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DISCUSSION.—DR. WALTER F. BECKER, New Orleans, La.: I have enjoyed these three fine papers on diseases of the gallbladder. Dr. Sparkman has emphasized that one of the most effective means of decreasing the mortality of gallbladder disease is to remove the calculous gallbladder in young patients before the development of certain complications. These complications are largely related to the advanced age of the patient and the advanced stage of the disease, and are to a considerable degree responsible for the deaths associated with gallbladder surgery. I wish to emphasize the extent to which this seems to be true of acute cholecystitis.

(Slide) Dr. Joseph Powell, Dr. Robert Turner and I have recently reviewed the Charity Hospital experience with 1,060 cases of acute cholecystitis. This slide shows the age in relation to the incidence of associated diseases. Note the greatly increased incidence of such diseases as arteriosclerotic heart disease, hypertensive cardiovascular disease, diabetes, etc., in the older patients.

(Slide) This is another chart relating to the age factor in acute cholecystitis. Patients more than 40 years of age comprised only 70 per cent of the material, but accounted for over 98 per cent of the deaths. The mortality rate in the group past 40 was thirty times as high as it was in the younger age group. Choledocholithiasis was twice as common in the group past 40. The compromise procedure of cholecystostomy was resorted to with much greater frequency in the older group. Perforation of the gallbladder was five times as common in the patients past 40; and the incidence of generalized bile peritonitis was eight times higher in the older patients.

(Slide) I agree with Dr. Massie that perforation of the gallbladder is an important complication of acute cholecystitis. This chart indicates the frequency of perforation of the gallbladder in the 679 operative cases of acute cholecystitis at Charity Hospital. The overall incidence of perforation of the gallbladder in this series was 9.3 per cent. We think this is a conservative estimate because it includes only those cases in which the operative note specifically described the presence of a gross defect in the gallbladder wall. In 21 cases there was free perforation with generalized bile peritonitis. The perforation was localized to the pericholecystic area in 30 cases, while in 14 cases the perforation was into an adjacent viscus, such as the duodenum or liver. One can only

speculate relative to the frequency with which gallbladder perforation occurred in the group of patients who were not operated upon, but we do know that one-third of the conservatively treated patients who died were proven at autopsy to have free perforation of the gallbladder with generalized bile peritonitis.

DR. JOSEPH M. DONALD, Birmingham, Ala.: I have enjoyed the excellent papers on gallbladder disease and wish to discuss briefly those of Dr. Sparkman and Dr. Massie. The title of Dr. Sparkman's paper immediately reminded me of a harrowing experience I had in 1949 with a young colored female, 23 years of age, suffering from gallstones and sickle-cell anemia. Without having previously been diagnosed as having sickle-cell anemia, this patient was admitted to the hospital for an elective cholecystectomy for gallstones which had apparently been causing symptoms for about two years. She gave a history of having been jaundiced on one previous occasion, but was not jaundiced at the time of operation. Laboratory examination showed a hemoglobin of 58 per cent (9 cm.) and a white cell count of 17,300. At the time of operation the gallbladder was found to be diseased and was filled with gallstones. The common duct was apparently normal and was not explored. The spleen was found to be quite small, measuring about one inch in diameter. A cholecystectomy and appendectomy were performed without difficulty. One unit of blood was administered during the operation. The day following operation, to my great surprise, the patient was jaundiced and her temperature was 103°. A few days later, when her anemia had increased, it suddenly dawned on me that I had better request examination for sickle-cell anemia. This was done and 85 per cent of the erythrocytes were found to be sickled. The patient was given further transfusions, which improved the blood picture. The jaundice disappeared in about ten days. It is believed that the operation, anesthetic, transfusion, or the combination precipitated the attack of sickle-cell anemia. The rather severe anemia occurring in a Negro patient and the finding of an atrophic spleen at the time of laparotomy should have directed our attention immediately to the probability of sickle-cell anemia. I recently learned that the patient became pregnant in 1953 and died from sickle-cell anemia at the age of 27.

In closing I would like to make one comment concerning Dr. Massie's excellent presentation. I recently treated a patient who had an acute free perforation of the gallbladder with bile peritonitis. At the time of operation I was surprised to find the cause of perforation to be due to an elongated, sharp pointed gallstone lying transversely in the gallbladder lumen with the sharp point of the stone sticking through the anterior wall of the gallbladder. There was no evidence of acute inflammation. This is the only time I have ever found such an explanation for acute perforation of the gallbladder.

DR. GEORGE G. FINNEY, Baltimore, Md.: I appreciate being allowed to say something since you have to see me up here all the time. I was very much interested in Dr. Burdette's paper. In 1944 my brother, Dr. John Finney, Jr., before this Association presented a series of cases of carcinoma of the gallbladder from the Union Memorial Hospital in Baltimore, over a ten year period up to 1941, and there were 18. In the succeeding ten year period at the same hospital there were 24 more cases which made a total of 42. During that same period of 20 years there were 1,920 operations for gallbladder disease and disease in the ducts, exclusive of carcinoma of the ducts and carcinoma of the head of the pancreas. That gave an incidence of approximately 1.8 per cent of carcinoma in this group of cases. It is interesting that at Johns Hopkins Hospital during the same 20 year period up to 1951, there were 2,303 operations for gallbladder disease and there were 49 cases of carcinoma, which makes an incidence of 2.5 per cent. It is also interesting in this series that about 73 per cent of the cases, when operated upon or coming to autopsy, showed evidence of spread of the disease of one kind or another as has been stated by Dr. Burdette.

In this series we know that there were 68 per cent of the cases that had gallstones, and I know that there was only one case that definitely did not have gallstones. Lord Moynihan, in his book on gallbladder disease published in 1904, stated "In cases of carcinoma of the gallbladder, 95 per cent have malignant change which is due to chronic irritation of gallstones." That statement may be open to question as to its complete accuracy. However, I would like to add a word to what has been said by all three of the essayists on this subject, that certainly if we know there are gallstones present it is probably better for the patient, no matter what the age, to get the gallbladder out. The only trouble with that statement is that it should be made to our medical conferees and not to a group such as this.

DR. JULIAN K. QUATTLEBAUM, JR., Baltimore, Md.: May I first express my appreciation for the privilege of the floor and say how much I have enjoyed these three papers. We recently have had

occasion to review cases of carcinoma of the gallbladder encountered at the Johns Hopkins Hospital since 1925 and up to the present. A number of these cases have been mentioned by Dr. Finney. There have been 67 such cases in the files at the Johns Hopkins Hospital since 1925 all of which have been proved either at operation or at autopsy. Analysis of these cases has brought out some interesting information of practical value, not the least of which has been the extremely lethal nature of the disease. In 11 cases in which no abdominal exploration was performed the average duration of symptoms, including two that had had symptoms for more than two years, was but eight months from the onset of symptoms until death. Diagnosis in these cases was made at autopsy.

The presenting symptoms of the disease, while usually insidious, were often acute. Twenty-two of the patients had had symptoms for less than one month prior to being first seen in our hospital, and nine had had symptoms for not more than one week. Only nine patients in the entire series had had previous symptoms suggesting biliary colic, despite the fact that in only two cases was there shown to be absence of stones from the biliary tree. Forty-nine patients, or 73 per cent of the series, had a palpable mass when first seen, and 35, or 54 per cent, had jaundice. Twenty-eight, or 42 per cent of the series, had both a palpable mass and jaundice. However, no direct correlation could be made between these findings and the length of survival of the patients having them. Laparotomy only, usually with biopsy or sometimes combined with a bypass procedure, was carried out in 31 cases in which the tumor was deemed inoperable. Cholecystectomy was performed in 22 cases, cholecystostomy in two, and right hepatic lobectomy in one case.

This last case was a 64-year-old diabetic woman thought to have acute cholecystitis. Hepatectomy was performed one week after cholecystectomy because of the known presence of residual tumor in the gallbladder fossa. The patient succumbed within 24 hours to shock which failed to respond to massive transfusions, glucose, pressor agents and cortisone. The overall operative mortality, that is to say patients not leaving the hospital alive, was 38 per cent. There were 56 cases operated upon and 34 are known to be dead. Seventeen additional patients are presumed dead, having been discharged with known residual tumor more than two years ago. Two cases have been lost to followup, one of which probably had residual tumor and one of which had a papilloma with early invasion removed by cholecystectomy in 1939. Three cases are known to be alive, one with residual tumor operated on four weeks ago. One is free of evidence of disease 26 months following cholecystectomy. One patient who had cholecystectomy for acute cholecystitis with hydrops on January 11, 1949; is the patient referred to by Dr. Rienhoff a few moments ago.

In his gallbladder was found a  $2 \times 3$  centimeter raised ulcerated carcinoma in the fundus on the side away from the liver, invading into but not through the muscularis. This patient was re-explored in the course of a ventral herniorrhaphy last Saturday, December 1, 1956, and no evidence of residual or recurrent tumor could be found. The only other patient known to have survived more than two years had cholecystectomy and removal of a common duct stone which was obstructing and causing jaundice. The gallbladder itself contained no stones, but had polypoid epithelial hyperplasia with one small area of anaplastic invasion of the muscularis. This patient lived nine years and three months, dying in a nursing home in Baltimore of heart disease not long ago.

The only common feature in the survivors for any length of time was the absence of involvement of the liver. Since 57 of our 67 cases had involvement of the liver when the tumor was first visualized, notwithstanding the fact that the duodenum and the hepatic flexure of the colon are often involved, it would seem necessary to include hepatectomy in selected cases of carcinoma of the gallbladder if one hopes to improve the survival rate.

DR. N. A. WOMACK, Chapel Hill, N. C.: I should like to comment on the subject so ably presented by Dr. Burdette. He has discussed the pathology of cancer of the gallbladder so clearly that one cannot help but agree with his findings. Only in the relationship between the presence of gallstones and cancer of the gallbladder has our experience been at variance.

A few weeks ago, Dr. Robert Zeppa and I presented a study at the meeting of the Southern Medical Association in which we described our efforts at the experimental production of gallbladder cancer in mice, not only by the insertion of stone fragments from a patient with cancer of the gallbladder, but by the use of more classical carcinogens as well. Approximately 165 of these mice were observed for a year or more after treatment and then sacrificed. We were unable to find a single incidence in which cancer had been induced in the gallbladder, although there was one animal in which the adjacent transverse colon presented adenocarcinoma.

It is unwise to transfer observations on carcinogenesis from animal to man without some qualification. Nevertheless, it did seem to us that perhaps stones alone were not the only factor involved in the pathogenesis of gallbladder cancer, and that it might be well to review clinical statistics with greater concern related to the bias in the way such data were studied. Where guilt is to be decided by association there must be no prejudice in the way data are collected and studied, and the mathematical probabilities must be overwhelming before firm conclusions are drawn.

By utilizing autopsy figures assembled from various authors, the probability of the development of gallstones with each successive decade was determined. In childhood, of course, stones are uncommon and, when present, are usually bilirubinate in type. Following puberty, cholesterol stones begin to make their appearance with a frequency increasing with each successive decade in an almost direct relationship. By the time the ninth decade is reached, approximately 48 per cent of women will possess stones in their biliary tract. The same relationship holds in the male, but not to such a high degree.

If we now examine the probabilities for the development of cancer of the gallbladder in a random population, we note that the frequency drops after the seventh decade rather than continues to rise as one would anticipate if there were a dominant and direct etiologic relationship with stones. This does not suggest, therefore, a very strong cause effect association.

If we now factor the probabilities of the development of cancer of the gallbladder against the probability of development of stones, it becomes less than 0.5 per cent, again, not a very strong cause effect relationship.

Such observations do not, of course, exclude the possibility of stones acting in a promoting fashion in the development of gallbladder cancer. They do suggest, however, that the role is not a dominant one, hardly warranting the removal of the gallbladder in cases of stones, for this indication alone.

DR. ROBERT S. SPARKMAN, Dallas, Texas (closing): I would like to thank the several discussants but have nothing further to add.

DR. J. ROBERT MASSIE, JR., Richmond, Va. (closing): I too would like to thank those who discussed these papers.

DR. WALTER J. BURDETTE, St. Louis, Mo. (closing): I wish to thank Drs. Finney, Quattlebaum and Womack for their discussion. Although I would agree with Dr. Womack that all cases of carcinoma of the gallbladder cannot be explained by antecedent gallstones, there is a significant correlation between cholelithiasis, and the occurrence of carcinoma which cannot be denied. The relative decline in incidence of carcinoma in older age groups which Dr. Womack mentions may possibly be explained by a prolonged induction time, so that those developing cholelithiasis late in life do not have an interval before death sufficiently long to develop carcinoma. However, the mere fact that the disease does occur in the absence of stones would suggest caution in concluding that a direct relationship exists between the two. Certainly more information about unknown parameters in the etiology of the disease is highly desirable.

A representative group of 93 surgeons, a number of whom are present in the audience, was

questioned concerning their experience with treatment of cancer of the gallbladder. Only five had no personal experience with the disease, one reported that he had had 20 personal cases, and one was treating a patient with this type of cancer when he was questioned. Thirty-four of the 868 cases seen in the institutions from which the reports were sent survived without evidence of residual or recurrent disease. At least ten of these were living five years after operation. Although 37 hepatic resections were performed in the entire group of cases, none of the survivors had more than a limited resection. This is somewhat at variance with the opinion that more frequent use of extensive procedures in advanced disease will improve survival considerably.

The one thing I would like to emphasize in closing is that the greatest possibility for improving survival figures immediately rests on careful examination of the extirpated gallbladder at the time of operation. Ten of the 74 cases reported were not recognized at the time of operation, and in at least six of these cases the chance of survival would have been increased considerably had the surgeon extended his operation at the time of original exploration, or if re-operation had been performed immediately. When small, early, and in situ carcinomas are recognized, extension of surgery may prove more rewarding than the radical procedures which have proved disappointing in more advanced disease.

