

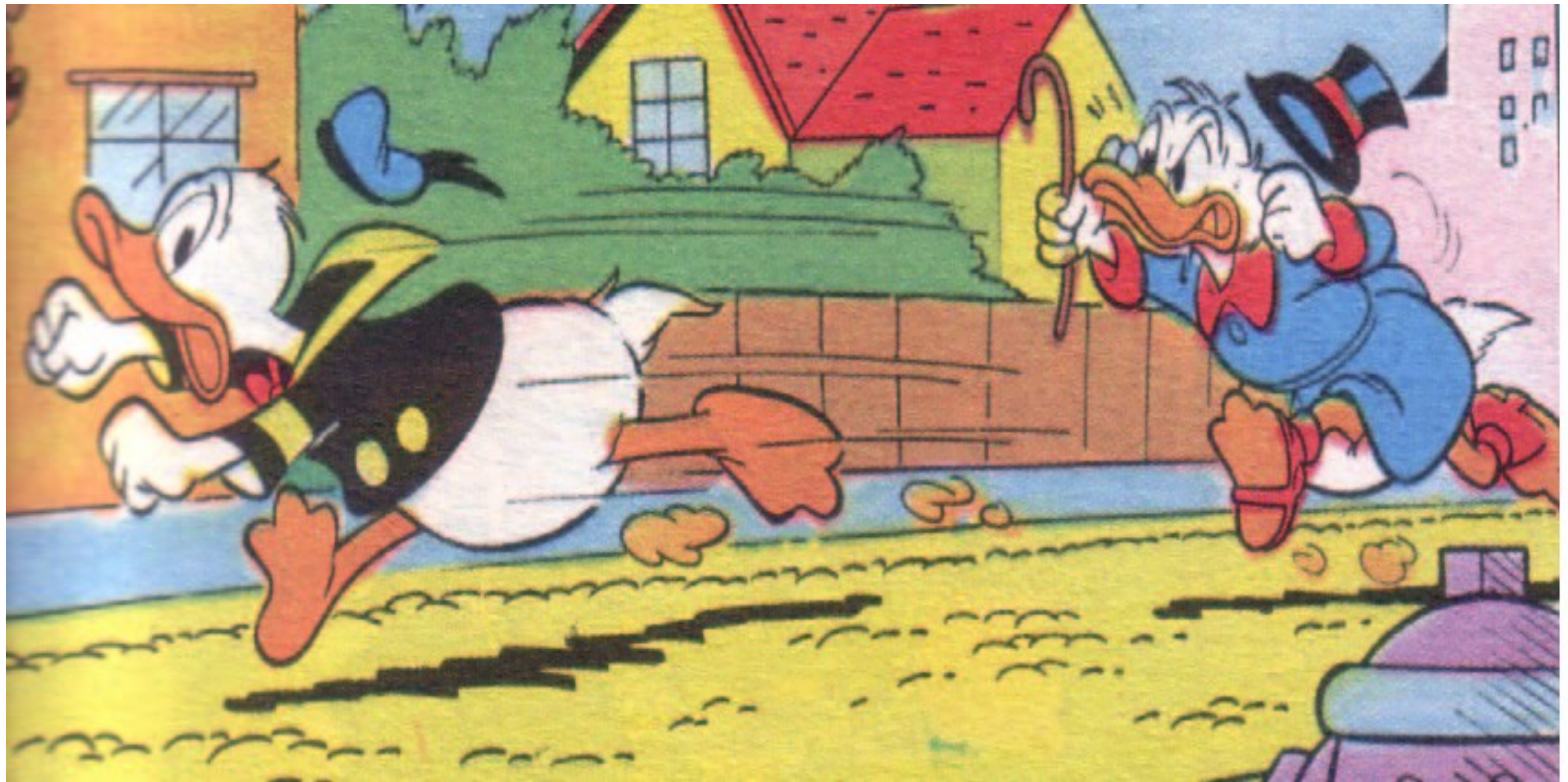
L-Carnitine and immune system

*Claudio De Simone, M.D.,
Professor Infectious Diseases
Dept. Experimental Medicina,
University of L'Aquila, Italy*

With the cooperation of :

Grazia Cifone, Giuseppe Famularo,
Vito Trinchieri, Hiroaki Mitsuya,
Marinos Dalakas, Emilio Jirillo,
Gino Santini

...and thanks to Mr Claudio CAVAZZA for his aggressive appreciation of our research



L-carnitine: where and when

Many studies have shown that L-carnitine could be used in a wide range of conditions:

- neurological diseases,
- alcohol-related disorders,
- diabetic complications,
- liver and kidney diseases,
- obesity and muscular dystrophy

and... what about immunity?

....Just a few Examples

Selimoglu MA

Plasma and liver carnitine levels of children with chronic hepatitis B.
J Clin Gastroenterol. 2004 Feb;38(2):130-3.

Athanassakis I

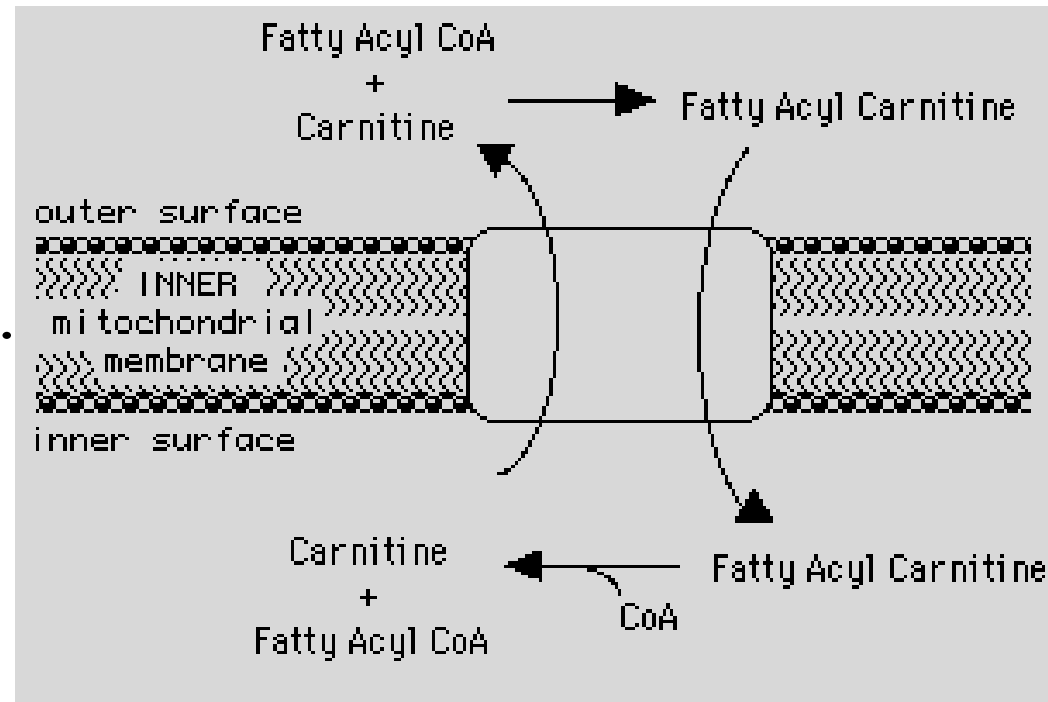
Early events of the exogenously provided L-Carnitine in murine macrophages, T- and B-lymphocytes: modulation of prostaglandin E1 and E2 production in response to arachidonic acid.
J Nutr Biochem. 2003 Jun;14(6):350-7

Arafa HM

Immunomodulatory effects of L-carnitine and q10 in mouse spleen exposed to low-frequency high-intensity magnetic field.
Toxicology. 2003 May 3;187(2-3):171-81.

L-Carnitine and Immune Response: The Energy Production Hypothesis

- High level immune function requires large amounts of cellular energy.
- Infections appear to deplete carnitine levels.
- Carnitine supplementation restores energy and then, the immune response.



Patients with active pulmonary tuberculosis (TBC)

- ALC was orally administered (2 g/day for 30 days) to 10 patients with TBC.
- Lymphocyte-mediated antibacterial activity and serum levels of TNF-alpha were evaluated before and after treatment, comparing with 10 TBC patients receiving placebo.
- Results: antibacterial activity (by day 30) remained unmodified or increased in ALC-treated subjects, while decreased in the placebo group. No influence of ALC on TNF-alpha levels was detectable.

Carnitine has more fun with.... old cells

- The effect of L-carnitine and acetyl-L-carnitine on cell proliferation was studied in peripheral blood lymphocytes from donors of different ages.
- The results showed that PHA-induced PBL proliferation was markedly increased in L-carnitine- or acetyl-L-carnitine-preloaded lymphocytes from young and especially from old subjects.
- Preliminary observations suggest that L-carnitine-preloading also protected peripheral blood lymphocytes from old donors when such cells were exposed to an oxidative stress.

Reversibility by L-carnitine of immunosuppression induced by an emulsion of soya bean oil, glycerol and egg lecithin. *Arzneimittelforschung*.1982;32(11):1485

Intralipid--an emulsion of soya bean oil, glycerol and egg lecithin--which is usually employed to improve caloric intake of parenteral nutrition regimens, may compromise human host defence mechanisms

....justify the inclusion of L-carnitine in parenteral nutrition regimens which, by abrogating some co-factor limitation, improves the immune responses of the host

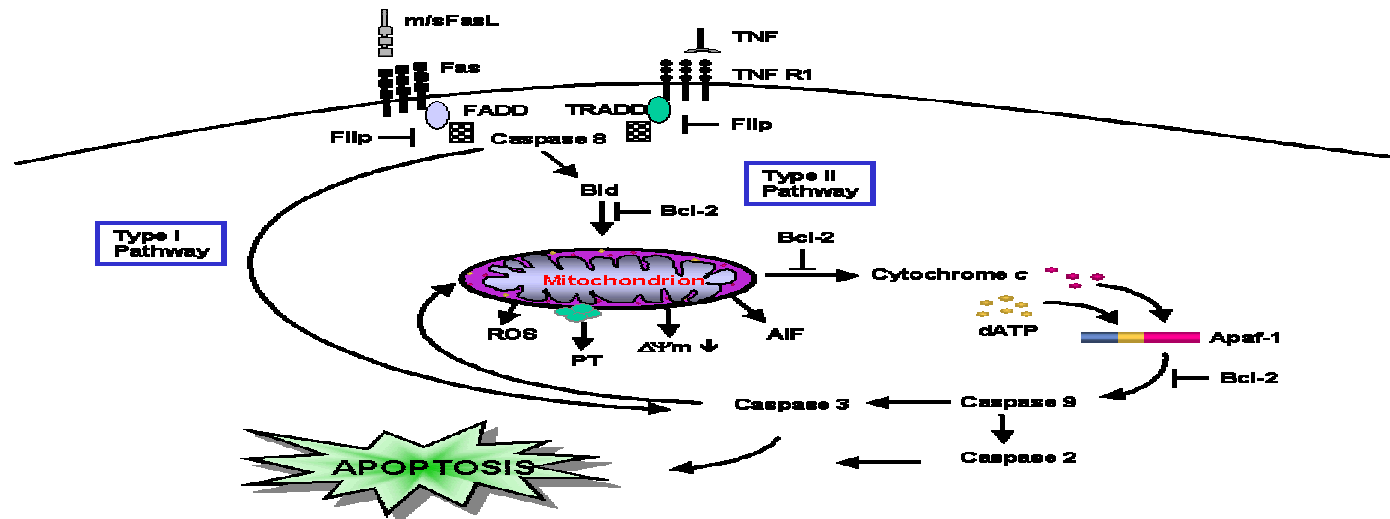
Are we in a good position ?



Or, can we do it better?

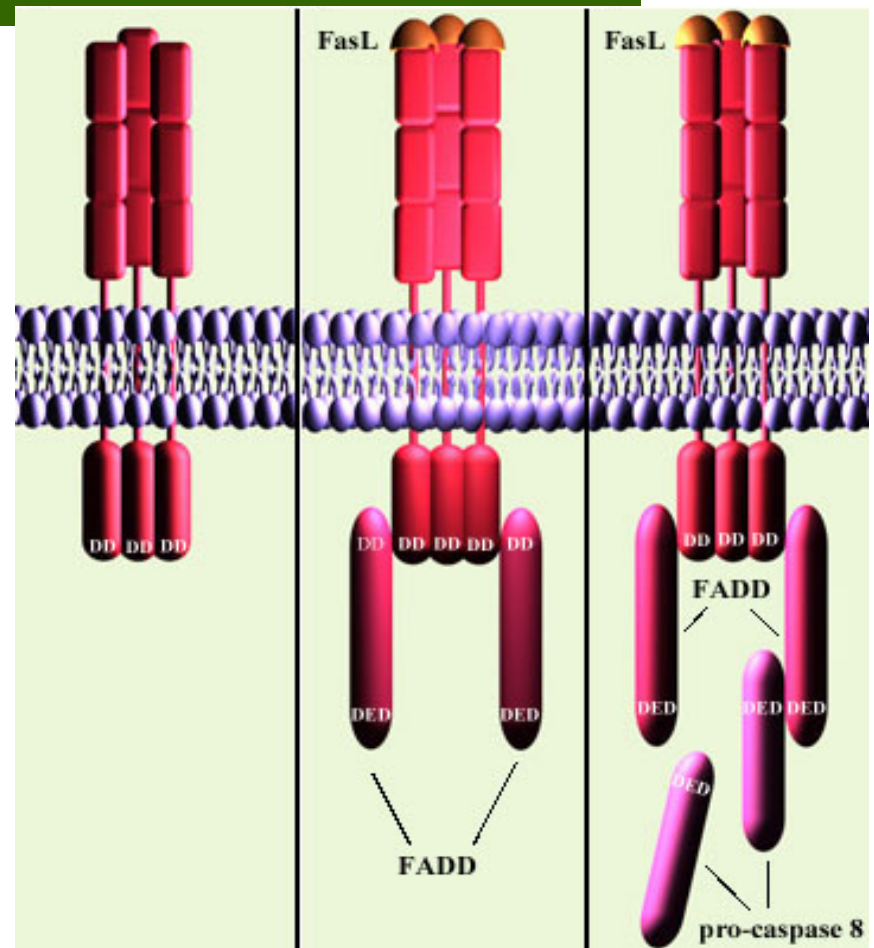
Apoptosis and AIDS

- A high degree of apoptosis has been detected in patients with AIDS in comparison with long-term non-progressors.



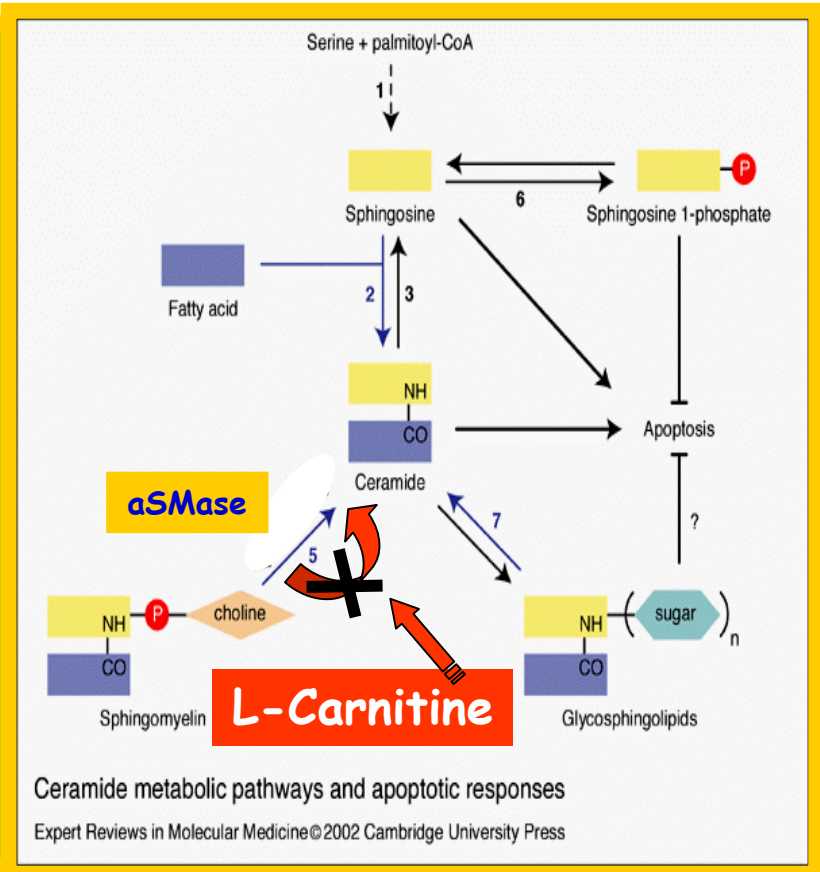
The FasL System

- The apoptotic signal transduced by Fas receptor involves the activation of an acidic sphingomyelinase, sphingomyelin breakdown, and ceramide production.
- Ceramide acts as an endogenous mediator of apoptosis and enhances HIV-1 replication



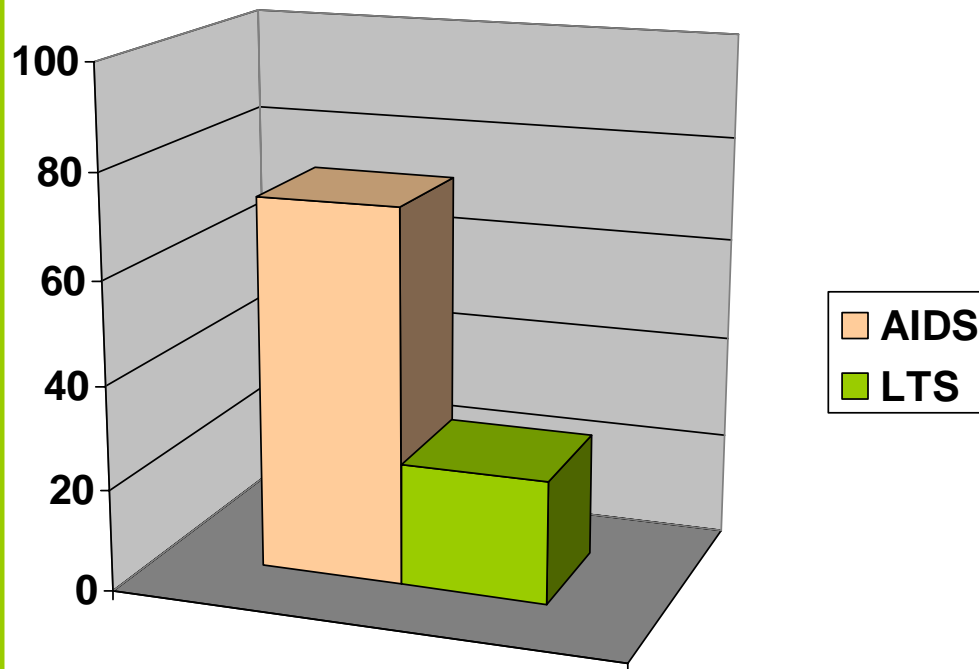
L-Carnitine inhibits ceramide generation

- In vitro effects of L-carnitine on CD95 cross-linking-induced apoptosis through an anti-CD95 mAb in Fas-sensitive cell lines (HuT78 and U937).
- L-carnitine is able to inhibit CD95-induced apoptosis of these cells, by preventing sphingomyelin breakdown and consequent ceramide synthesis.



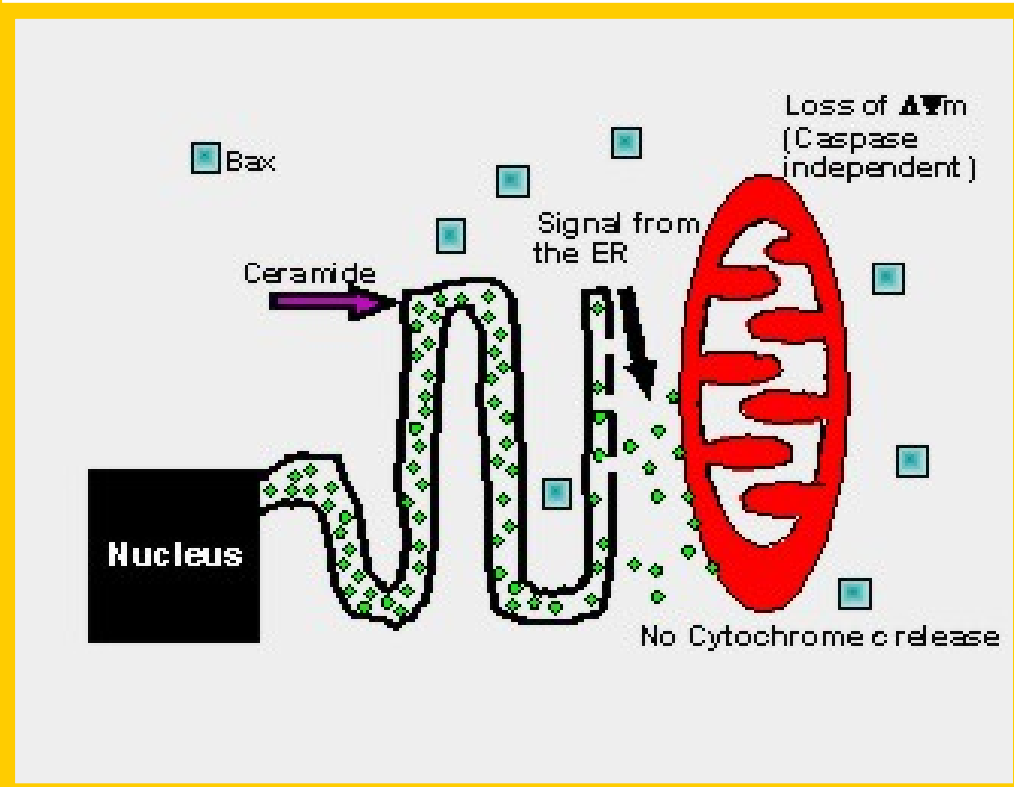
Ceramide, AIDS and long-term survivors.

- *Immunology Today*
1996 Jan;17(1):48
- *Immunology Today*
1996, Jun; 17(6): 256
- *AIDS. 1996*
Jun;10(6):675



Apoptosis and AIDS

- Healthy individuals and HIV-1-LTNPs have less elevated lymphocyte-associated ceramide levels than patients with AIDS.
- A lower frequency of apoptotic CD4 and CD8 cells in long-term nonprogressors than in patients with AIDS.

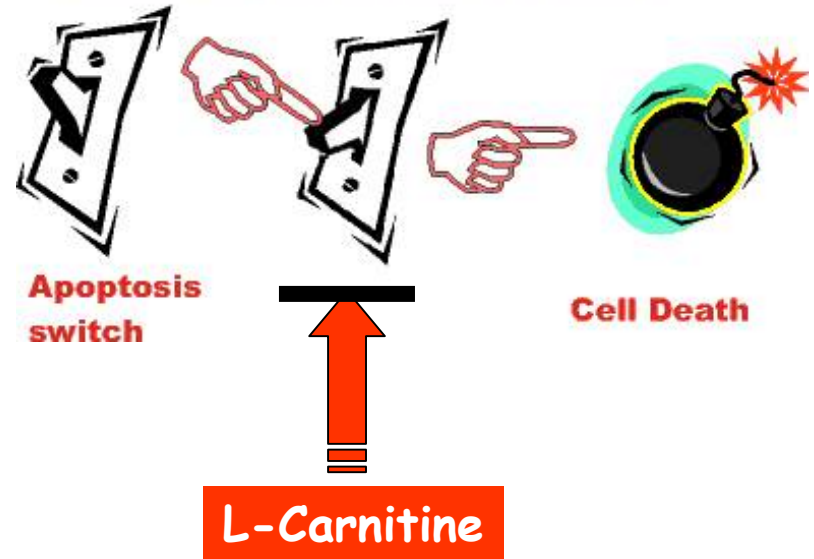


L-Carnitine:

AN EFFECTIVE ANTI-APOPTOTIC DRUG IN THE TREATMENT OF AIDS PATIENTS?

- A short-term (5-day) intravenous treatment with L-carnitine (6 g/day)
- Results: a strong reduction in the percentage of both CD4 and CD8 cells undergoing apoptosis.
- Significant reduction of peripheral blood mononuclear cell-associated ceramide

These results suggest that L-carnitine could be an effective antiapoptotic drug in the treatment of AIDS patients.



Effect of L-Carnitine on Human Immunodeficiency Virus-1 Infection-associated apoptosis: A pilot Study

Blood, Vol. 91, N. 10 (May 15) - 1998;3817-3824

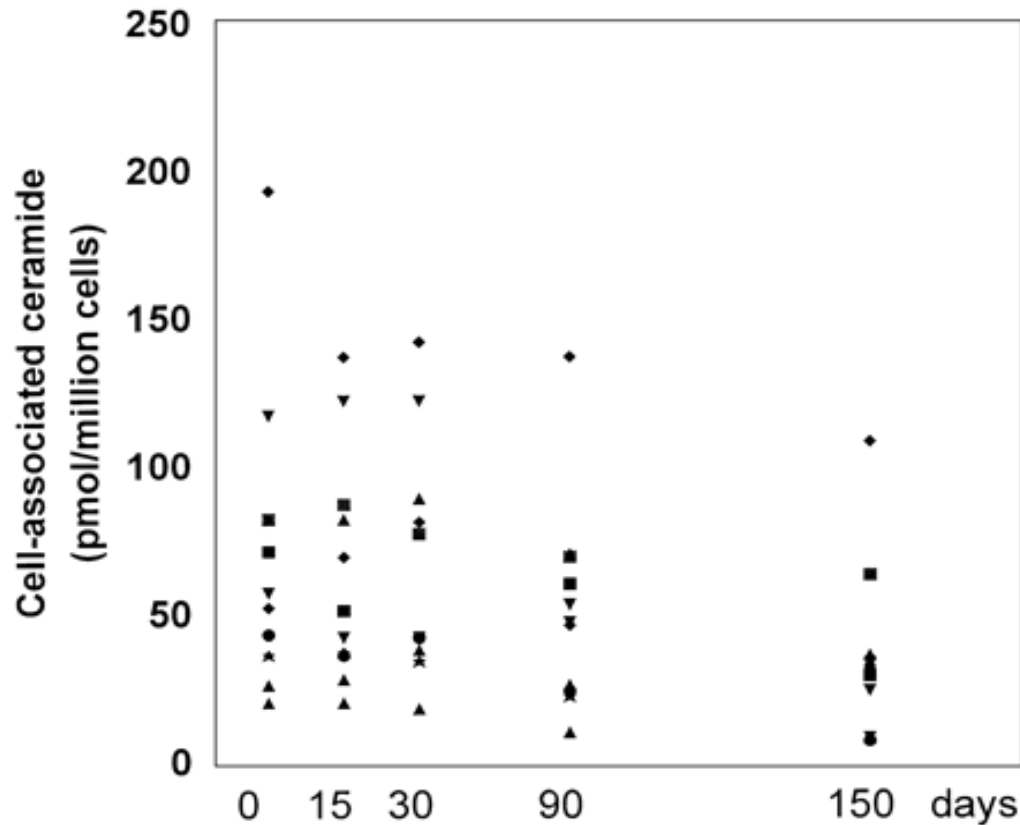
Eligibility criteria:

- (1) each subject had to be living in the community of San Patrignano, which is devoted to the rescue of drug addicts
- (2) each individual had rejected the opportunity of antiretroviral treatment despite experiencing a progressive decline in CD4 cell counts.

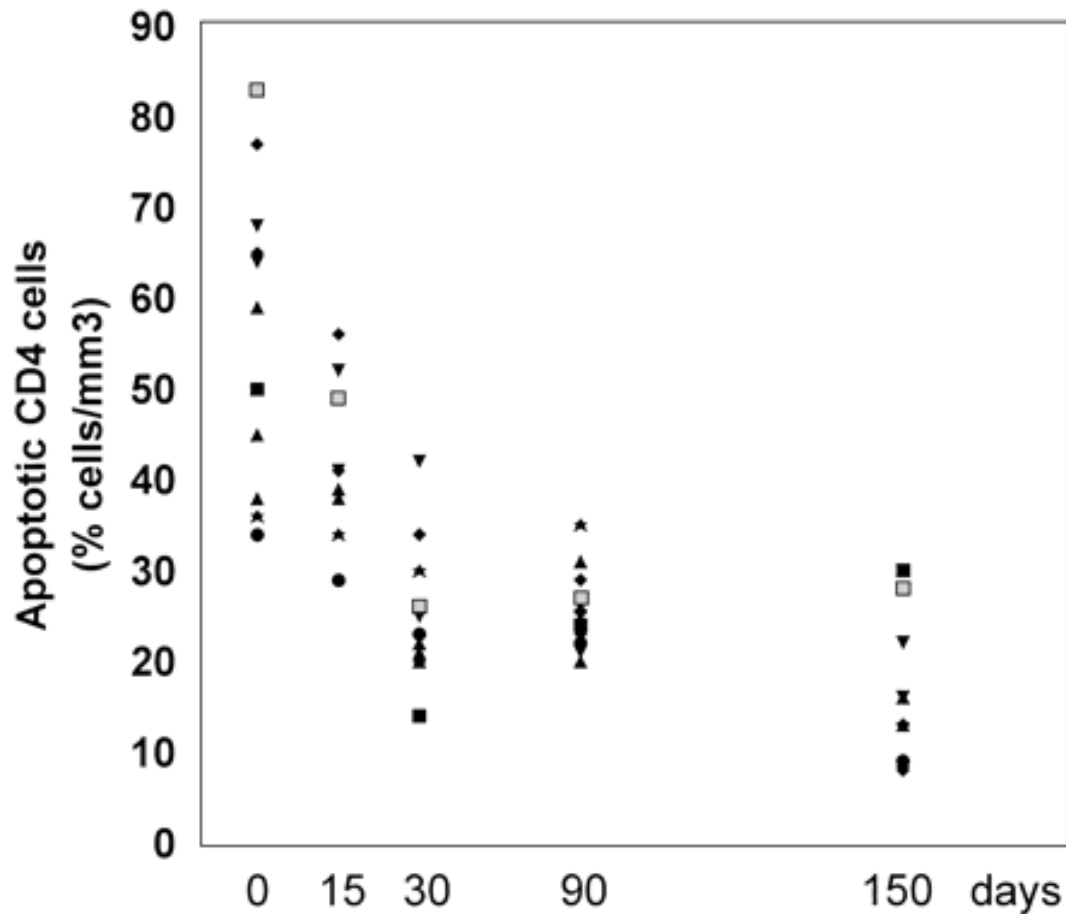


*The San Patrignano Community,
Rimini, Italy*

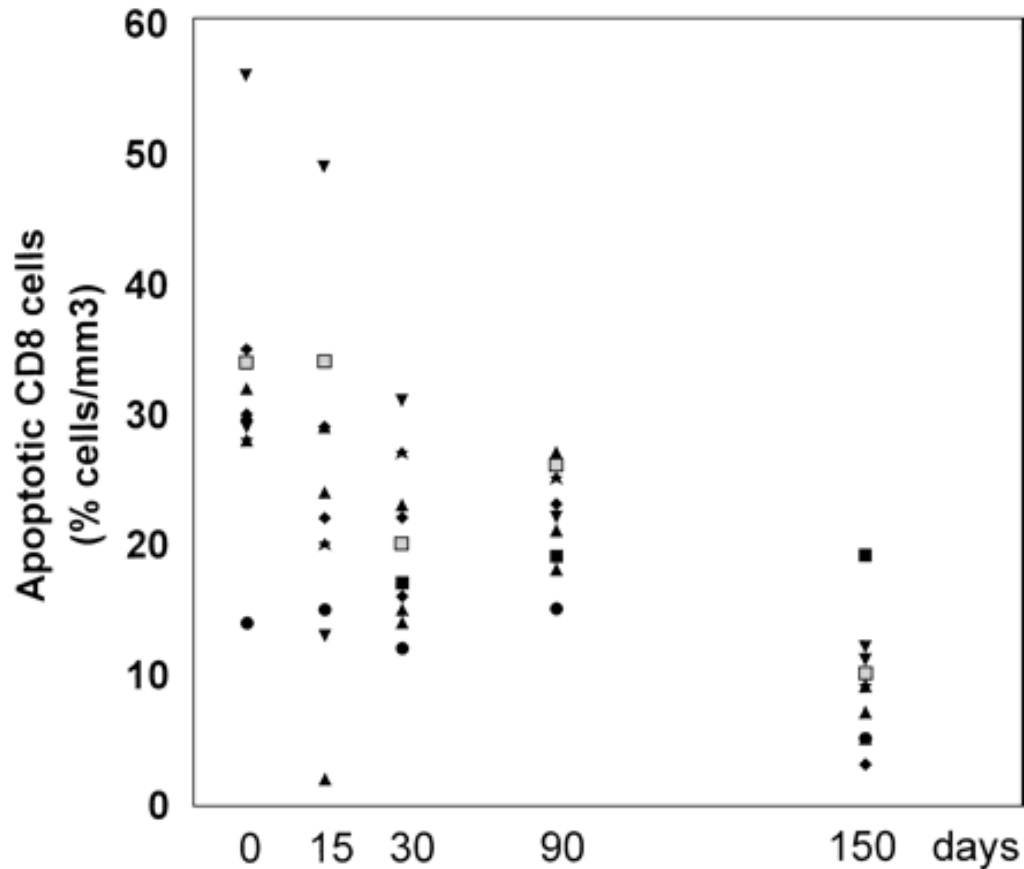
Cell-associated ceramide levels in peripheral blood mononuclear cells from AIDS patients before and after L-carnitine treatment (15-150 days).



Percentage of CD4 cells undergoing apoptosis in AIDS patients, before and after L-carnitine treatment (15-150 days).



Percentage of CD8 cells undergoing apoptosis in AIDS patients, before and after L-carnitine treatment (15-150 days).



SUMMARY

Unknown and multiple factors may promote a lipid imbalance in the cell

Lipid imbalance may result in an over production of ceramide

Ceramide is an ubiquitous second messenger that modulates :

- Cell differentiation
- Proliferation
- Survival
- Apoptosis

Ceramide generation is linked to loss of redox and cytokine balance

FUTURE RESEARCH:

**if ceramide plays a role...
will carnitine be an option for?**

- **Parkinson's disease**
- **Alzheimer's disease**
- **Demyelinating diseases (motoneuron disease, X-adrenoleukodystrophy and multiple sclerosis)**
- **Juvenile neuronal ceroid lipofuscinosis or Batten disease (JNCL)**
- **Hypertension and atherosclerosis**
- **Cardiomyocyte apoptosis induced by ischemia and reperfusion**
- **Stroke**
- **Multiple organ dysfunction syndrome (MODS)**

Perturbation of sphingolipid metabolism and ceramide production in HIV- Dementia

Haughey NG, Ann Neurol, 2004; 55:257

In patients with HIVD and pathological evidence of encephalitis, we found significant increases of sphingomyelins and ceramide in brain tissue and CSF.

..two inflammatory mediators that are induced in HIVD , TNF alpha and FasL are potent inducers of ceramide and can induce neuronal apoptosis ...

...because both cytokine and HIV protein-induced neuronal death can be prevented by inhibition of ceramide synthesis , this point of convergence is an attractive therapeutic target

Many thanks for your attention



...and that's all Folks!