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.

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Nervous System Mechanism for Epinephrine Secretion.

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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.

subcutaneously. Intravenous administration of the larger doses generally causes only the augmentation of epinephrine output.[3] This suggests a possible activity of an inhibitory mechanism during the phase of cerebral stimulation by strychnine. Such an inhibitory influence upon epinephrine secretion would be submerged by the more powerful action of the opposing spinal cord centre, when the predominant influence of strychnine on the cord is effected.

Other observations likewise indicated the possibility that an inhibitory centre, which influences epinephrine secretion, exists in the brain. For example, when experimental animals were rendered insensitive to pain by compression or destruction of the brain, after preliminary anesthesia, the epinephrine output from the adrenal glands was found to be within but near or at the maximum of the range of spontaneous liberation.[2a,8] Furthermore, the same observation was made when the rate of liberation of epinephrine was determined in animals with cerebral anemia induced by occlusion of the blood supply to the brain.[4]

In the present series of experiments, the rate of epinephrine secretion from the adrenal glands was determined before and after transection at various levels of the brain. Decerebration was performed with the special knife described by Karrer and Stevens.[5] All of the experiments were performed on cats. The animals were anesthetized with urethane administered by stomach tube. The results obtained are illustrated in Table I and Fig. 3.

The level of decerebration was verified at the end of each experiment, by post-mortem examination. In Experiments 1-16, inclusive, transection of the brain was at levels bounded by the superior colliculus and the optic chiasm. In the others, decerebration was at various levels anterior to this. In 6 of the 28 animals, a small area of cortex escaped section (No. 7, 17, 18, 20, 24, 26).

The rate of secretion of epinephrine was assayed by the method of Stewart and Rogoff. Adrenal blood specimens were collected via the "cava pocket," before and after transection of the brain. The amount of blood obtained and the duration of the collection were measured, thus determining the rate of blood flow from the adrenals. The concentration of epinephrine in the blood specimens was assayed by the quantitative inhibition of rabbits' intestine segments. From this information, the rate of epinephrine secretion was readily calculated. In a few of the experiments, assay of the adrenal blood specimens was confirmed employing the "sensitized eye" method.[6]

Table I illustrates the decided increase in the rate of liberation of epinephrine which follows transection of the brain between the superior colliculus and the optic chiasm (cats 1-16, inclusive). In 12 of the animals the epinephrine output rose to or near the maximum of the normal range of spontaneous liberation. In cats 1 and 15, the output did not approach the upper limit of the range, although there was an increase of 2 and 3 times the initial rate of epinephrine secretion.

In one cat (8) there was, if anything, a slight reduction in the output. The adrenal blood flow, following decerebration, was very low in cats 4, 8 and 15. Brain transection was associated with excessive hemorrhage in these animals. However, experimental shock due to loss of systemic blood was not found to alter the epinephrine output from the adrenal glands.[7]

The 12 experiments in which transection of the brain was performed through or anterior to the optic chiasm showed no significant alteration of the rate of liberation of epinephrine from the adrenals, except in cat 24. In this animal, a reduction to about one-fourth of the initial epinephrine output was found, although the blood flow from the adrenals was good. A reduction in output to about one-half was found in cat 17 but

[3] Stewart, G. N., and Rogoff, J. M., *J. Pharm. and Exp. Therap.*, 1919, **13**, 95.

[4] Rogoff, J. M., *Am. J. Physiol.*, 1924, **67**, 551.

[5] Karrer, E., and Stevens, H. C., *J. Lab. Clin. Med.*, 1928, **14**, 266.

[6] Rogoff, J. M., PROC. SOC. EXP. BIOL. AND MED., 1937, **36**, 441.

[7] Stewart, G. N., and Rogoff, J. M., *Am. J. Physiol.*, 1919, **48**, 22.

TABLE I.
Epinephrine Output from the Adrenals after Decerebration.*

	Before brain section							After brain section				
				Epinephrine						Epinephrine		
No.	wt kg	Blood pressure mm Hg.	Blood flow g/min	Concentration x 100,000	Output μg/min	Output μg/kg/min	Interval min	Blood pressure mm Hg.	Blood flow g/min	Concentration x 100,000	Output μg/min	Output μg/kg/min
1	3.0		2.32	1:64	0.33	0.11	10		2.31	1:21	1.1	0.37
2	2.9	86	1.36	1:32	0.42	0.14	12	90	1.87	1:8.3	2.25	0.8
3	2.9	120	3.28	1:58	0.57	0.2	5	78	2.45	1:8.5	2.88	1.0
4	2.7	93	2.52	1:80	0.31	0.11	15	40	0.62	1:30	0.21	0.09
5	3.2	156	7.09	1:52	1.37	0.43	5	96	5.8	1:20	2.9	0.91
6	3.2	140	6.2	1:46	1.35	0.42	10	68	2.25	1:6.5	3.46	1.08
7	3.3	154	6.8	1:33	2.06	0.62	8	44	1.07	1:4.3	2.49	0.75
8	2.3	142	3.0	1:35	0.86	0.37	8	38	0.54	1:10	0.54	0.23
9	2.4	120	5.2	1:42.5	1.22	0.51	10	72	2.88	1:7.5	3.84	1.6
10	2.7	97	4.3	1:51	0.84	0.31	8	52	2.7	1:7.0	3.86	1.43
11	2.7	74	2.08	1:32.5	0.64	0.24	4	58	1.55	1:9.0	1.72	0.64
12	3.1	150	2.7	1:45	0.6	0.19	6	77	1.0	1:4.2	2.38	0.77
13	2.8	85	4.2	1:47.5	0.88	0.31	5	88	4.5	1:11	4.1	1.46
14	2.7	102	7.1	1:90	0.79	0.29	7	93	7.0	1:21	3.33	1.23
15	3.3	118	3.8	1:65	0.58	0.18	4	44	0.46	1:4.2	1.1	0.33
16	2.8	96	2.6	1:30	0.87	0.31	6	90	2.51	1:8.75	2.87	1.03
17	2.6	95	1.74	1:21	0.83	0.32	15	36	0.45	1:10	0.45	0.17
18	2.7	150	4.41	1:53	0.83	0.31	10	84	2.48	1:37.5	0.66	0.24
19	2.3	125	4.6	1:70	0.66	0.29	7	64	2.0	1:31	0.64	0.28
20	2.2	90	3.1	1:30	1.03	0.47	8	68	1.3	1:9.7	1.34	0.61
21	2.9	145	5.9	1:55	1.08	0.37	5	126	4.4	1:35	1.26	0.43
22	3.2	122	6.41	1:56	1.14	0.36	5	84	2.93	1:22.5	1.3	0.41
23	2.4	130	6.2	1:55	1.13	0.47	4	95	3.82	1:33	1.16	0.48
24	3.7	112	4.4	1:37	1.19	0.32	5	88	2.4	1:70	0.34	0.09
25	3.1	130	2.16	1:25	0.86	0.28	5	66	1.01	1:12.8	0.79	0.25
26	2.9	122	3.8	1:40	0.95	0.33	4	70	1.15	1:9.75	1.18	0.41
27	3.9	110	3.2	1:28	1.14	0.29	6	82	2.9	1:20	1.45	0.37
28	2.5	122	3.41	1:52	0.66	0.26	6	97	2.86	1:40	0.71	0.28

* In cats 1-16, inclusive, decerebration was between the superior colliculi and the optic chiasm; in all the others, it was anterior to that level.

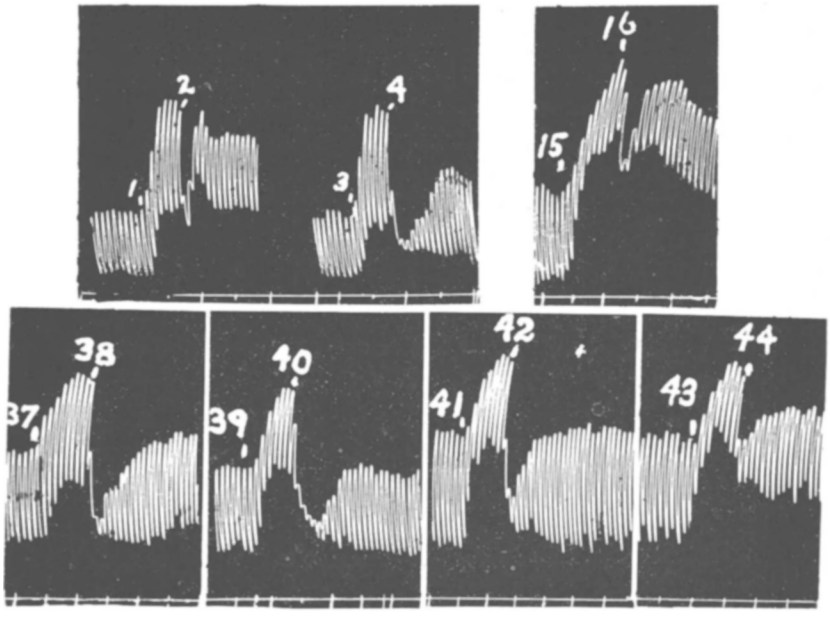

Fig. 1.

At the uneven numbers Ringer's solution was displaced by indifferent blood and this at 2 by adrenal blood specimen A, at 4, 38 and 42 by adrenal blood specimen B, at 16 by indifferent blood to which was added adrenalin to make a concentration of 1:7,000,000, at 40 a concentration of 1:1,450.000, and at 44 a concentration of 1:2,850,000. A was assayed at 1:6,400,000, and B at 1:2,100,000. Time in half-minutes. Reduced to two-thirds.

in this case, as in cats 4, 8 and 15, the adrenal blood flow was very slow. The question may be raised, in these cases, whether trauma of the brain, in a region near the inhibitory centre for epinephrine secretion, might not result in stimulation of that centre and consequent reduction of epinephrine output from the adrenal glands.

In 2 experiments (cats 3 and 5), in which the decerebration was between the superior colliculus and the optic chiasm, and in one (cat 19), in which the decerebration was anterior to this region, additional adrenal blood specimens were obtained for assay. In cat 3, a specimen obtained 25 minutes after decerebration, when the adrenal blood flow was 1.15 g per minute, was assayed at 1:450,000 adrenalin, corresponding to an output of 0.0025 mg per minute for the cat or 0.00086 mg per kg per minute. In cat 5, a specimen obtained 18 minutes after decerebration, when the adrenal blood flow was 1.02 g per minute, was assayed at 1:750,000 adrenalin, corresponding to an output of 0.00136 mg per minute for the cat or 0.00048 mg per kg per minute. In the case of transection of the brain through the optic chiasm (cat 19), a specimen obtained 35 minutes after decerebration, when the adrenal blood flow was 1.4 g per minute showed the same epinephrine output from the adrenals as before and 7 minutes after the decerebration.

To illustrate the results obtained, condensed protocols and some of the tracings (Fig. 1, 2) from the assay in 2 of the experiments are given (cats 1 and 13). In these animals the transection of the brain was between the superior colliculi and the optic chiasm. Cat 1 was a pregnant female and cat 13 a male. These animals were selected for illustration because the results are unequivocal. The rate of blood flow from the adrenal glands did not change after decerebration; nevertheless, the epinephrine concentration in the adrenal blood specimens obtained after the decerebration (B) was decidedly greater than that in the initial specimens (A).

Condensed protocol. Cat 1: pregnant fe-

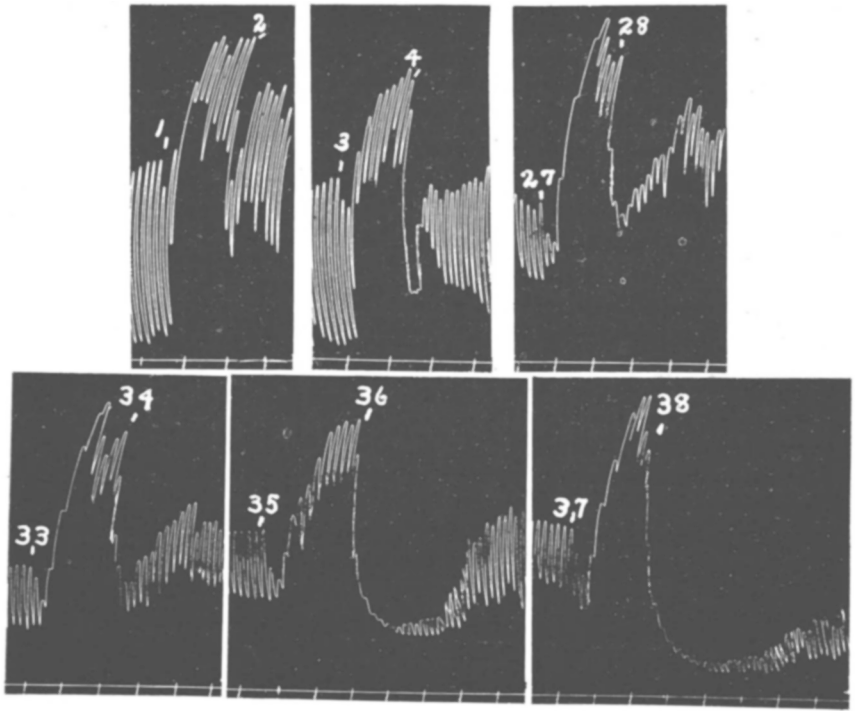

Fig. 2.

At the uneven numbers Ringer's solution was displaced by indifferent blood and this at 2 and 34 by adrenal blood specimen A, at 4 and 36 by adrenal blood specimen B, at 28 by indifferent blood to which was added adrenalin to make a concentration of 1:6,250,000, and at 38 a concentration of 1:700,000. A was assayed at 1:4,750,000, and B at 1:1,100,000. Time in half-minutes. Reduced to three-fifths.

male; weight 3.0 kg.

a.m.

8:45; Urethane (20 cc of 20% sol.) by stomach tube.

10:45; Anesthesia complete.

11:22; Collected adrenal blood specimen A, 5.8 g in 2½ min.; blood flow, 2.32 g per minute.

11:40; Inserted tracheal cannula and trephined skull.

11:42; Decerebration.

11:52; Collected adrenal blood specimen B, 5.78 g in 2½ min.; blood flow, 2.31 g per minute.

Complete transection of the brain, just anterior to the superior colliculi, verified by post mortem examination.

Specimen A, assayed at 1:6,400,000 adrenalin, corresponding to an output of 0.00033 mg per minute for the cat or 0.00011 mg per kg body weight per minute. Specimen B, assayed at 1:2,100,000 adrenalin, corresponding to an output of 0.0011 mg per minute for the cat or 0.00037 mg per kg body weight per minute (Fig. 1).

Condensed protocol. Cat 13; male; weight, 2.8 kg.

a.m.

9:30; Urethane (25 cc of 20% sol.) by stomach tube.

10:30; Anesthesia complete.

10:55; Collected adrenal blood specimen A, 8.4 g in 2 min.; blood flow, 4.2 g per minute.

11:12; Inserted tracheal cannula and trephined skull.

11:18; Decerebration.

11:23; Collected adrenal blood specimen B, 9.0 g in 2 min.; blood flow, 4.5 g per minute.

Complete transection of the brain, about ⅛ inch anterior to the superior colliculi, verified

TABLE II.
Statistical Summary of Epinephrine Output.

Cats	Decere-bration	Mean μg/kg/min	Squared standard deviation	Probable error of mean	Ratio of std.error of diff. to diff. of means		t	
					Observed	Significant	Observed	Significant
1-16	before	0.296	0.146	0.025				
1-16	after	0.858	0.451	0.076	7.02	3.0	4.736	2.131
17-28	before	0.339	0.069	0.013				
17-28	after	0.335	0.144	0.028	0.031	3.0	0.891	2.201
1-16	before	0.296	0.146	0.025				
17-28	before	0.858	0.069	0.013	1.529	3.0	0.939	2.201

by post mortem examination.

Specimen A, assayed at 1:4,750,000 adrenalin, corresponding to an output of 0.00088 mg per minute for the cat or 0.00031 mg per kg body weight per minute. Specimen B, assayed at 1:1,100,000 adrenalin, corresponding to an output of 0.0041 mg per minute for the cat or 0.00146 mg per kg body weight per minute (Fig. 2).

Although the results are sufficiently definite to support our conclusions, they are presented in the following statistical summary (Table II) for which we are greatly indebted to Dr. Paul L. McLain of the Department of

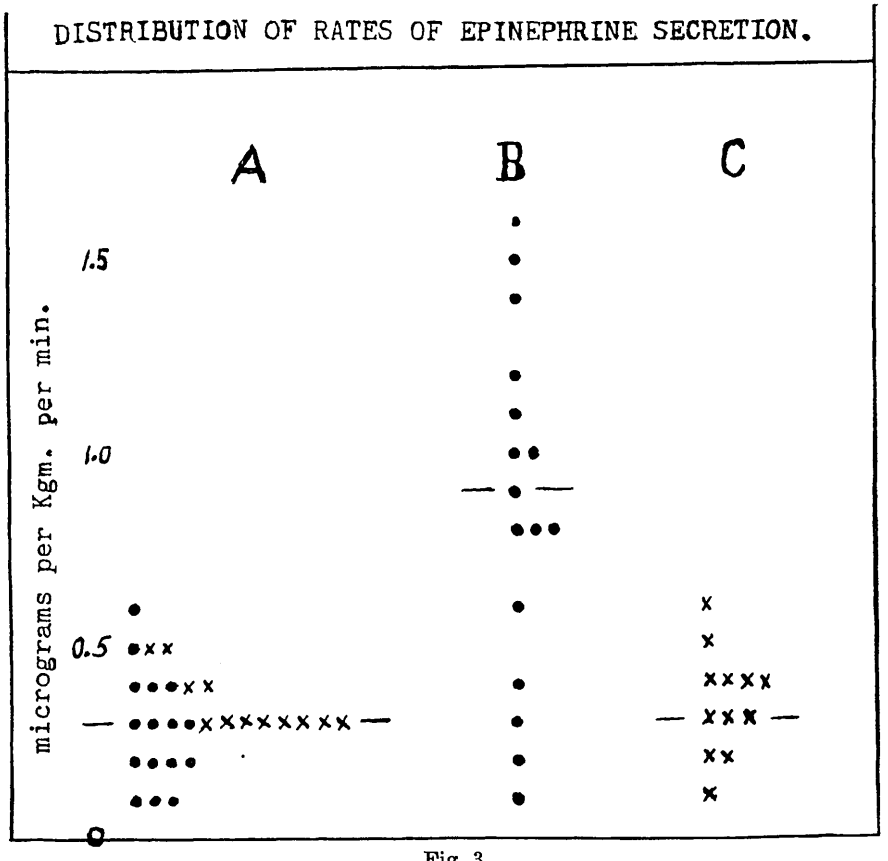

Fig. 3.

A—Before decerebration.
B—After decerebration between superior colliculi and optic chiasm.
C—After decerebration anterior to level of B.
●—Cats 1-16, inclusive.
X—Cats 17-28, inclusive.

Physiology. The distribution of the rates of epinephrine output is illustrated in Fig. 3.

Summary. These experiments indicate the existence of an inhibitory central mechanism, located in the region of the brain bounded by the superior colliculi and the optic chiasm, which influences epinephrine secretion from the adrenal glands. The existence of a central mechanism in the spinal cord, which exercises an opposite influence to that of this cerebral centre, was established earlier.[2] Removal of the influence of the brain centre, results in epinephrine output from the adrenals at the maximum rate of spontaneous liberation which can be sustained through the physiological activity of the spinal cord centre. This rate corresponds with the upper limit of the range of normal epinephrine secretion.[1]

Despite the fact that epinephrine was the first hormone to be isolated from its source, and to be synthesized, the functional significance of epinephrine secretion is still obscure. Physiological interpretations from pharmacological observations often have been misleading. Only quantitative experiments, yielding results within the limits of the physiological rate of liberation, can be expected to yield unequivocal information on the function of epinephrine secretion.

In the light of the experiments reported herewith, it can be seen why reflex augmentation of the rate of epinephrine secretion has not been demonstrated successfully in animals under the influence of asphyxia[8] or stimulation of sensory nerve trunks.[9] For, even if these stimuli might affect appropriate receptors, which could alter the rate of epinephrine secretion, there is no reason to assume that they might not equally influence the cerebral and the cord centres, thus defeating the possibility of eliciting reflexly either augmentation or diminution in the rate of epinephrine secretion from the adrenal glands. In preliminary tests, it was not found possible to elicit augmentation of the epinephrine output by stimulation of sensory nerves, following mechanical destruction or compression of the brain.[9a]

[8] Stewart, G. N., and Rogoff, J. M., *J. Pharm. and Exp. Therap.*, 1917, **10**, 49.

[9] Stewart, G. N., and Rogoff, J. M., a. *J. Exper. Med.*, 1917, **26**, 637; b. *Am. J. Physiol.*, 1924, **69**, 605.

15294 P

Inhibition of Experimental Drug Allergy by Prior Feeding of the Sensitizing Agent.

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In the course of studies on experimental drug allergy, it was noticed that sensitization was apt to be less successful in guinea pigs which previously had been treated briefly with the same chemical. Experiments were undertaken to establish at will such a refractory state.* For the preparatory, or blocking, treatment, the methods tried included the parenteral injection of soluble and insoluble protein conjugates of the incitant itself, repeated cutaneous application of the chemicals in very low (non-sensitizing) concentration, intravenous injections, and feeding experiments. After this preliminary treatment, a rest period of 2 weeks was allowed, and then the animals, in parallel with fresh guinea pigs as controls, were subjected to an active sensitizing course consisting of 6 or more intracutaneous injections of the incitant over a period of several weeks. Following

* In the case of neoarsphenamine, Sulzberger[4] had found that a single intravenous injection of the substance usually prevented the active sensitization sought by an intracutaneous injection made one day previously.