CHOLESTEROSIS OF THE GALL BLADDER *

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The wall of the gall bladder is structurally well adapted for absorptive purposes. The mucosa of the gall bladder is formed of tall, thin, villous structures, intricate in their extensive branching, and delicate in the supporting framework of the stroma. If anatomic structure is the result of physiologic need, then certainly this mucosa is well formed for the end in view, that of intensive absorption. Indeed, physiologists have agreed that the gall bladder is essentially an organ of concentration. Rous and McMaster have proved definitely that water is absorbed from the bile in the gall bladder, thus concentrating the latter six to ten times. Moreover, physiologists have demonstrated the absorption of solid matter through the wall of the gall bladder. In 1920, Harer, Hargis and Van Meter injected potassium sulfocyanid into the cavity of the gall bladder of dogs and recovered the salt in the cystic node within five minutes after injection, thus showing the passage of particulate matter from the lumen, through the wall and thence into the lymphatic structures of the biliary system. In 1921, Boyd, after injecting potassium ferrocyanid into the lumen of the gall bladder of dogs, obtained the Prussian-blue reaction in the epithelial cells of the mucosa and even in the connective tissue cells of the stroma of the wall within thirty minutes.

I have repeated the work of these investigators and obtained similar results. Finely powdered carmine powder, charcoal and India ink were also used in separate experiments. Solid particles of these were found in the lymphatic structures within a few minutes after the injection into the cavity of the gall bladder.

The passage of solid substances, thus demonstrated, lends weight to the opinions of Grigaut, Boyd, Dewey, Starling and Sweet who believe that lipoids such as cholesterol are absorbed by the epithelial cells of the mucosa of the gall bladder. On the other hand, many

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workers, notably Adami, Herter and Workman, believe that cholesterol is excreted by the mucosa. A parallelism is drawn between epithelial cells of various parts of the body and those of the mucosa of the gall bladder, and the presence of cholesterol crystals in epithelial structures is cited. For instance, such crystals have been found in the bronchi and their presence attributed to "excretion" of cholesterol by the epithelial cells lining the bronchi. They have been found in leiomyomas of the uterus and attributed to similar excretion there. But it seems more reasonable to believe that the cholesterol crystals found under these circumstances are the result of cellular disintegration, as the cholesterol found in arteriosclerotic patches of the aorta undoubtedly is.

The experimental data recorded here are positive evidence of actual absorption of lipoid material by the epithelial cells of the mucosa of the gall bladder. So far as I know there is no other experimental evidence substantiating this work, but numerous investigators have said that cholesterol is probably absorbed by the wall of the gall bladder. In March, 1924, at a staff meeting at the Mayo Clinic, I reported the following experimental data:

Laparotomy was performed on twenty-three dogs anesthetized with ether. Into the cavity of the gall bladder of four of the dogs, finely powdered carmine suspended in distilled water was injected through a fine hypodermic needle in amounts of 10, 15, 20 and 25 c.c. These animals were necropsied within five minutes after the injections and in each carmine was observed in the cystic node. Other similar experiments were performed, powdered charcoal and later India ink being used in each case, with the same recovery of particulate matter in the cystic node. Therefore it seemed justifiable to conclude, as had previous investigators, that the wall of the gall bladder is capable of absorbing solid substances as well as fluids.

These findings led to experiments with other substances. The absorption of fats by the wall of the gall bladder proved an inviting problem and the experiments were repeated, using lipoid substances instead of particulate matter. Dogs were anesthetized with ether, and highly emulsified Sudan-stained fat particles injected into the cavity of the gall bladder. But in no instance was microscopically demonstrable fat discovered in the cystic node, even several hours after the injection. However, fat-stained particles in fresh untreated sections were present in the epithelial cells of the mucosa of the gall bladder within a half hour after injection. And at varying intervals up to three hours, similar Sudan-stained globules were found in the connective-tissue cells of the stroma, and even in vascular endothelial cells. Similar observations were made by MacCarty in 1919 in a study of "strawberry" gall bladders. However, similar experiments with milk, olive oil and cholesterol esters were without success; in no instance was it possible to recover lipoid substances from the lymphatic structure of the wall of the gall bladder, even several hours after the injection.

However, the use of highly emulsified milk fat, deeply stained orange with Sudan III, produced astonishing results. Laparotomy was performed on anesthetized dogs and the fat-stained emulsion injected into the cavity of the gall bladder as in the previous experiments. Twenty-five minutes after the injection minute Sudan-stained globules were seen in the epithelial cells of the mucosa of the gall bladder, in otherwise unstained sections. And within one hour after injections these stained microscopic lipoids were seen as multiple, discrete masses throughout the epithelial cells, most numerous at the periphery of the cells, but present also at their base. In other sections, taken from the gall bladder of dogs necropsied two and three hours after injection, these tiny globules of previously stained fat were seen in the stroma and even endothelial lining of the blood vessels. Similar experiments, using cholesterol crystals dissolved in oleic acid, were not so satisfactory, but were sufficiently conclusive to verify the previous observations.

From these data, it was concluded that the wall of the gall bladder had the power to absorb lipoid substances, and that this absorption was effected, probably, by a direct passage of the lipoid through the epithelial cells of the gall bladder mucosa. Furthermore, it seemed likely that lipoid substances differed from particulate matter, in that they were not swept into the lymphatic stream, but were carried away through the blood vessels. At least, sufficient data were present to indicate that lipoid substances might pass through the wall of the gall bladder from its cavity.

The passage of lipoid through the wall of the gall bladder is probably a metabolic one, but our knowledge of the metabolism of lipoids is too indefinite to warrant any further speculation on this point. Suffice to say, physiologists are not in accord with the present theory of lacteal absorption of fats from the intestinal tract. Indeed, Mac-

Callum has proffered the suggestion that fats are probably absorbed directly by epithelial cells, and that this may be the method of their passage from the intestinal tract. However this may be, the factors concerned in such a passage are probably easily disturbed, and this disturbance would probably result in imperfect or incomplete passage of the lipoid through the wall of the gall bladder, with their resultant accumulation in the wall. Undoubtedly the lipoids would first accumulate in the epithelial cells of the mucosa, and later pile up in the connective-tissue cells of the stroma of the villi. Indeed, this is the characteristic picture of strawberry and papillomatous gall bladders on microscopic examination. The former shows the lipoid scattered diffusely over the surface of the mucosa, involving the distal or proximal portions of the epithelial cells and later the structure of the villi themselves. The papillomatous organ presents essentially the same picture, except that the areas of gross lipoid are localized in discrete polypoid masses.

However much we may be concerned with the direction of the passage of lipoid through the wall of the gall bladder, whether it passes from within the cavity into the wall, or vice versa, we cannot escape the fact that lipoids accumulate in the structures of the wall itself. Indeed, it is quite possible that the lipoid thus seen in the strawberry and papillomatous gall bladders is but an accumulation of cellular lipoid resulting from the degeneration of the cells themselves. It is difficult to believe such a contention, however, when one sees the relatively huge masses of lipoid that often distend the frail polypoid villi. It seems scarcely possible that such an amount of lipoid could come from the degeneration of the relatively few cells constituting their histologic structure.

Regardless of the method of accumulation, however, the fact is established that the gross appearance of the strawberry, fishscale and papillomatous gall bladders is due to lipoid substances piled up in the structures of the wall of the gall bladder, principally in the mucosa. MacCarty, in 1919, demonstrated that these lipoids are essentially cholesterin esters, and numerous observers have since verified this.

We are concerned, then, principally with an alteration in the cholesterol metabolism occurring in the wall of the gall bladder. The disturbance may be purely local, confined, so far as can be determined by our present methods, to the wall of the gall bladder itself.

That it is often associated with generalized disturbance in the fat metabolism of the body seems true.

In a study of 633 consecutive necropsies, in which I gathered the data myself, thereby reducing to a minimum the personal equation, 134 strawberry gall bladders, sixty-one papillomatous, and twenty-nine showing both conditions, were found. None of the persons was under fifteen years, and only three were under twenty; thus 34.7 per cent of adults showed this fat disturbance in the gall bladder. Also 21.6 per cent of the adults had gall stones, and 30 per cent of these also had fat alteration, making a total of 46.4 per cent of persons over the age of twenty that had some gross evidence of accumulated lipoid in the wall of the gall bladder. The lesion was found in 45.7 per cent of 150 consecutive men, whereas it was found in 53.9 per cent of women.

A majority of persons with fatty changes in the wall of the gall bladder also had fatty changes in other portions of the body. For instance, sixty-seven women had pathologic lipoid changes in the mucosa of the gall bladder. Fifty-eight of these (86.5 per cent) had been pregnant. It is well known that pregnancy is associated with fatty changes throughout the body, and that disease of the gall bladder frequently accompanies pregnancy. Likewise, the fat disturbance occurring in cases of obesity seems to be associated with the lipoid disturbance occurring in the wall of the gall bladder. In fifty-one necropsies, the subjects weighing over 200 pounds, 78.4 per cent had gross fatty changes in the wall of the gall bladder, and 94 per cent had abnormally large amounts of microscopic lipoid.

There is a slight increase in the frequency and amount of fatty changes in the liver in cases of lipoid disease of the gall bladder; the significance of this is not known. In 54.2 per cent of 315 cases in which there was no lipoid visible in the wall of the gall bladder, there were fatty changes in the liver, whereas in a series of 233 cases of strawberry and papillomatous gall bladders, fatty changes were present in the liver in 68.2 per cent. This is only a 14 per cent increase in the frequency of fatty changes in these cases, but the much greater extent and severity of the process was more striking.

That other organs in the body are concerned with these fatty changes is probable. It is known that certain organs contain relatively high proportions of lipoids, particularly the brain, adrenals, liver and blood vessels. Moreover, it is known that the cholesterin content of these organs varies considerably, and probably fluctuates from day to day. Certainly it is true that the cholesterol content of the blood and bile varies from hour to hour and can be readily influenced by fat food intake. It seems likely that the various organs of the body are influenced by the lipoid content of the blood, and therefore change their lipoidal content as does the blood.

To facilitate the study of lipoid changes in the body, and especially that of cholesterol metabolism, and to obviate the rather unscientific terms of "strawberry" and "fishscale" gall bladders, a term descriptive of these changes has been sought. Inasmuch as it has been proved that the lipoid disturbance seen in the strawberry gall bladder, and the similar conditions, fishscale and papillomatous gall bladders, is essentially a cholesterol one, and inasmuch as the cholesterol content of the brain, adrenal, liver and blood vessels at least, undergo quantitative changes, it seems advisable to select a name, scientific and universally applicable, that will be descriptive of such alterations. These conditions are fulfilled by the term "cholesterosis," which is formed from the Greek "kolesteron" and "osis," meaning respectively "cholesterol" and "dysfunction." Our present knowledge does not permit further speculation on the type of changes that occur in the fatty derangements of the body. But we know that the pathologic changes here referred to are concerned with cholesterol, and the word "cholesterosis" simply indicates this dysfunction without further commitment. Regardless of what future studies may reveal as to the mechanism of this dysfunction, we know that the disease is concerned with cholesterol, and so the term will always be appropriate.