had apparently healed within 24 hours. Altogether, 40 eyes were healed at the end of 6 days. In 6 eyes (13%) the inflammation persisted up to 17 days. A hypopyon appeared in only 5 eyes (11%) and in none did the cornea rupture. In 40 eyes (87%) the resultant scar did not exceed 2 mm in diameter.

In the second group of 82 eyes, in which treatment was begun 18 hours after inoculation, the course was usually more severe and the outcome less favorable. The maximum inflammation appeared later and the duration was more prolonged, being over 7 days in 37 eyes (45%). A hypopyon was present in 27 (33%) and the cornea ruptured in 7 (8.5%). The resultant scarring was generally more extensive than in the first group. In 28 eyes (34%) it did not exceed 2 mm in diameter, but in 20 eyes it exceeded 7 mm.

In 82 control eyes the infection occurred in the form of a rapidly progressing superficial ulcer, or less frequently as a ring abscess. A hypopyon, usually large, appeared in 62 eyes (75%) and the cornea ruptured in 46 (56%). The duration of inflammation ranged from 7 days in a few cases to as long as 3 weeks. There were no instances of panophthalmitis. The resultant scar occupied over half the cornea in 72 eyes and in all but 8 of these virtually the entire cornea was involved.

It may be concluded, therefore, that sulfapyridine had a significant effect in the prophylaxis and treatment of experimental pyocyaneus ulcer.

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Pathological Changes in the Gallbladder Wall Due to Action of Bile.

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For a long time the local cytotoxic effect of bile and many of its components on tissue has been recognized. With the exception of the more resistant and adapted mucosa of the intestinal tract and the excretory ducts of the biliary tract, there are few instances in which the production of cellular injury does not occur when bile comes in contact with such tissue. This local action is

to a large extent dependent upon the concentration of the bile or the several components of bile. For the most part it presents itself as edema, increased capillary permeability with extravasation of blood and direct tissue necrosis with fibroblastic proliferation and round cell infiltration chiefly of the monocytic series. This can be easily demonstrated when bile of various concentrations is injected intramuscularly or subcutaneously and the tissue studied at various time intervals.

Because of the failure of a purely bacteriological explanation of the etiology of cholecystitis to satisfy many of the experimental and clinical aspects of this disease, it has occurred to us that the local effects of bile might be of importance in this condition. That bile may act in this capacity in the production of cholecystitis has previously been suggested by Aronsohn and Andrews[1] and by Ravdin[2] and his co-workers. These investigators injected bile or bile salts into the gallbladder through the cystic duct or common duct and observed acute inflammatory changes in the wall. Cole[3] observed changes in the gallbladder wall following partial cystic duct obstruction. Because of the fact that acute cholecystitis is very rarely seen in the absence of cystic duct obstruction, it occurred to us that this factor must also be considered in the etiological aspects of this disease.

Accordingly, cystic duct obstruction with the injection of bile and several of its components was attempted. The animals were treated by ligation of the cystic duct, ligation of the cystic duct with replacement of the gallbladder bile by an equal amount of physiological salt solution and replacement of gallbladder bile by various concentrations of dog bile, commercial dried bile, cholesterol emulsions, sodium glycocholate and sodium deoxycholate with and without cystic duct obstruction. All injections into the gallbladder were made through the cystic duct in order that there should be no mechanical trauma to the gallbladder wall. In order to eliminate this mechanical trauma further that portion of the gallbladder adjacent to the liver was studied in detail giving an area of tissue far removed from any site of trauma. The animals were sacrificed at various intervals ranging from 24 hours to several months. Fifty dogs and 14 rabbits were used. Because of the closer resemblance of the dog's gallbladder to that of the human it its function and in the type of bile present, this animal

1 Aronsohn, H. G., and Andrews, E., *Surg., Gyn. and Obst.*, 1938, **66**, 748.

2 Markowitz, J., *Textbook of Experimental Surgery*, William Wood and Co., Baltimore, 1937, p. 264.

3 Cole, Warren H., personal communication.

was considered best suited for such a study. The results that we wish to report may be summarized as follows.

(1) With occlusion of the cystic duct after the gallbladder has been emptied and washed of bile and the lumen filled with physiological salt solution no pathological change of importance was noted in the gallbladder wall.

(2) Occlusion of the cystic duct without disturbing the contents of the gallbladder resulted in a moderate amount of edema, round cell infiltration and fibrosis of the gallbladder wall.

(3) Occlusion of the cystic duct with replacement of the gallbladder bile by a solution of commercial dried bile resulted in the various degrees of inflammation that are encountered clinically in cholecystitis depending, however, upon the concentration of the bile solution. Where this concentration was as great as twice that of normal gallbladder bile, complete necrosis of the gallbladder was often encountered. If the cystic duct was not occluded the observed changes were slight and for the most part transient.

(4) When concentrated dog's bile was used a similar change was encountered which likewise seemed to be dependent upon the concentration of the bile. Where this concentration was as great as twice that normally seen, complete necrosis of the gallbladder wall was often encountered. At times where such necrosis was not seen there was often seen either a precipitation in the form of small dark granules of portions of the bile solids or there was an extraordinary out-pouring of mucus with mucus gland hyperplasia on the part of the gallbladder epithelium.

(5) Similar types of reaction have been given by many components of bile. Among those studied have been sodium deoxycholate, sodium glycocholate and cholesterol emulsions with various concentrations as well as cholesterol dissolved in gallbladder bile. These reactions have not all been identical in degree, sodium deoxycholate being the most destructive often resulting in gangrene.

(6) Studies of human gallbladders removed at operation show inflammatory changes identical to the ones that we have produced experimentally in dogs.

From these studies we may conclude that while cholecystitis may be the result of primary bacterial invasion in certain instances it may also occur as a result of cystic duct obstruction, the intensity of the inflammation being dependent upon the composition of the bile imprisoned. This inflammatory process may also be modified by certain protective mechanisms on the part of the gallbladder epithelium and by secondary bacterial invasion.