indicate that the chronic administration of this simple chemical compound interferes with a hitherto unrecognized process, perhaps by making unavailable a component of some enzyme system.

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THE MECHANISM OF ACTION OF ALLOXAN ON BLOOD SUGAR

THE intravenous administration of alloxan induces a triphasic modification of the blood sugar level: (1) hyperglycemia; (2) hypoglycemia; (3) hyperglycemia. We have studied these phenomena in several species, particularly the chlorolosed dog (100 mg of alloxan/kg of body weight) and the toad *Bufo arenarum* Hensel (200 mg/kg).

The initial hyperglycemia did not appear in hepatectomized dogs or toads nor in eviscerated dogs. It was observed in adrenalectomized animals (5 dogs and 6 toads) and in 3 dogs with previous section of the splanchnic nerves (major and minor) so that it can not be attributed to either adrenaline or cortical hormones. It was also observed in recently hypophysectomized toads. If injected in the portal vein, alloxan produces a higher initial hyperglycemia (5 dogs) than if injected in the saphenous vein (8 dogs).

The secondary hypoglycemia is not due to liberation of insulin by the β cells of the islets undergoing destruction. Nine dogs totally depancreatized half an hour before injection of alloxan, showed a marked hypoglycemia beginning 1, 2, 2, 2, 2, 3, 3, 4 and 5 hours after injection; the blood sugar level reaching in 7 cases to 50 and 24 mg per 100 cc. Six of these dogs showed initial hyperglycemia. Pancreatectomized controls with no alloxan only in a few cases showed slight and brief diminution of the blood sugar level half an hour after the operation, followed by a gradual and steady increase from 2 to 6 hours after the operation, reaching at that time 0.149 and 0.180 g per 100 cc of blood.

In 7 dogs depancreatized 24 to 48 hours previous to the injection of alloxan there was no hypoglycemia: on the contrary, the blood sugar level was slightly increased. In only one case was there a moderate decrease (from 0.217 to 0.134 g per cent. between 5 to 6 hours after the injection).

In pancreatectomized toads, alloxan injected immediately after the operation either prevents or decreases the diabetic hyperglycemia during the next 24 hours. If injected 24 hours after pancreatectomy, the existing diabetic hyperglycemia decreases as shown by the blood samples 24 hours after injection. Alloxan also notably decreased the diabetogenic action of the *pars distalis* of the hypophysis when subcutaneously injected to the hypophysectomized and depancreatectomized toad.

The capacity of the pancreas to secrete insulin was investigated by grafting in the neck through vascular anastomosis the duodeno-pancreas of dogs to dogs rendered diabetic through pancreatectomy performed 24 hours before. Normal pancreas decreases the blood sugar to normal level within 3 to 5 hours. Pancreas from dogs injected with alloxan 24 hours (6 dogs) or 48 hours (2 dogs) before extraction and grafting did not secrete insulin in 4 cases, the secretion was very reduced in 3 cases and only in 1 was the secretion normal. It is interesting to note that the pancreas was taken in some cases from animals that were still hypoglycemic. The β cells of the islets showed lesions in all cases (Dr. Di Pietro).

The final rise of the blood sugar reaches sometimes (rats, rabbits and dogs) higher values to those usually observed after pancreatectomy. Values of 0.700 and 1.00 g per 100 cc of blood have been observed. Possibly the liver plays some part in this phenomenon.

Therefore: (1) The liver is essential for the initial hyperglycemia produced by alloxan. Hyperglycemia is observed in adrenalectomized animals and those with section of the splanchnic nerves. It must be attributed principally to a direct action of alloxan on the liver. (2) The secondary hypoglycemia is not due to liberation of insulin, but to an extrapancreatic effect: probably lack of glucose production by the liver. The liver of the animal already in a diabetic condition is generally insensible to this action of alloxan. (3) The final hyperglycemia is mainly due to the destruction of the β cells of the islets of Langerhans, and becomes permanent if the animal survives. (4) The liver plays an important role during the 3 phases of modification of blood sugar level.

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THE PRODUCTION OF ANTI-PENICILLINASE IMMUNE SERA

IT is well known that the injection of an antigen (precipitinogen) parenterally in animals stimulates the production of antibodies (precipitins). In order that a substance may be precipitinogenic, it apparently must contain a soluble protein.[1]

[1] F. P. Gay and Associates, "Agents of Disease and Host Resistance," Charles C Thomas, Baltimore, Md., 1935.