Sir,
Adverse drug reactions common in daily clinical practice (1) include allergic drug reactions characterized by underlying immune reactions, and account for about one-seventh of all adverse drug reactions (2). Their pathophysiology is not fully understood, but T cells have been found to play a crucial role (3).

Conclusive diagnosis of drug allergy remains a major problem. Currently, the lymphocyte transformation test (LTT) is the only available in vitro test for detecting drug sensitization at the cellular level, irrespective of the effector mechanisms and the clinical phenotype of the reaction (3, 4). A common clinical feature of drug allergy is eosinophilia (5), which is promoted by interleukin (IL)-5 secretion from antigen-specific activated T cells (6).

We report on a female who developed an erythema exudativum multiforme-like exanthem after receiving fenoterol for tocolysis due to preterm labour. Lymphocyte sensitization to fenoterol could be confirmed in vivo by a patch test and in vitro by a LTT additionally employing the chemically related terbutaline and propranolol, which did not induce lymphocyte proliferation. Determination of IL-5 concentrations in the culture supernatants of the LTT revealed – in addition to fenoterol – lymphocyte reactivity to terbutaline, which could be confirmed in a second patch test.

MATERIALS AND METHODS
The LTT was performed according to a standard protocol as described elsewhere (4). Briefly, peripheral blood mononuclear cells (PBMC) from the patient and healthy control were isolated and cultured for 6 days in 96-well round-bottom plates (Becton Dickinson, Le Pont de Claix, France) with various concentrations of the indicated drugs dissolved in phosphate-buffered saline (PBS) or with PBS alone. For the last 18 h, 0.6 µCi 3H-thymidine (NEN, Vilvoorde, Belgium) was added to each well. Cells were then harvested and incorporated radioactivity was measured as counts per minute (cpm). Stimulation index (SI) represents the ratio of average cpm in cultures with and without antigen. SIs exceeding 2.5 were considered as positive results, suggesting drug-specific T-cell proliferation (4).

Culture supernatant (100 µl) of each well with PBMC from the patient and the control were collected after 5 days. IL-5 and interferon-γ concentrations were determined using commercially available cytokine specific sandwich ELISAs (Immunotech, Marseille, France) in accordance with the manufacturer’s recommendations.

RESULTS
The patient showed twofold positive (+ +) reactions in the patch test to fenoterol after 48, 72 and 168 h. In the second patch test following detection of drug-specific IL-5 secretion to terbutaline the patient gave positive reactions to terbutaline (+, + +, +) on all three reading days, but not to propranolol.

Incubation of the patient’s PBMC with fenoterol in the LTT resulted in SIs of 2.7, 4.7 and 4.7 at concentrations of 0.1, 1 and 10 µg/ml, respectively (Fig. 1). No significant proliferative T-cell response to terbutaline or propranolol could be detected (data not shown). PBMC from a healthy control did not proliferate in response to any of the three substances. Incubation of the patient’s PBMC with fenoterol at concentrations of 0.01, 0.1, 1 and 10 µg/ml resulted in secretion of considerable amounts of IL-5, whereas in the culture wells incubated with PBS the IL-5 concentration was below the detection limit (1.5 pg/ml) of the ELISA (Fig. 2). Although with regard to the SI no drug-specific proliferation of the patient’s PBMC following incubation with terbutaline was observed, IL-5 could be detected in the supernatants of these cultures, namely 33.5, 7.1 and 3.7 pg/ml IL-5 at concentrations of 0.01, 0.1 and 1 µg/ml terbutaline. The IL-5 concentrations determined in the culture supernatants of the patient’s PBMC incubated with propranolol were below the detection limit of the ELISA. PBMC of the healthy control did not release significant amounts of IL-5 upon incubation with fenoterol, terbutaline or propranolol. Further on, neither PBMC of the patient nor of the control secreted significant amounts of interferon-γ when incubated with the three drugs.

DISCUSSION
The β2-adrenoceptor agonists fenoterol and terbutaline belong to the group of direct sympathomimetic drugs and are routinely

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Fig. 1. Lymphocyte transformation test with peripheral blood mononuclear cells from the patient and a healthy control incubated with fenoterol or with the solvent phosphate-buffered saline (PBS). SI: Stimulation index (see Methods for explanation).
in conjunction with recently published observations (9–11) suggest that in vitro determination of drug-specific IL-5 secretion may serve as an additional parameter for the in vitro detection of drug-sensitization in the LTT.

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REFERENCES