were not injured in any way by even large quantities of the substance.

After having established the maximum tolerated dosage and the toxic or lethal dosage of the compound and after having studied its action on the vital functions of the body, and in consideration of the wide margin of safety between the minimal effective pharmacodynamic and the toxic doses of the drug, carefully controlled clinical observations were made by a number of well-known physicians. Their preliminary reports indicated that the drug was efficacious in relieving spastic conditions, particularly of the gastro-intestinal organs and of the uterus (spastic dysmenorrhea). It was furthermore found by a number of surgeons to be a satisfactory local anesthetic for the performance of minor operations. The favorable preliminary results obtained with the drug render a further and more extensive clinical therapeutic study of the compound very desirable. Full data will be published elsewhere.

7172 C

Ergotoxine Excitement.

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The attention of investigators has been so centered on the peripheral effects of ergotoxine that the central action of this drug has received scant notice. Most of the studies of ergotoxine have been conducted upon anesthetized animals. In these its depressant action upon the respiratory center has been repeatedly reported. There have been few references, however, to central stimulation. Barger and Dale,[1] after intramuscular injection of ergotoxine in cats, observed vomiting and "hyperexcitability". They have recorded similar findings including fever in rabbits. Githens[2] considered this fever to be of central origin. Rothlin[3] found clonic and tonic convulsions 3 hours after large intravenous doses of ergotamine in rabbits. Koppanyi and Evans[4] reported vomiting and defecation of

[1] Barger, G., and Dale, H. H., *Biochem. J.*, 1907, **2**, 240.

[2] Githens, T. S., *J. Pharm. and Exp. Therap.*, 1917, **10**, 327.

[3] Rothlin—Cited by Barger, G. Ergot and Ergotism, Gurney and Jackson, London.

[4] Koppanyi, T., and Evans, E., PROC. SOC. EXP. BIOL. AND MED., 1932, **29**, 1181, 1183.

central origin in dogs and cats after the administration of small doses of ergotamine. Recent studies[5] in which ergotamine has been intramuscularly administered to unanesthetized animals in amounts sufficient to affect the sympathetic system make no mention of central action.

The observations here reported were made upon cats. Unanesthetized animals were tied to boards. No injection was made until the subjects had been calmed. Ergotoxine ethanesulphonate (1 mg./kilo)* was administered by intracardiac injection. This procedure can be accomplished without any excitement of the cat. The immediate manifestations of the action of the drug were those of sympathetic stimulation, wide dilation of the pupil and pilo-erection, especially in the tail. One minute after injection, the central effects became evident. The reflexes were hyperactive, the slightest touch causing a single spastic response in all voluntary muscles. More dramatic, however, were the emotional changes in the animal. The cats previously calm and unmindful of the injection, showed marked rage and apprehension. The slightest stimulation, visual, auditory or tactual, caused a savage hissing and snarling. Objects, brought near the head of the cat were ferociously attacked and bitten. The animals seemed at all times alert and followed all movements closely. Although the hyperactive reflexes and even the rage of the animal might be explained by cortical inhibition, the general demeanor of

FIG. 1.
Rage During Sympathetic Paralysis.

[5] Sawyer, M. E. MacKay, and Schlossberg, T., *Am. J. Physiol.*, 1933, **104**, 172.

* Kindly furnished by the Wellcome Research Laboratories, Tuckahoe, New York.

the cat was more suggestive of stimulation. The locus of this action has not yet been fixed.

The syndrome described above persisted for over an hour with diminishing intensity. It is of especial interest that the symptoms of rage were still apparent after sympathetic paralysis. The unusual picture of anger with extremely constricted pupils was presented (Fig. 1). The pupils remained fixed even after the intracardiac injection of large doses of epinephrine (0.4 mg./kilo). The stimulation described above was not followed by any extreme depression. At no time was there any evidence of clonic or tonic convulsions. The above phenomena have been a constant finding in the 12 cats studied.

7173

Vascular Lesions in Hemorrhagic Pancreatitis.

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The cause of the extensive hemorrhage which occurs in hemorrhagic pancreatitis has long been a matter of speculation. Diapedesis of red cells from capillaries has been said to occur as a result of the action of trypsin, but no one has demonstrated that trypsin has the power to destroy the walls of previously intact arteries and veins, and in the only histological study of the question which we have been able to find it is stated that the ferment does not attack vessels larger than capillaries.[1] Our microscopical studies of the pancreas in cases of hemorrhagic pancreatitis have revealed the constant and, as far as we can determine, hitherto unrecognized presence of a specific form of necrosis of the walls of arteries and veins, leading to the rupture of the vessels with consequent hemorrhage. We have found the same vascular lesions in experimental hemorrhagic pancreatitis produced by the injection of irritants into the pancreatic ducts of dogs, following the procedure of Opie[2] and Flexner[3]; and we have determined experimentally that this vascular necrosis is the direct result of the action of pancreatic juice upon the

1 Achalme, *Ann. Inst. Past.*, 1901, **15**, 737.

2 Opie, *Johns Hopkins Hosp. Bull.*, 1901, **12**, 182.

3 Flexner, *Univ. of Pennsylvania Med. Bull.*, 1901-2, **14**, 193.