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<p>(21) International Application Number: PCT/US90/06976</p> <p>(22) International Filing Date: 27 November 1990 (27.11.90)</p> <p>(30) Priority data: 441,110 27 November 1989 (27.11.89) US</p> <p>(71)(72) Applicants and Inventors: SHUG, Austin, L. [US/US]; 1201 Shorewood Blvd, Madison, WI 53705 (US). KEENE, Bruce, W. [US/US]; North NC State University, 4700 Hillsborough Street, Raleigh, NC 27606 (US).</p> <p>(74) Agent: GULBRANDSEN, Carl, E.; Stroud, Stroud, Wil-link, Thompson & Howard, 25 West Main Street, P.O. Box 2236, Madison, WI 53701 (US).</p>		<p>(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), NL (European patent), NO, SE (European patent).</p> <p>Published <i>With international search report.</i></p>
<p>(54) Title: METHOD FOR PREVENTING DIET-INDUCED CARNITINE DEFICIENCY IN DOMESTICATED DOGS AND CATS</p>		
<p>(57) Abstract</p> <p>A method is described for preventing diet-induced Carnitine deficiency in domesticated dogs and cats. A daily prophylactic amount of γ-butyrobetaine is administered to the pet either as a dietary supplement in an amount of 1.0 to 5.0 grams of γ-butyrobetaine per day, or γ-butyrobetaine is provided as an additional ingredient to a commercial pet food in an amount of 1.0 to 5.0 grams of γ-butyrobetaine per kilogram pet food.</p>		

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**METHOD FOR PREVENTING DIET-INDUCED CARNITINE
DEFICIENCY IN DOMESTICATED DOGS AND CATS**

DESCRIPTION:

5 **General Field of the Invention:**

The invention relates to the field of pet food compositions and more specifically to pet food enriched with L-Carnitine.

10 **Background of the Invention:**

L-Carnitine is a quaternary amine that promotes beta-oxidation of long-chain fatty acids by facilitating their transfer across the mitochondrial membrane. L-Carnitine has also been shown to promote oxidation of branched-chain amino acids and the utilization of acetyl-coenzyme A.

15 In mammalian species, L-Carnitine concentration in cardiac and skeletal muscle is much higher than in serum. In these tissues fatty acids are utilized as a major source of energy. Because of L-Carnitine's central role in transporting fatty acids to the site of oxidation, adequate levels of L-Carnitine are required for normal fatty acid and energy metabolism in mammalian hearts. This is evidenced by the restoration to normal of fatty acid oxidation in muscle homogenates of certain L-Carnitine deficient patients. A relationship between deficient levels of myocardial L-Carnitine and cardiomyopathy has been observed in both hamsters and dogs. Restoration toward normal of such deficient L-Carnitine levels has been shown to result in improved myocardial function in both species.

25
30 In mammals, L-Carnitine is derived from the diet and from biosynthesis in the liver, and in some species, kidney and other tissues. Neither cardiac nor skeletal muscle is

capable of synthesizing L-Carnitine, however. Thus, the L-Carnitine found in these tissues was either absorbed from the diet or biosynthesized endogenously by other tissues.

5 Our International Patent Application published as WO89/10065 is directed to a new use, in veterinary medicine for L-Carnitine and proposes a dietary supplement for domesticated dogs and cats, containing a prophylactic amount of L-Carnitine. The invention of WO89/10065 was based on the observation that dogs and cats were unable to
10 maintain a stable and optimum level of L-Carnitine in the same way as other mammalian species studied. The majority of mammalian species reabsorb, in the kidney, L-Carnitine from the urine. Renal reabsorption permits a stable and optimum level of L-Carnitine to be maintained. Dogs and
15 cats, however, did not have the ability of renal absorption to a sufficient degree, so that in the wild they were dependent on diet to replace L-Carnitine excreted in the urine and to maintain a stable and optimum physiological level. Previous researchers had relied the on L-Carnitine
20 levels in domesticated dogs and cats as indicating the stable and optimum physiological levels. The present inventors showed in WO89/10065 that in comparison with the same species in the wild, domesticated dogs and cats tended to suffer from acute L-Carnitine deficiency.

25 Studies have been made on the effectiveness of the biological precursors of L-Carnitine, ϵ -N-trimethyl-L-lysine and γ -butyrobetaine, as nutritional additives in the feeding of human babies. (A.L. Olson & C.J. Rebouch, Amer. Inst. of Nutrition, 1987 February.).

30 γ -butyrobetaine is a biological precursor of L-Carnitine in the biosynthetic pathway of the latter compound. See Nutrition Reviews, Vol. 36, No. 10, pp.305-

309, 1978, the teachings of which are incorporated herein by reference. γ -butyrobetaine has been used successfully to alleviate carnitine deficiency syndromes in humans as described in U.S. Patent No. 4,382,092 to Cavazza.

5 Olson and Rebouche compared L-Carnitine excretion rates in rats and in human infants when fed comparable doses of dietary γ -butyrobetaine and ϵ -N-trimethyl-L-lysine. They concluded that the γ -butyrobetaine was biologically converted to L-Carnitine in human infants at
10 a limiting rate greater than that at which it was isolated by renal activity. Conversely, with ϵ -N-trimethyl-L-lysine, the renal removal was the rate limiting step. In the absence of comparative tests on human adults, Olson and Rebouche declined to draw any conclusions on the uniqueness
15 of this pattern of renal behavior to human infants.

The inability of Olson and Rebouche to predict the renal activity of human adults from studies on human infants demonstrates the impossibility of extrapolating such results to other species, and particularly to species
20 such as dogs and cats which have been shown to exhibit quite unique renal activity in the handling of L-Carnitine itself.

With the above background, the inventors set out to investigate the possibility of using a low-cost biological precursor of L-Carnitine as a dietary supplement for
25 domesticated dogs and cats, to prevent diet-induced carnitine deficiency.

Summary of the Invention

30 The invention is based on a study of L-Carnitine levels established and maintained in domesticated dogs and cats fed with a dietary supplement of γ -butyrobetaine, from

which study it was deduced that the conversion of γ -butyrobetaine by the dog or cat is the rate limiting step, and not the removal of the γ -butyrobetaine by the kidneys.

The invention provides a method for preventing diet-induced carnitine deficiency in a domesticated dog or cat, comprising the step of: administering daily to said dog or cat a prophylactic amount of γ -butyrobetaine. The γ -butyrobetaine may be administered in the dog's or cat's drinking water or incorporated into the pet food. The invention therefore also provides a pet food composition for daily feeding to a dog or cat, said composition containing a prophylactic amount of γ -butyrobetaine.

The appropriate prophylactic amount of γ -butyrobetaine for incorporation into the pet food is preferably at least 1.0 gram of γ -butyrobetaine per kilogram of mixture and advantageously from 1.0 to 5.0 grams of γ -butyrobetaine per kilogram. Whether administered in the food or in the drinking water, the prophylactic amount is preferably sufficient to produce and maintain in the dog or cat a plasma total L-Carnitine concentration of at least 40 μM /liter of plasma.

Best Mode of Carrying Out the Invention:

Studies were made of the levels of serum L-Carnitine in dogs for a period following oral administration of 5 grams of γ -butyrobetaine. The blood serum level of L-Carnitine was found to rise markedly to a desirably high level within two hours of administration of the γ -butyrobetaine. Moreover, it was observed that the blood serum level of L-Carnitine was maintained at levels close to the initial peak level for at least six hours, indicating that secretion of the γ -butyrobetaine in the

kidneys was not the rate limiting step in the biological utilization of the γ -butyrobetaine.

The results are shown in the Table below.

TABLE

5 Changes in serum L-Carnitine following oral administration of 5 grams of gamma-butyrobetaine. Amounts are given in $\mu\text{M}/\text{l}$.

	0hr.	2hr.	4hr.	6hr.
10 Free Carnitine	15.8	60.2	51.4	40
Esterified	6.5	12.3	14.7	17.5
15 Total Serum Carnitine	22.3	72.5	66.1	57.5

20 Similar results were indicated from studies on cats.

In the preferred embodiment, sufficient γ -butyrobetaine will be administered orally to the pet dog or cat to raise the serum L-Carnitine level to 40.0 $\mu\text{M}/\text{liter}$ of plasma. Administration can be accomplished in the manner described in WO89/10065 for L-Carnitine, but the amount of γ -butyrobetaine needed for the same amount of rise in serum L-Carnitine will be greater. In practice, between 1 to 5 grams of γ -butyrobetaine should be administered daily, with the preferred amount being between 3 and 4 grams of γ -butyrobetaine.

30 The use of γ -butyrobetaine in lieu of L-Carnitine as a supplement provides a distinct economic advantage as the industrial preparation of γ -butyrobetaine is less complicated and less expensive than the preparation of L-Carnitine. The L-Carnitine preparation requires the optical antipode resolution of the racemic mixture which is unavoidably obtained in the chemical synthesis of

carnitine, and this necessarily increases the complexity and the expense of the synthesis.

CLAIMS

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A method for preventing diet-induced carnitine deficiency in a domesticated dog or cat, comprising the step of: administering daily to said dog or cat a prophylactic amount of γ -butyrobetaine.

5 2. A method as described in claim 1, wherein said γ -butyrobetaine is administered by adding said prophylactic amount of γ -butyrobetaine to said dog or cat's pet food so as to form a mixture and daily feeding said mixture to said dog or cat.

10 3. A method as claimed in claim 2, wherein said mixture has a γ -butyrobetaine concentration of at least 1.0 gram γ -butyrobetaine per kilogram of mixture.

15 4. A method as described in claim 1, wherein said L-Carnitine is administered by dissolving said prophylactic amount of γ -butyrobetaine in water so as to form a solution and feeding said solution to said dog or cat.

5. A method as claimed in claim 4, wherein said solution has a γ -butyrobetaine concentration of at least 1.0 gram γ -butyrobetaine per liter of solution.

20 6. A method as claimed in claim 1, wherein said prophylactic amount is an amount sufficient to produce and maintain in said dog or cat a plasma total carnitine concentration of at least 40.0 μ M/liter of plasma.

7. A method for preventing diet-induced carnitine deficiency in a domesticated dog or cat comprising the steps of: mixing a sufficient amount of γ -butyrobetaine with said dog or cat's food so as to form a mixture having a γ -butyrobetaine concentration of at least 1.0 gram per kilogram of mixture; and feeding daily said mixture to said dog or cat.

8. A pet food composition for daily feeding to a dog or cat, said composition containing a prophylactic amount of γ -butyrobetaine.

9. A pet food composition as claimed in claim 8 wherein said γ -butyrobetaine is in an amount from 1.0 to 5.0 grams per kilogram of pet food.

10. A pet food composition as claimed in claim 9, wherein said γ -butyrobetaine is in an amount of from 3.0 to 4.0 grams per kilogram of pet food.

11. γ -butyrobetaine for feeding to a domesticated dog or cat in a prophylactic amount to prevent diet-induced L-Carnitine deficiency.

12. A dietary supplement for a domesticated dog or cat, containing γ -butyrobetaine for feeding to the dog or cat in measured prophylactic amounts.

INTERNATIONAL SEARCH REPORT

International Application No **PCT/US90/06976**

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ³		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC(5) A23K 1/00 426/002		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁴		
Classification System	Classification Symbols	
U.S.	426/002,072,623,630,805 514/556	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁵		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ^{1*}		
Category [*]	Citation of Document, ^{1*} with indication, where appropriate, of the relevant passages ^{1*}	Relevant to Claim No. ^{1*}
Y	US,A, 4,382,092 (CAVAZZA) 03 May 1983 (See entire document).	1-12
A, P	US,A, 4,883,672 (Shug et al) 28 November 1989	1-12
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IV. CERTIFICATION		
Date of the Actual Completion of the International Search ²	Date of Mailing of this International Search Report ²	
04 March 1991	15 MAR 1991	
International Searching Authority ¹	Signature of Authorized Officer <i>Ruginto Nguyen</i>	
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