

Medicinal preparations containing the Vitamin B<sub>6</sub> complex factors, lipotropic factors, and various hormones in an aqueous phase in one and the same solution and method of making the same.

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The object of this invention is to provide to the Medical Profession for parenteral administration all at one time the important Vitamin B complex factors, the lipotropic factors and various hormones either male or female sex hormones, such as the natural estrogenic female sex hormone, and testosteronepropionate, the male sex hormone, as well as progesterone, stilbesterol, and pregnelone as well as other hormone factors.

It is of course a well known fact in medicine, that the Vitamin B ~~Complex~~ Complex factors, such as thiamine hydrochloride, riboflavin, pyridoxin, and niacinamide play an important role in many disturbances and diseases and are being given by intravenous as well as by intramuscular injections.

Recently lipotropic factors such as choline chloride, inositol and ~~and~~ and ~~M~~ d. l. methionine, have come to be used in medicine and are considered important substances which regulate the metabolism of fats and regulate the function of the liver and these lipotropic factors, together with some specific amino acids are also given by parenteral injection, either intravenously or intramuscularly.

Recent work has also shown, that certain types of cancer now appear to be intimately connected to excessive quantities of estrogen in the body. This excess of estrogen exists because of malfunction of the liver. It was found, that this liver malfunction is caused by an absence from the diet of certain essential nutritional factors.

A number of investigators have demonstrated, that it is the liver which is the responsible organ in the inactivation of estrogen in the body. . ~~KXH~~ As early as 1908, in Osler's Modern Medicine, reference is made to the effect that menorrhagia and metrorrhagia do not infrequently occur in women with cirrhosis of the liver. Menstrual disturbances have been reported in women intoxicated with liver poisons or substances which are believed to effect adversely certain functions

of the liver, such as lead.

Sterility in men and aspermatogenesis with atrophy and vascular degeneration of the germinal epithelium in male are common occurrences in lead poisoning.

If a defective liver then fails to inactivate estrogen, it becomes apparent, that the high estrogen level might be responsible for the initiation of malignancies, which in animals and in human beings are sometimes associated with the excessive administration of exogenous estrogen.

Therefore if adequate therapy for the damaged liver could be found, one would expect the liver to regain its power of inactivating estrogen.

The Biskinds and their group of investigators have demonstrated a partial solution of this problem.

They have shown that a significant interrelationship exists between ~~Vitamin B~~ Vitamin B Complex deficiency and the inactivation of estrogen. This has become now an accepted scientific fact. A deficiency of Vitamin B Complex could lead to a failure of the liver to inactivate estrogen.

Rhoads had shown, that when butter yellow, a naphthalene derivative is fed with a diet of polished rice and carrots to rats, cancer develops. However, when he added to the same diet liver and yeast, both rich in Vitamin B. Complex, the cancer did not develop. This is a proof, that a dietary constituent such as Vitamin B. Complex can protect against induced cancer.

In the Vitamin B. Complex factors, it is particularly the thiamine, which is not stored in the body. and is therefore particularly liable to temporary or chronic depletion and a daily intake of thiamine is necessary; such thiamine as it is needed immediately is used, the remainder is excreted or destroyed.

The demand for thiamine is particularly increased in alcoholics and in those who consume large quantities of carbohydrates.

On the other hand, a number of investigators have demonstrated the fact that certain ~~specific~~ specific amino acids have catalytic as well as synergistic action.

upon the effectiveness of the factors of the Vitamin B. Complex.

Furthermore it has been demonstrated, that certain substances such as ~~AA~~ choline hydrochloride, inositol, and ~~inositol~~ <sup>4. P. Methionine</sup> act upon the fat metabolism and are very helpful to a sluggish liver, causing a relief or a repair of such a liver. These factors have come to be known as lipotropic factors.

These lipotropic factors given by intravenous or intramuscular injections establish a relationship between high blood cholesterol and atherosclerotic plaque. . It is believed that regulation of the blood cholesterol appears to offer the most promising approach to the prevention of arteriosclerosis.

A number of cardiologists are convinced that there is a connection ~~XXXXX~~ between fat metabolism and intimal atherosclerosis, especially of the coronary arteries

It has been recently reported that individuals, in whom heart disease was a primary cause of death, arteriosclerosis was by far the most important contributory cause. Several investigators have noticed an increased incidence of atherosclerosis in diseases associated with high serum cholesterols, such as xanthomatosis and other lipoidosis, diabetes mellitus, myxedema and nephritis.

Lipotropic factors such as choline, methionine and inositol will reduce blood cholesterol levels and slight increases in phospho lipids occurred after ~~six~~ six to ten weeks.

Recently with the discovery of cortisone and A. C. T. H. factor, attention of the Medical Profession was directed to the treatment of arthritis with these hormones. Scarcity of these hormones and the difficulty in synthesizing cortisone, makes this still more or less a laboratory curiosity.

~~It is for this reason~~ <sup>It is for this reason</sup>, that workers of the Oklahoma University Medical School tried other sex hormones in the treatment of arthritis and they obtained most encouraging results with estrogenic substances, ~~with~~ progesterone and ~~with~~ testosterone propionate.

The results

The results that these workers reported with these hormones are so encouraging, that we conceived the idea, to combine in one and the same solution, the factors of the Vitamin B Complex with the lipotropic factors with the sex hormones.

As the factors of the Vitamin B. Complex are all soluble in water and also the lipotropic factors are also very easily soluble in water, it was of course obvious to use water as the common solvent.

Of course the sex hormones are oil soluble and so the idea occurred to us to use these hormones like the natural sex hormones, the testosterone propionate, the progesterone, the stilbesterol, the pregnolone, etc in aqueous suspension using as the dispersing medium, the water in which the Vitamin B. Complex factors and the lipotropic factors are dissolved.

As a matter of illustration of our invention, we are describing here with a few sample methods:

#### Illustration I.

Method for preparing Vitamin B factors and natural estrogenic suspension and lipotropic factors, to which we have given the name Vitramone.

We dissolve in distilled water into which previously 1% chloro-butanol has been dissolved, using about 400 cc of it, 100 gms of Inositol, Choline chloride, 20 gms, d. l. methionine, 20 gms, thiamine hydrochloride 20 gms, solubilized riboflavin, 4 gms, Pyridoxin, 10 gms, Niacinamide 80 gms, benzyl alcohol 6 cc. After everything has been brought into solution at room temperature by vigorous agitation, it is brought to a volume of 500 cc.

The natural estrogenic substance in macrocrystalline suspension, is prepared in the following way:

Dissolve 3.125 gms of sodium hydroxide in 250 cc of dist. water and bring to a boil. add 1.1 gms of total estrogenic substance to the boiling caustic, and when completely dissolved, filter solution through a # 52 Whatman paper, using vacuum filtration with a Buechner funnel. Cool immediately to 1-2 degrees C. in an ice bath, with care taken to avoid direct exposure to sun light.

Add 6.5 cc. of concentrated hydrochloric acid to 238.5 cc of distilled water, and 5 cc of liquid phenol, stir the solution vigorously, and filter through Selas 01. under ~~va~~ vacuum and transfer to a separatory funnel or aspirator bottle and add the hydrochloric acid drop by drop through a fine capillary tubing to the clear solution of the sodium salt of the estrogenic substance. As the hydrochloric acid is added through a small ~~cap~~ capillary tube with a very fine impinging stream, with agitation, the estrogenic substance is precipitated in the form of very fine glistening macro crystalline substance. the  $p_H$  is adjusted to 7.2-7.4 A total volume of the suspension thus prepared of 500 cc. is obtained and under constant stirring this is combined with the other 500 cc of the solution containing the Vitamin B. Complex factors and the lipotropic factors. and 1000 cc of a suspension is obtained containing per cct~~h~~ the following quantities:

Inositol 50 mgs.  
 Choline chloride 10 mgs  
 d. l. methionine, 10 mgs,  
 thiamine hydrochloride 10 mgs,  
 riboflavin 2 mgs.  
 pyridoxin 5 mgs.  
 niacinamide 40 mgs.  
 benzylalcohol 0.3%  
 chlorobutanol 0.5%  
 natural estrogenic hormone 1 mg or 10.000 Int units.

#### Example # 2

Just like in example # 1 except instead of natural estrogenic hormone, ~~xx~~ testosterone propionate is being used.

Each cc contains :

Inositol 50 mgs.  
 Choline chloride, 10 mgs  
 d. l. methionine, 10 mgs.  
 thiaminehydrochloride 10 mgs.  
 riboflavin 2 mgs  
 pyrodoxin 5 mgs  
 niacinamide 40 mgs.  
 benzylalcohol 0.3%  
 chlorobutanol 0.5%  
 sodium chloride 0.45%  
 testosterone propionate 12.5 mgs per cc.

In preparing this suspension, to which we have given the name Testramone, we proceed just as in example # 1 preparing the Vitamin B . Complex factors and the lipotropic factors in double strength with the benzyl alcohol and chlorobutanol in double strength and mixing it with a suspension of testosterone propionate, which was made in the following way:

25 grams of testosterone propionate ground finely and put through a 200 mesh sieve was added with vigorous stirring to a solution of 4.5 grams of sodium chloride and 5.0 grams of acacia in 500 cc of distilled water and to this was added the other 500 cc of double strength Vitamin B. Complex and lipotropic factors solution.

Example # 3.

is made like # 2 except that progesterone 12.5 mgs per cc is added in aqueous suspension. To this product we have given the name ~~Prog~~ <sup>Prog</sup>estramone. The process of preparing the suspension is similar to example # 2 .

Example # 4 is made like illustrations # 2 and # 3 except that stilbesterol is used in aqueous suspension. To this product we have given the name Stilbramon.

Example # 5 is made like # 2 , 3, 4. except that pregnelone is used in aqueous suspension.

The intramuscular injections of these products will produce a fairly rapid absorption of the Vitamin B. Complex factors and the lipotropic factors, but will give an exceedingly slow and prolonged absorption of the finely suspended particles of the hormones. These particles will act like pellet implantations at the site of injection and as a result will produce prolonged hormone action, which in conditions like rheumatoid arthritis etc is indeed most desirable.

#### Claims:

First : What we claim as a new and useful invention is the combination of Vitamin B Complex factors with lipotropic factors and various sex hormones

hormones in one and the same aqueous phase, so as to permit the intramuscular injection of all these medicinal ingredients at once and at the same time.

Second : The method of combining in aqueous solution the Vitamin B. Complex ~~IA~~ factors such as thiamine hydrochloride, riboflavin, pyridoxin, niacinamide, with d. l. methionine, choline chloride, and inositol as the lipotropic factors in aqueous solution with equal volumes of hormone suspension.

Third.

The method of combining in aqueous solution Vitamin B. Complex factors such as thiamine hydrochloride, riboflavin, niacinamide and pyridoxin with lipotropic factors such as choline chloride, d.l. methionine, and inositol in aqueous solution, in such a way that double quantities of the final strength of these factors are being used, so that upon dilution with the same volume of the aqueous suspension of the hormone the desired final strength is obtained.

Fourth.

These factors such as Vitamin B. Complex, and lipotropic factors are dissolved in distilled water and are diluted with equal volume of an aqueous suspension of natural estrogenic hormone or the female sex hormone, in such a way that each cc contains 1 mg of estrogen.

Fifth:

Vitamin B. Complex factors combined with lipotropic factors dissolved in distilled water are diluted with an equal volume of an aqueous suspension of testosterone propionate.

Sixth.

Vitamin B. Complex factors combined with lipotropic factors are dissolved in distilled water and are diluted with an equal volume of an aqueous suspension progesterone.

Seventh.

Vitamin B. Complex factors combined with lipotropic factors dissolved in distilled water are diluted with an equal volume of an aqueous suspension of stilbesterol.

Eighth :  
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Vitamin B. Complex factors combined with lipotropic factors dissolved in distilled water are diluted with an equal volume of an aqueous suspension of pregnelone.

Ninth:  
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Vitamin Complex factors and lipotropic factors dissolved in distilled water and diluted with an equal volume of an aqueous suspension of hormones of the type of cortisone, <sup>Factor E</sup> Reichstein hormone, Factor F, and desoxycorticosterone, all of which have recently become very prominent in the treatment of arthritis, provided these hormones may be prepared in an aqueous suspension.



Assignment of Patent rights ..

Be it known, that we , Dr. Max Jacobson of 155 East 72nd Street , New York City N. Y. and Frederick R. Greenbaum, of 548 Twickenham Road, ~~XXXXXX~~ Glenside, Pennsylvania, both citizens of the United States have invented certain ~~XXXXXX~~ <sup>medicinal</sup> preparations containing the Vitamin B. Complex factors, the lipotropic factors and various hormones in an aqueous phase in one and the same solution and method of making the same" do hereby declare to turn over all patent rights resulting from this invention to the Harvey Laboratories, Inc at 428 South 13th Philadelphia, Pa. or to their successors or assigns..

In witness thereof we have put our hand and seal.

Max Jacobson, M. D,

Frederick R. Greenbaum,

Harvey Laboratories, Inc.

Philip Bleecher, President..

Date,