Letters to the editor

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HILDA/LIF is present in the urine of rejecting kidney graft recipients

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Sir: Human interleukin for DA cells (HILDA, or LIF: leukemia inhibitory factor) is a 38 kDa cytokine produced mainly by activated T cells and macrophages [1]. The HILDA/LIF protein sequence has been deduced from cloned cDNA derived from HTLVI-infected cells [2] and partially confirmed by amino acid sequencing of natural molecules [3]. HILDA/LIF exerts pleiotropic effects, such as inhibition of embryonic stem cell differentiation, inhibition of lipoprotein lipase, stimulation of acute phase protein synthesis (HILDA/LIF is the hepatic stimulating factor III), stimulation of bone construction through osteoblasts, and stimulation of cholinergic neural differentiation [4]. In addition, preliminary results suggest that HILDA/LIF may intervene in inflammatory processes, probably exerting some of the same effects as IL6, whose receptor is related to the HILDA/LIF receptor [5].

Although HILDA/LIF was initially detected in the supernatants of all the allogeneic T lymphocyte clones derived from a rejecting kidney graft that we tested [1], its production by kidney graft recipients undergoing acute rejection episodes has never been studied. We obtained peripheral mononucleated cells from patients with unambiguous acute cellular rejection episodes (in the absence of any ongoing infectious process) immediately before treatment began. We assayed for both spontaneous release of HILDA/LIF and PHA/IL2-induced release by these cells. Although the presence of HILDA/LIF could be demonstrated in culture supernatants, its level, assessed by the DAIa bioassay [2], was indistinguishable from that observed in control recipients submitted to the same therapeutic regimen but with stable grafts (data not shown).

Since several other cytokines (or cytokine receptors) have been detected in urine during kidney rejection [6], we then studied HILDA/LIF levels in concentrated morning urine samples of rejecting patients ($n = 7$). In addition, serial urine samples were obtained at different times after treatment and once the rejection had been stopped. Figure 1 shows that rejecting patients had significantly increased HILDA/LIF levels in their urine at the time of rejection, whereas no HILDA/LIF could be evidenced 3 weeks after rejection was diagnosed. Urine samples from stable graft recipients matched with rejecting ones for time after transplantation ($n = 5$) from normal individuals ($n = 15$) and from pregnant women ($n = 20$) who were used as controls and did not have detectable levels of HILDA/LIF (not shown). Up to 300 IU/ml (37.7 ng/ml) recombinant human erythropoietin induced a DA1 a proliferative response that could not account for the level of proliferation observed in the urine samples. Interestingly, G-CSF, another cytokine acting on the HILDA-sensitive DA1 a cell and whose level was systematically assessed in the bioassay by using saturating amounts of an anti G-CSF monoclonal antibody [1], was not found in the urine samples studied.

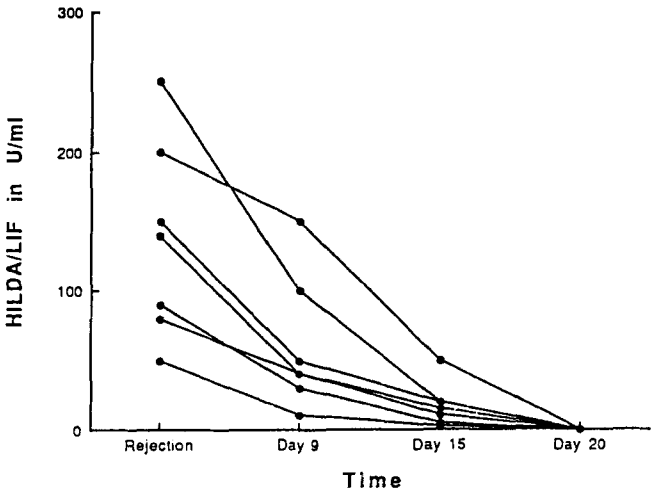

Fig. 1. Levels of HILDA/LIF in the urine of rejecting patients as assessed by the DA1 a bioassay. Data are given in U/ml of a morning sample of urine concentrated 25-fold

Our data suggest that macrophages and T cells, which infiltrate the graft during acute rejection episodes, produce HILDA/LIF upon allogeneic stimulation during the rejection process. They also suggest that this newly characterized cytokine may play a role in inflammatory lesions in rejection and that its presence may be a useful marker in the rejection process. Further studies are, however, needed to define HILDA/LIF production during infectious episodes.

In summary, our data show for the first time that HILDA/LIF is present in the urine of rejecting kidney graft patients.

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Foreigners on the waiting list

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Sir: As a retired nephrologist who took an active part in a kidney transplantation program for 25 years, I was quite amazed by point 2 of the resolution of the ESOT Council, presented by Dr. Gerhard Opelz in his preface to *Transplant International* (1991, 4:129).

The Council feels that the transfer of patients from low activity to high activity areas reduces the impetus to establish local transplantation services. I would rather believe that the opposite is true, namely, that patients returning home with transplants obtained elsewhere doubtlessly raises the following question among the local patients, doctors, and nursing staffs responsible for health and care: why not in our own country? Such circumstances and consequent thoughts constituted extremely potent factors leading to local achievements in the past in all types of human activities.

As a European citizen, I would strongly advocate the free circulation of patients from one state to another, as it has been achieved in the medical profession. Indeed, in the United States of America, nobody would object to the news that a Texan received a kidney transplant in Minneapolis.

Europe is made up of many countries with distinct characteristics in various fields. If some patients living in the South have received organ transplants in the North, many more healthy people living in the North have enjoyed the unmatched splendors of the climates, landscapes, and cities of the South, as well as the natural amenity of the populations living close to the Mediterranean Sea.

On the other hand, I certainly agree with point 3 of the Council's resolution: it is unacceptable for doctors or institutions to charge fees in excess of the usual fee in use locally.