patients had disappeared by the sixth, fourteenth, twenty-second and twenty-fifth days on therapy. Two of the patients developed neuritic pains in the lower extremities while the symptoms of pellagra were improving. All patients noted sensation of heat and tingling of skin within 10 minutes after ingesting nicotinic acid. These sensations lasted for 10 to 20 minutes. During this time there was distinct dilatation of peripheral blood vessels but only slight temporary fall in blood pressure.

Summary. Improvement in 4 patients with pellagra following administration of nicotinic acid was as satisfactory as that following administration of liver filtrate except for an increase in time required for complete disappearance of dermatitis.

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Hypoglycemic Action of Alloxan.

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The study of the physiological regulation of blood-sugar concentration embraces a complexity of independently variable factors whose individual influences are still incompletely understood. Many experimental substances and conditions will cause hyperglycemia, but none besides insulin are known which will cause hypoglycemia.

Alloxan will produce hypoglycemia in normal rabbits in a very characteristic fashion. If upwards of 70 mg. of alloxan monohydrate per kg. of body weight is injected intravenously the blood sugar level of the animal will fall below the normal value (less than 70 mg. %) in about 3-4 hours, and will continue to fall steadily during the next 2-4 hours until the convulsive level (less than 35 mg. %) is reached. It will keep falling further during the convulsive stage until the animal expires, and very low (less than 15 mg. %) values may be observed terminally. All normal rabbits respond in the same way, although some delay in the time of onset of convulsions is observed if the animals have not fasted for 12-24 hours before the experiment. The larger dosages of alloxan (150-200 mg./kg.) will not hasten the appearance of convulsions, but will very definitely cause the recurrence of convulsions after remissions induced by glucose.

Both the convulsions and the hypoglycemia are promptly relieved

by glucose intravenously administered. Animals in violent convulsions will return to a conscious and quite normal state within one minute after glucose has been given. After 5-10 minutes they will eat and drink in a normal manner. If the dosage of alloxan has been large hypoglycemia and convulsions may recur several times at intervals of 2-3 hours provided that each attack is treated with glucose. Large dosages of glucose or sufficient food intake tend to forestall subsequent seizures. The effect of alloxan persists for at least 24 hours in fasting animals.

The graphs in Fig. 1 illustrate the effect of alloxan on the blood-sugar concentration. Alloxan was dissolved in water and given to young adult rabbits intravenously. All the animals except No. 6

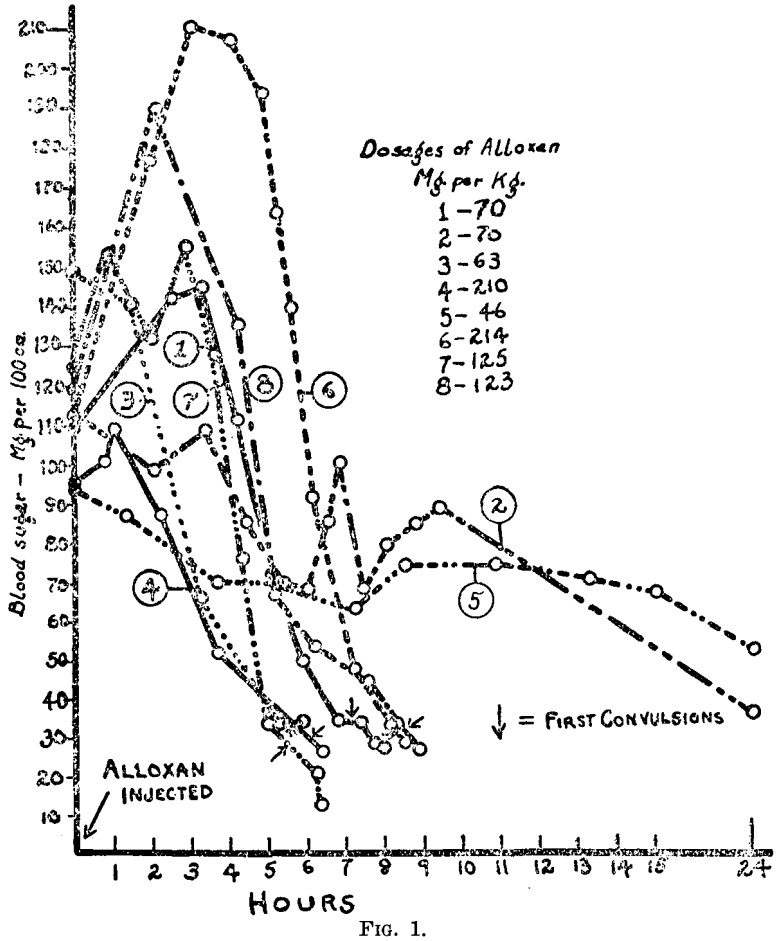

FIG. 1.
The Effect of Alloxan on the Blood-Sugar Level of Normal Rabbits.

fasted for 12 hours before the experiment. The first point on each curve gives the value for the blood-sugar concentration just before the injection. Blood sugar estimations were made by the method of Miller and Van Slyke[1] on samples drawn from the ear veins. Each curve represents an experiment with a fresh animal. Whether the transient hyperglycemia which precedes the fall in blood-sugar concentration in some of the animals is a specific effect of alloxan cannot be stated.

That the effects of alloxan are largely a consequence of the lowering of blood-sugar concentration is indicated by the specific antidotal action of glucose. Furthermore, after the acute effects of alloxan have subsided, the animals treated with it return rapidly to a normal state. In fatal experiments a marked rigor appears at once, but all the organs, and particularly the liver, look normal grossly.

In order to try to learn whether the described effects are due to alloxan itself or to one of its simpler decomposition products several likely derivatives of alloxan were also tested. Alloxanic acid, dialuric acid, isodialuric acid, barbituric acid, isobarbituric acid, alloxantin, murexide, mesoxalic acid, parabanic acid, oxaluric acid, formyl-oxaluric acid and formylurea exhibited no effects similar to those of alloxan when given to rabbits in substantial doses. As Cerecedo[2] noted, formylurea and formyl-oxaluric acid were extremely toxic.

At present there is no explanation for the hypoglycemic action of alloxan. There is no evidence to indicate that alloxan is chemically or physiologically related to insulin, or that the mechanism by which it produces hypoglycemia is a physiological one. Alloxan is an oxidizing agent credited with special affinity for the hydrogen of sulphydryl groups.[3-6] It is rapidly changed to alloxanic acid by alkalis. Insulin is sensitive to reducing agents and to alkalis. Whether the capacity for being readily reduced chemically, which is possessed by both alloxan and insulin, is related to the effect on the blood-sugar concentration remains to be settled. Labes and Friedberger[5] regard alloxan as a capillary poison.

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