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BENEFICIAL EFFECTS OF L-CARNITINE  
IN POST-DIALYSIS SYNDROME

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ABSTRACT

Patients subjected to intermittent haemodialysis present low muscle concentrations of carnitine. The purpose of our clinical study was that of investigating whether L-carnitine administration is able to affect some characteristic symptoms of the so-called post-dialysis syndrome.

One group of dialyzed patients received L-carnitine (60 days) and placebo (60 days) in sequence; the other group of 9 patients received the substances in the reverse order. The dosage used was 990 mg per day orally. The carnitine blood values, assayed prior to and during the different treatments, showed a distinct increase (approx. 80%) only during L-carnitine treatment.

Eleven symptoms were monitored by periodical interviews prior to and during the course of the investigation. The four symptoms which exhibited changes (asthenia, cramp, intradialysis hypotension, and dyspnoea after exertion) showed a ratio inversely proportional to the blood concentrations of carnitine: when such concentrations were increased a lower incidence of the characteristic symptoms of the post-dialysis syndrome occurred.

INTRODUCTION

It is commonly known that uraemic patients subjected to periodical haemodialysis after a time become affected by asthenia, easy muscular exhaustion, and dyspnoea after exertion. Such symptoms tend to be intensified and even persist for some hours during the post-dialysis period.

This so-called post-dialysis syndrome comprises low haematocrit values, metabolic shock provoked by rapid removal of fluids and urea, incomplete removal of some toxic substances or, on the contrary, the loss of useful metabolites.

In this regard Böhmer<sup>1</sup> in 1974 demonstrated that non-dialyzed

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patients with renal insufficiency displayed a higher than normal concentration of carnitine and that such a substance could be rapidly removed by dialysis.

Later, other researchers<sup>2-5</sup> carried out further investigations and found that patients subjected to periodical haemodialysis exhibited a constant loss of carnitine by filtration and successive endogenous biosynthesis did not restore basal levels.

Böhmer,<sup>3</sup> by comparing the carnitine content in the muscles of uraemic patients with that of healthy subjects, found that the former showed an average of 90% less carnitine versus controls.

We decided to investigate whether L-carnitine administration could prove useful for improving the post-dialysis syndrome.

#### MATERIALS AND METHODS

Eighteen subjects, 11 males and 7 females, between 20 and 45 years of age, were selected for the trial from a pool of approximately thirty patients periodically dialyzed at our Institute. All the patients had been undergoing 4-hour dialysis thrice weekly.

Dialysis was carried out using a Gambro AK 10 single unit dialyzer. The dialyzate contained the following ionic concentration: Na<sup>+</sup> 138 mEq/l, K<sup>+</sup> 2 mEq/l, Ca<sup>++</sup> 4 mEq/l, Mg<sup>++</sup> 1.5 mEq/l, C<sup>-</sup> 107.5 mEq/l, CH<sub>3</sub>COOH 38 mEq/l, Dextrose 12g/l.

The general clinico-metabolic conditions of the patients were satisfactory, and their cardiovascular state can be thus summarized:

- 9 normotensive patients with mean SAP  $\leq$  110 mmHg, not treated with cardiovascular active drugs;
- 9 hypertensive patients with mean SAP  $>$  100 mmHg, on hypotensive drugs, and with left ventricular hypertrophy without functional or haemodynamic failure.

Mean blood values: red cells 3,400,000 mm<sup>3</sup>, BUN 1.5 g/l, glucose 0.60 g/l, Na<sup>+</sup> 130 mEq/l, K<sup>+</sup> 4.8 mEq/l, SGOT 3  $\mu$ /ml, SGPT 2  $\mu$ /ml, creatinine 12 g/l.

The study was a double-blind cross-over trial. The patients were therefore divided into two groups (1 and 2) of 9, and selected in such a manner as to form as far as possible homogeneous groups as regards age, sex and general conditions.

#### *Treatment*

The group 1 patients were given (after basal monitoring) L-carnitine\* at the daily dosage of 990 mg p.o. in 3 equally divided administrations for 60 days. After a 10-day wash-out period the patients received placebo (3 tablets per day) for 60 days. Group 2 patients followed the same treatment design but with a reversed succession: placebo, wash-out, L-carnitine.

#### *Parameters*

Blood samples were drawn for determining carnitine concentrations at basal time, at

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\* L-carnitine (330-mg tablets) was kindly provided by Sigma Tau, S.p.A., Rome, Italy.

BENEFICIAL EFFECTS OF L-CARNITINE IN POST-DIALYSIS SYNDROME

2, 30 and 60 days of placebo or carnitine treatment and at 2, 30 and 60 days after the termination of the 10-day washout period, i.e., starting the cross-over. The Pearson method<sup>6</sup> was used for assaying the serum levels of carnitine. Special attention was given to overall symptomatology; the patients were interviewed fortnightly by a physician who recorded changes in symptoms by scoring from 0 to 3 according to intensity and duration (Table I). The interviewing physician was the same for the entire duration of the study.

Table I

Asthenia	<ol style="list-style-type: none"> <li>1. Rarely present at the end of dialysis and in any case not lasting for more than 30 minutes.</li> <li>2. Constantly present at the end of dialysis with a duration of approximately 2 hours.</li> <li>3. Constantly present with maximum intensity during the first 4 hours following dialysis.</li> </ol>
Intradialysis muscular cramp	<ol style="list-style-type: none"> <li>1. Present approximately every 10 dialyses.</li> <li>2. " " " 5 dialyses.</li> <li>3. " " at each dialysis.</li> </ol>
Intradialysis hypotension (SAP < 90 mmHg)	<ol style="list-style-type: none"> <li>1. Present approximately every 10 dialyses.</li> <li>2. " " " 5 dialyses.</li> <li>3. " " at each dialysis.</li> </ol>
Dyspnoea after exertion	<ol style="list-style-type: none"> <li>1. Occurring after 3 flights of stairs (10 steps each flight) or after strolling for about 500 metres.</li> <li>2. Occurring after 2 flights of stairs (10 steps each flight) or after strolling for about 100 metres.</li> <li>3. Occurring after 1 (or less) flight of stairs or after strolling for about 100 metres.</li> </ol>

The same method was used for other symptoms: precordial pain, cardiopalmus, insomnia, epigastric pain, nausea, vomiting and altered appetite.

RESULTS

Group 1 (Figs. 1, 3 and 5)

Figure 1 shows the carnitinaemia pattern during the dialysis performed prior to initiating the study, at 60 days of L-carnitine treatment and at 60 days of placebo.

The most significant differences were observed at the beginning of dialysis between post-therapy values with L-carnitine ( $91.1 \pm 10 \mu\text{moles/l}$ ) and basal values ( $49.3 \pm 8 \mu\text{moles/l}$ ) and after placebo ( $43.4 \pm 5.2 \mu\text{moles/l}$ ).

Once dialysis was initiated the carnitine values in the blood showed a considerable decrease, in all three cases, versus predialysis values, even though curve no. 2 at the first and second hour still indicates relatively high levels ( $41.8$  and  $36.3 \mu\text{moles/l}$ ). Figure 3 summarizes the predialysis values. It can be observed that in the first period (L-carnitine treatment) a progressive and constant increase in carnitinaemia occurred,

Figure 1 — Total carnitinaemia pattern in group 1 patients. Blood samples were drawn immediately prior to dialysis and at each of the 4 hours during dialysis. Monitorings: baseline, at 60 days of L-carnitine treatment (990 mg per day orally) at 60 days of placebo treatment. After 60 days of L-carnitine treatment a 10-day wash-out period was observed.

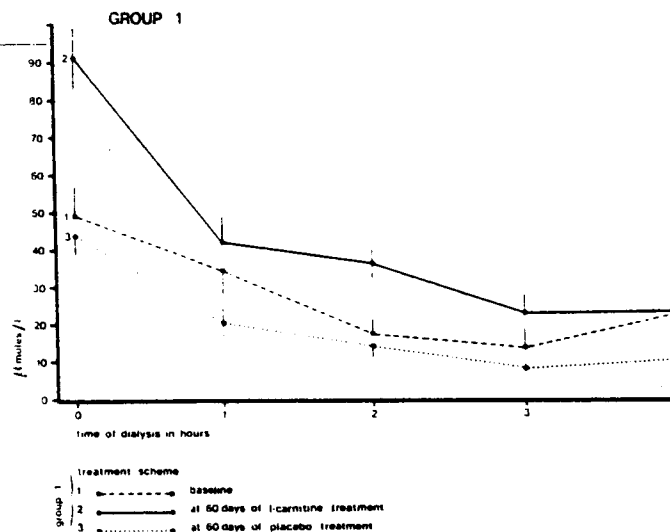
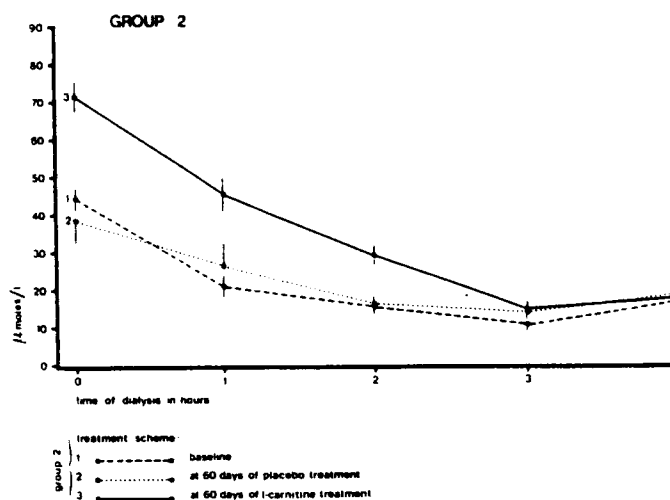


Figure 2 — Total carnitinaemia pattern in group 2 patients. Blood samples were drawn immediately prior to dialysis and at each of the 4 hours during dialysis. Monitorings: baseline and at 60 days of placebo treatment, at 60 days of L-carnitine treatment (990 mg per day orally). After 60 days of placebo treatment a 10-day wash-out period was observed.



BENEFICIAL EFFECTS OF L-CARNITINE IN POST-DIALYSIS SYNDROME

Figure 3 — The histograms only show carnitine levels of the blood samples drawn immediately prior to dialysis in group 1 patients. Monitorings: baseline, at 2, 30 and 60 days of L-carnitine treatment (990 mg per day orally), at 2, 30 and 60 days of placebo treatment. After 60 days of L-carnitine treatment a 10-day wash-out period was observed. Statistical evaluation: Student's t test.

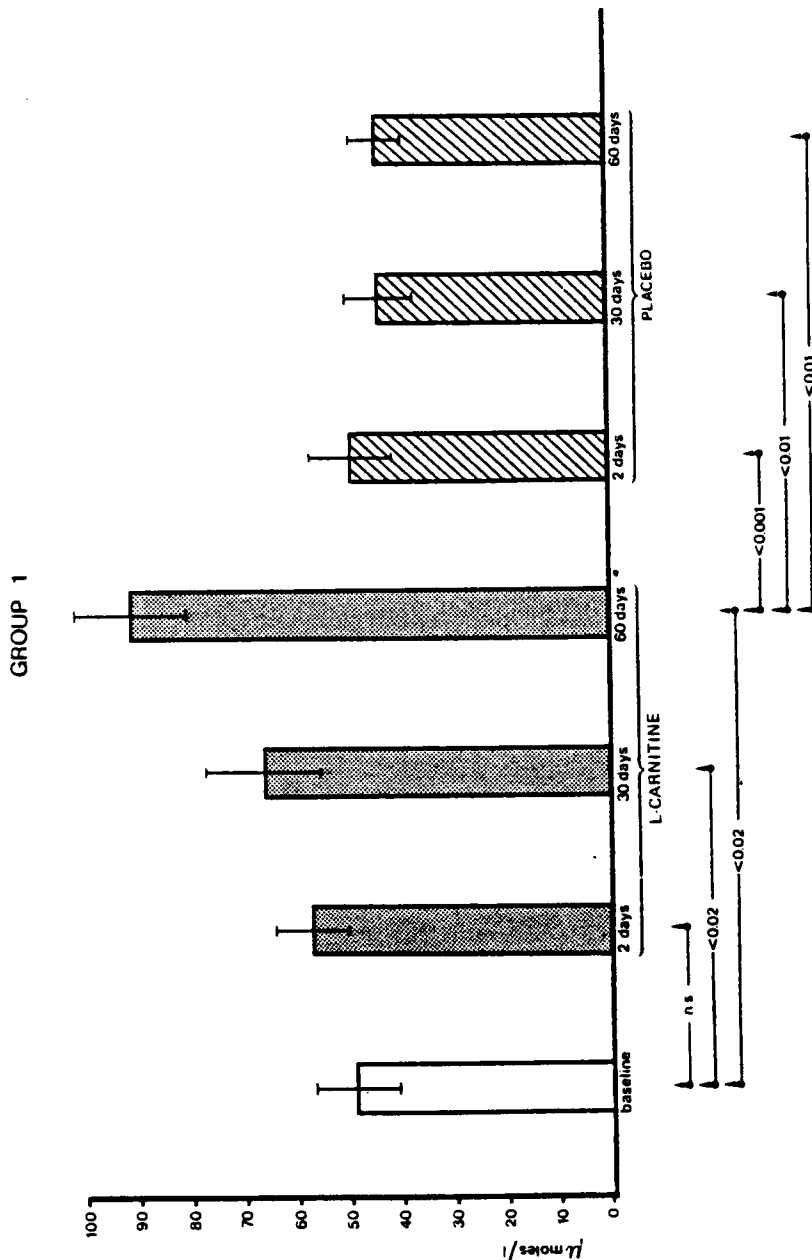
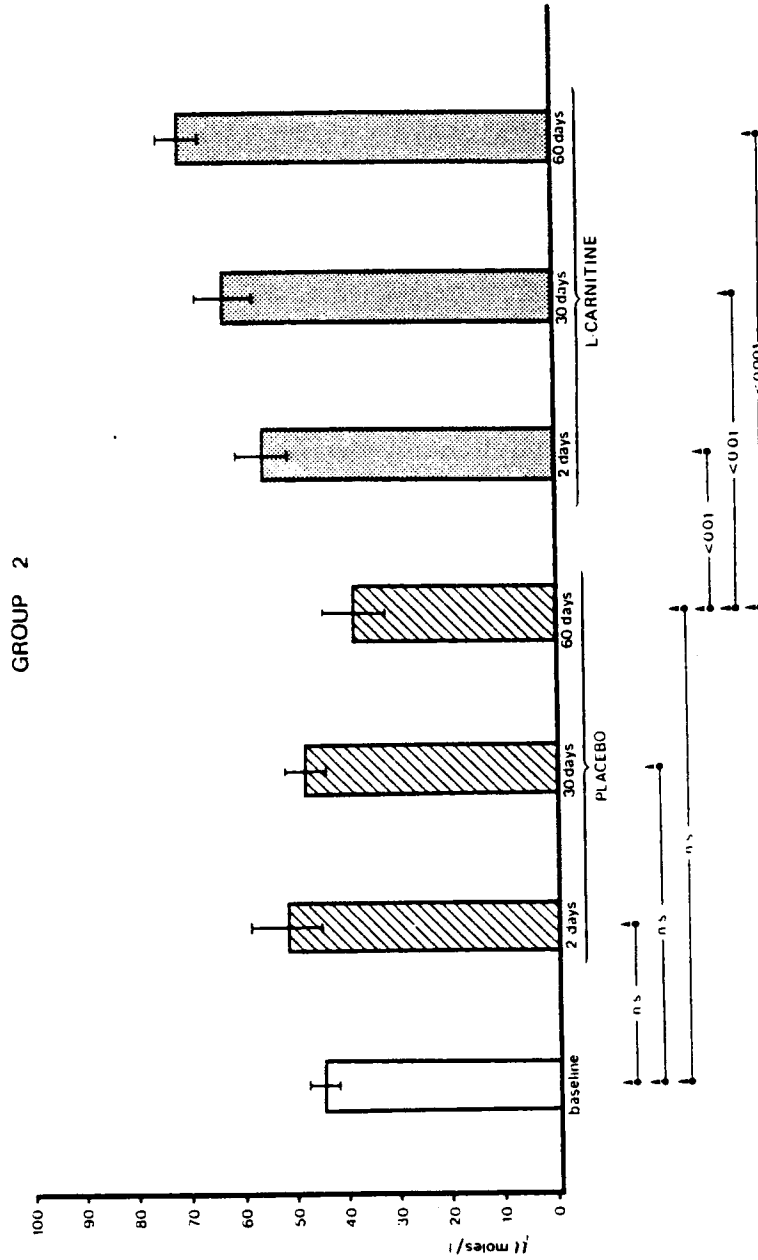
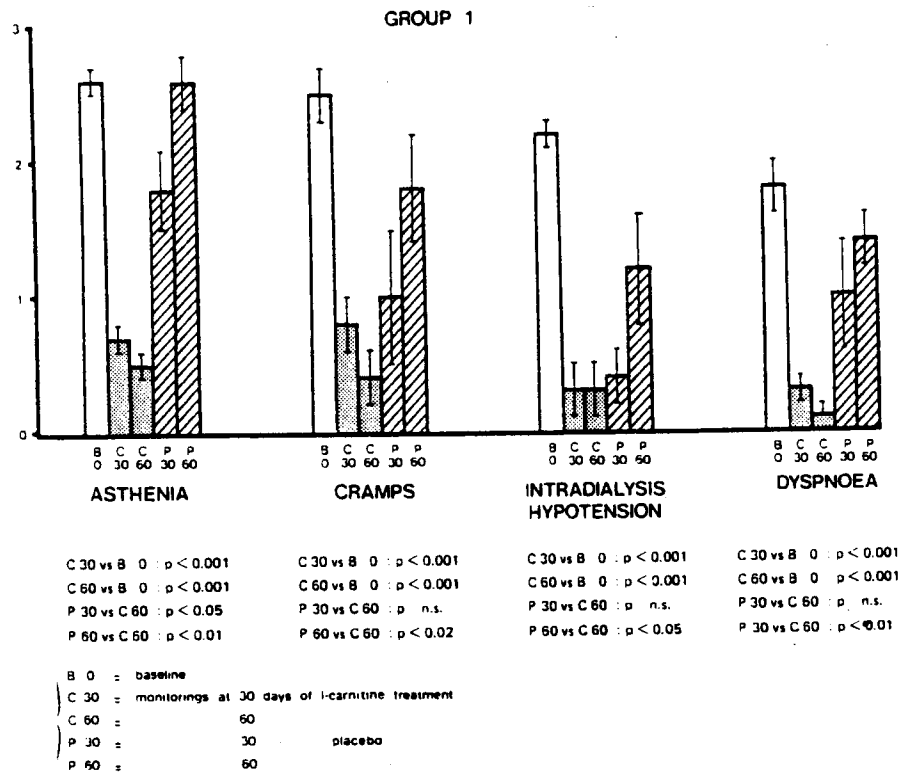


Figure 4 — The histograms only show carnitine levels of the blood samples drawn immediately prior to dialysis in group 2 patients. Monitorings: baseline, at 2, 30 and 60 days of placebo treatment, at 2, 30 and 60 days of L-carnitine treatment (990 mg per day orally). After 60 days of placebo treatment a 10-day wash-out period was observed. Statistical evaluation: Student's t test.



BENEFICIAL EFFECTS OF L-CARNITINE IN POST-DIALYSIS SYNDROME

Figure 5 — Group 1 symptomatology. Monitorings: baseline, at 30 and 60 days of L-carnitine treatment (990 mg per day orally), at 30 and 70 days of placebo treatment. After 60 days of L-carnitine treatment a 10-day wash-out period was observed. Statistical evaluation: Student's t test.



which was reduced after suspension of the drug practically returning to basal values.

In regard to symptomatology, Figure 5 gives the histograms referred to asthenia, cramp, dyspnoea and intradialysis hypotension only since the other symptoms did not display any important changes.

At 30 days and to a greater degree at 60 days the situation of a marked incidence of symptoms showed an extremely significant attenuation almost reaching disappearance as in the case of dyspnoea ( $1.8 \pm 2$  to  $0.1 \pm 0.1$ ).

Placebo treatment resulted in a somewhat deteriorated symptom situation at 30 days which showed a tendency to be more marked at 60 days.

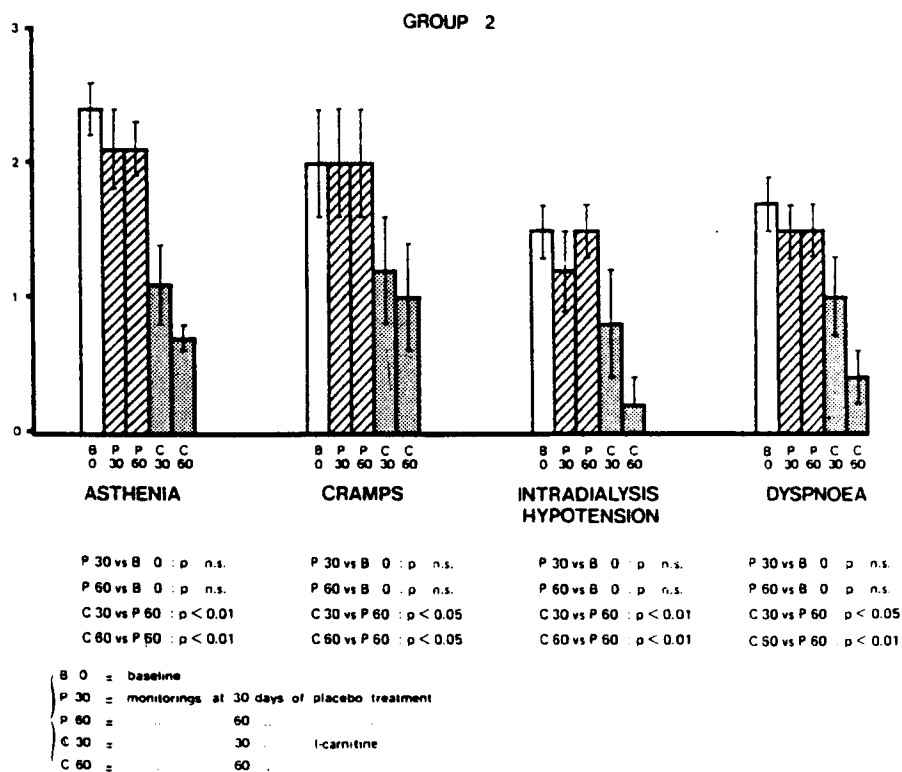
Group 2 (Figs. 2, 4 and 6)

The reversed treatment sequence (placebo, L-carnitine) employed in this group perfectly corresponded to the changes in symptomatology and carnitine levels in the blood. In fact, Figures 2 and 4 show that the blood concentration of carnitine increased only after L-carnitine treatment.

Likewise symptomatology (Fig. 6) did not exhibit significant changes after 60 days of placebo, whereas during L-carnitine treatment there was a considerable improvement at 30 days which became more marked at 60 days.

No side effects were observed in either group.

Figure 6 — Group 2 symptomatology. Monitorings: baseline, at 30 and 60 days of placebo treatment, at 30 and 60 days of L-carnitine treatment (990 mg per day orally). After 60 days of placebo treatment a 10-day wash-out period was observed. Statistical evaluation: Student's *t* test.

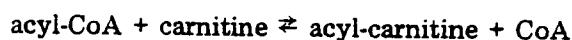




DISCUSSION

Carnitine ( $\gamma$ -trimethyl-ammonium- $\beta$ -hydroxybutyrate) is a naturally occurring substance whose main physiological role is that of transporting fatty acids from the cytoplasm to within the mitochondrial matrix<sup>7-8</sup> since the mitochondrial inner membrane is impermeable to acyl-CoA.

The importance of carnitine is evident in order to enable fatty acid oxidation and also, indirectly, to facilitate the tricarboxylic acid cycle since the exchange



makes available coenzyme A which is required for partial oxidation (up to acetate) and total oxidation ( $\text{CO}_2$  and  $\text{H}_2\text{O}$ ) of the fatty acids.

The highest concentrations of carnitine occur in the skeletal and cardiac muscles<sup>9-10</sup> and varied pathological situations deplete this muscle pool.

In addition to particular myopathies characterized by low carnitine levels and muscle lipid storage,<sup>11-14</sup> it has been found also that the myocardium during ischaemia loses carnitine.<sup>15</sup> Various experiments with animals<sup>16-19</sup> and man<sup>20-23</sup> suggest that carnitine therapy can be of considerable benefit in myocardial ischaemia.

It has also been observed that carnitine is chronically lacking in patients subjected to periodical haemodialysis.<sup>3</sup> This led to further clinical trials which demonstrated that carnitine therapy is capable of reducing hypertriglyceridaemia in dialyzed patients.<sup>24-27</sup>

Our clinical investigation had the purpose of evaluating the influence of carnitine on a series of symptoms which, in theory, could be affected by chronic muscle depletion of carnitine. The results appear to be encouraging even though clinical assessment of symptomatology always presents serious problems of interpretation and reliability. We tried to obviate this inconvenience as far as possible by employing the double-blind cross-over design and this enabled us to observe an almost mirror-like pattern in the two groups treated with the sequences: drug-placebo and placebo-drug.

It appears particularly interesting to emphasize that L-carnitine treatment has been shown to be capable of gradually reducing the incidence of various symptoms and that, in group 1, the successive placebo treatment did not restore initial values at 30 days, as if the exogenous carnitine which had accumulated in muscle tissue still continued to have some effect.

A recent study<sup>28</sup> showed that carnitine administration is able to elevate carnitine muscle concentrations in dialyzed subjects.

As regards three of the four symptoms — asthenia, cramp and dyspnoea — that varied with L-carnitine treatment, it may be hypothesized that muscular performance improved by increasing peripheral fatty acid utilization.

The lower incidence of intradialysis hypotension is more difficult to account for; the only datum in our possession is that carnitine exerts a positive inotropic effect.<sup>29-30</sup>

In conclusion, we could suggest that L-carnitine therapy is beneficial for treating the post-dialysis syndrome in addition to hypertriglyceridaemia in dialyzed subjects.

#### Acknowledgment

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BENEFICIAL EFFECTS OF L-CARNITINE IN POST-DIALYSIS SYNDROME

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C.U. CASCIANI, U. CARUSO, E. CRAVOTTO, M. CORSI, AND F. MACCARI

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*Key Words:*

cramps, asthenia, dyspnoea, intradialysis hypotension, L-carnitine.

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