

## Effect of Glycine Upon Action of Insulin in Rabbits.

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It was found by Pollak<sup>1</sup> that a pronounced hyperglycemia is produced in rabbits by the subcutaneous injection of a 5% solution of glycine. One gram of glycine was found to raise the blood sugar level of an animal weighing 1700 g from 90 to 160 mg % within 2 hours. Izumi<sup>2</sup> and Schenk<sup>3</sup> made further studies of the effect of amino acids upon the blood sugar level of rabbits. Izumi found that glycine administered intravenously (1.7 g per kg body weight) caused but a slight rise in the level of blood sugar, producing no subsequent lowering below the normal level, and that glycine administered perorally (2.675 g per kg) caused a slight lowering in the course of a 4 hour period. He pronounced the general effect of administering protein hydrolysates to be that of mobilizing blood glucose either from glycogen stores or by its formation from amino acids. Schenk<sup>3</sup> made a comprehensive study of the effect which the peroral administration of relatively large amounts of amino acids and of mixtures of these has upon the blood sugar level. Of those amino acids which were found to lower this level the effect of glycine was the most pronounced. In determining the amount of glycine to be administered the weight of the animal was not taken into account. The response was, however, interpreted in accordance with the amount administered. One gram was found to produce a *hyperglycemia* while the generally administered dose of 1.5 g was found to produce a *hypoglycemia* of varied degrees of intensity in different animals. Thus, the hypoglycemia produced by 1.5 g in an animal weighing 2810 g was more pronounced than that in one weighing but 1260 g. The hypoglycemic state disappeared within 8 hours

after the administration of the glycine. Self-administered doses were found to produce a similar hypoglycemia in man.

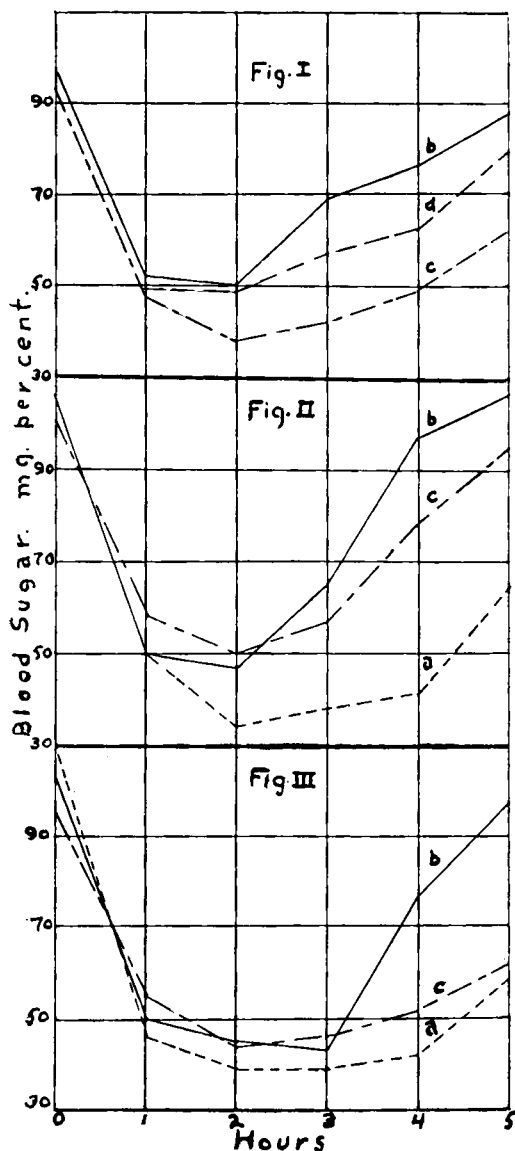
When relatively small amounts of insulin were injected subcutaneously immediately after the feeding of glycine the decrease in the level of blood sugar was found to be the summation of that produced independently by the insulin and by the glycine.

It was found in this laboratory, using rabbits which had been carefully standardized with respect to their insulin tolerance, that small amounts of glycine (3 mg per kg) which were injected simultaneously with insulin, either subcutaneously or intravenously, did not significantly affect the insulin tolerance of these animals immediately. When the same rabbits were retested some weeks later, however, the effect which the administration of glycine had produced was found to be so pronounced as to cause these animals to reach the convulsive state when they were injected with but one-half of the originally determined convulsive dose of insulin and to promote a corresponding decrease in the level of the blood sugar. Thus, three rabbits which had received from 3 to 5 intravenous injections of insulin and glycine on alternate days late in February did not exhibit any significant response due to the glycine at that time. The same rabbits, upon receiving one or two subcutaneous injections of a mixture of glycine and insulin late in May, reached a convulsive state when the amount of insulin administered was but one-half that of the originally determined convulsive dose, (0.6, 0.7, and 0.7 units per kg respectively). These amounts constituting but one-half of the original convulsive dose are smaller than any which had heretofore been found to be required in bringing any normal rabbit to a convulsive state. Two other rabbits, upon receiving subcutaneous injections of glycine

<sup>1</sup> Pollak, L., *Biochem. Z.*, 1922, **127**, 120.

<sup>2</sup> Izumi, K., *Biochem. Z.*, 1932, **248**, 383.

<sup>3</sup> Schenk, E. G., *Arch. Exp. Pathol. and Pharmacol.*, 1932, **167**, 201.



FIGS. 1-3.

Curve *a* of Figs. 2 and 3 shows the effect of a subconvulsive dose of insulin upon the blood sugar level of rabbits; curve *b* of each figure that of one-half the convulsive dose of insulin *before* treatment with glycine; curve *c* of each figure that of one-half of the convulsive dose of insulin *after* treatment with glycine; curve *d* of Fig. 1 that of one-half of a convulsive dose of insulin at a later period after treatment with glycine.

and insulin late in March, did not exhibit any significantly abnormal insulin response due to the glycine at that time. When the same rabbits received subcutaneous injections of insulin, with and without glycine, late in May,

they were found to reach a convulsive state upon receiving but one-half of the originally determined convulsive dose of insulin.

This effect of glycine upon insulin action is more fully demonstrated by the following more recent data which were obtained in more carefully controlled experiments. These data, which are illustrated by the curves of Fig. 1 to 3, indicate the progressive change in the blood sugar level of rabbits for a 5 hour period following the subcutaneous injection of insulin, of glycine, and of a mixture of these. In all instances where glycine was administered the dose consisted of 3 mg per kg body weight. Five per cent solutions of glycine were used.

The data represented in Fig. 1 were obtained with a group of 4 rabbits (male albinos) which, as in all other experiments, had been carefully standardized with respect to their insulin tolerance. The data of curve *b* were obtained on Nov. 10th after the injection of one-half of the convulsive dose of insulin. Each animal was then injected with a mixture consisting of one-half of its convulsive dose of insulin and the usual amount of glycine on each of the following dates: Nov. 12th, 15th, 18th, 20th. The average blood sugar data obtained on each of these dates showed no significant deviation from those indicated by curve *b*. On Nov. 27th and 30th each animal again received the same injection of insulin and glycine as on Nov. 12th through 20th. The average data of these 2 days are given by curve *c*. They indicate a pronounced lowering of the blood sugar level during this 5 hour period as a consequence of the previous treatment with glycine. On Jan. 17th these rabbits were again injected with the same dose as on Nov. 27th. The data obtained, which are those of curve *d*, indicate a sustained effect due to the earlier injections of glycine.

The data of Fig. 2 were obtained with a second group of 4 rabbits which received similar treatment to those represented by Fig. 1. Injections of a mixture of glycine and one-half of the convulsive dose of insulin were given subcutaneously on Jan. 4th, 6th, 8th, and 10th. A similar injection was given each animal on Jan. 18th. Two of these (male albinos) reached the convulsive state after re-

ceiving the injection of Jan. 18th and their data are not included among those of Fig. 2. The other 2 rabbits (male grey) appeared to be somewhat less susceptible to the treatment than were the 2 albinos. Their data are represented by Fig. 2. The data of curve *a* were obtained on Dec. 20th following the injection of a dose of insulin slightly less than the convulsive dose and those of curve *b* on Dec. 22nd following the injection of one-half of the convulsive dose of insulin. Those of curve *c* were obtained on Jan. 18th following the injection of glycine and one-half of the convulsive dose of insulin. A definite effect of glycine on insulin action is also indicated here.

The data of Fig. 3 were obtained with a third group of 2 rabbits (black, male). After determining the response to a subconvulsive dose of insulin (curve *a*) and to one-half of a convulsive dose (curve *b*) these animals were injected with glycine only on Jan. 6th, 7th, 8th, 10th, and 12th. On Jan. 18th they re-

ceived one-half of the convulsive dose of insulin but no glycine. A comparison of curve *c* with curves *a* and *b* indicates the effectiveness of the initial treatment with glycine upon the subsequent action of the injected insulin.

Many variables suggest themselves for further investigation. In view of the concern over the prediction of a possible shortage of insulin in the near future these experimental facts would seem of interest to a further search for a more favorable insulin economy. It should also be of interest to note how a similar treatment might affect humans who are predisposed to the conditions of diabetes.

*Summary.* Repeated injections of small amounts of glycine (3 mg per kg body weight) appear to increase the action of subsequent injections of insulin for a prolonged period of time.

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## 16950

### Production of Irritative and Destructive Changes in the Gastric Mucosa Followed by Regeneration.\*

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Some progress has been made in the last 3 decades concerning our knowledge of the normal and pathological physiology of the stomach. Special emphasis has been lent study of the functions of the peptic and parietal cells; by contrast, our knowledge of the gastric mucous epithelium and its function is meagre. Hollander and his associates have been probing with care for some time this aspect of the problem of functions and morphology of the gastric mucosa; with few ex-

ceptions the functions of the gastric mucous epithelium and the other mucous secreting cells have not been given due consideration.

In this study, investigations of some functions of the mucous secreting cells were carried out; also the mechanism of regeneration of the gastric mucosa was studied.

*Methods and experiments.* The gastric mucous secreting cells were stimulated by placing various substances into the stomach with both ends ligated. Cats and dogs were employed in the experiment. Mustard oil and clove oil in concentrations of from 0.5 to 2 % (in corn oil), and eugenol in watery solutions up to 10% were used.

The animals were anesthetized with nembu-

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