

THE PRODUCTION BY CHEMICAL MEANS OF A SPECIFIC CHOLECYSTITIS

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AN ACUTELY inflamed gall-bladder was found in a dog that had been injected intravenously with a solution of chlorinated soda (Dakin's solution). Further investigation showed that this occurred in a high percentage of instances. Many experimental investigations have been made of the condition of cholecystitis, in all of which bacteria have been employed in some manner or other. The present investigation of a chemically produced cholecystitis was carried out, not because of the possibility of its having any direct bearing on the condition as it occurs in man, but because it offered an opportunity to observe the production by a chemical, of an inflammation of a particular organ. Facts have been ascertained with regard to this phenomenon as follows:

Animals Used.—The solution was injected into dogs, cats, and rabbits, the most successful experiments were conducted on dogs. While definite gall-bladder changes were produced in a few cats, on the whole, they were not satisfactory animals to work with, because the solution is more toxic to this species. Carrel has noted that the intravenous injection of the chlorinated soda solution in rabbits produces marked toxic action and this was our experience also; thus they were of no value for this investigation.

Amount of Solution Necessary to Produce the Reaction.—From 5 to 12 c.c. for each kilogram must be injected. If less than 5 c.c. are injected, the gall-bladder is rarely affected, and if more than 12 c.c. are injected, the general effect of the solution may kill the animal. In most of our experiments from 8 to 10 c.c. were injected.

Time After Injection Necessary for the Gall-bladder to Be Affected.—The inflammatory reaction of the gall-bladder seems to occur almost immediately after injection, and is certainly completed within the first twenty-four hours. As a matter of fact, if the gall-bladder of an anesthetized dog is under observation and an intravenous injection of the solution is made, quite frequently it is possible to see the beginning injection of the blood-vessels, their rupture, and the infiltration of the tissues with blood. Well-marked gall-bladder reactions have been noted in a cat and in dogs within one-half hour after the injection of the solution into the blood-stream.

Route Taken by the Solution to the Gall-bladder.—It was at first thought that the chemical producing the reaction was excreted in the bile and thus reached the gall-bladder. This was shown not to be true, however,

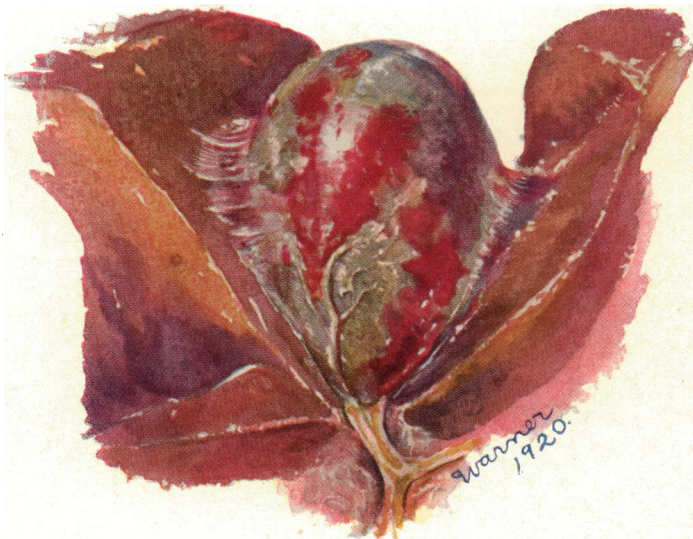


FIG. 1.—Drawing of a specimen of a gall-bladder two hours after the injection of chlorinated soda solution. Note the marked acute inflammatory reaction produced.

CHEMICALLY INDUCED CHOLECYSTITIS

because (1) the time at which the reaction occurs after injection is too short; (2) it is possible to observe the early stages of the reaction, and (3) in some animals the cystic duct was securely ligated and the gall-bladder changes took place after the injection, as when the cystic duct was patent. There can be no doubt that the chemical reaches the gall-bladder through the blood-stream.

The Chemical Substance Producing the Reaction.—The exact chemical in the solution which produces the reaction has not been determined definitely. Some of the evidence points to the chlorin. For instance, the solutions in which the available chlorin is less than 0.48 per cent., seldom produce any reaction on the gall-bladder. In several experiments chlorin water was injected. This solution is so toxic, however, that but little of it can be injected intravenously without causing the immediate death of the animal. If such a small amount were injected that the animal lived the gall-bladder was not found to have been affected. If larger amounts were injected, the animal invariably died in a short time. In one or two instances, a medium amount was reached and a few slight changes in the gall-bladder were noted. It would seem from this that the chlorin may be the active chemical agent, but the fact that the number of positive results obtained by different samples of the chlorinated soda solution was variable, seems to indicate that other factors were involved besides the chlorin. For example, with two solutions of practically the same chlorin content, one may give 100 per cent. gall-bladder reactions, while the other produces little or no effect.

The Involvement of Other Organs by the Solution.—The injection of the solution, of course, produces effects other than changes in the gall-bladder. Quite often a certain amount of nephritis may occur, and congestion of the liver has been noted. In a few instances, it was noted that the blood-vessels on the surface of the liver were injected in a manner similar to those of the gall-bladder. This was particularly true in cats, in which species these blood-vessels are sometimes quite prominent. None of the other changes appear prominently at necropsy and they certainly do not appear to differ essentially from the changes caused by the injection of some other toxic agents.

The outstanding feature usually noted at necropsy is the inflammation of the gall-bladder, which is not noted after the injection of other substances. For this reason it may be concluded that a specific chemical cholecystitis is produced, although the specific reaction seems to be on the blood-vessels on the surface of the liver and is most marked on the surface of the gall-bladder because that is more vascular.

Relation of the Blood Supply of the Gall-bladder to the Reaction Occurring After Injection.—Whether or not the gall-bladder is affected by the solution depends on several factors, one of the most important of which is the blood supply. A gall-bladder that does not have a good blood supply, particularly blood-vessels coming directly from the liver, rarely

has shown changes following injection, while a gall-bladder with a generous supply of blood-vessels from the liver that anastomose over the surface of the viscus has usually shown very marked changes. It has also been observed that gall-bladders of animals not in good condition, as those having distemper, usually develop few or no changes following injection.

Gross Appearance of the Acutely Inflamed Gall-bladder.—The gross appearance of the gall-bladder within the first twenty-four hours after the injection of the solution is that of intense inflammation. The lesions start at the fundus of the gall-bladder and on the exposed surface, usually at the point where the blood-vessels arising from the vessels in the liver on each side anastomose. The dilatation of the lymphatics usually is the first change noted after injection. The lymphatics of the gall-bladder become very prominent and are soon colored with the blood contained in them. These lymphatics can readily be traced in their course to the adjacent lymph-nodes. The reaction is not altogether specific for the blood-vessels of the gall-bladder; because the liver is shown to be also affected by the fact that the lymphatics draining the various lobes are somewhat injected, but not to so marked a degree as those of the gall-bladder. A breaking down of the small capillaries follows with a transudation of the contained blood, making minute petechiæ, which may gradually spread and involve the whole surface of the gall-bladder. At first these areas into which the blood has escaped from the vessels are red; changes then take place and most of the areas turn dark green and the entire gall-bladder has a gangrenous appearance. The organ becomes so tense in many instances that rupture seems imminent. There is usually very little, if any, œdema and adhesions to the omentum or other organs rarely form. The reaction seems to localize to a marked degree; seldom it has been seen to extend beyond the gall-bladder and cystic duct. The common and hepatic ducts do not seem to be involved in the reaction.

Microscopic Appearance of the Acutely Inflamed Gall-bladder.—The acutely inflamed gall-bladder shows first a marked breaking of the capillaries and infiltration of the wall of the gall-bladder. There are two areas of infiltration; in one the capillaries between the muscle and the serous coats are mainly or wholly affected and blood escapes and infiltrates between these two coats. In the other area the capillaries within the muscle coat are mainly affected, and the infiltration takes place between the bundles of muscle-fibres. At times this infiltration is so extensive that the whole section appears to be a mass of blood. The mucosa has not been found markedly affected primarily. In some cases, however, small hemorrhagic cyst-like areas are produced just under the mucosa; a definite ulceration of the mucosa may later occur, draining the extravasated blood into the gall-bladder.

Chronicity of the Lesions.—The reaction of the acutely inflamed gall-bladder may last for several weeks. It has been noted five weeks after

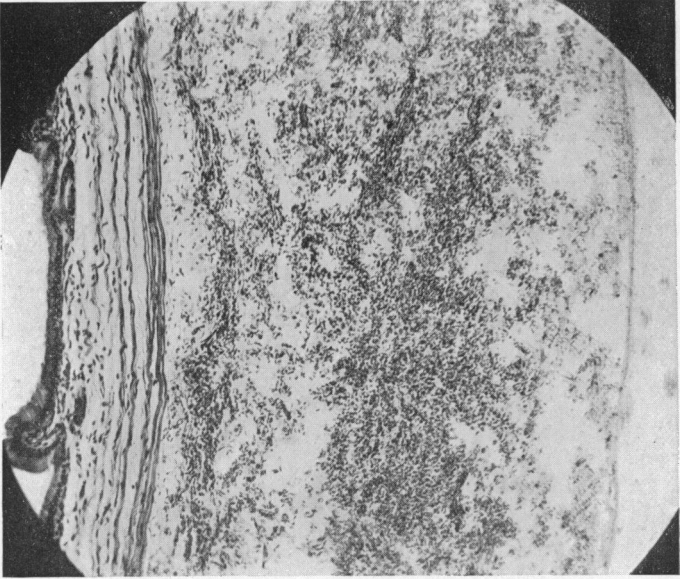


FIG. 2.—Photomicrograph of a section of the wall of the gall-bladder fifty hours after injection. In this case the infiltration of the blood took place between the serosa and the muscularis. This is the usual type of lesion produced. X100.



FIG. 3.—Photomicrograph of a section of the wall of the gall-bladder fifty hours after injection. The infiltration of the blood took place in the muscularis. X70.

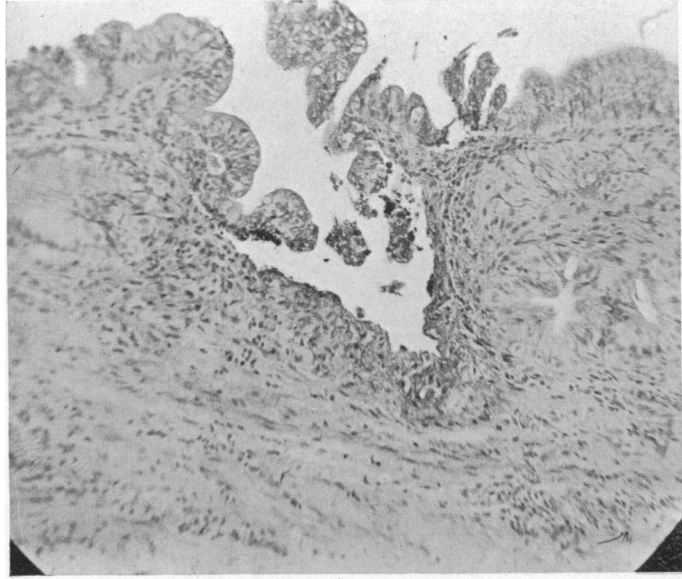


FIG. 4.—Photomicrograph of a section of the wall of the gall-bladder after injection. A small lesion of the mucosa has occurred. The base of the ulcer is infiltrated with blood in a manner similar though to less extent than is shown in Figs. 2 and 3. This type of lesion has rarely been noted. $\times 100$.



FIG. 5.—Photomicrograph of a section of the wall of the gall-bladder forty-three days after the production of the acute condition. The organization of the blood which had infiltrated in the muscle-wall is shown. $\times 50$.



FIG. 6.—A higher magnification of Fig. 5. Note the marked reaction which the intramuscular hemorrhage has produced. $\times 100$.

CHEMICALLY INDUCED CHOLECYSTITIS

injection that the gall-bladder had practically the same appearance as it had twenty-four hours after injection. Gradually the condition clears up, and in three months it may appear normal except for a few small white scars. In some cases, however, the condition becomes chronic. Although it has not been proved definitely, it seems as if the organs which apparently returned to normal were in animals in which the extravasation of blood took place between the serosa and muscle coat, while in those in which a definite chronic condition developed, the blood infiltrated the muscle coat. The end-result of these chronic lesions has not been studied fully.

In several experiments an exploratory operation twenty-four hours after injection showed a definitely inflamed gall-bladder; the animals are still alive and in good condition several months after the production of the acute lesion. It is hoped that these experiments will furnish material for a study of chronic gall-bladder lesions.¹

SUMMARY

It has been found that the intravenous injection of a solution of chlorinated soda in dogs produces a definite reaction of the gall-bladder in a high percentage of experiments. The reaction consists of a breaking down of the capillaries and infiltration of the wall of the gall-bladder with blood.

To produce the reaction in the gall-bladder it is necessary to inject relatively large amounts of the solution, at least more than 5 c.c. for each kilogram. The reaction takes place very shortly after the injection, and is completed within the first twelve to twenty-four hours.

The reaction is undoubtedly produced by some chemical in the solution; chlorin is suggested as the probable substance. All solutions, however, even though their chlorin content may be practically the same, do not give the same percentage of gall-bladder reactions; it would thus appear that a factor other than the chlorin content was involved.

The solution reaches the gall-bladder through the blood-stream and a gall-bladder in which the blood supply, particularly that coming from the liver, is generous, develops the most marked reaction. In some instances a definite chronic condition has followed the acute condition.

BIBLIOGRAPHY

Carrel, A., and Dehelly, G.: *Infected Wounds*. New York, Hoeber, 1917, 32.

¹ This observation probably has no bearing on the use of chlorinated soda solution in the treatment of wounds. The amount of such a solution necessary to produce the reaction in the gall-bladder would be so large that it does not seem probable enough could be absorbed from a wound to produce cholecystitis. It seems that the only condition in which a large amount of the solution might be absorbed is the treatment of acute empyema. We have injected quantities (5 c.c. per kilo) of the solution into the thorax of dogs daily for several days without producing a reaction in the gall-bladder. Our work in no way invalidates the legitimate use of the solution. Carrel has emphasized that it is very toxic when injected intravenously.