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Secondary or Compensatory Hypoglycemia.

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In contrast with true hypoglycemia, of which insulin hypoglycemia is an example, we suggest the term secondary or compensatory hypoglycemia for those conditions in which an initial rise in blood sugar is followed by a fall below normal. McGuigan and Ross[1] state that many investigators have reported a hyperglycemia, while others working with the same substance have demonstrated a hypoglycemia. Santos[2] finds that secretin exerts a hypoglycemic action in man, dog and rabbit. Lambert and Hermann,[3] however, show that injection of secretin causes transient hyperglycemia, followed by hypoglycemia. Such differences in observation may be due to the quantity of reserve glycogen in the animal, or to the time of withdrawal of the blood for analysis, after injection of the biologic mixture or compound under investigation.

We postulate that any biologic condition or chemical substance giving rise to persistent hyperglycemia may eventually produce hypoglycemia. Josephs[4] has demonstrated that the hyperglycemia developed during anesthesia results in post-anesthetic hypoglycemia. According to Herold,[5] a high blood sugar during obstetrical labor is followed by post-partum hypoglycemia. Maud L. Menten[6] has reported that the soluble toxic products of the enteritidis-paratyphoid B group produce an initial hyperglycemia and a secondary hypoglycemia. Taya[7] has shown that a rise in temperature causes an increase in blood sugar concentration, followed by a fall below

normal. Geiger[8] maintains that spontaneous fall of fever is accompanied by a hypoglycemia.

Adrenalin, known to cause a marked rise in blood sugar, is also capable of producing hypoglycemia. According to György and Herzberg,[9] the initial hyperglycemia occasioned by adrenalin is finally superseded by hypoglycemia. The latter results from depletion of the glycogen stores incident upon the increased glycogenolysis and increased glucose consumption. Collens, Shelling and Byron[10] found that ligating the hepatic artery causes a total depletion of the glycogen reserves of the body. During this process adrenalin injected intravenously has less and less effect the longer after ligation it is injected. When the hypoglycemia has developed, adrenalin does not affect the sugar level of the blood. According to Gatin-Gruzewska,[11] the liver and muscles in the rabbit can be rendered glycogen-free by injecting adrenalin after a one-day period of starvation.

The hormone of the thyroid gland behaves like the adrenal hormone with reference to its influence on blood sugar. Marks[12] followed the blood sugar curve of rabbits given thyroid extract. After the injection of glucose (1/6 gm. per kilo), there first appeared, in comparison with the controls, a definite rise in blood sugar during the first and second hours. The initial rise was followed, however, by a marked drop in blood sugar. If during the hypoglycemic stage no additional sugar was given, the animals became convulsive, went into coma, and finally died. Schwarz[13] recently reported a case of pregnancy complicated by hyperthyroidism, in which hypoglycemia developed.

Rabbits and frogs can also, according to Kulz, Zuntz and Vogelius, Frentzel[14] and others, be rendered glycogen-free by injections of strychnine. This alkaloid is known to cause hyperglycemia. If it can desugarize animals it should be able to induce secondary hypoglycemia. The following experiment proves the correctness of this supposition:

Morphine Sulphate.

Weight of rabbit, 1370 grams.

Dose: 30 milligrams per kilo, injected subcutaneously.

	Blood Sugar.
Before injection	0.124%
1½ hours after injection	0.167%
2½ hours after injection	0.104%
3½ hours after injection	0.060%
4½ hours after injection	0.060%

Since morphine produces hyperglycemia, it should also give rise to secondary hypoglycemia. The following experiment bears out the *a priori* reasoning:

Strychnine Sulphate.

Weight of rabbit, 2000 grams.

Dose: 3 milligrams per kilo, injected subcutaneously.

	Blood Sugar.
Before injection	0.104%
1 hour after injection	0.150%
3 hours after injection	0.118%
5 hours after injection	0.066%

Hydroxylamine hydrochloride we have found to behave like morphine and strychnine. As the experiment below shows, it gives rise to hyperglycemia and secondary or compensatory hypoglycemia.

Hydroxylamine Hydrochloride.

Weight of rabbit, 2150 grams.

Dose: 12 milligrams per kilo, injected subcutaneously.

	Blood Sugar.
Before injection	0.092%
1 hour after injection	0.138%
3 hours after injection	0.118%
4 hours after injection	0.079%
5 hours after injection	0.060%

When two substances giving rise to hyperglycemia are administered, the result is a summation effect, and secondary hypoglycemia may be more readily produced. Diesel[15] reports that extracts of pituitary reduce the hyperglycemia developed by adrenalin. Ross[16] states that ether given after morphine does not increase the blood sugar as much as if ether alone had been administered. György and Herzberg[9] find that the preliminary administration of ammonium chloride increases the secondary hypoglycemia produced by adrenalin. Ammonium salts, as the experiment suggests, may have a tendency to produce hyperglycemia.

Ammonium Carbonate.

Weight of rabbit, 1600 grams.

Dose: 25 milligrams per kilo, injected subcutaneously.

	Blood Sugar.
Before injection	0.098%
45 minutes after injection	0.167%

Among other substances producing initial hyperglycemia and secondary hypoglycemia may be mentioned thallium compounds (Mamoli[17]), hydrazine (Underhill and Karelitz[18]), chloroform and

phosphorus (Bodansky[19]). Very recently Izume and Lewis,[20] working with hydrazine and its derivatives, observed that when hyperglycemia and hypoglycemia were present the hyperglycemia occurred first, following a period of excitement, and the hypoglycemia later, during the stages of depression.

Hypoglycemia may be due to an increase in the rate of disappearance of the sugar in the blood resulting (1) from greater combustion of glucose (glycolysis), or from using up the glycogen reserves, as in fasting; (2) from greater withdrawal of glucose for storage purposes (glycogenesis); or (3) from greater elimination by the kidney of sugar (glycuresis) or its intermediate products of metabolism. Hypoglycemia may also be due to a decrease in the supply of sugar available in the system resulting (1) from interference with glycogenolysis (conversion of glycogen to glucose); or (2) from interference with glyconeogenesis (conversion into glucose of non-carbohydrate material, like amino acids).

Adrenalin causes secondary hypoglycemia because of glycogen depletion due to increased consumption of glucose. Lyman, Nicholls and McGann[21] state that this hormone causes a hyperglycemia accompanied by an increase in heat production and by a rise in the respiratory quotient. Hydrazine and its derivatives, according to Izume and Lewis, give rise to secondary hypoglycemia as a result of decrease in the supply of glucose available for combustion. At first hydrazine produces an increase in the consumption of carbohydrate. After the supply of reserve glycogen is used up, hypoglycemia results. No new sugar, or very little sugar, is formed as a result of the liver injury, which diminishes glyconeogenesis or the transformation of amino acids into glucose.

The mechanism of the production of primary hypoglycemia is probably not the same as that of secondary hypoglycemia. Substances producing secondary hypoglycemia should differ from insulin. In this connection it may be said that a review of the experimental data furnished by Collip[22] in relation to his plant glucokinin leads to the belief that it is not identical with insulin. Glycokinin gives at first a normal blood sugar or an increased blood sugar, and the hypoglycemia, which seems to be secondary, makes its appearance many hours or days after the injection. Insulin, on the other hand, yields an immediate hypoglycemia.

It is suggested that in all conditions where a secondary hypoglycemia is apt to occur, glucose or preferably glucose and insulin should be administered as a therapeutic measure. Such procedure should, therefore, be followed to prevent the symptoms of post-

anesthetic or post-partum hypoglycemia, and in poisoning or overdoses of such drugs as morphine or strychnine.*

* In all the experiments recorded the animals received no food except water for 24 hours prior to injection. Blood sugar was determined by the iodometric method of Shaffer and Hartmann.

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The Influence of the Thyroid Gland on Experimental Rickets.

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Histological studies of sagittal sections through the distal end of the femur of rats 69 days old, and thyroidectomized between 15 and 29 days after birth, reveal a marked overgrowth of the epiphyseal cartilage close to the junction with the metaphysis. This area is also characterized by deficient calcification and invasion of