

ORIGINAL PAPERS

## Effect of Low Doses and High Homeopathic Potencies in Normal and Cancerous Human Lymphocytes: An *In Vitro* Isopathic Study

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### ABSTRACT

**Objectives:** Biologic effects of high homeopathic potencies can be studied in cell cultures using cell lines or primary cells. We hypothesized that primary cells would be more apt to respond to high potencies than cell lines, especially cancer cell lines. We set out to investigate the effects of low doses and high homeopathic potencies of cadmium chloride, respectively, in an intoxication model with human primary lymphocytes compared to a human leukemia cell line (Jurkat).

**Design:** Cells were pretreated with either low concentrations (nM– $\mu$ M) or high potencies (pool 15–20c) of cadmium for 120 hours, following which they were exposed to a toxic treatment with a range of cadmium concentrations (8–80  $\mu$ M) during 24 hours. Cell viability was eventually assessed by use of the MTS/PES assay. Controls included a vehicle (NaCl 0.9%) for the low concentrations of cadmium or water 15–20c for cadmium 15–20c. A total of 34 experiments were conducted, 23 with low concentrations and 11 with high potencies of cadmium. Data were analyzed by analysis of variance.

**Results:** Pretreatment with low concentrations or high potencies of cadmium significantly increased cell viability in primary lymphocytes after toxic challenge, compared to control cells (mean effect  $\pm$  standard error = 19%  $\pm$  0.9% for low concentrations respectively 8%  $\pm$  0.6% for high potencies of cadmium;  $p < 0.001$  in both cases). The pretreatment effect of low doses was significant also in cancerous lymphocytes (4%  $\pm$  0.5%;  $p < 0.001$ ), albeit weaker than in normal lymphocytes. However, high homeopathic potencies had no effect on cancerous lymphocytes (1%  $\pm$  1.9%;  $p = 0.45$ ).

**Conclusions:** High homeopathic potencies exhibit a biologic effect on cell cultures of normal primary lymphocytes. Cancerous lymphocytes (Jurkat), having lost the ability to respond to regulatory signals, seem to be fairly unresponsive to high homeopathic potencies.

### INTRODUCTION

Homeopathy is an autonomous medical system of Western medicine that has been widely used for almost 2 centuries. Homeopathy's approach to treatment includes the use of suitably diluted substances to provoke the body's own defense and self-regulatory responses. Homeopathic remedies are prepared by successive steps of dilution and agita-

tion ("potentization"). Some homeopathic potencies are diluted beyond the molecular limit (so-called "high" potencies,  $\geq 23x$  or 12c, with a calculated concentration of  $< 10^{-23}$  M) and therefore are dismissed by critics as placebo. However several large reviews and meta-analyses of placebo-controlled clinical trials on homeopathy are pointing toward real effects, although the mechanism of action remains to be clarified.<sup>1–5</sup> Even in a recent meta-analysis

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claiming that “the clinical effects of homeopathy are placebo effects,”<sup>6</sup> almost three quarters of the examined homeopathic studies show positive results compared to placebo.<sup>7,\*</sup> *In vitro* research on homeopathy explores the effects of potentized remedies on molecular or cellular systems to test for differences between homeopathic potencies and appropriate controls and to understand the nature and mode of action of the potencies. One simplification of the homeopathic *similia* principle that can easily be applied to *in vitro* systems is the isopathic principle, which maintains that a low concentration of a toxic substance enhances self-recovery in a system damaged by a high dose of the same substance. Numerous preclinical studies have investigated the effect of low doses or homeopathic preparations in such intoxication models.<sup>8–15</sup> The available body of data suggests that the isopathic model is well suited for the investigation of potency effects.

The aim of the present study was to compare the sensitivity of normal primary cells with that of cancerous cells with regard to the effect of low doses and high homeopathic potencies of cadmium, using an intoxication model. Therefore, we implemented a cell culture system of human lymphocytes including primary T-lymphocytes, isolated from peripheral blood, and a human T-leukemia cell line (Jurkat). The cells were preexposed to either low doses (nM– $\mu$ M) or high homeopathic potencies (pool of potencies 15–20c, corresponding to a calculated concentration of  $\sim 10^{-31}$  M) of cadmium. Cytotoxicity was subsequently induced with toxic cadmium concentrations and cell viability assessed by the MTS/PES assay.

## MATERIALS AND METHODS

### Cell cultures

The following cells were used: peripheral human T-lymphocytes as euploid (normal) cells and a human T-leukemia cell line derived from the blood of a 14-year-old patient with acute lymphoblastic leukemia (Jurkat, ATCC) as cancerous cells. The cells were cultured in RPMI [Roswell Park Memorial Institute] 1640 medium (Eurobio; Courtaboeuf, France) supplemented with 2 mM of glutamine, 100 U/mL of penicillin and 100  $\mu$ g/mL of streptomycin (all from Sigma Aldrich, Lyon, France) and containing 5% heat-inactivated fetal bovine serum (Gibco BRL, Corgy-Pontoise, France). The cells were kept at 37°C in 5% CO<sub>2</sub> and 95% H<sub>2</sub>O.

The T-lymphocytes were isolated from leukocyte-enriched human peripheral blood (buffy-coat) based on previously described procedures.<sup>16</sup> In brief, mononuclear cells were obtained by Ficoll-Hypaque density gradient centrifugation (density = 1.077; Eurobio). Interleukin-2-dependent

cells were prepared by stimulation with 2  $\mu$ g/mL of phytohemagglutinin (Abbott, Rungis, France) for 48–60 hours. Primary T-lymphocytes were maintained by the addition of 300 U/mL of interleukin-2 (Proleukin,<sup>®</sup> Chiron, Emeryville, CA) to the culture medium. The T-lymphocytes were used for experiments after 2–2.5 days in culture following phytohemagglutinin stimulation.

### Cell-viability assessments

For pretreatment, the cells were incubated in 10 mL cell culture flasks ( $5 \times 10^5$  cells/mL) for 120 hours with low concentrations (1 nM–1  $\mu$ M) or with homeopathic potencies (pool 15–20c, 1 mL/10 mL) of cadmium chloride (Sigma). Following the pretreatment, the cells were washed with RPMI 1640 medium and exposed for 24 hours in 96-well plates ( $5-8 \times 10^5$  cells/mL, 200  $\mu$ L/well) to a toxic treatment with 10, 20, 40, and 80  $\mu$ M of cadmium chloride (for T-lymphocytes) or 8, 16, 32, and 64  $\mu$ M of cadmium chloride (for Jurkat). Cadmium chloride for low-dose pretreatment and for toxic treatment was added to the cells from a stock solution of cadmium chloride 10 mM in physiologic saline (NaCl 0.9%), prepared freshly for each experiment. Cell viability after the toxic treatment was assessed with a colorimetric assay (CellTiter 96<sup>®</sup> Aqueous One Solution Cell Proliferation Assay, Promega, Charbonnieres-les-Bains, France) composed of the tetrazolium compound MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt) and the electron coupling reagent PES (phenazine ethosulfate). Twenty-five (25)  $\mu$ L of the MTS/PES solution was pipetted into each well containing 200  $\mu$ L of cells. The plates were incubated for 1–6 hours at 37°C in 5% CO<sub>2</sub> and 95% H<sub>2</sub>O. The absorbance at 490 nm was recorded using a 96-well plate reader (Molecular Devices, St. Gregoire, France). The background absorbance was determined in wells containing medium without cells and subtracted from the experimental values. Six wells were used for each experimental condition. The assays with low-con-

TABLE 1. OVERVIEW OF ALL EXPERIMENTS PERFORMED

Cells	Pretreatment	Control	Design	Set	n
Lymphocytes	1 nM CdCl <sub>2</sub>	NaCl <sup>a</sup>	Open	A	3
Lymphocytes	10 nM CdCl <sub>2</sub>	NaCl	Open	A	1
Lymphocytes	0.1 $\mu$ M CdCl <sub>2</sub>	NaCl	Open	A	2
Lymphocytes	1 $\mu$ M CdCl <sub>2</sub>	NaCl	Open	A	4
Jurkat	1 nM CdCl <sub>2</sub>	NaCl	Open	B	3
Jurkat	10 nM CdCl <sub>2</sub>	NaCl	Open	B	1
Jurkat	0.1 $\mu$ M CdCl <sub>2</sub>	NaCl	Open	B	5
Jurkat	1 $\mu$ M CdCl <sub>2</sub>	NaCl	Open	B	4
Lymphocytes	CdCl <sub>2</sub> 15c	PW	Blind	C	6
Lymphocytes	CdCl <sub>2</sub> 15c	PW	Open	C	1
Jurkat	CdCl <sub>2</sub> 15c	PW	Blind	D	1
Jurkat	CdCl <sub>2</sub> 15c	PW	Open	D	3

\*See special issue of *The Journal of Alternative and Complementary Medicine*, Volume 11, Number 5, 2006.

<sup>a</sup>Vehicle NaCl, 0.9%  
PW, potentized water.

centration pretreatment were open because they were classical toxicologic experiments and constituted our frame of reference, whereas the assays with homeopathic potencies were performed blindly and openly (Table 1).

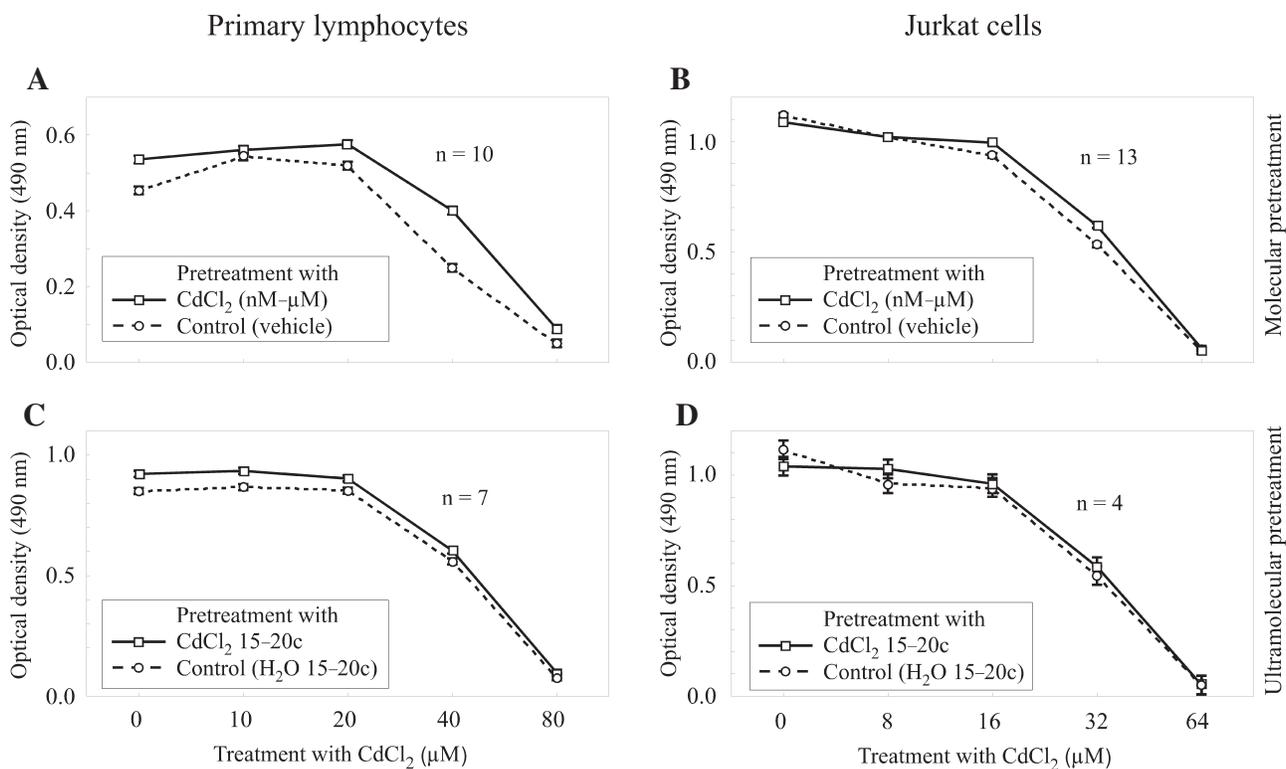
#### Preparation of homeopathic potencies and control

The homeopathic potencies of cadmium chloride were prepared by successive steps of dilution, agitation (potentization) and settling. The potentization medium was deionized water (MilliQ [Guyancourt, France] system) except for the last potentization step for which the cell culture medium was used. The potencies were prepared in 50 mL (for the first potency) or 15 mL (for all subsequent potencies) sterile polypropylene tubes (Falcon, BD Biosciences, Le Pont de Claix, France). The starting dilution was prepared by dissolving approximately 25 mg of cadmium chloride in the corresponding volume of deionized water to obtain a 1 mg/mL solution. The solution was agitated mechanically for 1 minute by vertical shaking at 300 succussions/min (Agitelec, Appareil de Baudard, type RTB, Society Carteau,

Laboratory Furniture, Bagnolet, France) to obtain the first potency level (1c). Each subsequent potency was made by adding 75  $\mu\text{L}$  of the previous potency to 7.5 mL of deionized water and agitating for 1 minute up to the potency level 19c. Two (2) minutes of settling was kept between each potentizing step. A pool of homeopathic potencies 15–20c ( $\sim 10^{-31}$  M) was prepared by adding 250  $\mu\text{L}$  of the potencies 14c, 15c, 16c, 17c, 18c, and 19c into 23.5 mL of cell culture medium and agitating for 1 minute. All pipetting was performed with sterile disposable tips under laminar flow, avoiding direct intense light.

As a control, a pool of homeopathic potencies of water 15–20c was prepared according to the procedure described above, except for the starting dilution in which cadmium chloride was omitted. The pretreatment effect was calculated with respect to potentized water in order to account for the physicochemical effects of the potentization procedure.<sup>17,18</sup>

The pool of cadmium chloride potencies and the control were stored separately at 4°C, wrapped in aluminium paper to protect them from light and other external influences. The



**FIG. 1.** Effect (mean values  $\pm$  standard error) of a 120-hour-pretreatment with low concentrations (1 nM–1  $\mu\text{M}$ ; **A** and **B**) or high homeopathic potencies (pool 15c–20c; **C** and **D**) of cadmium on the cellular viability of primary T-lymphocytes (**A** and **C**) and Jurkat cells (**B** and **D**). Following the pretreatment, the cells were exposed to a 24-hour-treatment with a range of cadmium concentrations (X-axis). Cell viability was assessed with the MTS/PES colorimetric assay (optical density at 490 nm, Y-axis). Cell viability was 19% higher in primary lymphocytes ( $p < 0.001$ ) and 4% higher in Jurkat cells ( $p < 0.001$ ) pretreated with low cadmium concentrations compared to control cells. The pretreatment with high homeopathic potencies increased cell viability significantly only in primary lymphocytes (8%;  $p < 0.001$ ) and had no significant effect on Jurkat cells. The standard error is, in general, smaller than the icons used and therefore is not visible.

potencies and the control were used for experiments within 2 months after preparation. A total of 4 different preparations were used. For blind manipulations, the tubes containing the potencies and the control were random coded by a person not connected to the study. The code was broken only after analysis of the results.

### Statistical analysis

The raw data were analyzed by analysis of variance (ANOVA) with type VI (effective hypothesis) sums of squares and  $\alpha = 0.05$ . For each set of experiments as defined in Table 1, an overall mean pretreatment effect ("unweighted means") was calculated by essentially averaging data, either from all corresponding experiments and all pretreatment cadmium concentrations (for low-dose cadmium pretreatment, sets A and B), or from all corresponding experiments (for high-potency pretreatment, sets C and D). Specific comparisons between groups were made using the least significant difference (LSD) test only if the preceding global F-test was significant. A *p*-value of  $<0.05$  was considered to represent a significant difference. The statistical analysis was performed with the software package Statistica 6.0. (Statsoft, Inc., Tulsa, OK)

## RESULTS

### Experiments performed

An overview of all experiments performed is given in Table 1. A total of 34 experiments were performed, divided in 4 sets (A, B, C, D). Twenty-three experiments were conducted with a pretreatment with low cadmium concentrations, thereof 10 in primary T-lymphocytes (set A) and 13 in Jurkat cells (set B). Eleven assays included a pretreatment with homeopathic potencies, 7 in primary lymphocytes (set C), and 4 in Jurkat (set D). The experiments with low-concentration pretreatment were open, whereas most of the experiments with homeopathic potencies were blinded. In a few cases (1 of 7 in primary lymphocytes and 3 of 4 in Jurkat), open experiments were conducted with homeopathic potencies in an exploratory attempt to compare the outcome of blinded versus open experiments. However, no difference was observed between the results obtained with the 2 types of design.

All experiments were performed at least two times independently with exception of the experiments with the 10 nM pretreatment in primary lymphocytes and in Jurkat.

TABLE 2. EFFECT OF A 120 HOUR PRETREATMENT WITH LOW CONCENTRATIONS (1 nM, 10 nM, 100 nM, 1  $\mu$ M) OR HIGH HOMEOPATHIC POTENCIES (POOL 15c–20c) OF CADMIUM ON THE CELLULAR VIABILITY OF PRIMARY T-LYMPHOCYTES AND JURKAT CELLS

Pretreatment	Primary lymphocytes				Jurkat cells			
	Set	n	Treatment with CdCl <sub>2</sub> [ $\mu$ M] <sup>a</sup>	Cell viability <sup>b</sup>	Set	n	Treatment with CdCl <sub>2</sub> [ $\mu$ M] <sup>a</sup>	Cell viability <sup>b</sup>
Molecular (CdCl <sub>2</sub> 1 nM–1 $\mu$ M)	A	10	0	0.535 $\pm$ 0.005	B	13	0	1.087 $\pm$ 0.006
			10	0.561 $\pm$ 0.005			8	1.020 $\pm$ 0.006
			20	0.576 $\pm$ 0.005			16	0.995 $\pm$ 0.006
			40	0.400 $\pm$ 0.005			32	0.618 $\pm$ 0.006
			80	0.088 $\pm$ 0.005			64	0.063 $\pm$ 0.006
Control <sup>c</sup>			0	0.454 $\pm$ 0.005			0	1.117 $\pm$ 0.006
			10	0.543 $\pm$ 0.005			8	1.019 $\pm$ 0.006
			20	0.519 $\pm$ 0.005			16	0.936 $\pm$ 0.006
			40	0.249 $\pm$ 0.005			32	0.531 $\pm$ 0.006
			80	0.050 $\pm$ 0.005			64	0.050 $\pm$ 0.006
Ultra-molecular (CdCl <sub>2</sub> pool 15–20c)	C	7	0	0.922 $\pm$ 0.006	D	4	0	1.040 $\pm$ 0.021
			10	0.934 $\pm$ 0.006			8	1.028 $\pm$ 0.021
			20	0.903 $\pm$ 0.006			16	0.961 $\pm$ 0.021
			40	0.004 $\pm$ 0.006			32	0.585 $\pm$ 0.021
			80	0.096 $\pm$ 0.006			64	0.050 $\pm$ 0.021
Control <sup>d</sup>			0	0.851 $\pm$ 0.006			0	1.115 $\pm$ 0.021
			10	0.867 $\pm$ 0.006			8	0.961 $\pm$ 0.021
			20	0.852 $\pm$ 0.006			16	0.944 $\pm$ 0.021
			40	0.559 $\pm$ 0.006			32	0.546 $\pm$ 0.021
			80	0.078 $\pm$ 0.006			64	0.049 $\pm$ 0.021

<sup>a</sup>Following the pretreatment, the cells were exposed to a 24-h-treatment with a range of cadmium concentrations.

<sup>b</sup>Cell viability was assessed with the MTS/PES colorimetric assay (optical density at 490 nm). Mean optical density values  $\pm$  standard error for pretreated and control cells are shown for each treatment cadmium concentration.

<sup>c</sup>Vehicle NaCl, 0.9%.

<sup>d</sup>Potentized water.

*Effect of low-dose pretreatment on cadmium toxicity*

Low cadmium concentrations for pretreatment included 1 nM, 10 nM, 100 nM, and 1  $\mu$ M of cadmium. Given that the effect was not significantly dependent on pretreatment concentration, an overall pretreatment effect was calculated using data from all experiences and all pretreatment cadmium concentrations, for primary T-lymphocytes and for Jurkat cells, respectively.

Viability of primary T-lymphocytes exposed to low-dose cadmium pretreatment (1 nM–1  $\mu$ M) was significantly higher (mean effect  $\pm$  standard error [SE] = 19%  $\pm$  0.9%;  $p < 0.001$ ;  $n = 10$ ) than the vehicle-pretreated control cells when cadmium toxicity was induced (Fig. 1A; Table 2/Set A). Interestingly, the global pretreatment effect was manifest also in nonintoxicated cells (mean effect  $\pm$  SE = 18%  $\pm$  1.9%;  $p < 0.001$ , for the treatment cadmium concentration 0).

Jurkat cells pretreated with 1 nM, 10 nM, 100 nM, or 1  $\mu$ M of cadmium were more resistant toward subsequent intoxication with cadmium than control cells (Fig. 1B, Table 2/Set B). The pretreatment effect was significantly lower than in primary cells (mean effect  $\pm$  SE = 4%  $\pm$  0.5%;  $p < 0.001$ ,  $n = 13$ ).

*Effect of high homeopathic potency pretreatment on cadmium toxicity*

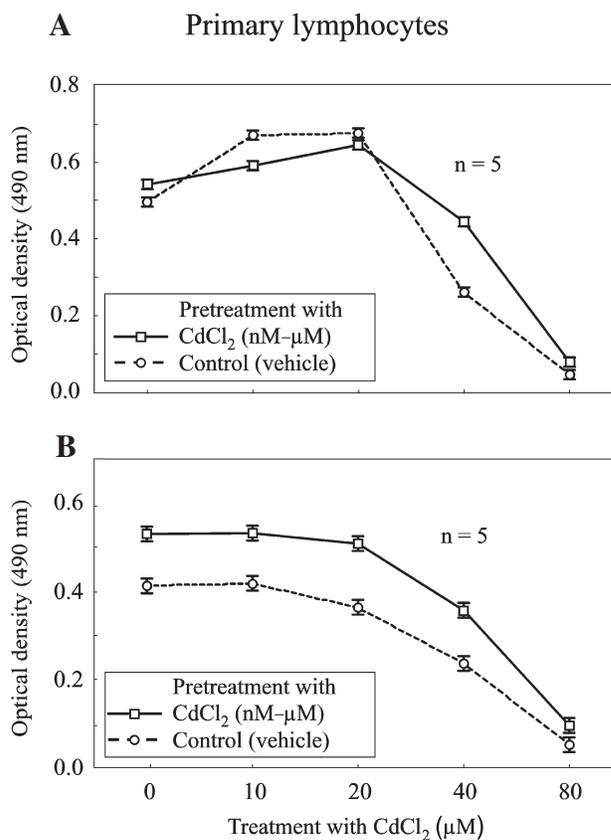
Pretreatment with the pool of homeopathic potencies 15–20c of cadmium resulted in a significantly increased viability of primary T-lymphocytes after exposure to toxic cadmium concentrations compared to control cells pretreated with potentized water 15–20c (mean effect  $\pm$  SE = 8%  $\pm$  0.6%;  $p < 0.001$ ,  $n = 7$ ; Fig. 1C, Table 2/Set C). As seen with low-dose pretreatment, the effect of the homeopathic potencies was observed also in nonintoxicated cells (mean effect  $\pm$  SE = 8%  $\pm$  1.1%;  $p < 0.001$ , for the treatment cadmium concentration 0).

However, the pool of homeopathic potencies had no significant effect on Jurkat cells (Fig. 1D, Table 2/Set D). The leukemic cells pretreated with homeopathic potencies did not show any enhancement of their viability following intoxication with cadmium compared to control cells pretreated with potentized water (mean effect  $\pm$  SE = 1%  $\pm$  1.9%;  $p = 0.45$ ;  $n = 4$ ). The pretreatment effect was significantly lower in Jurkat cells than in primary lymphocytes.

*Stimulatory effect of the cadmium treatment in primary lymphocytes*

Independently of the pretreatment, the 2 lower concentrations of the toxic cadmium treatment (10  $\mu$ M and 20  $\mu$ M) induced an increase of cell viability in primary lymphocytes (Fig. 1A). When the data were pooled for the pretreated and nonpretreated cells, a stimulatory effect was observed for 10  $\mu$ M and 20  $\mu$ M of cadmium (mean effect  $\pm$  SE = 12%  $\pm$  1%;  $p < 0.001$ , for 10  $\mu$ M of cadmium, and

11%  $\pm$  1%;  $p < 0.001$ , for 20  $\mu$ M of cadmium). This so-called hormetic effect was visible in some, but not all, experiments. We thus classified the single experiments into two groups, depending on the presence or not of a hormetic effect at 10–20  $\mu$ M of cadmium and analyzed the two groups separately (Fig. 2). Strikingly, in the experiments showing a hormetic effect at 10–20  $\mu$ M of cadmium, the pretreatment effect in nonintoxicated cells was weak, implying that, in these experiments, the stimulatory effect was induced mainly by the cadmium treatment (10–20  $\mu$ M) rather than by the low-dose pretreatment (Fig. 2A). However, the pretreatment effect in nonintoxicated cells was prevalent in the experiments in which the hormetic effect was not observed for the treatment cadmium concentrations (Fig. 2B). The observed hormetic effect seemed to be restricted to normal lymphocytes. No hormetic effect was seen in Jurkat cells (Fig. 1B).



**FIG. 2.** Effect (mean values  $\pm$  standard error) of a 120-hour-pretreatment with low concentrations (1 nM–1  $\mu$ M) of cadmium on the cellular viability of primary T-lymphocytes exposed to a 24-hour-treatment with a range of cadmium concentrations (X-axis). Cell viability was assessed with the MTS/PES colorimetric assay (optical density at 490 nm, Y-axis). In 5 experiments, an enhanced cellular viability (a hormetic effect) was induced by the treatment cadmium concentrations 10  $\mu$ M and 20  $\mu$ M compared to nonintoxicated cells (A). In the other 5 experiments, no hormetic effect was found (B).

## DISCUSSION

The present study was aimed at investigating, in normal and cancerous lymphocytes, the effect of a pretreatment with low concentrations and high homeopathic potencies of cadmium, respectively, with regard to a subsequent intoxication with cadmium. In both primary T-lymphocytes isolated from peripheral blood and Jurkat leukemic cells, a stimulatory effect of low-dose cadmium exposure was found compared to vehicle-treated cells. These results are in line with previous observations that an exposure to cadmium doses 2–50,000 times lower than the toxic dose applied, significantly enhances cellular survival.<sup>8,9,12</sup>

We found a dose-independent effect of the low-dose cadmium pretreatment for the concentration range we used (1 nM–1  $\mu$ M), both in primary lymphocytes and in Jurkat cells. In contrast, Pellegrini, et al., have reported a dose-dependent increase of the cellular survival rate in an immature T-cell line (CEM-C12) after exposure to toxic doses of cadmium for pretreatment concentrations ranging from 0.1 nM to 1  $\mu$ M.<sup>8</sup> Similarly, Wiegant, et al., found a dose-dependent effect of the low dose cadmium pretreatment for concentrations from 30 nM to 1  $\mu$ M in Reuber H35 rat hepatoma cells.<sup>12</sup> The discrepancy between their results and the results of the present study may be owing to a different sensibility to low cadmium doses of the various cell types used.

Pretreatment with the high homeopathic potencies of cadmium had a significant stimulatory effect on primary T-lymphocytes, whereas no effect could be found in Jurkat cells. These results suggest that cancerous cells are less responsive to low doses than normal cells and are fairly unresponsive to high homeopathic potencies. Similarly, Delbanco, et al., demonstrated in a noncancerous pig kidney cell line (LLC-PK1) a protective effect of a pretreatment with high homeopathic potencies of cadmium (10c, 15c, 20c) against subsequent toxic treatment with cadmium.<sup>11</sup> Other reports of potency effects in cell cultures using the isopathic approach include the studies by Then, et al., and Jonas, et al.<sup>10,13</sup> Then, et al., investigated a cancer cell line (HeLa/human cervix adenocarcinoma) and 2 normal cell lines (EBL/embryonic bovine lung, and MDBK/bovine kidney). They found a significant effect only with low-molecular potencies; ultramolecular potencies had no effect even in the normal cell lines.<sup>10</sup> In contrast, Jonas, et al., obtained positive results with high potencies in primary neuronal cells.<sup>13</sup> Taken together, these data corroborate the current authors' assumption that cancerous cells, having lost the ability to respond to regulatory signals, do not respond to high homeopathic potencies. Noncancerous cell lines seem to respond inconsistently, whereas primary cells are probably the best model to test the action of high potencies *in vitro*.

There are actually a few reports demonstrating an effect of ultramolecular potencies in cancer cell lines: the study by Kandefér-Szerszen, et al., performed in lung carcinoma

cells with potencies up to 40c, and the study by Carmine in neuroblastoma cells with potencies up to 100x.<sup>19,20</sup> These studies, however, cannot directly be compared with the current study because they were performed with high potencies of cytokines ( $\alpha$ -interferon respectively tumor necrosis factor- $\alpha$ ), and thus transcend the isopathic model. High homeopathic potencies carry nonmolecular information that can only be understood by an organism or by isolated cells in a given framework.<sup>21</sup> In the isopathic approach, the framework is provided by the identity between the exogenous toxic agent and the high potencies prepared from the same toxic agent. In experimental models using high potencies of cytokines, the cells understand the informational content of the potencies because cytokines are endogenous molecules and belong to the self.<sup>21</sup> It is a higher level of information that can seemingly be understood even by cancer cells.

In the present study, pretreatment with high homeopathic potencies had a stimulatory effect also on nonintoxicated cells; the effect was not more pronounced in intoxicated cells. Thus, it is not a protective effect, as was expected. The authors hypothesize that the stimulatory effect observed is the result of a real homeopathic effect according to the *similia* principle. Primary cells kept in culture experience a continual stress from the culture conditions, which mimic the *in vivo* conditions only incompletely. The cells survive only for a limited period of time. Cadmium as a homeopathic remedy (*Cadmium sulphuratum*) is prescribed in cases of great exhaustion when the disease runs toward death as an outcome.<sup>22</sup> Thus, the primary lymphocytes were stimulated by the cadmium potencies applied in the framework of the *similia* principle. As the similitude cannot be perfect for a cellular system, the effect induced is not very large. Cancerous cells, on the other hand, were apparently not capable to recognize the informative content of the high homeopathic potencies.

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