

The minimal lethal dose during the months of June a year apart was from 0.002 to 0.003 mg. per kilo. This amount again killed approximately 8 out of 10 animals and all died with 0.004 mg. per kilo.

If the toxin be thought to change spontaneously on long standing, it of necessity should become either less or more potent. Since identical figures were obtained during the same seasons a year apart, *i. e.*, greater toxicity both summers and lesser toxicity both winters, we are forced to conclude that the differences observed reside in the conditional state of the animals and not to changes in the toxin.

It seems to us, therefore, that there is a sufficient variation in the seasonal susceptibility of guinea pigs to tetanus toxin to justify special care in its standardization.

By contrast to the above data on tetanus toxin, it may be noted that diphtheria toxin appears to be more toxic to pigs in winter than in summer.¹ The two toxins, however, are obviously quite different in character and in mode of action, hence further knowledge is required in order to correlate the differences in the two toxins with respect to seasonal variations of susceptibility of guinea pigs and rabbits.

8929 P

Epinephrine Secretion in Animals with Experimental Diabetes.

J. M. ROGOFF* AND E. NOLA NIXON.

From the Physiological Laboratory, University of Chicago.

Rogoff and Ferrill¹ have shown that the development and course of diabetes following total extirpation of the pancreas, in dogs, is not modified by reduction or suppression of epinephrine secretion, from the adrenal glands. Further, they observed that in depancreatized dogs, not subjected to operations for interference with epinephrine secretion, a marked reduction in the epinephrine output may occur after various periods, under treatment with insulin on a constant diet.

We are investigating the probable causes for this disturbance of

¹ *British System of Bacteriology*, 1931, **6**, 108.

* Aided by the G. N. Stewart Memorial Fund and a grant from Mr. Max Manischewitz.

We are grateful to Eli Lilly & Company for generous supplies of insulin.

¹ Rogoff and Ferrill, *Proc. Soc. Exp. Biol. and Med.*, 1936, **34**, 100.

the epinephrine secretion from the adrenals and have attempted to determine whether the following factors play a rôle: *a*, the diabetic state, *b*, a possible influence of insulin, *c*, integrity of the splanchnic innervation. This report is a summary of the results obtained by us in experiments on 39 dogs.

Sixteen animals (Group 1) were totally pancreatectomized and kept on a diet consisting of 500 gm. boiled beef lung, 100 gm. cane sugar and 75 gm. fresh raw beef pancreas daily. Insulin was administered in doses necessary to maintain the daily excretion of sugar in the urine below about 5 gm. and below about 1%. At different periods of observation, ranging from 11 to 77 days following pancreatectomy, experiments were terminated and the animals sacrificed for determination of the epinephrine output from the adrenal glands by the method of Stewart and Rogoff.

Thirteen dogs (Group 2) were totally pancreatectomized and kept on a diet of 500 gm. boiled beef lung and 75 gm. fresh raw pancreas daily. Sugar was not added, nor were they treated with insulin. The animals were sacrificed for determination of epinephrine output from the adrenals when they showed evidence of severe diabetes, 4 to 23 days after pancreatectomy.

Ten normal, unoperated dogs were kept on a diet of 500 gm. boiled beef lung and 100 gm. sugar daily. Five of these animals (Group 3) were injected with insulin in doses comparable with those employed in depancreatized animals of Group 1. The other 5 animals (Group 4) received no insulin. Epinephrine output from the adrenals was determined after 22 to 64 days of observation in Group 3 and after 21 to 55 days in Group 4.

Under ordinary experimental conditions, the average epinephrine output in dogs (and cats) is approximately 0.0002 mg. per kg. body weight, as determined by Stewart and Rogoff.² In about 85% of a large series of determinations the limits were 0.0001 to 0.0003 mg. per kg. These figures may be used for comparison with the figures for epinephrine output in the present series of experiments, since the determinations were made with the same method.

Of the 16 animals in Group 1, the epinephrine output was within the ordinary range for normal animals in 4 experiments. Six showed an output corresponding to about 1/3 to 1/2 of the lower level of the normal range, or about 1/6 to 1/4 of the average. The epinephrine output in the other 6 animals ranged from 1/10 to 1/75 of the average for normal dogs. In Group 2 (13 dogs), 10 showed a normal epinephrine output, in one the output was 1/5 and in 2 approximately 1/20 of the normal average. Of the 5 animals in

² Stewart and Rogoff, *Am. J. Physiol.*, 1923, **66**, 235.

Group 3, one showed a normal output and the others ranged from 1/20 to 1/100 of the average epinephrine output for normal dogs. In Group 4 (5 dogs) a normal output was found in 3 animals, about 1/8 of the normal average in one and 1/50 in the other.

It appeared, at first, that insulin might be responsible for the low epinephrine output, since most of the treated depancreatized animals showed a marked reduction. However, in 3 of the 13 untreated depancreatized dogs there was a definitely reduced epinephrine output. The animals in this group did not live nearly as long as the treated animals, which may explain the smaller number of instances of reduction in output in the untreated dogs. On the other hand, a similar difference is seen in the case of unoperated dogs on a diet rich in sugar, between Groups 3 (receiving insulin) and 4 (untreated). Of course, it is possible that this difference might be less striking in larger series of experiments. Nevertheless, whatever the reason may be for the greater number of instances of reduced epinephrine output in the insulin-treated groups, it is evident that this reduction can occur without the action of insulin. That the liver may play a rôle and other probable factors remain for further investigation.

The evidence indicates that the diabetic state of the animal is primarily responsible for the reduction or suppression of epinephrine secretion from the adrenals. We have found that electrical stimulation of the splanchnic nerve is capable of increasing the epinephrine output up to or above the normal level, in those animals that show a marked reduction in output.

8930 C

Electrocardiographic Changes in Rats Deficient in Vitamin B₁.

PAUL M. ZOLL AND SOMA WEISS.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston.

Vitamin B₁ deficiency in rats and pigeons has been found to be associated with bradycardia (Birch and Harris¹; Drury, Harris and Maudsley²; Carter and Drury³; and Méhes and Péter^{4, 5}). Changes

¹ Birch, T. W., and Harris, L. J., *Biochem. J.*, 1934, **28**, 602.

² Drury, A. N., Harris, L. J., and Maudsley, C., *Biochem. J.*, 1930, **24**, 1632.

³ Carter, C. W., and Drury, A. N., *J. Physiol.*, 1929, **68**, i (Proceedings).

⁴ Méhes, J., *Arch. f. Exp. Path. u. Pharm.*, 1934, **176**, 141.

⁵ Méhes, J., and Péter, F., *Arch. f. Exp. Path. u. Pharm.*, 1934, **176**, 226.