

April 10, 1945.

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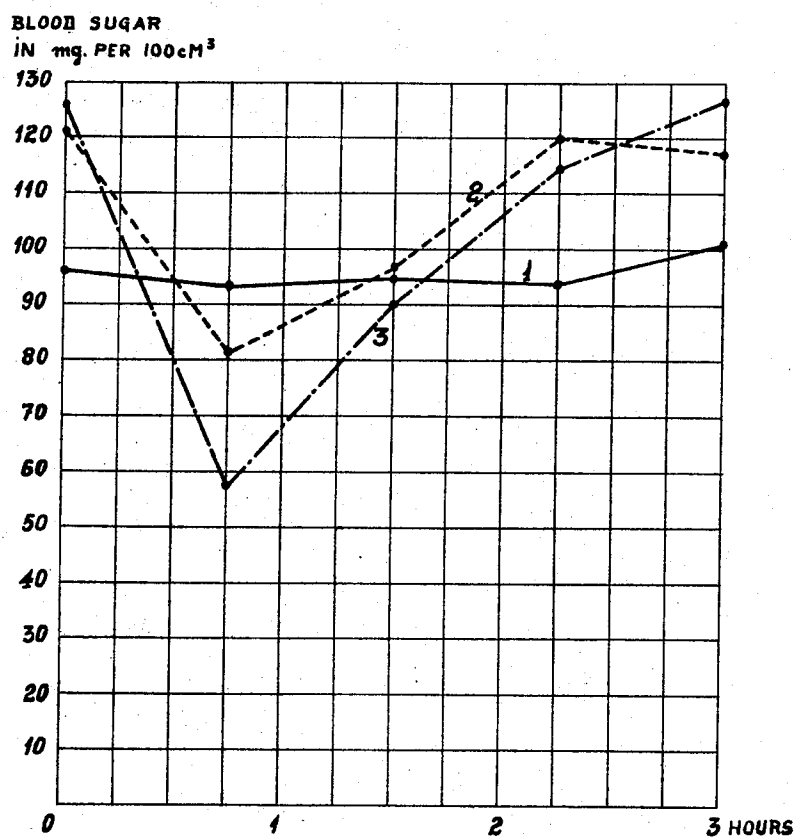
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SUPPOSITORIUM CONTAINING INSULIN

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2 Sheets-Sheet 1

Fig. 1.



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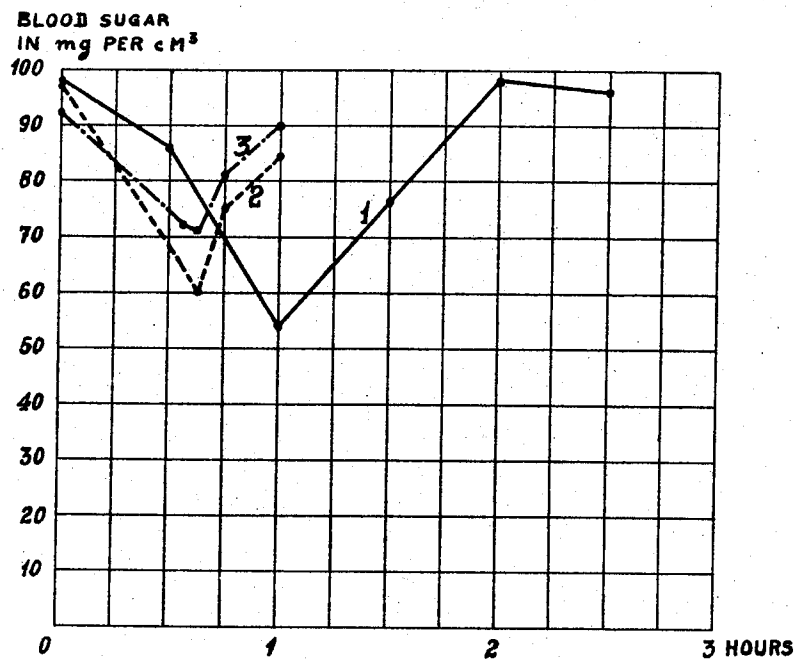
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Fig. 2.



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SUPPOSITORIUM CONTAINING INSULIN

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11 Claims. (Cl. 167-64)

Up to the present it has only been possible to introduce insulin into the human system by means of injections, and not by way of the stomach or the intestinal tract. In the latter two cases the insulin was very soon rendered inactive by the peptic and tryptic enzymes, so that this treatment could not be applied in cases of diabetes.

It has now been found that insulin may be successfully administered in the form of suppositories, provided certain substances producing a favorable effect on the resorption of the insulin are added.

The present invention relates to suppositories containing besides the insulin and a substance serving as a carrier, a small proportion of acid. This acid will either neutralize or greatly reduce the inactivating action on the insulin by the intestinal ferments, so that by administering the said insulin suppositories the sugar content of the blood is materially reduced.

Various materials may be used as carriers for the insulin and the additional substances. For this purpose use is preferably made of substances that will melt in the intestine, such as a carrier material or vehicle conventionally used for making suppositories, or which will dissolve in the contents of the intestine at body temperature, such as e. g. fats having a low melting point, soaps, glycerol soaps, agar-agar, gelatine and the like. Very suitable for the purpose is cocoa-butter which is very consistent, but nevertheless will melt at a temperature of 31-32° C.

Suitable organic acids are lactic acid, citric acid or tartaric acid. For suppositories on cocoa-butter basis the addition of higher fatty acids, such as e. g. palmitic acid or oleic acid, etc., is also very suitable.

It is true that palmitic acid has a melting point of 60-62° C., but a mixture of 85 parts by weight of cocoa-butter and 15 parts by weight of palmitic acid will melt at approx. from 33-34° C., i. e. below body temperature. With mixtures of cocoa-butter and 15% of palmitic acid and small quantities of lactic or citric acid excellent results have been obtained in practice.

The favorable action of the insulin suppositories containing an organic acid may be further improved by the addition of non-haemolytic acting saponins. Guajac saponin, the saponin of hippocastanum and glycyrrhizine have proved very satisfactory for this purpose. They have a favorable effect on the resorption of the insulin in the intestines.

The effect of the suppositories according to the

invention is illustrated in Fig. 1, which shows the results of tests made on rabbits. In this graph the ordinates represent the sugar content of the blood, the abscissae the time elapsed since the administration of the suppositories. The curves indicating the blood sugar content after different intervals are averages of several determinations.

Curve 1 shows the results of a test in which suppositories consisting of 1.5 grams of cocoa-butter and 15 units of insulin were administered. This curve clearly shows that the said suppositories do not reduce the sugar content of the blood.

Curve 2 relates to suppositories containing 1.5 grams of cocoa-butter, 15 units of insulin and 0.0625 gram of lactic acid. These suppositories have a considerable reducing influence on the sugar content of the blood, the said sugar content going down to approximately $\frac{2}{3}$ of its original value and returning to the said value only after a period of about 2 hours.

A still better effect will be obtained when the suppositories also contain saponin. This is shown by curve 3 showing the results of test in which suppositories comprising 1.5 grams of cocoa-butter, 15 units of insulin, 0.0625 grams of lactic acid and 0.05 gram of guajac saponin, were used.

Similar results were obtained with healthy humans. Fig. 2 represents the curves for the sugar content of the blood after the administration of suppositories according to the invention having the following composition:

Curve 1

35	Cocoa-butter	gram	1.0
	Insulin	units	120
	Lactic acid	gram	0.15
	Citric acid	do	0.1
	Palmitic acid	do	0.18
40	Guajac saponin	do	0.8

Curve 2

	Cocoa-butter	grams	1.2
	Insulin	units	90
45	Lactic acid	gram	0.1
	Saponin of hippocastanum	do	0.05

Curve 3

	Cocoa-butter	grams	1.2
50	Insulin	units	90
	Lactic acid	gram	0.1

The favorable action of the suppositories according to the invention is evident once more from the said tests, particularly if they contain both organic acid and a non-haemolytic saponin.

In comparison with subcutaneous, intramuscular and intravenous administration of insulin, the use of insulin suppositories not only has the advantage that the latter are far less objectionable in the long run than injections, but also that the preparations used may be less pure. Various substances which may be harmful in the first case, such as e. g. foreign albumens, may be present in the suppositories without the least danger.

I claim.

1. An insulin suppository for rectal administration comprising insulin, a solid carrier of the group of materials conventionally used for making suppositories, a substantially non-toxic and non-irritating weak organic acid of the type of lactic acid, citric acid and tartaric acid in quantity sufficient by its acidity to protect the insulin against inactivating ferments in the intestines, and a non-haemolytic saponin surface tension reducing agent.

2. A suppository as defined in claim 1 in which the carrier is cocoa butter.

3. A suppository as defined in claim 1 in which the acid is lactic acid.

4. A suppository as defined in claim 1 comprising a plurality of acids of the group named.

5. A suppository as defined in claim 1 in which the carrier is cocoa butter and the suppository also contains a higher fatty acid.

6. A suppository as defined in claim 1 in which the carrier is cocoa butter and the suppository also contains palmitic acid.

7. A suppository as defined in claim 1 in which

the carrier is cocoa butter, the acid is lactic acid, and the suppository also contains palmitic acid.

8. A suppository as defined in claim 1 in which the carrier is cocoa butter, and the suppository comprises lactic acid, citric acid and palmitic acid.

9. A suppository containing insulin, a solid carrier of the group of materials conventionally used for making suppositories and a substantially non-toxic and non-irritating organic acid in quantity sufficient by its acidity to protect the insulin against inactivating ferments in the intestines, said acid being present in quantity insufficient to exert a noxious effect upon the mucous membrane of the intestine.

10. A suppository containing insulin, a solid carrier of the group of materials conventionally used for suppositories and an acid, said acid being present in quantity sufficient by its acidity to protect the insulin against inactivating ferments in the intestines and in quantity insufficient to exert a noxious toxic or irritating effect upon the mucous membrane of the intestine.

11. A suppository comprising insulin, a solid carrier of the group of materials conventionally used in making suppositories, an acid which in the quantity present by its acidity protects the insulin against inactivating ferments in the intestine and is innocuous to the mucous membrane of the intestine, and a non-haemolytic surface tension reducing agent which promotes the absorption of the insulin through the intestine wall.

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