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Part II A clinical study

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SUMMARY In the present study of 241 patients submitted for gallbladder and biliary tract surgery, it is found that choledocholithiasis in cases in Singapore presents with a wide spectrum of clinical manifestations. It is essential that the less common clinical presentations should be recognized.

Recurrent pyogenic cholangitis, a syndrome infrequently encountered elsewhere, is a major biliary tract disease in the Orient. This entity has attracted much attention and there are several reports on various aspects of this syndrome (Cook, Hou, Ho, and McFadzean, 1954;

Huang, 1959; Jessen, 1961; Maki, 1961; Ong, 1962; Stock and Fung, 1962). However, information on the general pattern of biliary diseases in Oriental populations has been scanty and incomplete, and for the number of individual reports it is evident that such information is essential for a better understanding of the nature and pathogenesis of Oriental cholelithiasis.

This paper presents an analysis of gallstone disease in a multiracial Oriental population and is based on patients admitted to the Professorial Surgical Unit, General Hospital, Singapore, from 1 August 1962 to 31 December 1966.

Materials and Methods

The clinical records of patients with biliary diseases were reviewed. Patients with neoplasia, trauma, or malformation of the biliary tract were excluded.

Singapore has a multiracial population of about 1·5 million people. Chinese are in the majority, 75% of the total; Malays form 14%, Indians and Pakistanis 9%, and others, ie, Europeans, Eurasians, Ceylonese, Arabs, etc, 2%. The Chinese and Malay populations show a slight excess of males, but in the Indian and Pakistan population there is a twofold excess of males (Singapore, Chief Statistician, 1959).

The Singapore Government maintains a comprehensive medical service. Consultations and treatment in government hospitals are mostly free; there are a few fee-paying wards where those having the means and senior government officials may be admitted. It may be reasonably assumed that the fee-paying patients are of a higher socio-economic group in Singapore.

Other forms of bias, such as types of patients admitted, hospital utilization rates of the various races, etc, have been more fully discussed elsewhere (Muir, 1962, 1963).

Age	*Cholecysto-lithiasis*		*Choledocho ± Cholecysto-lithiasis*	
	Male	*Female*	*Male*	*Female*
0-9	0	0	0	0
10-19	0	2	0	2
20-29	3	2	1	2
30-39	7	8	5	9
40-49	11	13	7	12
50-59	20	10	19	7
60-69	3	8	19	11
70-79	2	2	3	7
80+	0	2	0	0
Total	46	47	54	50
No. of paying patients	16	16	3	3

Table I *Cholelithiasis in Chinese by sex, age, and site*

	No. of Cases		*Born in China*		*Paying Class*		*Opium Addicts*	
	Male	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*
Cholecystolithiasis without choledocholithiasis	46	47	28[1]	23	16[2]	16[3]	6[4]	1
Choledocholithiasis with/without cholecystlithiasis	54	50	47[1]	31	3[2]	3[3]	23[4]	1

Table II *Frequency of choledocho- with/without cholecystolithiasis related to sex, place of birth, paying class, and opium addiction.*

[1] $\chi^2 = 7{\cdot}729$, n = 1, P < 0·01.
[2] $\chi^2 = 11{\cdot}953$, n = 1, P < 0·01.
[3] $\chi^2 = 7{\cdot}779$, n = 1, P < 0·01.
[4] $\chi^2 = 9{\cdot}149$, n = 1, P < 0·01.

Results

There were 241 patients who had undergone surgery of the biliary tract for conditions other than neoplasia, trauma, and malformations of the biliary tract. The lesions studied fell in three main groups: (1) gallstones limited to the gallbladder (cholecystolithiasis without choledocholithiasis), 120 cases; (2) gallstones or biliary 'mud' in the bile ducts with or without similar involvement of the gallbladder (choledocholithiasis with or without cholecystolithiasis), 109 cases; (3) cholecystitis without stones, 12 cases.

The distribution of Chinese patients by race, age, and sex is shown in Table I.

As the pattern of biliary disease differed among the various races, a more detailed presentation of the results is accordingly divided into major groups by race.

Biliary Tract Diseases in Chinese

CHOLECYSTOLITHIASIS WITHOUT CHOLEDOCHOLITHIASIS (93 CASES)

The male patients in the 50-59 age group outnumbered the female patients by 2 to 1. There were three male opium addicts in this age group. Significant findings in this group see also Table II are: the presence of 33 radiopaque stones detected by plain *x*-ray of the abdomen, and 19 cases of pure pigment stones found at operation.

Analysis of the Chinese series showed that these 93 patients were made up of 82 'uncomplicated' cases, six of empyema of the gallbladder, and one of cholecystoduodenal fistula with gallstone ileus. Of the six patients with empyema of the gallbladder, four were opium addicts.

Four patients (two males, two females) died postoperatively. There was one male opium addict. The causes of death were acute pancreatititis, bronchopneumonia, myocardial in-

farction, and paralytic ileus with acute dilatation of the stomach.

CHOLEDOCHOLITHIASIS WITH OR WITHOUT CHOLECYSTOLITHIASIS (104 CASES)

The age, sex distribution of these cases, and their relationship with place of birth, type of ward to which they were admitted, and addiction to opium is shown in Table II. The male patients in the 50-69 age groups outnumbered the female patients by 2·1 to 1. There were 12 male addicts in the 50-69 age groups.

In 53 cases, discrete stones were present in both the gallbladder and the bile ducts. Gallstones were limited to the bile ducts in 30 cases. The remaining 21 cases had no formed stones, but had biliary 'mud' and infected bile in the biliary tract.

Histological examination showed acute cholecystitis or acute and chronic cholecystitis in 19 cases and chronic cholecystititis in 85 cases. Liver biopsy done in 14 cases showed cholangitis (5 cases), biliary stasis with portal fibrosis (3 cases), cirrhosis (4 cases), and pyogenic abscess (2 cases).

Bile cultures were done in 60 cases, of which five proved to be sterile. The organisms isolated were *E. coli* (37 cases), *A. aerogenes* (9 cases), *B. alkaligenes* (8 cases), *P. pyocyanea* (6 cases), and *S. typhi* (1 case).

Seventeen patients (15 males, two females) died postoperatively, six within 24 hours of surgical intervention. The 11 late postoperative deaths were due to septicaemia (6 cases), hepatorenal failure (2 cases), hepatic failure (1 case), subphrenic abscess (1 case), and intestinal obstruction (1 case). Of the 15 male patients who died, seven were opium addicts.

Twelve patients continued to have symptoms after definitive surgery. Three of them died during an acute exacerbation of the disease.

Further analysis of this group of patients showed four clinical patterns. Eighty patients presented with a typical history of Charcot's intermittent biliary fever. In 24 patients, presentation was atypical: 19 patients were admitted with acute epigastric or right upper quadrant pain, hyperpyrexia but little or no jaundice, and all went into septicaemic shock which proved to be fatal in four cases in spite of emergency laparotomy; in another nine patients, the clinical history simulated that of malignancy causing biliary obstruction; the remaining six patients were admitted with symptoms and signs of acute generalized peritonitis but abdominal radiographs failed to show free air in the peritoneum and the correct diagnosis was made at emergency laparotomy.

STONELESS CHOLECYSTITIS (11 CASES)

These were seven males, one of them born in China, and one an opium addict, and four females, one of them Chinese.[1] None was an opium addict.

Ages ranged from 7 to 80 years (7, 34, 63, 48, 50, 51, 55, 58, 62, 80). One woman and three men were admitted to a fee-paying ward.

The clinical picture was that of acute cholecystitis but no stones were found in the gallbladder or the bile ducts.

Cholelithiasis in Other Races

CHOLECYSTOLITHIASIS (27 CASES)

The clinical symptoms and laboratory and other findings resembled those of the Chinese patients.

CHOLEDOCHOLITHIASIS WITH CHOLECYSTOLITHIASIS (5 CASES)

Four patients presented with a typical clinical picture of recurrent pyogenic cholangitis with biliary mud and stones in the biliary tract. One patient was admitted with severe acute epigastric pain and vomiting. Physical examination revealed generalized abdominal tenderness and guarding. Laparotomy was done following a clinical diagnosis of generalized peritonitis. Acute impaction of the terminal bile duct by gallstones was found at operation.

STONELESS CHOLECYSTITIS (1 CASE)

This patient was admitted with a five month-history of painless jaundice with an enlarged firm liver. Laparotomy was done following a clinical diagnosis of liver carcinoma. A large thick-walled gallbladder was removed and it showed chronic cholecystitis histologically. The liver was cirrhotic. His recovery was uneventful after cholecystectomy and choledochostomy where no gallstone was found.

Discussion

The number of non-Chinese patients in the present study is too small for a reliable statistical analysis, but two features are noteworthy: (1) it was found in the present study that recurrent pyogenic cholangitis or oriental cholangiohepatitis does occur in the local Singapore population which is not exposed to clonorchis infestation; (2) bearing in mind the two-fold excess of male Indians in the Singapore population and a higher hospital utilization rate in the male Malays, it

[1]The Chinese in Singapore are of two types, those born in China who migrated to Singapore, and those born of Chinese parents in Singapore or Malaysia.

appears that the preponderance of cholelithiasis in women is maintained in these two races in contrast to the equal involvement of both sexes in the Chinese.

The present study shows a significantly large percentage of pigment stones occurring in the Chinese. Pigment stones being metabolic in origin occur more frequently in patients with haemolytic diseases, eg, sickle cell anaemia (Barrett-Connor, 1968). It has been shown by Wong (1966) that 1·6% of all the Singapore Chinese newborns are deficient in glucose-6-phosphate dehydrogenase and are thus more liable to intermittent haemolytic episodes. The relationship of this deficiency and pigment stones is uncertain and is at best speculative.

In the occidental experience, choledocholithiasis occurs in 6 to 18% of patients submitted to cholecystectomy for gallstones (Le Quesne, 1964). Choledocholithiasis is much more frequently encountered in Singapore, occurring in 44·3% of patients with stones in the gallbladder (excluding 30 patients with stones limited to the bile ducts).

Socio-economic conditions appear to be related to the site of stone formation. Whereas 34% of the patients with stones limited to the gallbladder were admitted to a paying ward, only 6% of the patients with choledocholithiasis were fee-paying. A diminishing incidence of pigment stones and choledocholithiasis has been reported in Japan and it has been attributed to a higher dietary fat intake due to an improvement in living standards (Maki, 1961). While dietary intake of fat may be important in the pathogenesis of gallstones, one also has to consider other factors related to poor socio-economic conditions, eg, poor environmental health, the prevalence of gastrointestinal infections, and opium addiction.

The present study further substantiates the association between cholelithiasis and opium addiction, an association which is particularly significant in the male patients with choledocholithiasis. Most of the addicts in this study were men in the 50-79 age groups in which the female preponderance of cholelithiasis was much diminished or even reversed.

Opium addicts are generally unreliable persons who tend to deny their addiction. The history of addiction is often obtained only during the post-operative period when addicts are prevented from swallowing opium preparations and no analgesics other than morphine can afford any relief of the pain. There is a disproportionately high mortality rate in the male patients with ductal stones. The reason for this is not obvious but it is felt that opium may contribute by masking symptoms.

Clonorchiasis does not occur in Singapore except in the Chinese immigrants or in persons who have been to the endemic areas. The relatively higher proportion of China-born patients with ductal stones lends some circumstantial support for clonorchiasis as an aetiological factor in choledocholithiasis. However, it is our experience in Singapore that clonorchiasis is seldom encountered during biliary tract surgery, and therefore cannot account for more than a small number of cases with choledocholithiasis in Singapore.

While the triad of Charcot's intermittent biliary fever is the usual presentation of choledocholithiasis in Singapore, other forms of presentation are by no means uncommon. A significant number of patients may not receive surgical treatment and to appreciate the full spectrum of the clinical manifestations of choledocholithiasis we include those cases from our previous necropsy series. Ong (1962) has emphasized the importance of recognizing the group of patients presenting with septicaemic shock. This is in fact the commonest atypical presentation which usually runs a rapidly fatal course. Accurate diagnosis is essential, for early surgical drainage of the common bile duct may be life saving. However, this is often rendered difficult because jaundice is usually minimal or absent and the site of pain may be atypical, thus leading to a misdiagnosis of myocardial infarction, acute pancreatitis, or basal pneumonia. On the other hand, jaundice may be a prominent symptom. Four such cases were associated with hyperpyrexia and rapidly progressive hepatorenal failure ending fatally with a clinical diagnosis of leptospirosis; 12 other cases were not associated with pain or fever and they were suspected of having malignant tumours obstructing the bile ducts. To complete the spectrum of presentations, Lai, McFadzean, and Yeung (1968) recently reported 15 cases of recurrent pyogenic cholangitis complicated by microembolic pulmonary hypertension.

Oriental choledocholithiasis or pyogenic cholangitis is a serious condition with a post-operative mortality of more than 16%. Surgery appears to be the only satisfactory treatment though the recurrence rate remains high. A better approach to the problem probably lies in the prevention of its occurrence by improving enviromental health and by limiting the abuse of opium.

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Reprints may be obtained from the Department of Pathology, University of Singapore.

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