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THERAPEUTIC METAL CEVITAMATE COMPOSITIONS

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The present invention relates to the manufacture of new preparations for use in human therapy and more particularly to a new and improved medium for the introduction of therapeutic metals into the animal organs.

This application is a continuation-in-part of my prior applications Serial No. 745,527 filed September 26, 1934, which issued on October 28, 1941, under No. 2,260,870; Serial No. 50,237, filed November 16, 1935, which issued on May 14, 1946, under No. 2,400,171, and Serial No. 210,772, filed May 28, 1938, which issued on October 21, 1941, under No. 2,259,492.

It is a general object of the invention to provide therapeutic preparations containing metals in combinations which are highly efficient for their intended purposes, are non-toxic, in the indicated dosages, and can be administered parenterally without irritation and without danger of sloughing.

More specifically, it is an object of the invention to provide preparations for use in metal therapy in which the metal is combined with or associated with an organic radical which is a normal component of the blood stream and of various tissues of the human body, whereby a more rapid and more normal absorption of the metal by the body is ensured.

It is a further object of the invention to provide therapeutic preparations composed in whole or in part of compounds containing therapeutic metals which are distinguished over compounds of such metals now in general use by at least one of the following characteristics: greater compatibility with the components of the blood stream and of the tissues; reduced toxicity, greater solubility, greater absorbability with resultant improved therapeutic efficiency, and fortified therapeutic action of the metal by reason of the nature of the medium to which it is chemically united or with which it is otherwise associated.

In accordance with the invention, the various metals now employed in chemotherapy are introduced into the human body, by injection or by mouth, with the aid of a medium in the form of the unsubstituted or substituted laevo-ascorbate or cevitamate radical, the metal being associated with such radical in any suitable and effective combination, being either directly combined with such radical in the form of a salt, or in the form of a base or of a salt of another acid associated or compounded with unsubstituted or substituted cevitamic acid or with a salt of cevitamic acid.

By "therapeutic metals" as employed in this specification and in the appended claims are to

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be understood those metals whose compounds are employed in the field of chemotherapy; that is, compounds which are administered internally, either by mouth or parenterally, for the treatment of various diseases or systemic or functional disorders. A large number of these metals are referred to hereinbelow; the enumeration of these metals is, however, to be understood to be given solely by way of example and not as excluding other metals whose compounds have been used in human therapeutics.

It is known that cevitamic acid, also known as "vitamin C," normally occurs in the free condition in the human body. I have found that this acid and certain derivatives thereof form salt or salt-like combinations with metals and thereby yield therapeutic agencies for the introduction of such metals into the human system which are characterized by valuable and unsual properties. In addition to the therapeutic values imparted to these products by the therapeutic metal itself, the compounds in general have also anti-scorbutic effects. That the neutralized vitamin will still possess anti-scorbutic action, was not to be expected in view of the fact that the vitamin occurred universally as a free acid in fruits and vegetables and in the animal tissues; still less was it to be expected that, as I have found, the cevitamate radical will enhance the therapeutic efficiency of the metal.

Thus in the case of calcium cevitamate, I have found over a long course of clinical investigations that this compound increases the calcium content of the blood much better than any other calcium compound heretofore employed for calcium therapy. Calcium cevitamate is more readily absorbed and maintains the calcium content at a higher level than similar quantities of other calcium salts, this being due in large part to the very high solubility and high degree of ionization of the salt. Compared with calcium gluconate, one of the salts heretofore most commonly employed in calcium therapy, calcium cevitamate is far more soluble and hence can be used in more highly concentrated solution so that smaller volumes need be injected. Even when used in strong solution, calcium cevitamate does not have any irritating or other untoward effects on injection. I have found that in the treatment of rickets, calcium cevitamate is more effective than other calcium salts and quickly gives evidence of more rapid clinical improvement. In the treatment of pyorrhea alveolaris, calcium cevitamate diminishes the tendency toward bleeding of the gums, stops the recession of the alveolus from

the crown of the tooth and effects rapid improvement of this condition. This calcium salt effects also a more rapid deposit of calcium in tooth formation; and it is, further, an active agent in strengthening the structure of the blood vessels and in promoting clotting of the blood, thereby reducing hemorrhages.

Whereas, in the case of certain metal preparations heretofore employed in metal therapy, it was inadvisable to inject the preparations otherwise than intravenously, the corresponding cevitamic acid compounds of these metals can be injected not only intravenously but also intramuscularly. Thus, calcium gluconate usually had to be employed intravenously because of the danger of producing sloughs; while calcium chloride could be injected only intravenously. Calcium cevitamate, on the other hand, is not limited in the method of its administration and can be repeatedly injected intramuscularly without danger of sloughing. This mode of injection is favored by the high solubility of calcium cevitamate. This compound is also exceptionally stable in the presence of carbon dioxide, phosphoric acid and other chemical substances in the human tissues with which calcium normally forms insoluble compounds.

A further and quite unexpected property of calcium cevitamate is the fact that the calcium and cevitamate portions of the compound show an almost completely parallel action in bone metabolism, hemorrhagic diathesis, cell membrane permeability and detoxicating action. Investigations have indicated that the cevitamate radical is a physiological carrier for calcium. This explains the remarkable parallelism in the physiological behavior of the calcium cevitamate radicals. As further parallel actions may be mentioned and the fact that both increase the coagulability of the blood, inhibit allergic reactions, possess a detoxicating action on heavy metals and on arsenic and participate in tooth and bone growth. In fact, their actions in allergy are so alike as to make calcium cevitamate a double acting agent wherewith there is obtained an intensification of calcium action hitherto unobtainable with other calcium compounds in similar dosage. Both ions have a similar physiological action on the vegetative nervous system and have shown favorable action in reducing diarrhea in intestinal tuberculosis. Similarity of action has been found also in a number of other diseases showing a striking parallel action in two otherwise quite dissimilar ions. This parallel action indicates a definite correlation; and further, that the cevitamic radical is a stabilizing agent for calcium in the body and participates or facilitates absorption and maintenance of the ionized calcium in serum calcium.

Calcium cevitamate has proved to be highly effective in the treatment of acute rhinitis. See Ruskin, "Annals of Otology, Rhinology and Laryngology," vol. 47, No. 2, page 502.

Recent research has shown that calcium cevitamate is absorbed by the blood proteins and thus becomes available for use in the body metabolism to the extent of four times as much as calcium gluconate. In fact, researches with an improved Abbe refractometer have indicated that calcium cevitamate has a higher degree of re-activity with the blood serum proteins than vitamin C itself.

In the case of the compounds bismuth, antimony and arsenic, hitherto employed for the treatment of various diseases such as syphilis, and trypanosomiasis, the administration of these

compounds has frequently been attended by irritation and even poisoning and sometimes gives rise to dermatitis, gingivitis, and other affections. While these side effects are in certain cases due to the susceptibility of the patients to bismuth, antimony and arsenic poisoning, they are frequently due, either entirely or in part, to the other constituents of the medicinal. It is my belief that the untoward effects, or a great part of them, obtained with the use of the known compounds of these metals can, to a great extent, be traced to the fact that the remainder of the molecule is just as foreign to the human organism, and particularly to the blood stream, as the metal it is sought to introduce and just as poisonous or difficultly tolerable, so that the system receives a double shock from both the therapeutic metal and the organic radical to which it is joined. By combining these ordinarily toxic metals with the cevitamate radical, where necessary with the aid of sodium hydroxide, for solubilization, there is obtained, in accordance with the invention, compounds which are considerably less toxic and less irritating on injection than the known compounds of these metals, while at the same time a high therapeutic efficiency is maintained and the efficiency even increased. The cevitamate compounds of bismuth, antimony and arsenic have been found by me to be more readily tolerated by the human organism and possess the property of inhibiting the tendency to dermatitis, and gingivitis, frequently observed in bismuth, antimony and arsenic therapy. It appears that the peculiar structure of the cevitamate radical, which supplies both oxidation and reduction mechanisms, makes it an effective detoxicating agent; the administration of the cevitamates of bismuth, antimony and arsenic is thus attended with less danger and discomfort than heretofore. The oxidation-reduction properties of the cevitamate radical also appear to increase the activity of the metal, while at the same time reducing its toxic effects.

I have found further that the cevitamic acid compounds of bismuth, antimony and arsenic, in contrast to many of the organic compounds of these metals now employed in therapy, are quite soluble in water and with the aid of a stabilizing agent, and particularly at a pH value of about 7.6 or slightly higher, can be kept indefinitely in solution. Like the corresponding salt of calcium and also of other metals referred to hereinbelow, the cevitamates of bismuth, antimony and arsenic possess also the physiological action of the free acid, and thus simultaneously act to correct morbid conditions arising from a deficiency of vitamin C.

The iron and copper compounds of cevitamic acid, prepared in accordance with the invention, either individually or in combination, with or without the corresponding cobalt compound, have proved to be remarkably efficient and easily tolerated agents for the treatment of various anemias, and particularly of nutritional anemias. They can be administered by mouth and also parenterally and especially intramuscularly, and without discomfort. Because of the high rate of absorption, considerably smaller dosages are required than of hitherto employed medicinals for similar purposes. The administration of iron, or iron-copper or iron-copper-cobalt cevitamates is relatively free from the gastric and intestinal disturbances which frequently accompany the administration by mouth of known iron and copper compounds; and they are also quite free of the

disturbances both at the point of injection and systemically, which frequently occur in the parenteral introduction of the known preparations. The efficiency of the known compound is quite low and correspondingly large doses must therefore be employed. Thus, although the average daily requirement of iron to secure 1% hemoglobin use is one-half grain, the dosage of iron ammonium citrate is 90 grains per day. In the case of iron cevitamate, on the other hand, the dosage need be only 10 grains. Although cevitamic acid is a relatively unstable compound and its salts were accordingly to be expected to be similarly unstable, this relative instability, far from being a disadvantage in the therapeutic preparations of the present invention, is in all probability responsible, at least in large part, for the unusual efficacy and efficiency of my new preparations, and particularly of the iron and copper compounds. This fact is closely associated with the circumstance, referred to hereinabove, that the cevitamic radical is a normal agency whereby metals and metallic compounds become combined with blood proteins and thereby become assimilable by the body tissues. The substances utilized by the body must first be converted into a protein complex, and as I have found, the cevitamate radical has the unique tendency toward the formation of protein complexes and thus improves assimilation (see Ruskin, "Studies on the parallel action of vitamin C and calcium," American Journal of Digestive Diseases, vol. 5, page 408 (1938); Ruskin, "Studies in calcium metabolism. Further contribution to comparative studies of physical-chemical properties of gluconate and cevitamate of calcium and of vitamin C," Ibid., vol. 5, page 676 (1938); Ruskin and Jonnard, "Etude physico-chemique comparee du gluconate, du sel de calcium de la vitamine C et la vitamine C," Compt. Rend. de Biol. 28, 266–268 (1938)). As in the case of the other compounds discussed above, the ready assimilability of the iron, copper and cobalt cevitamates is likewise due to the fact that the cevitamate radical is a normally occurring substance in the human blood stream. As the metal and other ions forming part of the metal cevitamates are likewise normal constituents of the blood stream, the metal cevitamates may be said to represent substances indigenous to the blood stream and this accounts for their easy toleration on injection and for their ready assimilation on oral administration.

According to this embodiment of the invention, therefore, the therapeutic metals indicated in the treatment of anemias are introduced into the animal organism in the form of their cevitamic acid compounds, either as simple salts of the acid or in more complex metal combinations with the cevitamic acid radical, or with organic derivatives of cevitamic acid. The anti-scorbutic action of these metal cevitamates appears to be lower than that of free vitamin C; however, their vitamin C action is considerable and they are accordingly particularly indicated in the treatment of nutritional anemias accompanied by scurvy. The patient is thus benefited not only by the supply of iron and the other anti-anemic metals, but the anemia is improved in a synergistic manner by the vitamin C factor. The iron salt of cevitamic acid is quite soluble and it is especially effective in the ferrous condition. This can be ensured by an excess of free cevitamic acid which exerts a reducing action. The iron, copper and cobalt ions in combination with the cevitamate radical has the property of increasing the number

of red blood corpuscles to a greater extent than any of these elements alone. Thus, although copper will increase the efficacy of iron in the elevation of the number of red blood corpuscles and the hemoglobin content, the addition of cobalt will produce a still further increase. It will be noted that the iron compound is an organic ferrous salt, the iron being combined with an organic acid having reducing properties; this preparation is thus of a quite different nature from the inorganic compounds heretofore employed for the treatment of anemia.

Unless otherwise indicated herein, the dosage of any particular metal cevitamate can correspond to the usual known dosage for the metal in the known compounds, even where this will indicate a large excess of vitamin C radical over the normal body requirements. Contrary to early views, I have found that a large excess of vitamin C radical, at least in combination with therapeutic metals, has no deleterious effects in so far as the dosage of the metal itself is within safe limits; in other words, there is practically no danger of an over-dose of the cevitamate radical. In most instances, it will be found that, as indicated above, considerably smaller dosages of the various metals will be necessary in view of the greater efficiency of absorption of the metals in the form of the cevitamate compounds or complexes. Thus in the case of calcium cevitamate, a usual dose is 3 cc. of a 15% solution, injected intramuscularly or subcutaneously. This represents a considerable excess of cevitamate radical over the normal daily vitamin C requirements (20–60 mg.).

The compounds may be prepared in any of the known ways for the manufacture of metal salts, as by reacting free cevitamic acid with the hydroxide or carbonate of the metal. In certain cases, the sodium salts of cevitamic acid may be reacted with a suitable salt, such as the chloride, of the metal whose cevitamate is to be formed. With certain metals these reactions form precipitates i. e. compounds insoluble in water and, in such case, the compounds may be brought into solution by suitable adjustment of the pH, as by the addition of sodium hydroxide to raise the pH above 7 but within limits still suitable for injection. With other compounds it may be necessary to add solubilizing agents like the sugars, for example sucrose, calcium saccharate, and the like, where these are compatible with the metal cevitamate. Excess of cevitamic acid may be present in certain cases, the reducing nature of such acid causing it to act as an anti-oxidant and stabilizer.

It is generally advisable, especially where the preparations are marketed in the form of solutions, to include suitable anti-oxidants or stabilizers in such solutions. Suitable stabilizers for the various cevitamates, are the amines and amine derivatives, such as acetanilid, phenyl alanine, adrenalin, mono-, di-, and tri-ethanolamine and other amido and imino compounds. Among the inorganic anti-oxidants, alkali metal sulfites and metasulfites, such as the sodium compounds, may be mentioned. In general, compounds having a reducing action are suitable for this purpose provided that they are not toxic in the concentrations and quantities employed. Only small proportions of these stablizers may be employed, say up to several percent of the weight of the metal cevitamate. Various known buffer substances may be employed to maintain the pH within more or less predetermined limits.

In most cases the reaction between the cevi-

tamic acid or its alkali metal salt with the compound of the metal whose cevitamate is to be produced takes place spontaneously without the application of heat or pressure. However, it is sometimes desirable to heat the reaction mixture moderately in order to render the reaction more complete. The reactions are preferably conducted in an inert atmosphere, for example, of carbon dioxide or nitrogen; and pressure may be employed, especially where the cevitamic acid is caused to react with a carbonate, so as to cause the solution of considerable amounts of carbon dioxide which aid in stabilizing certain of the salts, especially of calcium cevitamate. In the latter case the reaction should take place in the cold so as to keep as much as possible of the carbon dioxide in solution. The water employed is preferably de-aerated, as by boiling or by passing a current of an inert gas therethrough. Free oxygen destroys to a large degree the potency of the cevitamates and for best results the process should be carried out in the absence of oxygen. The final product may be either a solution, which can be packaged in ampules, capsules, etc., preferably in an inert gas, or in the form of a solid, obtained by evaporation of the solution to dryness, preferably with the aid of a vacuum. The solid material can be prepared for the market in tablet form and the tablets may be coated with a soluble film which is impervious to air, for example, a coating of gelatin.

The following examples set forth various embodiments of the invention but it will be understood that the same are presented by way of illustration and not as indicating the limits of the invention:

Example 1

12.896 grams of laevo-ascorbic or cevitamic acid are dissolved in water, for example, to a 10% solution. Into this solution there is then introduced, at room temperature, 3.354 grams of calcium carbonate, which represents a slight deficiency over the theoretical. The reaction is conducted in the cold so that the CO_2 formed in the reaction is kept in solution. The calcium cevitamate is passed cold through the Berkfeld filter and filled in ampules in an inert atmosphere, preferably of CO_2. An atmosphere of carbon dioxide is especially advantageous as the gas appears to increase the normally high solubility of the salt in water, thereby enabling solutions of higher concentration to be obtained as the final product. To obtain a solid product, the solution is evaporated, preferably under vacuum in the cold. This product may likewise be packages in an inert atmosphere and as already indicated, when prepared in tablet form, it may be given a gas-impervious coating, although the product may be prepared also in uncoated or unstabilized form.

The amount of water can, of course, be varied within wide limits. I have found that calcium carbonate yields a clear solution of calcium cevitamate when reacted with cevitamic acid, and similar results are obtained with calcium hydroxide. Calcium gluconate and phosphate, on the other hand, do not give as clear solutions, although they may, if desired, be used.

Example 2

1.8 grams cevitamic acid (about .01 mol) are dissolved in 20 cc. glycerol and 10 cc. N NaOH. To this are then added under stirring and cooling 35 cc. N NaOH and 22.5 cc. of aqueous $Bi(NO_3)_3 5H_2O$ (containing $\frac{2}{300}$ mol) in the following order:

NaOH:		$Bi(NO_3)_3 5H_2O$
(1) 5 cc	(2)	2.5 cc.
(3) 5 cc	(4)	2.5 cc.
(5) 5 cc	(6)	2.5 cc.
(7) 5 cc	(8)	2.5 cc.
(9) 5 cc	(10)	2.5 cc.
(11) 5 cc	(12)	2.5 cc.
(13) 5 cc	(14)	7.5 cc.

In this way the solution is always kept alkaline until the final addition of the $Bi(NO_3)_3$. The orange-colored precipitate is centrifuged, and then washed four times with distilled water by centrifugation. The moist precipitate weighing approximately 5 g. when dry (theory 5.5 g.) is suspended in 100 cc. 50% glycerol and 5N NaOH is dropped in under stirring until a faint cloudiness persists. The solution is filtered through a filter cell and to the filtrate 2.5 cc. Na_2SO_3 solution (containing 250 mg.) are now added to stabilize it and it is brought down to a pH around 7.6 with excess cevitamic acid. It is then made up to 150 cc. with distilled water and bottled immediately. The preparation should contain approximately 20 mg. Bi per cc.

Example 3

1.8 g. cevitamic acid are dissolved in 10 cc. saturated saline (NaCl) solution. To this is added slowly under stirring 4.3 g. $SbCl_3$ dissolved in 20 cc. saturated saline solution. The acid solution is cooled with ice, and under stirring and cooling 12 cc. 5N NaOH saturated with salt are added. This leaves the solution still acid. The precipitate is centrifuged, and is then washed three times by centrifugation with distilled water. The moist precipitate weighing 4.8 g. when dry (theory 4.9 g.) is now suspended in 100 cc. of 50% glycerol solution and 5N alkali solution is dropped in under violent stirring until a faint permanent cloudiness remains. The solution is filtered through a filter cell until clear. It should have a pH around 9.6. There are then added 2.5 cc. Na_2SO_3 (containing 250 mg.) to stabilize the solution. If a lower pH is desired a little excess cevitamic acid can be added. The solution is then made up to 150 cc. and bottled immediately. This solution should contain approximately 16 mg. Sb per cc.

Example 4

20 g. (10 cc.) arsenious chloride are dissolved in 50 cc. absolute alcohol and the solution shaken up with 1.8 g. cevitamic acid. Practically all the acid goes into solution which would not be the case if the arsenious chloride were absent. This indicates the formation of arsenic cevitamate. The arsenic cevitamate is less toxic than currently used arsenic preparations in the treatment of syphilis. The pH may be adjusted with sodium hydroxide or other alkali to a value at which the solution is stable and non-irritating on injection.

Example 5

The gold salt may be prepared in the following manner: Methyl alcohol is added to concentrated hydrochloric acid in the proportion of 1:1 by volume, and to this mixture a solution of gold chloride is added. An equivalent amount of solid cevitamic acid is now mixed in. A clear solution is obtained. The pH is adjusted with NaOH to a point short of precipitation but within limits suitable for injection. If desired, the solution

may be buffered with protein complexes, like gelatin. The amount of gold chloride employed is such that 1 cc. of the final solution contains ½ grain of gold, which constitutes a dose for injection. The gold cevitamate is indicated in the treatment of tuberculosis and asthma.

Example 6

A solution of 27.8 grams of $FeSO_4.7H_2O$ in 60 cc. of water are treated under stirring with a solution of 10.6 grams Na_2CO_3 in 50 cc. of water. The precipitated ferrous carbonate is allowed to stand for an hour and is then separated from the supernatant liquid by centrifugation. It is then washed three times with distilled water in the centrifuge. The moist precipitate is then slowly added under stirring to 17.6 grams of cevitamic acid dissolved in 100 cc. of water. The solution of ferrous carbonate should be practically complete. The solution is then filtered and made up to 186 cc. To this solution there are added 2 grams of sodium citrate, which acts as a stabilizer. The solution contains 2 grains of ferrous cevitamate per cc. although any other suitable concentration can be prepared. The dosage may be considered lower than the usual dosage for iron; for example, 10 cc. of the solution. In place of the sodium citrate, catechol and chlorophyl may be used as stabilizing agents in correspondingly small quantities.

When prepared in the absence of air, as in an inert atmosphere of nitrogen or carbon dioxide, the solution is quite colorless and may be ampuled as such.

Example 7

There is first formed the sodium salt of cevitamic acid, for example by the mixing of 175 parts by weight of cevitamic acid in 400 cc. of water with a concentrated solution of 40 parts by weight of sodium hydroxide. The mixture should be stirred constantly and the sodium hydroxide is preferably added slowly. The solution of the acid in the water may be aided by gentle heating. To this solution there is added an approximately combining proportion of cupric chloride, for example 67 parts by weight, either in a solid state or as a concentrated solution in water. As the reaction proceeds, there is noted a change of color of the solution to a light blue, the solution remaining clear. The solution is then warmed gently and an excess of sodium hydroxide is added, causing precipitation of the copper compound of cevitamic acid. This is filtered and redissolved in water containing a small amount of a solubilizing or stabilizing agent, such as sodium citrate. The copper cevitamate may be prepared also by the reaction of cevitamic acid on freshly prepared copper carbonate. The resulting solution may be evaporated to dryness in a vacuum desiccator or added to a solution of ferrous cevitamate. In like manner, the cobalt cevitamate may be prepared through its carbonate and added to the solution of iron and copper, or evaporated to dryness in a vacuum desiccator. The iron, copper and cobalt cevitamate combination may be used dry in the form of tablets or capsules or employed in the form of a solution, packaged in ampules for injection. Especially where solutions are prepared, either in the course of preparation or for marketing, the operations are preferably conducted in the absence of oxygen. The dosages may correspond to the known dosages of iron and copper mixtures heretofore employed in the treatment of anemia, both when administered parenterally and by mouth. However, because of the greater efficiency of absorption, considerably smaller dosages of the cevitamate compounds will be found effective.

Although the copper and cobalt cevitamates have been described above as forming part of an anti-anemic preparation, it will be obvious that these compounds can be used for any therapeutic purpose for which copper and cobalt are indicated.

To maintain the reduced state of the iron, as well as of the other multi-valent metals whose cevitamic acid salts are prepared in accordance with the present invention, various anti-oxidant stabilizers which are non-toxic in nature may be added to the solutions or even to the solid preparations of the compounds. These anti-oxidants include catechol, chlorophyl, various amines and amino compounds, including glycine, acetanilide, and the like.

For the treatment of anemia and related diseases the iron, copper, and cobalt may be administered simultaneously in the form of their cevitamates; however, in certain cases it may be desirable to administer only one of them at a time, or combination of only two of them. Where two or more of the metals are introduced simultaneously, only one may be in the form of the cevitamate, the other or others being commonly employed compounds, such as the chloride, sulphate, or an organic derivative. Thus, iron cevitamate may be administered simultaneously with copper chloride and/or cobalt chloride, or with the sulphates of copper and/or cobalt. The copper and cobalt salts exert an activating effect on the iron compound, and are used in smaller amounts than the iron. If desired, the cevitamates of copper and cobalt may be administered without any iron, or the cevitamate of copper or cobalt may be administered alone. In other words, in accordance with the invention, the material administered is one ccontaining the cevitamate radical, or the radical of an organic derivative of cevitamic acid, and one or more of the metals iron, copper and cobalt.

Example 8

A solution is made of 175 parts by weight of cevitamic acid in water and to this are added slowly and with stirring 155 parts of calcium gluconate. The originally clear solution gradually becomes cloudy and a precipitate forms. The precipitate is filtered and is suspended in water to which is added a small amount of sucrose. The mixture is heated to a moderate degree, whereupon the precipitate dissolves. The amount of water employed is such that the mixture contains about 15% of calcium cevitamate. The resulting solution is then ready for use.

Bronchiolar reaction tests have shown that calcium cevitamate has an unusually strong strong histamine antagonism. Measurements made of the areas of bronchial tubes following injections of histamine and followed by injections of calcium cevitamate, and separately also of cevitamic acid and of neo-calglucon, under careful control, shows that calcium cevitamate caused a much greater recovery in the cross-sectional area of the tubes than did the cevitamic acid or the neo-calglucon.

In similar fashion, the corresponding compounds of magnesium, strontium, barium, zinc, manganese, silver, mercury, tin, aluminum, etc., may be prepared. All of these compounds have therapeutic values by reason of the character of

the metal and, in addition, have a greater or less anti-scorbutic action. The manganese salt is indicated in inadequate functioning of bone marrow to stimulate the formation of such marrow. The silver and mercury compounds are suitable as antiseptics, whereas the zinc and aluminum compounds may be used as dusting powder and mouth washes. The sodium salt itself represents a non-irritating compound which is easily injected and is easily absorbed by the body and is valuable for its anti-scorbutic action. The tin compound is suitable for the treatment of infections, particularly of staphylocci infections.

The bismuth, antimony and arsenic cevitamates are administered parenterally, preferably intramuscularly. The dosage may amount to 20 to 40 mg. of the metal once or twice weekly. They are all suitable for the treatment of syphilis and protozoan diseases, like trypanosomiasis.

In syphilis, various known arsenic and bismuth preparations will not influence the Wassermann reaction in some cases. These "Wassermann fast" cases responded better to bismuth cevitamate than to known bismuth and arsenic preparations.

The product obtained may, if desired, be purified in any known manner, for example, by fractional crystallization, by precipitation, by pouring into organic water-miscible solvents in which they are insoluble, etc. Where sodium chloride is formed as a by-product of the reaction, no purification is necessary since this salt aids in making the solution isotonic. The solutions can, of course, be rendered isotonic by the addition of sodium chloride or other salts.

The use of buffers in connection with solutions of the cevitamates is recommended. The amounts of the buffer compound or compounds may be varied at will and within wide limits. With certain compounds the solubility is dependent upon the hydrogen ion concentration and such buffers tend to prevent changes of solubility of the compounds by preventing changes of pH. Thus certain citrates and other alkali metal salts of relatively weak organic acids aid in solubilizing iron cevitamate. Other solubilizing agents are the various carbohydrates such as sucrose, dextrose, glucose, mannose, and other compounds of the sugar type.

Various organic acids, in addition to cevitamic acid can be employed for adjusting the pH to a lower alkalinity, but short of precipitation, as in the case of the arsenic, antimony and bismuth cevitamates. Among these acids are tartaric, citric, gluconic and other injectable organic acids. To bring the pH down from above 9 to 8, tartaric or citric acid is satisfactory; gluconic acid on the other hand may in such case cause precipitation.

The buffers and anti-oxidants may be used in various combinations, provided that they form no precipitates in the cevitamate solutions. Thus sodium sulfite and sodium meta-bisulfite are suitable stabilizing agents for the various cevitamates, and particularly for the arsenic, antimony and bismuth compounds, and can be used either alone or together with citrates, tartrates, sugars, etc. In certain cases organic acids like tartaric and citric acids and various combinations with salts may be used as buffer mixtures.

Where the alkali metal salt of cevitamic acid is reacted with another compound of another metal, such other compound may in general be the chloride, sulphate, nitrate, acetate or other inorganic or organic non-toxic substance. In place of cevitamic acid the organic derivatives thereof such as the mono-acetone derivative can be employed where these derivatives do not split up to yield toxic compounds.

Local anesthetics such as chlorbutanol or benzyl alcohol may be added to the various cevitamates to reduce tissue sensitivity where this should be necessary. They likewise have a desirable effect on the stability of the solution.

From the foregoing it will be seen that I have provided new therapeutic preparations of new and improved properties, such preparations being marketable either in solid forms or as solutions suitable for injection, these materials, and especially the solutions, being stabilized against degenerative influences. Of course, the cevitamates may be marketed in the form of the free acid and a suitable base of the therapeutic metal, packaged separately and designed to be mixed by the physician; or sodium cevitamate may be associated in this fashion with a salt of the metal called for by the treatment, the two salts on mixing in water yielding the cevitamate of such metal. The cevitamates may also be manufactured in the form of ternary and quaternary compounds, for example, as calcium glycerocevitamate, calcium glycerophosphate-cevitamate, and as other organic complexes.

I claim:

1. A therapeutic composition prepared for administration into the animal organism, comprising the iron compound of cevitamic acid, said composition being indicated in the treatment of scurvy and anemia.

2. A therapeutic composition prepared for administration into the animal organism, comprising the copper compound of cevitamic acid, said composition being indicated in the treatment of scurvy and anemia.

3. A therapeutic composition prepared for administration into the animal organism, comprising a gold compound of cevitamic acid.

4. A preparation for the treatment of anemia, comprising a mixture of iron and copper compounds, at least one of said compounds having the cevitamate radical.

5. A preparation for the treatment of anemia, comprising a mixture of iron, copper and cobalt compounds, at least one of said compounds having the cevitamate radical.

6. A composition prepared for injection into the animal organism, comprising a metal compound of cevitamic acid mixed with a stabilizing agent in the form of a non-toxic, inorganic salt having reducing properties.

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