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Hyperglycemia Following the Portal Injection of Insulin.

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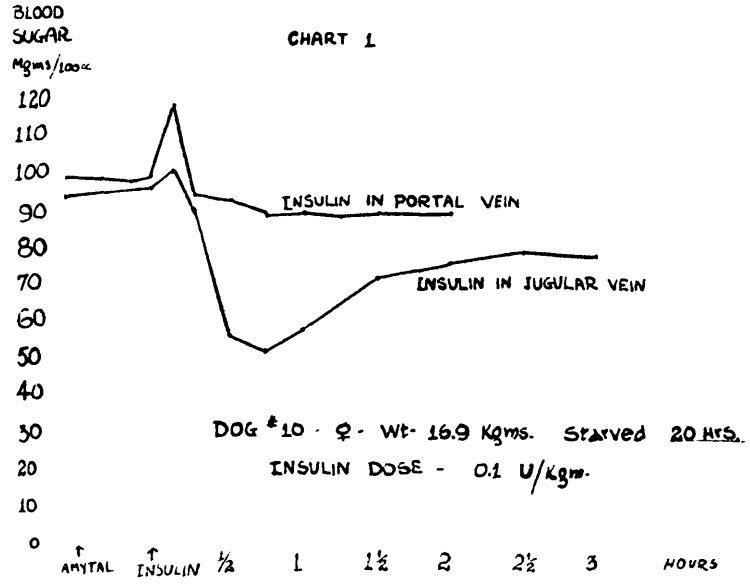
Experimental and clinical reports have appeared in the literature to indicate that the liver plays a part in regulating the activity of insulin. If it were conclusively proven to be so, then diabetes mellitus might be considered in part as a result of a disturbance of this regulatory mechanism of the liver.

Arborelius and Akerren[1] injected insulin into the serous coat of the intestine of rabbits and compared the drop in blood sugar with that which occurred following subcutaneous injections. They observed that hypoglycemia did not occur as readily following subserous injections and inferred that the liver had an inhibiting influence upon insulin. Brugsch and Horsters[2] noted a decrease in the potency of insulin, when insulin was incubated with liver pulp suspensions. Loewi,[3] although much questioned, claims to have iso-



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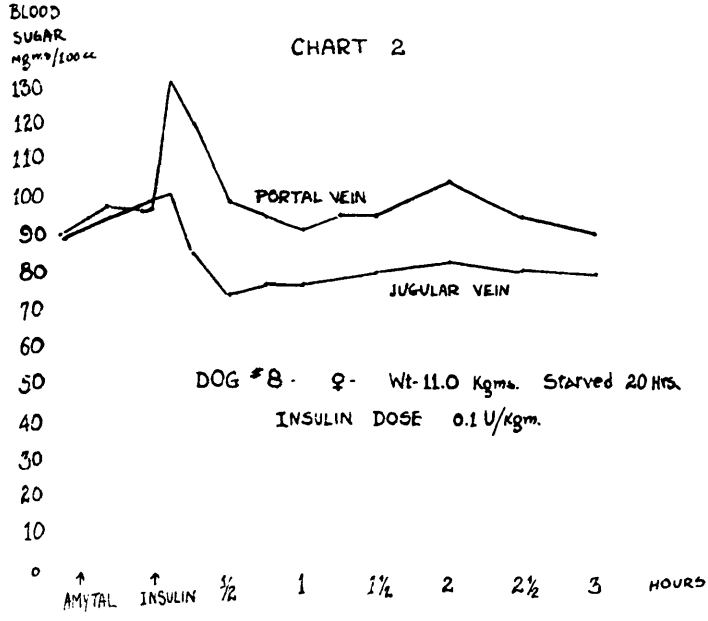
[1] Arborelius, M., and Akerren, Y., *Skand. Arch. f. Physiol.*, 1927, l, 35.

[2] Brugsch, T., and Horsters, H., *Biochem. Z.*, 1927, clxxxviii, 147.

[3] Loewi, O., *Klin. Woch.*, 1927, vi, 137.

lated a hormone from the liver which is antagonistic to insulin, particularly as regards its effect on the uptake of glucose by the red blood corpuscles. He calls this substance glykamin. His premise that insulin causes a fixation of sugar in the red blood corpuscles, was not confirmed by Harpuder.[4] Shope[5] studied the distribution of sugar between the corpuscles and plasma of normal and diabetic bloods. He found an equal amount of sugar in the plasma and the cells of all cases and observed no significant alteration in its distribution following insulin therapy. Zuelzer[6] also questions the nature of this hormone and suggests that it must first be proven that it is not adrenalin. A transient initial hyperglycemia following the subcutaneous injection of insulin has been observed by Guardabassi[7] in normal dogs and by Rosello[8] in a diabetic dog.

This study was undertaken to determine, by the direct introduction of insulin into the portal circulation, whether the liver plays any part in regulating insulin activity. Dogs which had been previously starved for 24 hours were used in all the experiments. Amy-



[4] Harpuder, K., *Klin. Woch.*, 1928, vii, 266.

[5] Shope, R. E., *J. Biol. Chem.*, 1928, xxviii, 111.

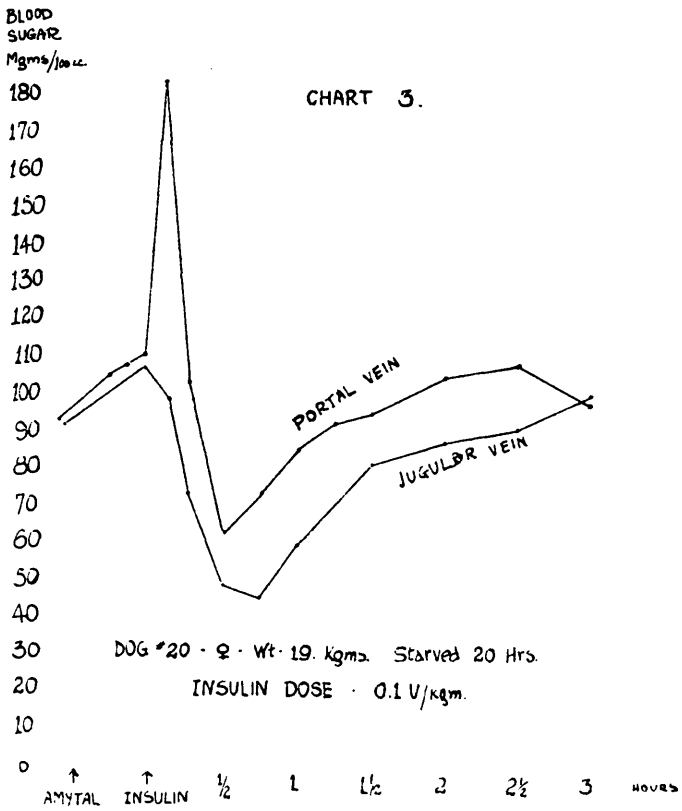
[6] Zuelzer, G., *Klin. Woch.*, 1928, vii, 312.

[7] Guardabassi, M., *Ber. Ges. Physiol. Exp. Pharm.*, 1927, xli, 86.

[8] Rossello, H., Benatti, D., Balea, S. E., *Ann. de la Facultad de Med.*, 1926, xi, 259.

tal was the anesthetic used because it has no influence on the blood sugar. The Folin Wu method was employed for the blood sugar determinations. Each experiment consisted of the alternate injection of the same amount of insulin into the portal or jugular vein at weekly intervals. The volume of solution of insulin injected was never greater than 1 cc. Insulin was made up in a solution of HCl at a pH of approximately 3.0. A large stock solution of insulin obtained from the Eli Lilly Co. was prepared and aliquots of the same solution were used in all the experiments.

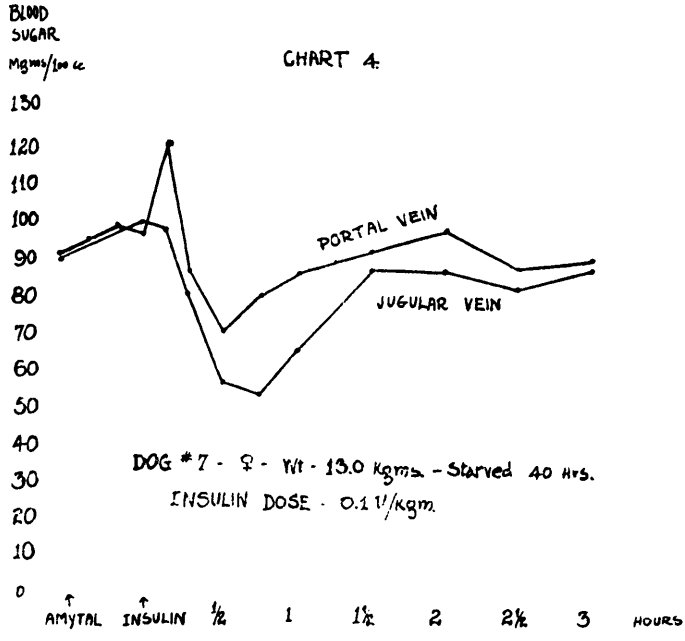
Results: Five experiments were performed. The constancy of the results obtained may be seen from Charts I to V. It will be noted that in every experiment, the portal injection of insulin results in an immediate sharp *rise* in the blood sugar of 20 to 80 mgm. This rise occurred within 5 minutes after the injection of the insulin and was then followed by a rapid decline. No such rise occurred following the systemic injection of the same dose of insulin. In order to rule out the possibility that the rise in blood sugar resulted from the mechanical effect of the injection, or the slightly acid state of the



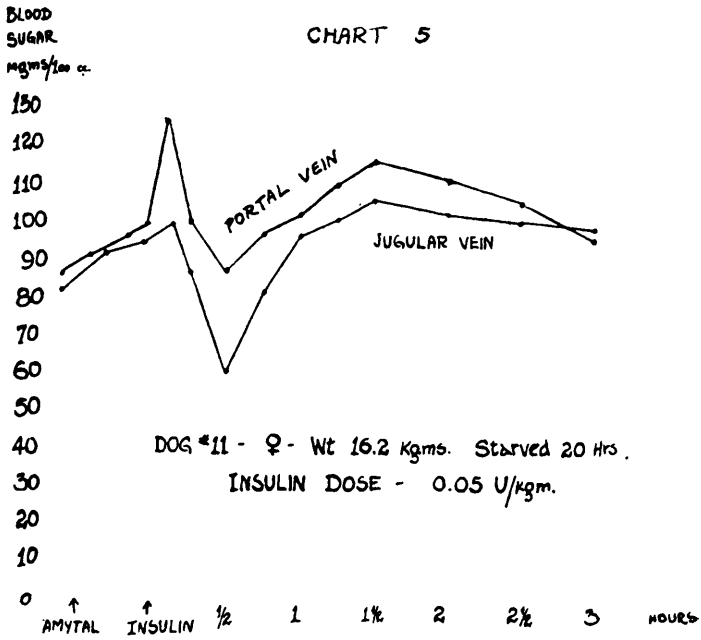
solution in which the insulin was kept, saline and HCl (pH 3.0) were injected into the portal vein but no effect upon blood sugar was noted (Chart VI).

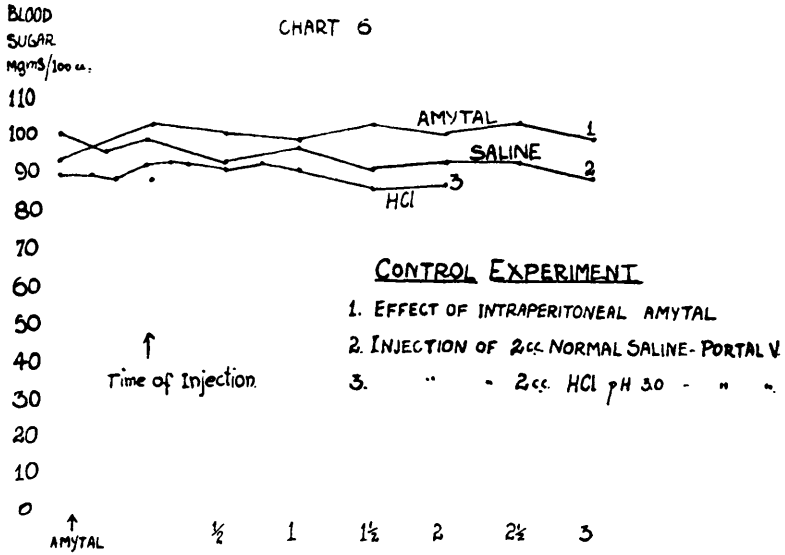
As an additional control, the blood sugar was studied 5 minutes after injection and over a 5 hour period following the intraperitoneal injection of amytal and it was observed to remain at a normal stationary level. Mechanical manipulation of the liver was avoided, for this alone was found to cause a rise in the blood sugar.

Discussion: It is quite obvious that the portal injection of insulin produces a distinct temporary rise in the blood sugar. This phenomenon permits of only 2 explanations; either that the insulin causes the discharge of an anti-insulin substance in the liver which is antagonistic to its action, or the sudden introduction of insulin into the liver causes a rapid glycogenolysis. The latter explanation is at present regarded as the more probable one—first because of the transient nature of the phenomenon, and second because it has been demonstrated that large doses of insulin even when injected systemically not only lower the blood sugar, but reduce the glycogen deposits in the liver. McCormick and Macleod[9] gave subconvulsive doses of insulin to normal rabbits and they observed an average glycogen content in the liver of 2.9% as compared with 4.1% glyco-



[9] McCormick, N. A., and Macleod, J. J. R., *Trans. Royal Soc. Canada*, Sec. V., 1923, xvii, 63.





gen in control animals. Dudley and Marrian[10] found 5.5% liver glycogen in normal rabbits and only 1.9% in insulinized rabbits. Bodo and Marks[11] observed, in perfusion studies of the isolated

[10] Dudley, H. W., and Marrian, G. F., *Biochem. J.*, 1923, xvii, 435.

[11] Bodo, R., and Marks, H. P., *J. Physiol.*, 1928, lxv, 48.

mammalian liver, that added insulin causes a breakdown of glycogen. The glycogenolytic properties of insulin have also been observed by Brugsch,[12] Nitzescu[13] and Gigon and Staub.[14] Macleod[15] believes that glycogenolysis is the most important single factor in restoring the blood sugar during the hypoglycemic state. Our experiments, by the direct introduction of insulin into the portal circulation, lend further confirmatory evidence to the conception that insulin in contact with liver cells, is an active glycogenolytic principle.

Conclusion: A transient hyperglycemia follows the portal injection of insulin.

We wish to express our appreciation to Mrs. Gladys Havens for her technical assistance in the work.

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The Source of Fibrinogen.

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The formation of fibrinogen has been ascribed to many tissues and organs of the body. Whipple,[1] Goodpasture[2] and others suggested that this substance takes its origin from the liver and intestinal tract; and recently Foster and Whipple[3] have presented excellent evidence that the liver is the main if not the sole source of fibrinogen. Schultz, Nicholes and Schaefer[4] have produced corroboratory data. Final proof in the matter has waited, however, upon the findings in liverless animals.

In 4 hepatectomized rabbits[5] we have determined the concentration of blood fibrinogen before operation and at various periods thereafter. A postoperative decrease in the substance was always

[12] Brugsch, T., Benatti, A., Horsters, H., and Katz, R., *Biochem. Z.*, 1924, cxlvii, 117.

[13] Nitzescu, L. I., and Popescu-Inotesti, C., *Compt. Rend. Soc. Biol.*, 1923, lxxxix, 1403.

[14] Gigon, A., and Staub, *Klin. Woch.*, 1923, ii, 1670.

[15] Macleod, J. J. R., "Carbohydrate Metabolism and Insulin," Longmans, Green and Co., 1926, 171.

[1] Whipple, G. H., *Am. J. Physiol.*, 1914, xxxiii, 50.

[2] Goodpasture, E. W., *Am. J. Physiol.*, 1914, xxxiii, 70.

[3] Foster, D. P., and Whipple, G. H., *Am. J. Physiol.*, 1922, lviii, 407.

[4] Schultz, E. W., Nicholes, J. K., and Shaefer, J. H., *Am. J. Path.*, 1925, i, 101.

[5] Drury, D. R., *J. Exp. Med.*, 1929, in press.