown to specifically express surface ligands to ELAM-1 (24). There is also a tendency of prolonged in vivo ELAM-1 expression associated with chronic inflammatory skin lesions (25). Notably, patch-testing to gold in hypersensitive individuals may result in long-lasting tissue reactions, with persistence of lymphocytic infiltrates (cf 10). In other words, ELAM-1 may sustain a certain influx of circulating T-cells. Our findings at the gold patch test site indicate that persisting T-lymphocytes and induced endothelial ELAM-1 have a close spatial relationship, suggesting that the induced ELAM-1 may play a role in the persistence of the lymphocytic infiltrate.

Indirectly, we found that the persistent ELAM-1 may be functionally associated with the increase of CD68+ mono-

Fig. 2. (*a-f*) Placebo. (*a*) HE-staining showing a few lymphocytic foci in papillary/upper reticular dermis (X140). (*b*) UCHL-1-stained "memory T-cells" in papillary dermal perivascular focus (X275). (*c*) ELAM-1-stained vascular endothelium in small lymphocytic papillary dermal focus (X275). (*d*) Tryptase+ mast cells in papillary/upper reticular dermis (*arrows*, X140). (*e*) CD1a-stained epidermal dendritic cells (*arrows*, X400). (*f*) CD68-stained cells (*arrows*) at small perivascular papillary dermal focus (X275). (*g-m*) GSTM. (*g*) HE-staining showing dense lymphocytic infiltrates in papillary and reticular dermis, cf fig 2a (X140). (*h*) HE-staining showing oedema of papillary dermis and apoptotic epidermal cells (*arrows*, X275). (*i*) FXIIIa-stained cells (*arrows*) associated with papillary dermal lymphocytic infiltrate (X275). (*k*) Tryptase+ mast cells (*arrows*) closely associated with dermal lymphocytic infiltrates, cf *d* (X140). (*l*) CD1a, weak staining of a few epidermal cells (*arrows*) and an occasional dermal cell (*arrowhead*), cf *e* (X275). (*m*) CD68-stained large number of cells at papillary dermal lymphocytic infiltrate, cf *f* (X275).

cytes/macrophages at the flare-up site. It is well known that multiple receptor-ligand systems are involved in monocytic adherence to endothelium (26) and that ELAM-1 may be involved in monocyte adherence (27). Goebel et al. (8) have suggested that susceptibility to adverse immunologic side-effects of gold is related to tissue uptake not in lymphocytic cells but in macrophages/accessory cells (APC). In positive patch tests to different allergens, Sterry et al. (28) found a significant decrease of CD1a+ LC in the epidermis and a significant increase of dermal macrophages/monocytes (CD68+) as well as basal keratinocyte ICAM-1 expression. These findings are surprisingly similar to the present flare-ups, suggesting overlapping tissue changes in the two types of lesions. The reduced CD1a epidermal staining may reflect migration of LC from the epidermis, suggested to occur following skin sensitization (29). In papillary and upper reticular dermis, all fixed dendritic cells express FXIIIa as well as HLADR but not S-100 (30–32). The functional significance of the redistribution of such cells which we observed in the flare-ups is unknown but may be associated with the spatial rearrangements caused by the lymphocytic infiltration. Interestingly, this seemed to be closely associated with S-100-stained peripheral nerves. There is evidence suggesting that LC may take up gold (33), but it is not known if uptake of gold occurs locally in connective tissue macrophages/APC following a patch test to a gold salt. It is tempting to believe that this may be the case. Also, following a systemic injection of GSTM, it is logical to consider blood-borne monocytic cells carrying some of this gold into the ELAM-1-expressing previous patch test site, thereby contributing to the the flare-up lesion.

To summarise, gold is stored as a conjugate (8, 11) at the initial patch test site of a contact allergy patient, presumably in macrophages/APC. For reasons unknown, some of this gold may persist locally for long periods, resulting in a continuous expression at macrophage/APC surfaces of "contact allergy-specific" peptides (34). T-cells, some having a memory phenotype (UCHL-1, cf 35, 36), also infiltrate the gold-elicited patch test site. Locally expressed "gold-specific" peptides would favour persistence of these T-cells, as long as the gold effect persists upon the macrophages/APC. This could partly explain the clinical long-lasting of gold patch test reactions (cf 10) and may represent a pathomechanism different from occasional long-lasting Ni test reactions (37). Lymphocyte-produced cytokines may also explain the initial ELAM-1 induction. This situation corresponds to "the primed tissue", in which a flare-up will later occur following a parenteral gold injection. Some of the injected gold is distributed to the primed site (15). Part of the priming may also involve IgE bound to mast cells (16, 17), and the injected Au may somehow activate such "Au-conditioned" (and closely nerve-associated?) mast cells, resulting initially in mediator-released vascular activation accompanied by oedema and upregulation of endothelial adhesion molecules. These initial events will favor influx of more T-cells, including further memory type cells but also probably Au-carrying monocytic cells, corresponding to the presently observed perivascular T-ly and CD68-cell-rich infiltrates. Gradually, some of the T-cells will become reactivated by APC-expressed gold-specific peptides (cf above), further amplifying the reaction.

Well compatible with these morphological findings is our recent demonstration of a significant release in blood of several cytokines and leukocyte proteins during the endogenous flare-up in contact allergy to gold (38). In particular, the rapid increase in blood of IL-1 and TNF-α in allergic patients provoked with GSTM may constitute a functional equivalence to the immunohistochemical changes. Further research should aim at identifying functional connections between possibly gold-activated mast cells (IgE?) and locally cell-borne gold (macrophages/APC), as pathogenetically potential factors in the development of flare-up to gold.

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