

TABLE I.

Injected Solution	pH	Result
1. Sod. desoxychol. 10, 8%	pH after adjust. with 0.1 mol. citr. acid:	7,3 severe cholecystitis
2. " " 9%		7,2 " "
3. Cholic acid 12, 6%		7,8 medium "
4. " " " 5%		7,4 " "
5. Purif. B. S. 15%	pH without adjust. •	5,7 moderate "
6. " " 15%		5,7 " "
7. Citric acid-NaOH	1 M. citric acid adjust. with NaOH 10%	7 normal gallbladder
8. " " "		7,4 " "

than 10, cause a gangrene of the gall bladder wall. 2. When an acid solution at pH 3 is injected into the empty gall bladder and bile through patent ducts is allowed to reenter the gall bladder, the buffering action of this bile is sufficient to convert the acid bile mixture into a harmless solution. 3. The toxicity of bile salts on the gall bladder wall is not changed by adjustment to the pH of gall bladder bile previous to injection. 4. Citric acid solution, in concentration even higher than that used for the adjustment, does not affect the gall bladder wall.

*Conclusion.* The toxic action of the bile salts on the normal gall bladder is not affected by alteration of the pH unless it exceeds the normal pH range of gall bladder bile.

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## Relative Toxicity of Different Bile Salts on the Normal Gall Bladder.\*

EDMUND ANDREWS AND HANS G. ARONSOHN.

*From the Department of Surgery, The University of Chicago.*

In a previous publication<sup>1</sup> we have shown that an experimental increase of the bile-salt concentration in the bile produces changes in the gall bladder wall similar to "human cholecystitis" Sixteen experiments had been performed, using "commercial bile-salts" (Armour and Company), and so-called "purified bile-salts", *i. e.*, the commercial variety freed from non-alcohol soluble impurities by alcohol precipitation. The latter proved the more effective prepara-

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<sup>1</sup> Andrews, E., and Aronsohn, H. G., *loc. cit.*

tion of the two. The technique employed consisted of the retrograde introduction of a fine ureter catheter into dog's gall bladders through an opening in the common duct and introduction of the bile-salt solution through this catheter.<sup>2</sup>

To elucidate this action further, we have made a more thorough investigation using different bile-salt fractions. The following results were obtained from 55 additional experiments:

The process of hydrolyzing increases rather than decreases the effectiveness of the bile salts. While a 20% solution causes a tremendous reaction on the gall bladder wall, a concentration as low as 8.7% still produces a marked effect. Two cases of bile peritonitis occurred in this group.

In a series of 13 experiments, a special study was made of Na desoxycholate. This proved to be the most powerful fraction, a concentration of 15% causing gangrene of the gall bladder wall, bile peritonitis, or even death, while even a concentration of 7.5% gave a marked reaction. Cholic and apocholic acid are slightly weaker in their actions than desoxycholic acid, apocholic being the stronger of the two. Positive reactions were obtained with 7% apocholic acid, while higher concentrations of cholic acid were necessary to produce similar changes. Glycocholic acid, on the other hand, has much less effect on the gall bladder wall than the fractions described above. An 8% solution yielded a normal gall bladder regularly, a reaction being obtained only with a 13% solution. Injection of taurocholic acid, obtained by evaporation of dog bile to about one-third of its volume, however, gave strongly positive results, *i. e.*, bile peritonitis and death accompanied by a marked change in the gall bladder wall. For the sake of completeness, we

TABLE I.

Fraction	No. of Exp.	Reaction
1. Desoxycholic acid	13	Severe reaction; gangrene of gallbl., bile peritonitis and death.
2. Apocholic and cholic acid	17	Same
3. Conc. dog bile (taurocholic acid)	4	Severe cholecystitis, bile peritonitis and death.
4. Hydrolyzed bile salts	6	Severe cholecystitis and death.
5. Purified " "	4	Same
6. Commercial " "	12	No death. Bile peritonitis and cholecystitis.
7. Glycocholic acid	9	Cholecystitis occasionally on high concentration, mostly normal gall bladder.
8. Decholin (dehydrocholic acid)	6	Normal gall bladder.

<sup>2</sup> Aronsohn, H. G., and Andrews, E., PROC. SOC. EXP. BIOL. AND MED., 1935, 32, 1629.

examined the action of Decholin (Dehydrocholic acid), which is used in the medical management of human cholecystitis. A 20% solution can be injected into the dog's gall bladder without producing a marked reaction in the gall bladder wall.

Table I shows the different fractions in decreasing order of their toxicity.

Grossly, the changes involve mainly the outer layers of the gall bladder wall. The usual findings were thickening of the wall, especially the serosa; thick fibrinous membranes, with fresh adhesions to the surrounding organs, duodenum and liver; and a serous or seropurulent exudate around the gall bladder. Bile peritonitis, either localized around the gall bladder, or a diffuse form without visible perforation of the gall bladder wall, was often seen. On microscopic examination, edema of the serosa was found with great regularity. In addition, the serosa, covered with a fresh fibrinous exudate, showed hyperemia, hemorrhages, dilatation of lymphatics, and round-cell infiltration. These changes were regularly found in those gall bladders which had been diagnosed as pathological on gross examination. There were no qualitative differences found in the appearance of the gall bladders after injection of the various fractions, the only differences being quantitative. There was, however, some difference in the character of the reaction produced by desoxycholic acid. In this case, apparently all of the layers were involved, there being leucocytic infiltration and hyperemia in the mucous membrane and muscular layer as well as in the serosa. It cannot be decided from the anatomical appearance whether this involvement of the inner layers was produced by secondary extension of the inflammatory process from the serosa to the muscular layer and mucous membrane, or by primary action on the latter.

We may conclude, in comparing the relative toxicity of different bile salts on the normal gall bladder wall, that desoxycholic acid has the strongest action.