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THERAPEUTIC COMPOSITION AND PROCESS
OF MAKING IT

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It is the object of our invention to enhance utility of "Insulin"-protamine compositions.

It has been demonstrated by Hagedorn and has co-workers that the blood-sugar-lowering action of "Insulin" may be prolonged by using protamine with the "Insulin". See The Journal of the American Medical Association for January 18, 1936, volume 106, page 177.

Experience has shown that all or a part of "Insulin"-containing precipitates in "Insulin"-protamine compositions will often adhere to the inside of containers in which the compositions are stored. Experience has shown, also, that in "Insulin"-protamine compositions the precipitates commonly form aggregates which cannot readily be adequately disintegrated. The utility of "Insulin"-protamine compositions in which precipitates either form such aggregates or adhere to the inside of containers is limited, since obviously the precipitates in the compositions should remain completely and homogeneously suspended during withdrawal of doses of the compositions.

We have discovered that such limitation of utility of "Insulin"-protamine compositions can be avoided, and in consequence that utility of such 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 "Insulin"-protamine compositions is greatly lengthened. Moreover, we find that by the presence of this amount of either zinc or cadmium in "Insulin"-protamine 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 protamine components.

According to our invention, in preparing "Insulin"-protamine compositions we ensure the presence in the compositions of an amount of zinc, cadmium, nickel, and/or cobalt, per unit of "Insulin", that is larger than the amount of such metal present per unit of "Insulin" in ordinary preparations of "Insulin" or in "Insulin"-protamine compositions as made prior to our discovery, and 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,

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.] Beneficial results are obtainable by having present in "Insulin"-protamine 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 the "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:

In any desired way we make a preparation of "Insulin" and protamine—as by adding to a solution of "Insulin" any suitable protamine, such as salmiridine or scombrine or salmine, commonly in the range of about 2 to 40 mg. of protamine per 1000 units of the "Insulin". During or following the operations of making this preparation, we add zinc in an amount ringing 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 preparing our new compositions the hydrogen-ion concentrations of the several components and of their mixtures are not of prime importance, but in making such compositions available for clinical use and in using these, we find it desirable to attain and maintain a reaction which is on the alkaline side of the isoelectric point of the "Insulin", desirably a reaction of between pH 6.9 and pH 7.4. The desired reaction may be attained by adding an appropriate solution, such as a solution of a suitable buffer (a

phosphate buffer for example), to one or more of the components or to our otherwise complete preparation.

We claim as our invention:

- 5 1. The process of producing an "Insulin"-protamine composition, which consists in putting "Insulin" and protamine together, and ensuring the presence therewith of an amount of metal of the class consisting of zinc, cadmium, nickel, and
10 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"-protamine composition, which consists in adding
15 a protamine to "Insulin", and also adding metal of the class consisting of zinc, cadmium, nickel, and cobalt.
3. The process of producing an "Insulin"-protamine composition, which consists in adding
20 a protamine 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
25 quantity of metal present per unit of "Insulin" in crystals of "Insulin".
4. The process of producing an "Insulin"-

protamine composition, which consists in adding to "Insulin" a protamine and zinc.

5. The process of producing an "Insulin"-protamine composition, which consists in adding to "Insulin" a protamine and cadmium. 5

6. A composition of matter, comprising "Insulin", protamine, and added metal of the class consisting of zinc, cadmium, nickel, and cobalt.

7. A composition of matter, comprising "Insulin", protamine, and 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". 10

8. A composition of matter, comprising "Insulin", protamine, 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". 15 20

9. A composition of matter, comprising "Insulin", protamine, and added zinc.

10. A composition of matter, comprising "Insulin", protamine, and added cadmium. 25

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