probably an invariable accompaniment of adolescent changes in boys. It was noted in 73% of boys in the 14.25 age group, in which the height of the nipple and the incidence of marked enlargement were maximal, and in 100% of boys in the 15.75 and 17.5 age groups, in which both the height of the nipple and the incidence of marked enlargement had declined. Older age-groups will have to be examined to observe the complete regression of the phenomenon.

8410 C

A Note on the Analysis of Sympatheticomimetic Action.

MICHAEL G. MULINOS AND RAYMOND L. OSBORNE.

From the Department of Pharmacology, College of Physicians and Surgeons, Columbia University.

Langley[1] enunciated the broad rule that the pharmacological activity of suprarenal medullary extracts upon plain muscle simulates that of electrical excitation of the sympathetic nerves supplying each particular muscle. Dale[2] discovered that ergot depressed or paralyzed the motor sympathetic nerves, leaving the inhibitory effects relatively unaffected. After ergot, epinephrine no longer raises the blood pressure, but lowers it. Froelich and Loewi[3] made the further discovery that cocaine magnifies the effect of epinephrine on blood pressure.

These peculiarities of epinephrine after ergotamine or cocaine have been advanced as criteria of sympatheticomimicity,[6] despite the fact that the inhibitor activity elicited by epinephrine is but slightly affected by these drugs. In analyzing sympatheticomimicity Tainter[7] especially has emphasized the value of the ergot reversal and of the cocaine synergism. He used anesthetized animals, so that reflex and brain stimulants were not so easily separated from drugs acting peripherally. It is obvious that when a drug is injected into anesthetized animals, the resulting effects are more complex than would be the case in adrenalectomized animals with the central nervous system destroyed. Ergot reverses the motor effects of stimulation of the sympathetic nerves, and of injected epinephrine, while cocaine augments both of these. It is possible to elicit the effects

1 Langley, *J. Physiol.*, 1901, **27**, 237.

2 Dale, *J. Physiol.*, 1905, **32**, lvii.

3 Froelich and Loewi, *Arch. f. exp. Path. u. Pharm.*, 1910, **62**, 159.

of sympathetic stimulation by drugs which stimulate the central nervous system directly or reflexly; and also by a nicotine-like action on the sympathetic ganglia. Furthermore, the blood pressure

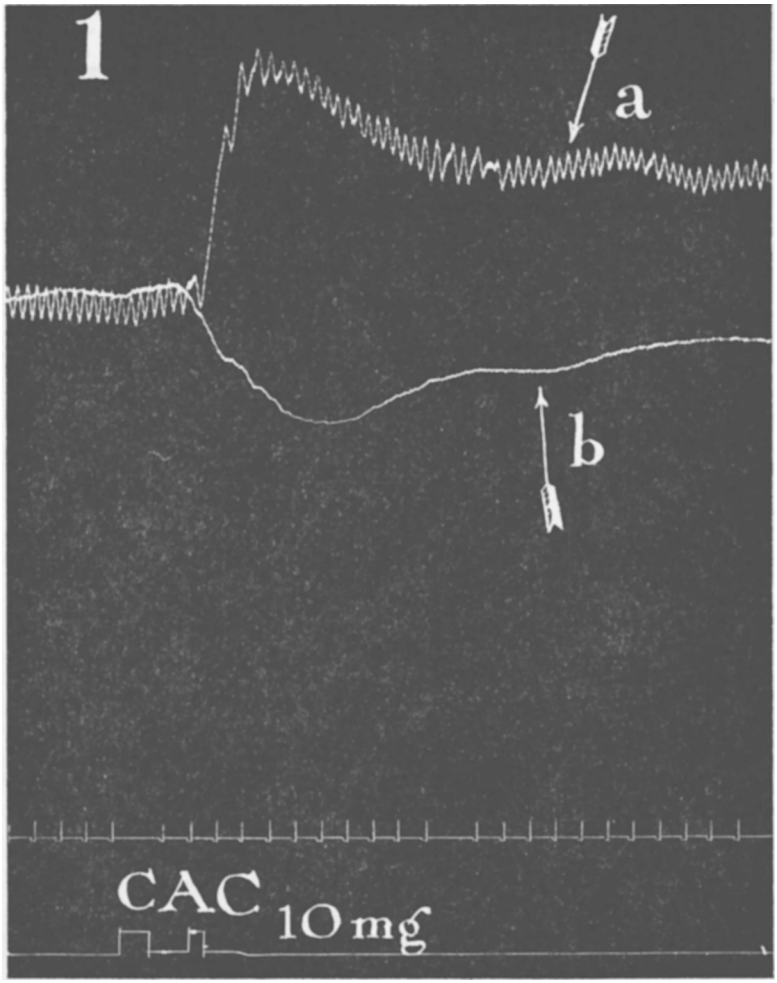

FIG. 1.
Blood pressure of cat anesthetized with Nembutal, 40 mg. per kilo. Atropine sulphate 5 mg. s. c. Tracing *a* was made before ergotamine. Tracing *b* was made after 1 mg. ergotamine tartrate. *CAC* is chloracetylcatechol. The "reversal" occurs also if the medulla is destroyed.

rise following stimulation of the central nervous system may be reversed by ergot and augmented by cocaine, as may that from electrical excitation of the splanchnic nerves.

Mulinos and Osborne[4] pointed out that chloracetocatechol (3,4-dihydroxyphenylchlormethylketone), designated for brevity as CAC, had properties suggestive of sympathetic stimulation. Ergot reverses the rise of blood pressure elicited by CAC on intact anesthetized cats (Fig. 1), while cocaine augments it (Fig. 2). From

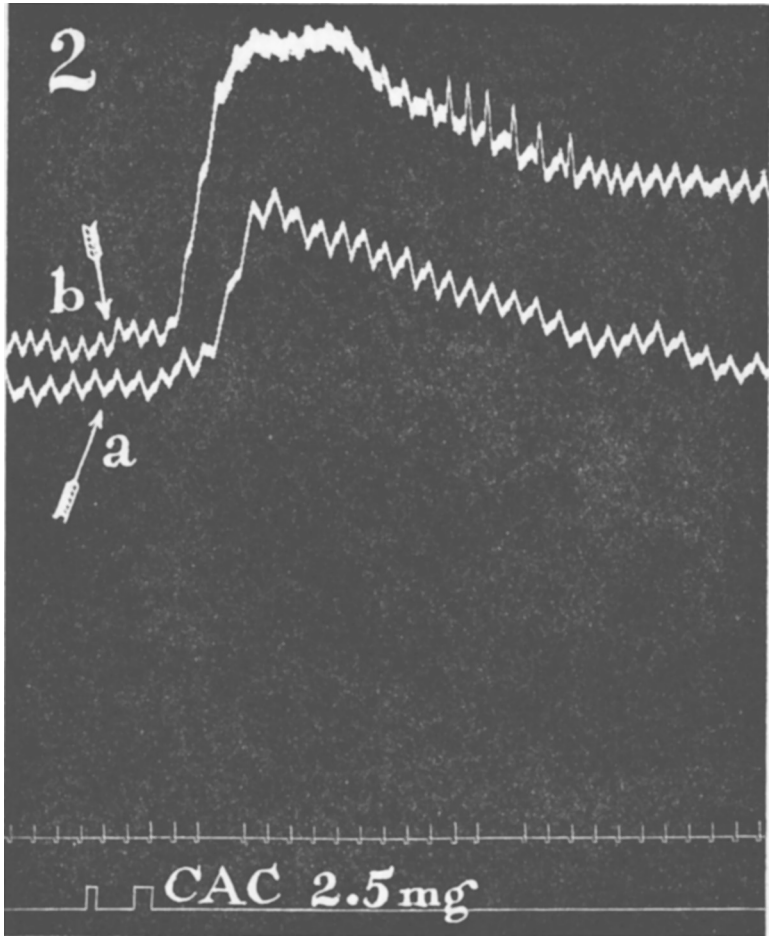

FIG. 2.
Cat blood pressure as for Fig. 1. Tracing *a* was made before cocaine. Tracing *b* was made after 5 mg. cocaine per kilo. The "synergy" does not occur if the medulla is destroyed. Compare with Fig. 1.

this it might be concluded that CAC resembles epinephrine in its action on blood pressure and in its behavior after ergotamine and

[4] Mulinos and Osborne, PROC. SOC. EXP. BIOL. AND MED., 1935, **32**, 1344.

cocaine. Table I shows clearly how erroneous this conclusion might be were it arrived at according to the criteria suggested by Tainter.[5-8]

TABLE I.
Summary of Blood Pressure Changes in Anesthetized Cats.

Drug	Intact Cat	Pithed Cat	Ergotamine Cat	Cocaine Cat	Increase after cocaine
Chloracetocatechol	+140	—27	— 8	+ 94	+37
Catechol	+ 41	+ 7	+ 4 — 1	+ 27	To be reported
Epinephrine	+141	+90	—14	+113	+32
Neosynephrine	+ 45	+70	+10	+ 5	

The numbers refer to total injections in 31 cats. + means a rise. — means a fall. A blank means not tried.

Our experiments indicate that chloracetocatechol raises the blood pressure by stimulation of the medulla oblongata. Its action is "reversed" by ergot, and also by pithing; and "increased" by cocaine only if the medulla is intact. On the other hand, catechol acts to raise the blood pressure both in intact and in pithed animals, and its action is not reversed by ergot. Therefore we believe that experiments with arylamines and catechol derivatives, substances which stimulate also the medulla, must be performed on pithed animals in order that the criteria of ergotamine reversal and cocaine synergism may be applicable for the analysis of sympatheticomimetic activity.[6] When the precautions of pithing and of adrenalectomy are observed, an action on the sympathetic ganglia must be guarded against.

Conclusion. In the intact animal, ergot reversal and cocaine synergy of a blood pressure rise indicate that the impulses eliciting the rise reached the blood vessels by way of the sympathetic nerves; they do not indicate the site of origin of the impulses.

[5] Tainter, *J. Pharm. Exp. Therap.*, 1929, **36**, 569.
[6] Tainter, *J. Pharm. Exp. Therap.*, 1930, **40**, 43.
[7] Tainter, *J. Pharm. Exp. Therap.*, 1932, **46**, 27.
[8] Wirt and Tainter, *J. Pharm. Exp. Therap.*, 1931, **44**, 299.