

This invention relates to compositions useful in combating symptoms of fatigue, particularly symptoms occurring in cases suffering from exhaustion caused by physical strain, delayed convalescence after infectious diseases and surgical interventions, malnutrition and anemic conditions, including pregnancy anemia.

I have found that in the treatment of the above symptoms, compositions in which the vitamin B-complex is combined with certain specific amino acids described hereinafter, have a cumulative effect which cannot be obtained by the use of the here described amino acids alone or the B-complex alone, or by the use of other mixtures or combinations of said amino acids of B-complex, respectively. In addition to the objective clinical improvements, almost immediate effects are noted in the relief from nervous tension, increase of ability of coordinated action and thinking, increased appetite, and relief from insomnia.

The problem of achieving an evaluation was solved by checking the subjective improvements simultaneously with a series of blood counts. The results of these blood counts invariably substantiated the subjective claims by showing an increase of hemoglobin and red blood cells, often after the first injection. The improvements obtained have proved to be permanent.

In order to test the response of a nerve accessible to objective clinical observation, patients with hearing disorders, as well as persons of normal hearing, were treated with the above mentioned compositions and subjected to clinical observation by means of the audiometer. In all cases an increase in hearing acuity was observed upon such treatment. In normal persons, this effect appeared as hyperacousis. The improved hearing was evidenced for the most part in the higher octaves.

The specific amino acids used in the before mentioned compositions are: betaine, glutamic acid, glycine, histidine, methionine,

tyrosine and cysteine. One single acid or a mixture of several amino acids may be used. Cysteine must be preferably used either in combination with betaine or with choline, and it is preferable to use two or more amino acids in mixture with the vitamin B-complex.

As mentioned above, the vitamin B-complex is used in combination with one or more specific amino acids of the group here described in order to obtain the above described effects. In addition to the vitamin B-complex and the amino acids, certain other ingredients of the beneficial effect may be used in my compositions, as described hereinafter.

It has been found that the compositions of the here described type have the disadvantage that they are not sufficiently stable and undergo certain undesired chemical changes upon storage in solid or dissolved condition. I have now found that this disadvantage can be overcome by adding to the compositions a small amount, 0.01-0.05%, of p-hydroxybenzoic methyl ester or p-hydroxybenzoic ethyl ester. Derivatives of these compounds in which the hydroxy group is converted into the -ONa group may also be used. Amounts of about 0.01 to 0.02% by weight based on the total weight of the ingredients in undissolved condition proved to be sufficient to obtain a satisfactory stabilizing effect and these amounts of 0.01 to 0.02% are preferably used. The stabilizing effect is essential as it permits the preparation of stable compositions having uniform properties and being free from undesired changes during the necessary storage period.

The compositions according to this invention may be used by oral or by parenteral administration.

Example 1 Capsules to be used by oral administration consist of

Vitamin A	(Fish Liver Oil)	4,000 USP units
Vitamin D	(Irradiated Ergosterol)	400 USP units

Vitamin B ₁ (Thiamine HCL, 666 USP units)	2 mg
Vitamin B ₂ (Riboflavin)	2 mg
Vitamin B ₆ (Pyridoxine HCL)	0.1 mg
Vitamin C (ascorbic acid, 750 USP units)	37.5 mg
Niacin amide	20.0 mg
Calcium pantothenate	1 mg
Cysteine hydrochloride	8 mg
Urea	75 mg
Tyrosine	60 mg
Choline	30 mg
Glutamic acid	60 mg
Liver Conc. 1:20	25 mg
Yeast-dried USP	50 mg
p-hydroxybenzoic methyl ester 0.015% of the total weight of undissolved ingredients.	

Example 2 A 2 cc solution for intramuscular injection is prepared by dissolving in distilled water

Vitamin B ₁	20 mg
Vitamin B ₂	5 mg
Vitamin B ₆	10 mg
Niacinamide	50 mg
Urea	200 mg
Histidine HCL	40 mg
Sodium glutamate	100 mg
Choline citrate	20 mg
Methionine	40 mg
p-hydroxybenzoic methyl ester 0.015% of the total weight of undissolved ingredients.	
Benzyl alcohol	2 % of the total weight
Chlorobutanol	0.4 % of the total weight
Propylene glycol	25 % of the total weight

Example 3 A 2 cc solution for intramuscular injection is prepared by dissolving in sterile distilled water

80 mg histidine hydrochloride

5 mg vitamin B₁

5 mg vitamin B₂

0.5 mg vitamin B₆

25.0 mg nicotine amide and

2.0 mg calcium pantothenate

p-hydroxybenzoic ethyl ester 0.02% of the total weight of undissolved ingredients.

Example 4 A composition is prepared by mixing

100 mg cysteine hydrochloride

300 mg glutamic acid hydrochloride

5 mg vitamin B₁

5 mg vitamin B₂

40 mg vitamin C

30 mg choline

170 mg vitamin B filtrate factor of liver

170 mg rice polish

170 mg yeast

p-hydroxybenzoic ethyl ester 0.02% of the total weight of undissolved ingredients.

The mixture is administered in the form of capsules, for example three times a day.

Example 5 A composition is prepared by mixing

100 mg cysteine

300 mg methionine

5 mg vitamin B₁

5 mg vitamin B₂

40 mg vitamin C

30 mg choline

170 mg vitamin B filtrate factor of liver

170 mg yeast

170 mg rice polish

p-hydroxybenzoic methylester 0.013% of the total weight of undissolved ingredients,

Example 6 A 2 cc solution for intramuscular injection is prepared by dissolving in sterile, distilled water

80 mg methionine

20 mg vitamin B₁

5 mg vitamin B₂

10 mg vitamin B₆

30 mg nicotinamide

2 mg calcium pantothenate

p-hydroxybenzoic methylester 0.01% of the total weight of undissolved ingredients.

Example 7 A 2cc solution for intramuscular injection is prepared by dissolving in water

80 mg histidine hydrochloride

5-10 mg vitamin B₁

5 mg vitamin B₂

0.5-1.0 mg vitamin B₆

20-30.0 mg niacin amide

2.0 mg calcium pantothenate

400.0 mg urea

667.0 mg propyleneglycol

40.0 mg Na₂HPO₄

6.0 mg H₃PO₄ (85%)

100.0 mg chlorobutanol

0.71 mg nipagin

p-hydroxybenzoic ethylester 0.02% of the total weight of undissolved ingredients.

It will be understood that the invention is not limited to the proportions, ingredients or other details described above and permits of various modifications without departing from the spirit thereof within the scope of the appended claims. It is to be understood that the term "amino acid" is used in the present specification and claims to include the free amino acids as well as salts of the acids.

Reference is made to my co-pending application Ser.No. 581,945 filed March 9, 1945, of which this is a continuation-in-part.

The p-hydroxybenzoic methylester mentioned above has the formula $\text{HO-C}_6\text{H}_4\text{-COO.CH}_3$ and the p-hydroxybenzoic ethylester has the formula $\text{HO-C}_6\text{H}_4\text{-COO.C}_2\text{H}_5$.

What I claim is:

1) A therapeutically active composition which comprises in combination compounds of the vitamin B-complex and at least one sex hormone.

2) A therapeutically active composition which comprises in combination compounds of the vitamin B-complex, at least one sex hormone, and at least one amino acid selected from the group consisting of betaine, glutamic acid, glycine, histidine, methionine, tyrosine and cysteine.

3) A therapeutically active composition which comprises in combination compounds of the vitamin B-complex, at least one sex hormone, choline, and at least one amino acid selected from the group consisting of betaine, glutamic acid, glycine, histidine, methionine, tyrosine and cysteine.

4) A composition as claimed in claim 2, in which the amino acids present are cysteine, tyrosine and glutamic acid.

5) A composition as claimed in claim 2, in which the amino acids present are histidine, glutamic acid and methionine.

6) A composition as claimed in claim 2, in which the amino acid present is histidine.

7) A therapeutically active composition which comprises in combination compounds of the vitamin B-complex, at least one sex hormone, at least one amino acid selected from the group consisting of betaine, glutamic acid, glycine, histidine, methionine, tyrosine and cysteine and a small amount of a stabilizer selected from the group of p-hydroxybenzoic methyl ester and p-hydroxybenzoic ethyl ester.

8) A therapeutically active composition which comprises in combination compounds of the vitamin B-complex, at least one sex hormone, choline, at least one amino acid selected from the group consisting of betaine, glutamic acid, glycine, histidine, methionine, tyrosine and cysteine and a small amount of a stabilizer selected from the group of p-hydroxybenzoic methyl ester and p-hydroxybenzoic ethyl ester.