Himsworth and Glynn used lard in the high fat diets and arachis oil in the low fat diets, and used cod liver oil as a source of fat soluble vitamins. In the present study lard was used in all diets and the vitamins were supplied by oleum percomorphum.

*Summary.* 1. Groups of rats were fed diets of 16% protein and 51% fat; 6% protein and 6% fat; and 4% protein and 6% fat. These diets resulted in a fatty infiltration of the liver, and in the long term experiments this was accompanied by a diffuse, progressive, hepatic fibrosis.

2. The hepatic lesions produced by all 3 of these diets appeared to be the same type and probably had the same basic pathogenesis.

3. Hepatic necrosis was not produced by the diets used, and deaths from acute hepatic necrosis were not obtained with a low protein intake.

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## Susceptibility of the Guinea Pig to Action of Alloxan as Compared with the Rat.*

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(Introduced by Fredrick J. Stare.)

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The susceptibility to the diabetogenic as well as the general toxic action of alloxan has been studied in several species[1-9] including the human being.[10] Goldner[5] reported lesions in the islets of the guinea pig after alloxan administration but no diabetes was produced because the animals died within 24 hours. Other workers[11,12] observed changes in the blood sugar levels after alloxan injections in this species but West and Highet[13] were unable to produce alloxan diabetes in the guinea pig.

The work presented in this paper is in agreement with that of West and Highet and compares the susceptibility of the guinea pig and the rat to the action of alloxan.

*Experimental.* Twenty-five male guinea pigs weighing between 500 and 600 g each and kept in individual cages were divided into 5 groups. Group I consisted of 6 guinea pigs which were injected with alloxan monohydrate intravenously at various doses as shown in Table I; Group II of 7 animals partially depancreatised prior to alloxan administration. One month after the operation the animals were injected with 200 mg per kg body weight alloxan intravenously and

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TABLE I.
Blood Sugar Values Following Alloxan Administration.

| Treatment | Dose of Alloxan | Blood glucose in mg %: Hr after Alloxan inj. 3 | 8 | 24 | 48 | Fasting† | Time of sacrifice after Alloxan injection |
|---|---|---|---|---|---|---|---|
| Group I | mg/kg B. wt | | | | | | |
| 24-hr fast | 250 | 132 | 112 | 100 | 104 | | 2 days |
| ,, | 225 | 128 | 120 | 131 | | 110 | 3 ,, |
| ,, | 225 | 103 | 88 | | | | 4 ,, |
| ,, | 200 | 150 | | 150 | | 100 | 7 ,, |
| ,, | 200 | 112 | | 150 | | 130 | 13 ,, |
| ,, | 200 | 100 | 115 | 108 | | 120 | 21 ,, |
| Group II | | | | | | | |
| 50% pancreatect. and 24-hr fast | 200 | | 120 | 112 | 135 | | 2 ,, |
| ,, | 200 | 100 | 109 | 115 | | 90 | 4 ,, |
| ,, | 200 | 120 | 118 | 115 | | 130 | 8 ,, |
| ,, | 200 | 125 | 118 | 108 | | 136 | 29 ,, |
| ,, | 200 | | 125 | | 112 | 108 | 16 ,, |
| Group III | | | | | | | |
| 24-hr fast | 2080* | | | | | 110 | 2 ,, |
| ,, | 2080* | | | | | 105 | 2 ,, |
| ,, | 2080* | | | | | 115 | 2 ,, |
| ,, | 2080* | | | | | 100 | 2 ,, |
| ,, | 2080* | | | | | 112 | 2 ,, |
| ,, | 2080* | | | | | 118 | 2 ,, |
| Group IV | | | | | | | |
| Vit. C deficiency and 24-hr fast | 200 | 115 | 112 | | | 100 | 3 ,, |
| ,, | 200 | 125 | 135 | | | 113 | 20 ,, |
| ,, | 200 | | 125 | 110 | | 85 | 24 ,, |
| ,, | 200 | | 115 | | | 90 | 2 ,, |
| Group V | | | | | | | |
| 3-day fasting | 200 | | 95 | 110 | 120 | | 2 ,, |
| ,, | 200 | | 100 | 132 | 130 | | 2 ,, |

* Intraperitoneal injection at intervals over a 10-week period. All other groups received one intravenous injection.

† Mean value of several determinations in those cases where the time of sacrifice was later than 4 days.

were sacrificed at various intervals thereafter. Group III consisted of 6 animals which were injected repeatedly with alloxan intraperitoneally over a period of 10 weeks. A total of 2080 mg per kg was given to each guinea pig and the animals sacrificed 2 days after the last injection which was 500 mg per kg body weight. Group IV was 4 animals which were kept on a vitamin C deficient diet for a period of 36 days, prior to injection of 200 mg per kg alloxan, and Group V was 2 animals which were fasted for 3 days and then injected with 200 mg alloxan intravenously.

The intravenous injections of alloxan in all cases were made in the jugular vein after exposure of the vein with a small skin incision under ether anaesthesia. Blood samples were drawn by heart puncture and the glucose concentration was determined using the micromethod of Reinecke.[14] Urine collections were made at weekly intervals during the whole experimental period and tested for glucose using the method of Somogyi.[15]

Cytologic examination of the pancreas was made in all cases after fixing the tissue in Bouin's solution and staining by Gomori's method.[16]

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TABLE II.
Effect of Age on Response of Rats to Diabetogenic and General Toxic Action of Various Doses of Alloxan Given Intravenously.

| No. of rats used | Wt, g | Dose, mg/kg | Failures, % | Mild* % | Severe† % | Deaths within 2 days % |
|---|---|---|---|---|---|---|
| 60 | 80-110 | 50 | 25.0 | 58.3 | 16.7 | 0.0 |
| 30 | 90-105 | 60 | 16.7 | 0.0 | 83.3 | 0.0 |
| 20 | 87-100 | 70 | 0.0 | 0.0 | 90.0 | 10.0 |
| 20 | 85-110 | 80 | 0.0 | 0.0 | 75.0 | 25.0 |
| 20 | 280-300 | 40 | 10.0 | 72.5 | 17.5 | 0.0 |
| 30 | 280-300 | 50 | 10.0 | 0.0 | 73.3 | 16.7 |
| 20 | 290-305 | 60 | 0.0 | 3.0 | 7.0 | 90.0 |

* *Under mild* are classified those young rats which drank 40-60 cc water daily and excreted 3-5 g of sugar daily in the urine, among the adult rats those that drank 60-90 cc water and excreted 5-9 g of sugar daily.

† *Under severe* are grouped those rats that drank water and excreted glucose in the urine in amounts greater than the ones stated above.

The diet consisted of stock rabbit pellets supplemented with fresh green vegetables, carrots and 8 cc of orange juice daily, the last given by pipette. The animals in Group IV received the rabbit pellets only.

*Results.* Table I summarizes the data with regard to treatment, size of alloxan dose, route of administration, blood sugar levels at various intervals after alloxan, and time of sacrifice in days after the last dose of alloxan was given. The blood sugar concentration at all intervals after alloxan injection ranged from 85 to 150 mg per 100 cc of blood. These values represent post-alloxan *fasting blood sugar levels* and lie in the normal range for the guinea pig. Glycosuria was never observed.

The survival of the animals following the injections of alloxan was influenced by the size of the dose, the route of administration and the previous nutritional status. A dose of 250 or 225 mg per kg body weight killed the animals within 3 days. A dose of 200 mg was well tolerated by animals fasted for 24 hours but the same dose was fatal after a 3-day fast although the blood sugar level was in the normal range. Following the administration of 400 mg per kg by the intraperitoneal route, the animals became ill and refused to eat but had recovered by the following day.

All of the animals which received over 200 mg of alloxan per kg and those which received 200 mg per kg following a 3-day fast and which were examined during the first week after injection showed gross lesions in the lungs, liver, and kidneys. The histological examination of the pancreas showed no lesions following the intravenous administration of a 200 mg per kg dose of alloxan. The animals which received the 250 and 225 mg per kg doses had lesions of various degrees of severity ranging from cloudy swelling to necrosis and disappearance of $\beta$-cells. It was observed that doses of alloxan which were fatal produced damage in a third of the islets and only 16% of the islets were classified as severely damaged.

*Discussion.* The data presented indicate the resistance of the guinea pig to the diabetogenic and to the general toxic action of alloxan. The maximum tolerated dose under the conditions of these studies is approximately 200 mg per kg intravenously. Slightly higher doses cause death within a few days, the blood sugar remaining normal. For comparison, data which have been collected with rats of various sizes during the past few years are shown in Table II. It will be observed that optimum dosage for the production of diabetes in the rat apparently varies with age. Young rats tolerate 60 to 70 mg per kg of body weight in agreement with the previous studies of Mann and Stare.[17] In adult animals similar results are obtained with a dosage level between 45 and 50 mg per kg of body weight.

Several other factors besides age and dosage level are known to affect the toxity and diabetogenic action of alloxan such as the con-

[17] Mann, G. V., Stare, F. J., *J. Lab. Clin. Med.*, 1948, **33**, 1161.

centration of the alloxan solution, fasting prior to alloxan injections, and the composition of the diet.[18-21]

The development of alloxan diabetes apparently depends upon the difference in the susceptibility of the islet tissue as compared to other body tissues. If the range is sufficiently great so that marked islet destruction with only minor damage to other tissues can be obtained, diabetes can be produced. This differential is apparently found in most mammalian species. In the guinea pig, however, the islet tissue appears no more susceptible than other tissues and the resistance of both to alloxan is much greater than is found in the rat.

*Summary.* The parenteral administration of various dosages of alloxan, up to those which were fatal, failed to produce diabetes in guinea pigs. Neither glycosuria nor hyperglycemia was observed. Animals deficient in ascorbic acid, partially pancreatectomised or starved prior to alloxan administration, also failed to develop diabetes, although starvation apparently increased the toxicity of alloxan.

The guinea pig is much more resistant to the diabetogenic and the toxic action of alloxan than is the rat, and the pancreatic islet cells appear no more susceptible to alloxan than the cells of several other tissues.

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## Anaphylactoid Shock Produced by Anti-Platelet Serum.*

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Decrease or even absence of platelets is well known during anaphylactic, peptonic and tryptic shocks. The rate of platelet disappearance is very rapid[1] and a relationship between the severity of anaphylactic shock and the amount of blood platelets removed from circulation has been emphasized.[2] The role of the platelet in the mechanism of these types of shock is not yet clear, but its interference has been verified.[3-5] Our purpose was to produce an anaphylactoid shock using a substance known as capable of inducing an experimental thrombocytopenic purpura. Substances known as producing experimental thrombocytopenia and purpura are estradiol benzoate[6] or urethane in the dog.[7] These substances act only after at least a week of daily administration and seem to be specific to dogs. These substances are not indicated to removing the platelets abruptly from the circulation with its sudden destruction and

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