

Effect of Epinephrine on the Neutrophile Count of Normal and Adrenalectomized Mice.* (18403)

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The role of epinephrine in the regulation of the number of leucocytes in the blood and thus in relation to the problem of stress has been discussed by various investigators(1,2). It is well known, and has been confirmed by the present study, that epinephrine injections result in a lymphopenia and an eosinopenia in intact animals and there is also evidence in the literature that this response is prevented by adrenalectomy(3-5). According to Speirs and Meyer(5) the occurrence of an eosinopenia following epinephrine injection in an adrenalectomized animal indicates either incomplete removal of the glands or the presence of accessory adrenal cortical tissue. It is interesting that in the majority of their adrenalectomized mice epinephrine actually caused an eosinophilia. An absolute neutrophilia has also been reported to occur after injection of epinephrine, cortical extracts and following conditions of stress(6,7). According to some investigators adrenalectomy prevents this response of the neutrophils to epinephrine(8) but this has not been confirmed by later work(9,10) nor by the present study. In the series of experiments reported

here it has also been observed that the neutrophilia resulting after epinephrine, both in intact and adrenalectomized mice, was more extreme than that caused by other agents, and an attempt has been made to discover the reason for this difference.

Materials and Methods. The mice used for these experiments came from various sources. Some were albino but the majority were hybrids of unknown ancestry. Many of the latter had been made trichinous by forced feeding with infected muscle. Adrenalectomy or splenectomy were performed on different groups (Table I). In the adrenalectomized series only those individuals which failed to show an eosinopenia after epinephrine injection, and which therefore could be considered completely adrenalectomized(5), were included. Injected substances, in addition to epinephrine or adrenaline, included ACE (lipoadrenal cortex)[†], sex hormones (testosterone propionate, estradiol dipropionate and estradiol benzoate) and sesame or peanut oil. Epinephrine was administered either hourly for 4 hours according to the method of Long and Fry(11), or as a single dose; other substances always as single subcutaneous injections. Total white counts were made in the usual manner from tail blood and differentials from smears stained in May-Grunewald-Giemsa. Monocytes were not distinguished from lymphocytes; mononuclears in Table I includes both. One thousand granular leucocytes (all stages) were differentiated as neutrophilic or eosinophilic in bone marrow smears made directly from sternum or femur and stained like the blood smears.

Results. The results (Table I) indicate that the neutrophilia supervening after

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[†] We are indebted to Dr. H. F. Hailman of the Upjohn Company for the Lipo-Adrenal Cortex.

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TABLE I. White Blood Counts of Mice Before and After Injections.

Substance injected	Dosage	No. and type	Time between counts	Avg No. cells before inj.			Avg No. cells after inj.		
				Total	N.	E.	Total	N.	M.
ACE in oil (Upjohn)	1/20 cc	8 trich.	Intact mice. 4 hr	24800	4960	1240	18600	10600	2540
	1/10	13 "	6 "	17350	4500	1350	11500	18600	3350
	0.02 mg	4 "	6 "	19100	5100	2700	11300	9900	3550
Epinephrine hydrochloride	100 g in 4 inj. (hourly)							18700	400
	1 dose	13 "	5 "	12450	3500	750	8600	7800	10500
	25 mg	5 norm.	5 "	6700	2300	250	4150	350	8040
Adrenaline chloride	70 mg	3 "	2 "	9900	2100	500	7300	300	14950
	1/10 cc	8 trich.	6 "	16500	4950	1150	10400	200	6250
		5 "	6 "	19100	3050	1450	14600	950	10850
♀ hormone		9 "	6 "	16000	4000	1000	11000	1050	14400
Testosterone								900	12200
Oil									
Adrenaline chloride	0.02 mg ^s	7 "	Adrenalectomized mice. 5 "	13000	3100	300	9600	7800	8300
	100 g in 4 inj. (hourly)	10 norm.	5 "	13900	1800	150	11950	350	11700
	1 dose	6 "	5 "	9200	1850	150	7200	450	9450
	0.005 mg	4 "	2 "	18400	4800	450	13200	1000	10500
	100 g 1 dose		5 "				26550	7200	18300
Adrenaline chloride	As above*	5 norm.	Spleneetomized mice. 5 "	15200	4150	350	9700	9350	7000
	1/10 cc	5 "	6 "	25500	7400	1500	16600	7000	9000

Trich.—trichinous; Norm.—normal; N.—neutrophiles; E.—eosinophiles; M.—mononuclears.

epinephrine was greater than that occurring after the other agents tested. This response was present in adrenalectomized as well as in intact animals. Adrenal cortical extract produced a relative though not the absolute neutrophilia noted by Dougherty and White(7). This does not seem explainable on the basis of dosage. Variation in the content of different samples of ACE may possibly be involved, although the 2 different samples utilized for the present study gave markedly uniform results, especially considering the amount of variation in the experimental animals. Though an absolute increase occurred in some individuals after sex hormones the average results, like those after sesame or peanut oil, showed no significant increase.

An attempt has been made to discover the mechanism by which epinephrine exerts its action. Obviously the spleen was not involved since splenectomized animals showed a neutrophilia corresponding to that found in normal and adrenalectomized mice (Table I). It is possible, as suggested by other investigators(12,13) that the effect of epinephrine in increasing the blood flow may serve to send into the actively circulating blood cells which ordinarily remain close to the vessel wall and are not dislodged in the process of taking blood for counts. This might also account for the eosinophilia observed after epinephrine in adrenalectomized animals by Speirs and Meyer(5) and in the present study (Table I). It would indicate the presence peripherally of a larger

proportion of polymorphonuclear cells than of lymphocytes, since an absolute lymphocytosis was not found in adrenalectomized animals injected with epinephrine except in one group after 5 hours. A comparison of the bone marrows of ACE and epinephrine injected intact mice indicated that after ACE injection there is an increase in the proportion of eosinophilic to neutrophilic cells while after the epinephrine injection a slight tendency toward a decrease in the ratio of these two types occurs. Since both substances caused an eosinopenia in the circulating blood, the differential effect on the bone marrow can perhaps be interpreted as a direct one of greater stimulation of neutrophile formation by epinephrine.

Summary. Adrenal cortical extract in doses which caused a similar or greater decrease in eosinophiles of intact mice did not produce as extreme a degree of neutrophilia as epinephrine. Even in animals which had been completely adrenalectomized, as indicated by the lack of an eosinopenia after epinephrine, this substance produced a marked increase of neutrophiles in the circulating blood. Neither sex hormones nor peanut oil had this effect. Since epinephrine also caused marked neutrophilia in splenectomized mice its influence was not exerted through the spleen. Preliminary observation of bone marrow smears of intact injected animals indicated a higher proportion of neutrophilic to eosinophilic cells in the marrow of epinephrine injected mice as compared with those injected with ACE. This suggests a direct effect of epinephrine on the bone marrow.

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