striking effect on the temperature responses of rabbits that had been previously "trained" by repeated daily injections of vaccine. A typical result is illustrated in Fig. 1. Here it will be noted that a considerable modification in response was manifest by the 7th day. Each animal was then given Thorotrast. On the following day administration of typhoid vaccine caused high, prolonged temperature elevations. After a rest of one day their febrile responses to the vaccine were again considerably lessened. This brief effect of the blocking agent is in line with other experience on functional interference with the reticulo-endothelial system.[2]

[2] Jaffe, R. H., *Physiol. Rev.*, 1931, **11**, 277.

These experiments show that rabbits can develop a tolerance to typhoid bacterial pyrogen, and that the tolerance is most marked when injections are given frequently. The mechanism of development of this state is not yet explained. Certain other observations, which cannot be given in detail here, indicate that the production of specific humoral antibodies is not responsible, and furthermore, that the development of tolerance to typhoid vaccine carries with it a similar alteration in response to other bacterial pyrogens. Possibly the process involves a change in the functional activity of the reticulo-endothelial system, providing for more rapid disposal of the foreign material.

15292

Effect of Penicillin on Blood Urea in the Rat

JACK RALPH LEONARDS AND FLORENCE WILLIAMS.
(Introduced by Victor C. Myers.)
From the Department of Biochemistry, School of Medicine, Western Reserve University, Cleveland.

Early in 1943 the Floreys[1] reported that 4 out of 5 patients treated with 120,000 or more Oxford units of penicillin manifested a rise in blood urea. The elevated values returned rapidly to normal when the drug was withdrawn. Although no explanation was advanced for this phenomenon it was not thought to be due to renal damage.

The present study demonstrates that penicillin has no significant effect on the blood urea level of normal rats even though exceedingly large amounts of the drug are administered.

The penicillin employed was a rather impure preparation assaying 300 Oxford units per mg of total solids.* Normal adult albino rats of both sexes were used and the penicillin was injected intraperitoneally in a solution containing 25,000 Oxford units per ml. Samples of blood (0.1 or 0.2 ml) for urea determinations were obtained from the tail vein directly into a pipette and the urea was analyzed by the colorimetric method described by Ormsby.[2]

The results are presented in Table I. It is immediately evident that no significant increase in blood urea results even after the administration of 500,000 Oxford units per kg of body weight. This dosage represents the largest amount of our preparation of penicillin that could be tolerated by the rat without any apparent toxic manifestations. It should be emphasized that this is a tremendously large dose. When a group of rats were given 1,000,000 Oxford units of penicillin per kg of body weight over a period of 10 hours, 4 of the 6 rats died on the same day and the 2 surviving animals were severely

[1] Florey, M. E., and Florey, H. W., *Lancet*, 1943, **1**, 387.

* Kindly supplied by Ben Venue Laboratories, Inc., Bedford, Ohio.

[2] Ormsby, A. A., *J. Biol. Chem.*, 1942, **146**, 595.

TABLE I.
Average Blood Urea Levels Following Intraperitoneal Injections of Penicillin.

Penicillin Oxford units per kg Time after penicillin	No. of rats	Blood urea mg per 100 cc 0 hr	3 hr	7 hr	11 hr	30 hr
0	10	37	34	29	36	37
50,000*	6	34	32	29	28	30
100,000†	6	41	31	31	31	40
250,000†	6	38	51	—	52	38
500,000†	8	39	36	41	49	40

* Single injection.
† Divided into 5 equal doses. Two hours apart.

ill for several days.

Summary. The intraperitoneal injection of penicillin into adult albino rats had no significant effect on the blood urea level, even when doses as high as 500,000 Oxford units were administered per kg of body weight.

15293

Nervous System Mechanism for Epinephrine Secretion.

J. M. ROGOFF, PHILIP WASSERMAN, AND E. NOLA NIXON.

From the Laboratory of Experimental Endocrinology, School of Medicine, University of Pittsburgh.*

The rate of liberation of epinephrine from the adrenal glands, under ordinary experimental conditions, has been determined as an average of about 0.00025 mg per kg of body weight per minute, in cats and dogs.[1] In the absence of experimentally induced alteration of the rate of secretion, the range of physiological epinephrine output was found to be approximately 0.0001 to 0.001 mg per kg per minute.

This spontaneous, constant secretion of epinephrine is sustained through the influence of a centre, or centres, located in the upper portion of the thoracic division of the spinal cord and can be considered as the normal, physiological secretion. Transection of the cord between the last cervical and the fourth dorsal segments abolishes epinephrine secretion from the adrenals. This centre is bilateral; semisection of the spinal cord, in this region, results in suppression of epinephrine secretion from the ipsilateral adrenal without detectable influence upon the secretion from the contralateral gland.[2]

Incidental observations made in the course of some other investigations suggested the probability of the existence of an inhibitory centre for epinephrine secretion, located in the brain. For example, the large increase in epinephrine output which is induced by the action of strychnine usually is preceded by a preliminary decline in the rate of secretion if a minimal effective dose of the drug is injected intravenously, or a larger dose

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A preliminary note was published in the *Proc. Am. Physiol. Soc.*, 1931. The study was interrupted when the Department of Experimental Medicine, at Western Reserve University, was discontinued. Some of the experiments were performed at the University of Chicago. The investigation was resumed and continued in this laboratory.

1 Stewart, G. N., and Rogoff, J. M., a. *J. Pharm. and Exp. Therap.*, 1916, **8**, 479; b. *Am. J. Physiol.*, 1923, **66**, 235.

2 Stewart, G. N., and Rogoff, J. M., a. *J. Exper. Med.*, 1917, **26**, 613; b. *Am. J. Physiol.*, 1920, **51**, 484.