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THERAPEUTIC COMPOSITION AND PROCESS OF MAKING IT

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This application is a continuation in part of our application Serial No. 135,106, filed April 5, 1937.

It is the object of our present invention to enhance the utility of 'Insulin'-histone compositions.

It has been demonstrated that the blood-sugar-lowering action of 'Insulin' may be prolonged by using with the 'Insulin' such substances as protamine, histone, and (in some animals) spermine. At certain hydrogen-ion concentrations, the substances named form with the 'Insulin' insoluble precipitates which, as experience shows, often adhere to the inside of containers in which the compositions are stored. Further, these precipitates commonly form undesirably large aggregates which can not readily be adequately disintegrated. This tendency of the 'Insulin' compositions to adhere to the walls of the containers and to form aggregates interferes with satisfactory use of the preparations; since, as is obvious, the precipitate should remain completely and homogeneously suspended during withdrawal of doses of the compositions.

We have discovered that the disadvantageous features noted above can be avoided, and in consequence the utility of the 'Insulin' compositions can be enhanced, by having present in the compositions an adequate amount of metal of the class consisting of zinc, cadmium, nickel, and cobalt. Also we have discovered that by the presence of this amount of metal of the class defined the period of utility of the 'Insulin' compositions is greatly lengthened. Moreover, we find that by the presence of this amount of either zinc or (sometimes) cadmium in the 'Insulin' compositions the prolonged blood-sugar-lowering action of the compositions is extended. We here assert no theory as to the nature of the actions of the metal present, or as to whether or not there is any chemical combination between the metal and either or both of the 'Insulin' and the other component or components.

This present application is directed to the use of these metals in connection with 'Insulin'-histone preparations; for the use of those metals in connection with 'Insulin'-protamine compositions is the subject of our Patent No. 2,179,384, granted November 7, 1939.

In preparing 'Insulin'-histone compositions embodying our present invention we ensure the presence in those compositions of an amount of zinc, cadmium, nickel, and/or cobalt, per unit of 'Insulin', that is at least twice as large, molecularly, as the amount of such metal present per unit of 'Insulin' in crystals of 'Insulin'. ('Insulin' crystallized with zinc contains about 0.52% of zinc, 'Insulin' crystallized with cadmium contains about 0.77% of cadmium, 'Insulin' crystallized with nickel contains about 0.41% of nickel, and 'Insulin' crystallized with cobalt contains about 0.44% of cobalt, in terms of dry weight of the crystals; and one milligram of a dry preparation of 'Insulin', whether in crystalline form or in substantially pure amorphous form, contains between 20 and 25 international units, the units used on this Continent.) Beneficial results are obtainable by having present in the 'Insulin'-histone compositions as little as half a milligram of zinc (or molecularly equivalent amounts if the other metals are used) per thousand units of the 'Insulin'; and desirably, in order to ensure that not less than this quantity of metal be present, we add at least this quantity. We may add any larger quantity of metal provided only that the quantity added be not so large as to induce untoward reactions, such as undue pain from injections. We have obtained satisfactory results from adding 20 mg. of zinc (and also from adding molecularly equivalent quantities of the other metals) per 1000 units of 'Insulin'. Most desirably we ensure the presence of a total of about 2 mg. of zinc per 1000 units of the 'Insulin'.

Illustrations of our invention are as follows:

1. In any desired way we make a preparation of 'Insulin' and histone, such as thymus histone,—as by adding the histone to a solution of 'Insulin', commonly in the range of about 4 to 80 mg. of histone per 1000 units of the 'Insulin'. The histone employed may be prepared by any suitable process, such, for example, as that described by Nelson (Arch. f. exper. Path. u. Pharmakol., 59, 336, 1908). During or following the operations of making this preparation, we add zinc in an amount ranging between about 1 and about 5 mg. per 1000 units of the 'Insulin'. Instead of zinc, we may add cadmium; and instead of either zinc or cadmium, we may add nickel or cobalt; but zinc is our first choice, and cadmium our second. Instead of only one of these four metals, we may add two or more. Preferably we add metal of the defined class in the form of chlorides, but we may add metal in elemental form, or in other forms, such as acetates, oxides, or hydroxides. Further, it is possible to ensure the presence of sufficient metal by conducting some of the production operations in equipment made of or containing the desired metal or metals.

In any of the compositions above described, the metal has the function of preventing adherence

of the suspended particles to the walls of the container and also of preventing the formation of undesirably large aggregates. Our 'Insulin' compositions are of utility over longer periods than in the absence of the added metal. Moreover, the prolonged blood-sugar-lowering effect of the compositions is materially extended by the addition of zinc or (sometimes) cadmium.

In preparing our new compositions the hydrogen-ion concentrations of the several components and of their mixtures are not of prime importance. In making such compositions available for clinical use, however, the hydrogen-ion concentration can be adjusted to control the character of the resultant product. If it is desired to administer the composition in the form of a suspension, a desirable reaction is on the alkaline side of the isoelectric point of 'Insulin'—say a reaction between pH 6.9 and 7.4. If, on the other hand, it is desired that the composition be in the form of a solution, the hydrogen-ion concentration should be kept on the acid side of the isoelectric point of 'Insulin'—say at a reaction of about pH 4.0. If desired, a suitable buffer may be added to maintain the hydrogen-ion concentration at the determined reaction.

We claim as our invention:

1. The process of producing an 'Insulin'-histone composition, which consists in putting 'Insulin' and histone together, and ensuring the presence therewith of an amount of metal of the class consisting of zinc, cadmium, nickel, and cobalt sufficient to correspond molecularly to at least half a milligram of zinc per thousand units of the 'Insulin'.

2. The process of producing an 'Insulin'-histone composition, which consists in adding to 'Insulin' a histone, and also adding metal of the class consisting of zinc, cadmium, nickel, and cobalt.

3. The process of producing an 'Insulin'-histone composition which consists in adding to 'Insulin' a histone and zinc.

4. A composition of matter comprising 'Insulin', histone, and added metal of the class consisting of zinc, cadmium, nickel, and cobalt.

5. A composition of matter, comprising 'Insulin', histone, and a quantity of metal of the class consisting of zinc, cadmium, nickel, and cobalt which per unit of 'Insulin' is at least twice as large molecularly as the quantity of metal present per unit of 'Insulin' in crystals of 'Insulin'.

6. A composition of matter, comprising 'Insulin', histone, and added zinc.

7. The process of producing an 'Insulin'-histone composition, which consists in adding a histone to 'Insulin', and also adding metal of the class consisting of zinc, cadmium, nickel, and cobalt in sufficient amount to make the total quantity of such metal present per unit of 'Insulin' at least twice as large molecularly as the quantity of metal present per unit of 'Insulin' in crystals of 'Insulin'.

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