traumatization. In about 20% of the cases, however, it is not possible to introduce the catheter successfully into the gall bladder without special manipulation. If the catheter encounters any great resistance about 6-8 cm. from the opening in the duct, it is fairly certain that it has entered one of the hepatic ducts. The catheter should then be withdrawn, and the particular hepatic duct clamped off. This procedure usually allows the catheter to proceed in the right direction, *i. e.*, into the gall bladder.

Control experiments were run to show that the technique of this operation does not produce any reaction or traumatization in the gall bladder. In some cases, bile was aspirated and nothing was injected, while in others saline was injected through the catheter as a control. In all instances, there was a complete absence of reaction in the gall bladder.

In summary, this operation can be accomplished in 60-70% of the cases without any traumatization, as the technique is quite simple. In 20% of the cases, there is necessary a special skill on the part of the surgeon which, too, can be quite readily mastered. The operation cannot be accomplished in only a very few per cent of cases, in which the common duct is too fine for even the smallest catheter to be introduced.

8207 P

Studies on Non-Bacterial Cholecystitis. Protein Injection into Gall Bladder and Reaction of Gall Bladder in Anaphylaxis.*

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In spite of the previous failure to find a correlation between the nitrogen content of the gall bladder and cholecystitis, it was thought advisable to approach the matter experimentally by increasing the nitrogen content and observing the effects. This was done by the injection of egg albumen.

Fifteen dogs were operated upon. The egg albumen solutions used were first the undiluted white of egg and second, a 6% solution in Ringer's of crystalline purified egg albumen. They were injected either directly into the gall bladder cavity or into the wall. In 9 of

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the 15 cases the introduction was done by means of a needle puncture and in 4 cases a catheter was introduced into the gall bladder through an opening in the common duct and the material introduced through this. In some instances either the common or cystic duct was ligated and in others the gall bladder was allowed to remain patent. The amount of egg albumen solution used was 6 cc. in every instance. Before the introduction of this material 6 to 10 cc. of bile were aspirated from the gall bladder. When the injection was made into the wall of the gall bladder, 6 or 8 different spots were injected with about ½ cc. either subserously or into the deeper layers. The dogs were electrocuted in 48 hours and cultures and sediment tests of the bile made as well as microscopic examinations of the gall bladder.

Thirteen of the 15 gall bladders showed active recent inflammatory processes in the wall. These were characterized by edema, fibrinous exudate and hemorrhage. The gall bladder contained thick, deep green bile clouded with large bile-stained albumen flakes. Histologically, in all of the cases inflammatory reaction was present. This was much more pronounced in the outer layers. The most constant finding was a marked edematous thickening of the serosa with round cell infiltration which was not so marked. The lymphatics were often greatly dilated and fibrinous deposits in and over the serosa were frequent. The mucosa was normal while a minimal round cell infiltration was seen in the muscularis. This histological picture resembles that described in man by Boyd,[1] Graham,[2] Feinblatt,[3] Andrews,[4] and Denton[5] much more closely than does cholecystitis produced by bacterial infection, although the picture is not as extreme as the experimental chemical cholecystitis produced by other agents to be reported later. That this reaction in the gall bladder is not due merely to the local mechanical effects of the needle puncture is obvious when one considers that the same results were obtained on the free surface or when the puncture was made through the hepatic surface or even when the material was introduced through a catheter in the common duct. Similarly the effects were not due to duct ligation alone since the same results were obtained in other instances where the connection was left patent.

The possibility was considered that this is an anaphylactic reac-

[1] Boyd, Textbook of Surgical Pathology.

[2] Graham, Diseases of the Gallbladder and Bile Ducts.

[3] Feinblatt, H. M., *New England J. Med.*, 1928, **109**, 1073.

[4] Andrews, E., *Trans. West. Surg. Assn.*, 1934.

[5] Denton, T., *Arch. Surg.*, 1927, **14**, 1.

tion and for this reason 2 dogs were given intravenous injections of egg albumen previous to the time of operation. The local reaction to egg protein, however, remained unchanged. Furthermore, other animals received 2 injections into the gall bladder after 3-day intervals and the effects observed were no greater than one would expect on a purely additive basis.

These experiments seem to indicate that the reaction obtained by injection of protein into the gall bladder is not anaphylactoid in character. Clinical observations, however, suggest the possibility that in man a reaction may occur on the biliary system based on an anaphylactoid condition.

Alvarez[6] has recently described 4 cases in which pain, apparently in the gall bladder, was due to an anaphylactic response against certain foodstuffs (chicken, milk and eggs), omission of these from the diet affording relief. A series of cases of very similar nature has recently been observed by Croutch.[7] However, the specific anaphylactic reaction of the gall bladder has never, as far as we know, been produced in the experimental animal. For that reason, the following experimental observations may be of interest:

Each of 3 dogs received 4 intravenous injections of crystallized egg albumen within a period of 3 days, each injection consisting of 5 cc. of a 6% solution. No particular reactions were observed either during or after these injections. After an interval of 6 days, there was injected again a 6% solution of the same crystallized egg albumen, but this time in much larger quantities, sufficient to produce visible and marked anaphylactic response. In 2 of the animals, the reaction consisted of vomiting, trembling, irregular respiration, and passage of feces, while in the third dog, the response was considerably more pronounced, with vomiting, loss of consciousness, cessation of respiration for 3 minutes, and generalized convulsions. The quantity of the last injection was 15-20 cc. in the first 2 dogs, and 25 cc. in the last. The animals were electrocuted one-half hour following the last injection, and post-mortem examination made immediately. In all 3 cases, there was found a marked edema of the gall bladder wall, more specifically of the serosa. The thickness varied from 3 to 6 mm. Microscopic examination of the liver revealed markedly constricted arterioles.

As a control experiment, egg albumen was injected in large amounts into 3 other dogs, which had not, however, received any

[6] Alvarez, W. C., *Proc. Staff Meetings of the Mayo Clinic*, 1934, **9**, 45.

[7] Croutch, personal communication.

previous injections. In 2 of these animals, no symptoms were visible until 40 cc. had been injected, while after 45 cc. the reaction was marked but consisted only of vomiting and passage of feces. In the third dog, these symptoms were not present until the injection of 60 cc. Electrocution was performed one-half hour later, and this time post-mortem examinations revealed perfectly normal gall bladders. A comparison of the results in the 2 series of animals leads us to the conclusion that the reaction obtained after the last injection in the first series was an anaphylactic response, since it required much less albumen to produce a response in the previously sensitized dogs than in the control animals. Furthermore, the constriction of the arterioles in the liver in the first series of animals is suggestive of anaphylactic change.

8208 C

Effects of Phenacetin and Aspirin Respectively upon Action of Phenobarbital.

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Some practical advantages of combining an analgesic with a hypnotic drug have been suggested by the work of Loewe and others. In particular, Käer and Loewe[1] investigated the hypnotic and toxic effects of members of 2 different analgesic groups in combination with barbital, namely, aspirin and phenacetin.

Aspirin was found to antagonize to a similar extent both the hypnotic and toxic effects of barbital. Phenacetin, on the other hand, while also antagonizing the toxic effects of barbital, appeared to enhance the milder hypnotic effects of the latter drug. This would suggest a better "therapeutic ratio" for a mixture of barbital and phenacetin than for barbital alone. In addition, such a mixture would have the additional therapeutic advantage of supplementing the hypnosis with analgesia.

We have completed an investigation along this line in which aspirin and phenacetin have respectively been used in combination with another member of the barbiturates, namely phenobarbital.

Rats were used as experimental subjects. The animals were

[1] Käer, E., and Loewe, S., *Arch. f. exp. Path. und Pharm.*, 1926, **116**, 140; 1926, **118**, 108.