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PANCREATIC HORMONE PREPARATIONS AND THE PRODUCTION THEREOF

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This invention relates to pancreatic hormone preparations for oral administration, and methods of producing the same. More particularly the invention relates to a pancreatic hormone preparation for oral administration, in which anti-enzymic principles are added to the pancreas hormone (Insulin) for the purpose of cancelling or inhibiting the activity of the digestive ferments, and to a method of producing the preparations of this nature. As anti-emzymic bodies organic dyestuffs may for example be employed in accordance with our earlier discoveries in this direction (cf. U. S. Patent application, Serial No. 69,722, filed March 19, 1936), and we have found acid organic dyestuffs to be capable of cancelling the action of the stomach ferments when the preparation is administered per os, while basic dyestuffs have the power of inhibiting the action of the intestinal ferments during the time the preparation is passing through and being absorbed in the intestine. Experiments have it is true been made with other substances which inhibit the action of proteolytic enzymes, but these substances, as is known from the literature on the subject, have proved to be entirely unsuitable for the present purpose or to be of such slight efficacy that it takes a very large dose of Insulin to bring about an observable reduction in the concentration of sugar in the blood. Thus economic considerations were alone sufficient to mark these methods down as failures, and numerous clinical tests have proved conclusively that therapeutically useful results can only be obtained with the use of organic dyestuffs.

When organic dyestuffs are added to the Insulin used in making a pancreatic hormone preparation they have the effect of completely or almost completely inhibiting the action of the digestive ferments after ingestion of the preparation, so that the Insulin is safeguarded from the destructive action of these ferments during its passage through the digestive tract; we have also ascertained that the greater part of the active principle of the Insulin is absorbed by the intestinal wall, particularly if a suitable resorption-promoting substance be added to the preparation, so that the quantity of Insulin required to obtain a desired lowering of the sugar concentration in the blood need only be slightly increased over and above that required when the Insulin is administered subcutaneously.

As far as the therapeutic applicability is concerned the mechanism of the efficacy of an ingested pancreatic hormone preparation is quite different from that of a subcutaneously injected preparation. After injection the blood sugar curve reaches its lowest point some 1½–3 hours after administration, and then rises again relatively rapidly, so that in serious cases it is necessary to repeat the injection in the course of a day. When the preparation is administered per os, on the other hand, absorption takes place only gradually and is consequently extended over a longer period of time, so that the blood sugar curve only falls off gradually, reaches its lowest point after about 6–8 hours, and then rises again only very gradually; thus under otherwise similar conditions the intervals between successive administrations of a pancreatic hormone preparation can be longer in the case of an ingested preparation than in the case of an injected preparation.

As regards the economy of an orally administered Insulin preparation it should be noted that the manufacturing thereof may well be rendered somewhat more expensive owing to the requisite addition of anti-enzymic principles. The present invention, however, is also based on the discovery that in the production of a pancreatic hormone preparation for oral administration to which anti-enzymic principles have been added to inhibit the action of the digestive ferments it is not necessary to start from a perfectly purified final product fit for use for injection purposes, as is the case with Insulin prepared for administration by injection, but that quite on the contrary a protein containing intermediate product may be used, with the result that, without the slightest detriment to the therapeutic efficacy, the manufacturing of the preparation is very much simplified and quite considerably cheapened. In consequence of this fact the manufacturing of a pancreatic hormone preparation destined for administration per os remains an economic proposition even when a considerably larger quantity of Insulin has to be used than in the case of a preparation destined for administration by injection.

As is well known, Insulin for administration by injection is obtained from the pancreatic gland by first extracting the active hormone from this gland, for example by suitable treatment with acid-containing alcoholic solutions. The resulting extract must then be subjected to certain purifying methods, since apart from the active hormonal principle it also contains a number of protein bodies which (if the product is to be injected) must be eliminated without fail since they

would otherwise give rise to dangerous secondary effects after injection.

These treatment steps serving for the removal of protein, such as repeated ammonium sulphate fractionation, electrodialysis for precipitating out protein, and so forth, are very complicated and time-consuming, and therefore tend to render the production of Insulin expensive. In addition, this purification treatment also results in a very large proportion of the active hormone responsible for reducing the concentration of sugar in the blood becoming lost.

The extracting itself must be very carefully carried out for the reason that the pancreas contains digestive ferments, particularly trypsin, which destroy the Insulin unless they are rendered inactive. Now we have found that if anti-enzymic principles are added during the preparing of the initial extract from the pancreas gland, so that the concomitant ferments present therein are rendered inactive, it is not necessary to add any further anti-enzymic principles for the purpose of cancelling or inhibiting the action of the digestive ferments in the stomach and intestine of the patient.

One of the main features of the present invention consists in interrupting a process serving for the recovery of the hormone from the pancreas before the stage at which a final product fit for use as an injection is obtained, and adding anti-enzymic principles, preferably dyestuffs, to the protein-containing intermediate product thus obtained. The process may for example be carried out in such a manner that an intermediate product containing the active substance together with protein bodies is obtained from the pancreas in the manner hitherto usual, and adding anti-enzymic principles to this intermediate product which still contains protein; it is also possible to do without the hitherto usual method of obtaining an extract, and to add the anti-enzymic principles directly to the comminuted fresh pancreas after appropriate preliminary treatment with a water-absorbing substance, for instance acetone.

Examples

(1) Immediately after slaughtering, the fresh pancreas is frozen in a refrigerating mixture. The frozen product is passed through a fine mincing machine, and the resulting pulp intimately mixed in a moist state with an acid and an alkaline dyestuff (e. g. trypan red and malachite green, there being used for every 100 g of pancreas substance at least 0.5 g of trypan red and 0.3 g. of malachite green). The mixture is then dried on flat dishes at a temperature of about 40° C, and the dried product made up into tablets in the usual manner with the use of a suitable filler such as secondary sodium phosphate. Before or during tabletting there may be added a resorption-promoting substance, e. g. a saponin (5 g of saponin per 100 g of substance).

(2) Fresh pancreas is frozen in a refrigerating mixture immediately after slaughtering. An extract is prepared from the frozen product in the usual manner, e. g. with alcohol containing hydrochloric acid, with trituration; to the resulting alcoholic extract there are then added appripriate quantities of dyestuff (0.5 g of trypan red and 0.3 g of malachite green per 100 g of the glandular substance). The solution is then evaporated in vacuo at low temperature, and drled. The product thus obtained is made up into tablets as in Example (1) with the addition of a resorption-promoting substance.

By the present invention a very considerable simplification and cheapening of the manufacturing process is achieved. One kilogram of neat's pancreas contains about 4000 units of Insulin, while the intermediate product obtained by extracting only contains about 2500 units, and the purified final product (entirely free from protein bodies) only has about 1200 units still left therein. Thus in the course of the hitherto usual method of production, as practised for the manufacturing of a final product fit for use in injections, a loss of more than 50% of the active principle is incurred during the purifying stage. With our improved method this loss of substance is completely or almost completely avoided and a product used as the starting material in the manufacturing process, which can be produced in a simpler and more economical manner. It thus becomes possible to produce an ingestible Insulin preparation economically even in cases in which, to bring about the desired lowering of the sugar concentration in the blood a considerably larger Insulin dose has to be taken than would be necessary in the case of a preparation administered by injection.

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