increased NK-cell activity in these mice by i.p. GM-CSF administration was found to have a greater effect than that of immunomodulator PS-K administration. Thus, i.p. GM-CSF certainly did enhance NK cell activity in immunosuppressed mice.

Effect of GM-CSF on γ-IFN Production

We also tested for the production of γ-IFN in serum after GM-CSF administration to mice. As shown in Fig. 5, when GM-CSF was intraperitoneally administered (on day 0), an increase in the γ-IFN titer was confirmed. This production increased with time, and 4.15 U of γ-IFN activity were observed on day 7.

DISCUSSION

It has been reported that administration of cyclosporine can induce a marked reduction of various types of immunocompetent cells in mice.[12] In our previous study,[13] we used mice as an experimental animal model to study the mechanism of action of cycloporine in anti-systemic *C. albicans* infection. Meanwhile, we determined the LD_{50} of cyclosporine, and studied the dose-response relationship of cyclosporine (data not shown), but we found that cyclosporine had no effect on anti-systemic *C. albicans* infections.

Therefore, we used cyclophosphamide in this study as an immunocompromising agent in the immunocompromised mice model according to the method described by Deepe et al.[3] These results confirmed those of our previous report that macrophages play a major role in anti-systemic *C. albicans* infection.[13]

GM-CSF is a kind of glycoprotein cytokine that promotes proliferation and maturation of myeloid progenitor cells, primarily giving rise to neutrophils, eosinophils, and monocytes and stimulating erythroid progenitors and megakaryocytes in vitro.[14] GM-CSF also enhances the function of mature myeloid effector cells. GM-CSF receptors have been identified on both hematopoietic (e.g., neutrophils, eosinophils, and monocytes)[15] and non-hematopoietic cells,[16] such as on squamous cell lung carcinoma[17] and on human melanoma cells.[18] Potential clinical roles of GM-CSF in vivo were largely based on indirect evidence, such when it was as used for treatment of refractory aplastic anemia,[19] myelodysplastic syndromes,[20] acquired immunodeficiency syndrome,[21] idiopathic neutropenia,[22] and bone marrow transplantation.[23] Therefore, GM-CSF is considered worthy of further evaluation as an active BRM for anti-*Candida* therapy, although detailed studies are necessary for its advance application.

Most BRMs can be classified into 2 groups based on their immunomodulating activity: one has the ability to activate macrophages, the other has an apparent direct effect on T cells.[4] Since systemic candidiasis is a significant complication of immunodeficiency syndromes, surgical procedures, and immunosuppressive medical therapies, we are interested in investigating the immunomodulating activities of cytokine,[8] because some researchers have reported that injection of lipopolysaccharides (LPS) may either enhance or suppress antibacterial resistance.[24, 25] In our present study of GM-CSF solution, LPS was not detected (at the detection limit of less than 0.2 ng/ml by the Limulus Lysate assay); we thus conclude that contaminating LPS was unlikely to be responsible for the enhanced anti-candidal activity.

Having confirmed that GM-CSF has highly enhanced anti-candidal activity, we began to analyze the possible effectors which are responsible for the activity of the resistance in mice. We first analyzed the kinetics of cell populations in whole blood and in the peritoneal cavity. Numbers of white blood cells decreased after cyclophosphamide administration. GM-CSF (100 U/mouse) was i.p. administered 4 days after i.p. cyclophosphamide, then the numbers of WBCs and the percent ages of monocytes, lymphocytes, and PMN were observed on days 0, 2, 4, and 8. As shown in table 1, the percent ages of lymphocytes decreased, whereas the percent ages of monocytes gradually increased after GM-CSF administration, until the maximum appeared on the 6th day. The percent ages of PMN also increased significantly on days 2, 4, and 6. All WBC populations (monocytes, lymphocytes, and PMN) returned to normal levels on day 8 after i.p. GM-CSF. Collectively, all white blood cell numbers decreased on days 2 and 4, but returned to normal levels on days 6 and 8 after i.p. GM-CSF. It was suspected that macrophages and monocytes may play a key role in the mani-