

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.

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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 Opie² and Flexner³; 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.

walls of the vessels, and that the agent in the juice responsible for the necrosis is trypsin. Pancreatic juice, or pancreatic trypsin freed from lipase, when injected subcutaneously produces in the vessels at the site precisely the same vascular necrosis with hemorrhage as that which occurs regularly in hemorrhagic pancreatitis, and when trypsin is injected into the pancreas hemorrhagic pancreatitis results. The activation of trypsinogen by enterokinase is not necessary for the production of the vascular necrosis, for pancreatic juice obtained by cannulating the pancreatic duct outside the duodenum produces local vascular necrosis and hemorrhage when injected into the subcutaneous tissue. We have not yet determined precisely what it is that serves to activate trypsinogen when it is injected into the tissue. It is, however, clear from our experiments that if pancreatic juice escapes about blood-vessels in the substance of the pancreas, necrosis of the vessels with hemorrhage (hemorrhagic pancreatitis) can occur.

Study of the pancreas in our unselected routine autopsy material has revealed an unexpected frequency of duct obstructions caused by concretions and by the type of epithelial metaplasia described by Baló and Ballon.⁴ Localized dilatations of the ducts and acini behind these obstructions, and the rupture of the thin-walled, dilated acini is not at all uncommon in our routine material. If the juice escaping from such ruptured acini flows about arteries, necrosis of their walls with resulting hemorrhage may occur, leading to widespread or to localized hemorrhagic pancreatitis depending upon the size of the vessels affected and the degree to which their walls are damaged by the escaping trypsin. If no arteries are present in the immediate vicinity of the rupture, localized fat necrosis, produced by the lipase, may be the only result, and this is most frequently the case in our material. That hemorrhagic pancreatitis can result from certain conditions which do not involve duct obstruction there is no question, but we believe that the rupture of acini dilated as a result of obstruction plays a rôle in the pathogenesis of hemorrhagic pancreatitis more frequently than has been appreciated. We have found histological evidence of obstruction in nearly 50% of our cases of hemorrhagic pancreatitis.

It is of interest that by means of the local injection of trypsin or of pancreatic juice we have been able to produce in the arterioles of the pancreas and of the subcutaneous tissue a lesion which is identical histologically with the familiar hyaline arteriolosclerosis which, in the human being, commonly occurs diffusely in association with

⁴ Baló and Ballon, *Arch. Path.*, 1929, **7**, 27.

hypertension and arteriolosclerotic nephritis. We are attempting to determine whether generalized hyaline arteriosclerosis can be produced by repeated injections of trypsin, and whether the proteolytic enzymes of bacteria are able to cause this lesion.

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Spinal Anesthesia in Winter Frogs.*

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In a previous communication¹ a simple method for producing spinal anesthesia in the frog was described. In addition, a series of 10 local anesthetics were studied in summer frogs, kept at temperatures of from 26° to 29°C. The data obtained on each drug included the determination of the minimal anesthetic dose, minimal lethal dose, duration of anesthesia produced by a sublethal dose, and the calculation of a therapeutic coefficient from the fraction M.L.D./M.A.D. Comparatively, this coefficient gives evidence of the usable therapeutic range for each local anesthetic.

In this paper similar results are described in which 7 local anesthetics were injected intraspinally into winter frogs kept before, during and after the experiments at 10° to 12°C. This series includes those local anesthetics showing, experimentally, the best possibilities for use in human spinal anesthesia. Five of these drugs had been studied previously in summer frogs, but because of the relatively high temperature prevailing at that time, it was thought advisable to repeat the work at a lower temperature and perhaps a more satisfactory one for frogs. Because of great variations noted in frogs, which are ascribed to seasonal and temperature changes, a further check on uniformity was attempted by carrying out the complete series during two winters. Consequently the first series was carried out between October 10, 1931, and February 20, 1932, and the second, between the same periods of 1932-33. As can be seen from the table no great variations are to be observed between the 2 series. It might also be added that the results obtained on winter frogs

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¹ Bieter, R. N., Harvey, A. M., and Burgess, W. W., *J. Pharm. and Exp. Therap.*, 1932, **45**, 291.