

Cholelithiasis in Singapore

Part I A necropsy study

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SUMMARY The present necropsy study shows an oriental pattern of gallstone disease in Singapore, namely, a relatively low overall frequency, an equal involvement of both sexes, a high proportion of pigment stones, and the common occurrence of choledocholithiasis associated with pyogenic cholangitis.

There is a close association between opium addiction and cholelithiasis in the adult male Chinese in Singapore, and the long-term abuse of opium may be an important aetiological factor in the pathogenesis of oriental cholelithiasis.

While a necropsy study would estimate a roughly comparable frequency of cholelithiasis in any population (Newman and Northrup, 1959) the few such studies that have been done in the Orient are based on small numbers of cases; the largest series is that by Stitnimankarn (1960) which is based on 1,427 necropsies on individuals above the age of 20. The first aim of the present study is to provide basic data on cholelithiasis in an Asian population based on a review of 12,767 consecutive necropsies, 5,957 of which were on individuals more than 20 years of age, over a five year period (1962-66) in Singapore.

Clinical studies suggest a peculiar pattern of cholelithiasis in the Orient: equal involvement of both sexes, a high percentage of pigment stones, and the common occurrence of choledocholithiasis which is often complicated by the syn-

drome of recurrent pyogenic cholangitis or cholangiohepatitis. The role of biliary stasis in the pathogenesis of oriental cholelithiasis has been widely recognized (Digby, 1930; Snapper, 1941; Cook, Hou, Ho, and McFadzean, 1954; Maki, 1961; Harrison-Levy, 1962; Ong, 1962; Stock and Fung, 1962; Hur, Rice, and Hong, 1963). However, the causes of biliary stasis peculiar to the Orient are not well understood.

Although it is known that morphine induces a prolonged spasm of the sphincter of Oddi (Goodman and Gilman, 1965) and thereby causes biliary stasis, opium addiction has not been postulated as a possible aetiological factor in the pathogenesis of cholelithiasis. The second aim of the present study is to evaluate the relationship between cholelithiasis and opium addiction.

Materials and Methods

FIVE-YEAR NECROPSY REVIEW

The necropsy records of the University and Government Department of Pathology from 1962 to 1966 were reviewed. There were 12,767 necropsies representing virtually all the necropsies done in Singapore during the period studied. The distribution of these cases according to age, sex, and race is shown in Table I.

Consultations and treatment in all Government hospitals in Singapore are mostly free but there are a few paying wards in these hospitals. In the present study, less than 2% of the adults necropsied were from the paying wards. Hence the incidence and pattern of cholelithiasis in the present study may not be representative of persons in the upper socio-economic groups in Singapore. The structure of the necropsy population and the various forms of bias in the selection of cases are more fully discussed elsewhere (Muir, 1964).

In most necropsies, full postmortem examination was carried out including a gross inspection of the gallbladder and biliary tract. No chemical or microscopic studies on the gallstones were done. The gallstones described in the necropsy protocols could be classified into three main groups: (1) cholesterol stones, these were small yellowish, spherical or ovoid stones with a crystalline surface; (2) pigment stones, these were usually small, multiple, dark greenish black, irregular, hard, or friable stones; and (3) mixed stones, these varied in number and size. Some were large, greenish black, soft, earthy stones of varying shapes; some were faceted and multiple with a dark greenish hard outer coating and laminating internal structures. This group also included five cases where the gallbladders had been surgically removed but no descriptions of the stones were available.

The full clinical records and histological sections of the relevant cases were also reviewed.

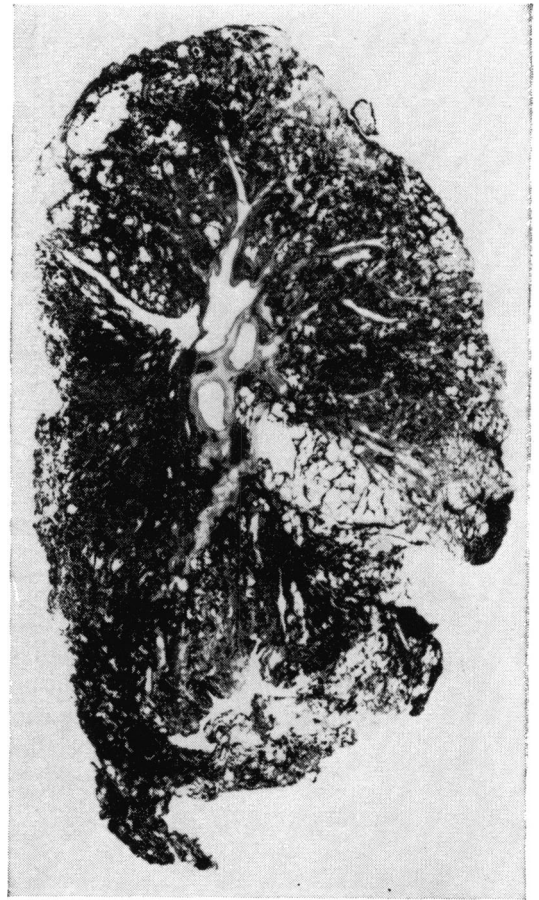


Fig. 1 Large lung section showing severe anthracosis with emphysema in an opium addict.

Age (years)	Chinese		Malays		Indians & Pakistanis		Others	
	Male	Female	Male	Female	Male	Female	Male	Female
0-9	3,322	2,403	33	27	126	121	16	11
10-19	358	182	27	8	23	10	6	4
20-29	480	197	59	23	61	13	30	3
30-39	373	197	44	14	119	27	27	6
40-49	512	190	47	11	205	18	20	3
50-59	926	251	31	4	195	18	32	3
60-69	867	232	14	4	82	8	17	5
70-79	307	124	6	2	31	3	8	3
80+	61	36	0	0	8	0	2	0
Unknown	82	24	8	0	18	0	1	0
Total	7,288	3,836	269	93	868	218	157	38
Age 20 & above	3,526	1,227	201	58	701	87	134	23

Table I Number of necropsies for the period 1962-66 by race, sex, and age

OPIUM ADDICTION AND CHOLELITHIASIS

As clinical records in coroner's necropsies are sometimes sketchy and inadequate, this investigation was restricted to elective necropsies performed by the University Department of Pathology in 1967. In this series enquiries were made into any history of opium addiction.

Opium addicts are generally unreliable persons who tend to deny their addiction because of the social taboos and of the law which prohibits the unauthorized sale and possession of opium. If only the clinical history is relied upon, a number of opium addicts would be missed. It is our experience in Singapore that habitual opium smokers frequently, though not invariably, have severe pulmonary anthracosis in which the lungs are jet black with a metallic sheen (Fig. 1), and as Singapore is a non-industrialized island city, severe pulmonary anthracosis is extremely unusual in persons other than opium addicts. It seems therefore reasonable to include as presumptive opium addicts those cases with no clinical history of opium smoking but found to have severe pulmonary anthracosis at necropsy.

Results

FIVE-YEAR NECROPSY REVIEW

Frequency

Gallstones were found in 398 cases in a total of 12,767 necropsies, constituting an overall frequency of 3.12%. However, after excluding those necropsies on individuals under the age of 20 and those of unknown age, the frequency was 6.6%.

Race, Age, and Sex

The frequency of gallstones by race, age, and sex is shown in Table II.

SITE AND TYPE OF GALLSTONES

The distribution of stones by site and type of stones in Chinese and Indians is shown in Table III. The small number of gallstones in other races were all found in the gallbladder. It may be of interest to note that 20% of the Chinese with choledocholithiasis did not have cholecystolithiasis.

Age	Chinese		Malays		Indians & Pakistanis		Others	
	Male	Female	Male	Female	Male	Female	Male	Female
	No. with Gallstones	No. with Gallstones	No. with Gallstones	No. with Gallstones	No. with Gallstones	No. with Gallstones	No. with Gallstones	No. with Gallstones
0-9	0	0	0	0	0	0	0	0
10-19	1 (0.28%)	0	0	0	0	0	0	0
20-29	2 (0.41%)	0	0	0	0	0	0	0
30-39	6 (1.61%)	11 (5.58%)	0	0	1 (0.84%)	1 (3.70%)	0	0
40-49	20 (3.91%)	12 (6.32%)	1 (2.13%)	0	6 (2.92%)	0	0	0
50-59	73 (7.88%)	31 (12.35%)	3 (9.68%)	1 (25.0%)	9 (4.62%)	1 (5.56%)	1 (3.13%)	0
60-69	98 (11.30%)	30 (12.93%)	1 (7.14%)	0	6 (7.32%)	1 (12.50%)	5 (29.53%)	1 (20.0%)
70-79	49 (13.03%)	14 (11.29%)	0	0	3 (9.70%)	0	1 (12.50%)	0
80+	7 (11.48%)	7 (19.44%)	0	0	2 (25.0%)	0	0	0
Unknown	1 (1.22%)	0	0	0	0	0	1 (100%)	0
Totals	248 (3.40%)	105 (2.74%)	5 (1.86%)	1 (1.08%)	27 (3.11%)	3 (1.38%)	8 (5.10%)	1 (2.90%)
Age 20 & above	246 (7.00%)	105 (8.56%)	5 (2.49%)	1 (1.72%)	27 (3.85%)	3 (3.45%)	7 (5.97%)	1 (4.35%)

Table II The frequency of gallstones by race, age, and sex

Type of Stone	Gallbladder Only		Gallbladder and Common Bile Duct		Bile Ducts Only	
	Male	Female	Male	Female	Male	Female
Cholesterol	5 (0) ¹	3 (0)	1 (0)	1 (0)	0 (0)	0 (0)
Pigment	86 (16)	37 (0)	6 (1)	6 (0)	5 (0)	0 (0)
Mixed	77 (6)	28 (1)	34 (4)	13 (2)	34 (0)	17 (0)
Total	168 (22)	68 (1)	41 (5)	20 (2)	39 (0)	17 (0)
No. without symptoms	159 (21)	62 (1)	13 (2)	6 (0)	9 (0)	3 (0)
No. with symptoms	9 (1)	6 (0)	28 (3)	14 (2)	30 (0)	14 (0)

Table III Types of stones related to sites in Chinese and Indians

Frequency in Indians given inside brackets

SYMPTOMS AND POSTMORTEM FINDINGS

Cholecystolithiasis

Six percent of the cases with stones confined to the gallbladder gave the following clinical history: acute cholecystitis (6 cases), previous cholecystectomy (5 cases), perforated gallbladder (2 cases), empyema of gall bladder (2 cases), and cholecystoduodenal fistula (1 case). The gallbladders of the asymptomatic cases were unremarkable on gross inspection but all of them showed chronic cholecystitis histologically.

Choledocholithiasis with or without cholecystolithiasis

Symptoms were present in 75% of these cases. Detailed analysis of the symptoms was carried out only in the 86 Chinese patients because they provided an adequate number of cases for study.

Sixty-six patients gave a typical history of Charcot's intermittent biliary fever, 49 of them experiencing a gradual onset, repeated attacks, and prolonged course, and 17 of them experiencing acute onset, rapid course, and stones impacted in ampulla. In ten of the 20 patients who gave an atypical history jaundice was absent or minimal and they were in shock. Of these patients, three died before the cause of shock was known. Four patients had fever,

rapidly progressive jaundice, anuria, uraemia, equivocal SEL titre, and the provisional diagnosis was leptospirosis. Three patients were afebrile, and presented with painless and progressive jaundice. Two patients were dead before arrival at hospital, and one patient was admitted with hyperpyrexia.

The anatomical findings in choledocholithiasis varied with the duration of symptoms, exact location of stones, and the presence of complications subsequent to obstruction. In cases of acute obstruction by stones impacted at the ampulla of Vater, the bile ducts were moderately dilated up to about 2 cm in diameter and filled with biliary mud or even pus (Figure 2). Histological sections showed acute cholangitis, cholangitic abscesses, areas of necrosis, and, in some cases, multiple thrombosis of the hepatic vein and portal vein radicals (Figures 3 and 4). In the more chronic cases, the bile ducts often appeared fibrotic and irregularly dilated with stricture, and the lumens were filled with casts of dark, earthy, pigment stones (Figure 5). Periductal fibrosis, acute and chronic cholangitis, and cholangitic abscesses were seen on microscopic examination (Figure 6). The gallbladders were markedly distended in more than a third of the 86 cases.

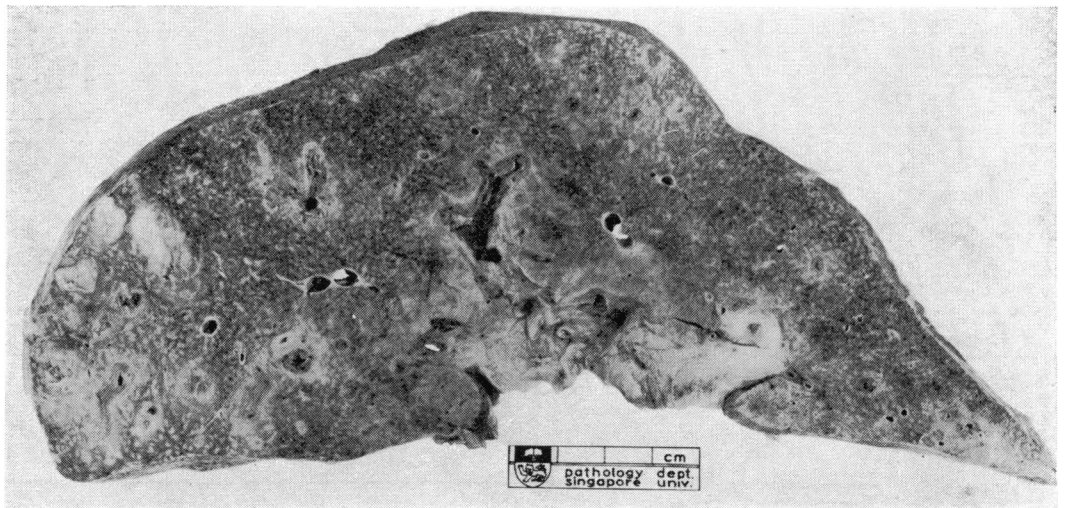


Fig. 2 Cholangitis in acute obstruction of biliary tract by stones. Note the moderate dilatation of the bile ducts which contain biliary mud and pus.

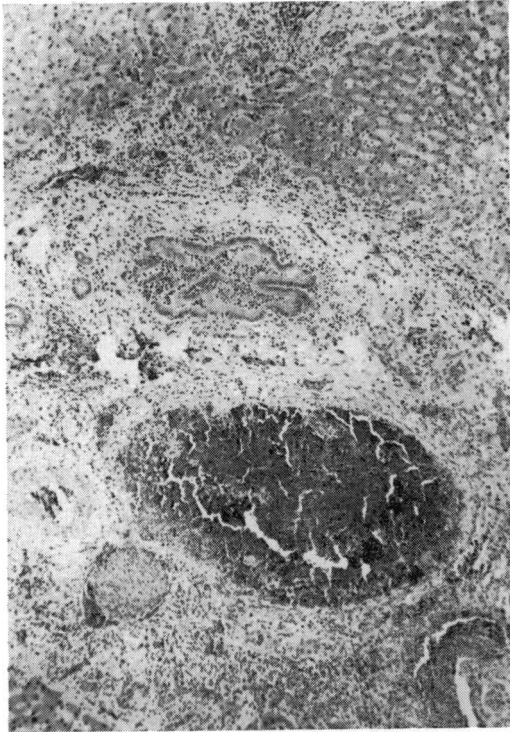


Fig. 3 Liver showing acute cholangitis and portal vein thrombosis. Haematoxylin and eosin $\times 45$.

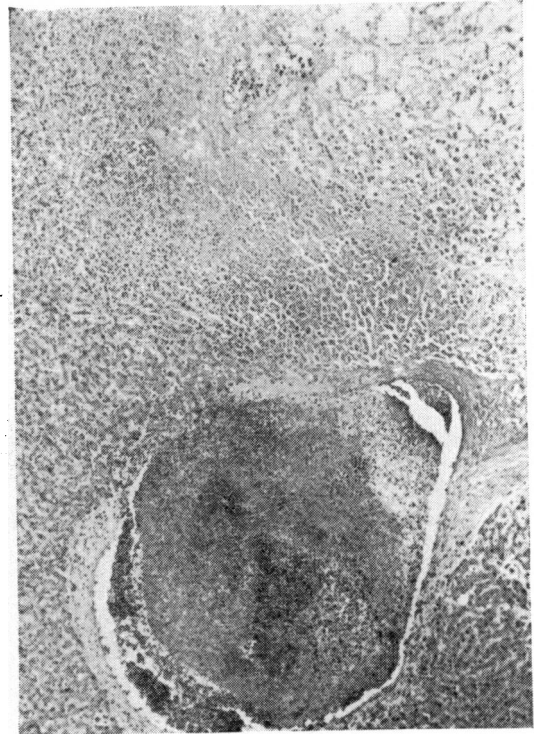


Fig. 4 Liver showing liver necrosis and hepatic vein thrombosis. Haematoxylin and eosin $\times 45$.

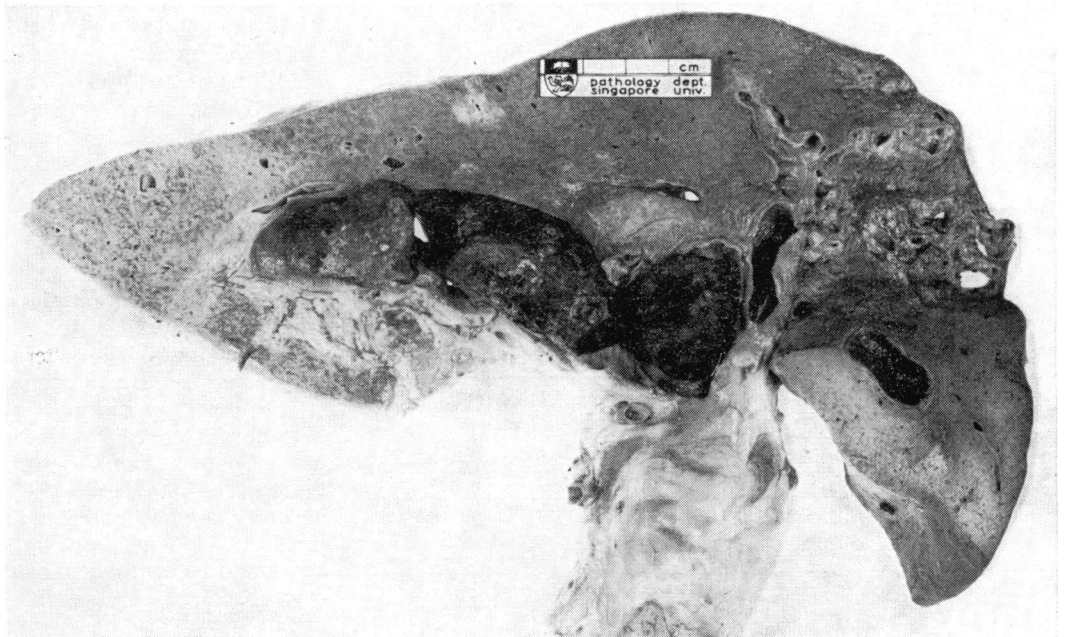


Fig. 5 Liver showing marked dilatation of bile ducts which are filled with cast of pigmented stones.

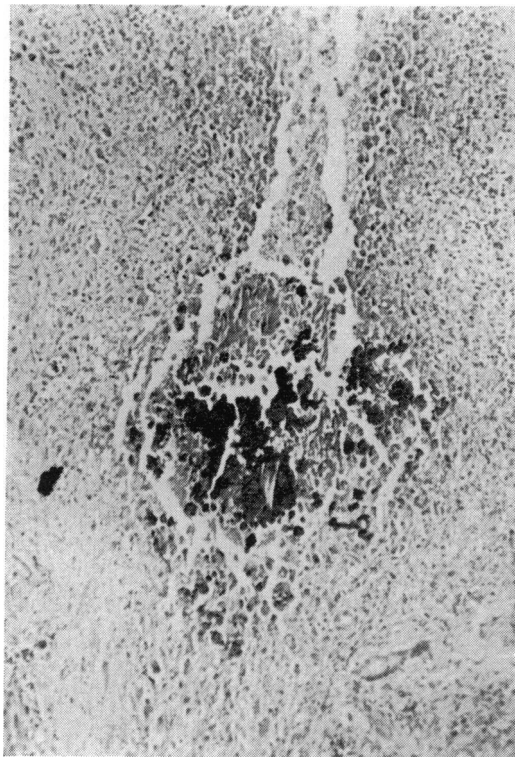


Fig. 6 Liver showing a cholangitic abscess. Haematoxylin and eosin $\times 45$.

Age (years)	Male		Female	
	Addicts	Non-Addicts	Addicts	Non-Addicts
	No. with Stones	No. with Stones	No. with Stones	No. with Stones
20-29	0 (0) ¹	1 (7) (14.3%)	0 (0)	0 (11)
30-39	0 (1)	0 (9)	0 (0)	0 (9)
40-49	1 (2) (50%)	1 (15) (13.3%)	0 (0)	0 (14)
50-59	2 (8) (25%)	4 (23) (17.4%)	0 (1)	0 (16)
60-69	9 (25) (36%)	0 (20)	0 (0)	4 (14) (28.5%)
70+	6 (7) (85.7%)	5 (23) (21.7%)	0 (1)	6 (18) (33.3%)
Total	18 (43) (41.9%)	12 (97) (12.2%)	0 (2)	10 (82) (12.2%)

Table IV Frequency of cholelithiasis in Chinese addicts and non-addicts by age and sex

¹Number of cases necropsied inside brackets.

Investigator	Race Studied	Incidence		Female: Male Ratio
		Female	Male	
Torvik & Høivik (1960)	Scandinavian	28.6	13.5	2.1
Lieber (1952)	American 'white'	21.7	9.67	2.2
Cleland (1952)	Australian	19.3	10.0	1.9
Gross (1929)	British	18.5	8.8	2.1
Hwang (1970)	Chinese	8.56	7.0	1.2
Lieber (1952)	American 'coloured'	8.7	3.25	2.7
Kozoll, Dwyer, & Meyer (1959)	American 'coloured'	6.6	2.3	2.9
Stitnimanakarn (1960)	Thai	3.93	1.77	2.2

Table V Necropsy frequency of gallstones in various races (excluding individuals below age 20)

ASSOCIATED CONDITIONS

Seven out of 39 cases of male Chinese with pure choledocholithiasis, and three out of 41 cases of male Chinese with both gallbladder and ductal stones were opium addicts. No opium addicts were noted in all the other groups.

There were 46 cases of clonorchiasis in the period studied; 14 of these had gallstones—seven in the gallbladder, two in both the gallbladder and bile ducts, and five limited to the bile ducts.

One dead ascaris was found in a Chinese woman with cholecysto- and choledocholithiasis. There were another four cases of liver and biliary ascariasis; three in young children and one in an adult aged 70. All four died of suppurative cholangitis without cholelithiasis.

Twenty cases of acute pancreatitis were recorded in the period studied. Six of these cases were associated with choledocholithiasis.

No significant associations were demonstrated between cholelithiasis and liver cirrhosis, carcinoma of liver, bile duct or gallbladder.

OPIUM ADDICTION AND CHOLELITHIASIS

Forty-five opium addicts (33 definitive and 12 presumptive) were noted in this series. All the addicts were Chinese above 30 years of age. Except in two cases, all the addicts were male. In this same series there were 40 cases of cholelithiasis in the Chinese. The incidence of cholelithiasis in the addicts as compared with the non-addicts is shown in Table IV.

All the gallstones were either pigment stones or 'mixed' stones. In 10 of the 18 addicts with cholelithiasis, gallstones were present in the bile ducts. Ductal stones were present in six out of 22 cases of cholelithiasis in the non-addicts.

Discussion

As the number of necropsies in races other than Chinese is inadequate for a reliable study, the present analysis of the pattern of cholelithiasis in Singapore is done mainly on the Chinese.

The overall frequency of cholelithiasis in Singapore is low compared with most Occidental necropsy series (Table V), particularly marked in the female Chinese. In the male Chinese the incidence approaches that of the Caucasians. The relatively high incidence in the male Chinese appears to be contributed by the large number of cases in the 50-79 age groups where the female preponderance is much diminished or even reversed.

Most of the gallstones found in Singapore are mixed stones and pigment stones associating with a high incidence of choledocholithiasis. These findings are in accordance with oriental clinical experience.

The aetiology of oriental cholelithiasis has been

postulated as starting as a portal bacteraemia; the bacteria after reaching the liver are localized in the biliary tree by unknown factors, one of which appears to be mechanical obstruction of the common bile duct (Cook *et al.*, 1954; Ong, 1962; Dineen, 1964; Flemma, Flint, Osterhout, and Shingleton, 1967). To verify this hypothesis, Chou and Gibson (1968) successfully produced lesions resembling human pyogenic cholangitis in rabbits and rats by constricting the common bile duct and injecting *E. coli* into the portal vein, and so biliary stasis appears to be an important aetiological factor in Oriental cholelithiasis. However, what are the causes of biliary stasis peculiar to the Orient?

The equal involvement of both sexes in oriental cholelithiasis is an outstanding feature which should deserve more attention. Female preponderance is a constant feature demonstrated in various races with different patterns of cholelithiasis (Robertson, 1945; Lieber, 1952; Cobo, Hall, Torres, and Cuello, 1964). It appears that in the Orient, there exist certain aetiological factors which act predominantly on either the male or the female in such a way that the usual female preponderance is nullified. Any postulated aetiological factors which affect both sexes equally will seem inadequate to explain the oriental pattern of cholelithiasis. The present study suggests an unusually high incidence of cholelithiasis in the male Chinese, particularly of the 50-79 age groups, in a population where the overall frequency of gallstone disease is relatively low.

The first part of the present study shows an undue number of opium addicts among the male Chinese with choledocholithiasis, and the second part that 41.9% of male Chinese addicts had gallstone disease in contrast to 12.2% of male Chinese non-addicts having gallstones. The association between opium addiction and cholelithiasis appears statistically significant ($\chi^2 = 13.570$, $n = 1$, $P < 0.01$) although the number of cases is small. Most addicts in the present study were male Chinese in the 50-79 age groups coinciding with the groups having an unduly high incidence of cholelithiasis. It is further demonstrated in that choledocholithiasis occurred three times as frequently in the addicts than in the non-addicts, indicating a higher tendency for the addicts to form ductal stones. If opium addiction contributes to the formation of oriental gallstones, a high incidence of chole-

docholithiasis is to be expected in the Orient.

Most opium addicts in Singapore are males (male:female ratio = 10:1), and practically all the opium addicts are Chinese in the poor socio-economic groups (Leong, 1959). Apart from its habitual use in addiction, opium is widely used in Chinese folk medicine for the treatment of diarrhoea to such an extent that it constitutes a common form of poisoning in Chinese children (Wallnöfer and von Rottauscher, 1965; Lam, 1967). The use and abuse of opium have been widespread among the ethnically related oriental races. It seems probable that the widespread use of opium, especially among the addicts who often consume large daily doses over a long period of time, may be important in the pathogenesis of cholelithiasis in the Orient, accounting for the type and site of gallstones, the male preponderance, and the common occurrence of pyogenic cholangitis.

Parasitic infestations of the biliary tract have also been postulated to cause biliary stasis in the Orient (Teoh, 1963; Maki, 1961). The present study shows that 30% of cases with clonorchiasis were associated with stones. However, it is obvious that while clonorchiasis may well play a part in some cases of cholelithiasis, it cannot account for more than a small number of cases in the present study. Biliary ascariasis is uncommon in Singapore, and it seems unimportant in the pathogenesis of gallstones.

The relatively high incidence of cholelithiasis found in opium addicts may partly be due to a higher proportion of older subjects, because of the exclusion of coroners' cases which cover a significant number of young adults killed in accidents. It may also be due to a more careful search for gallstones during necropsy examination. A great proportion of gallstones in Singapore are small pigment stones which can be easily missed when mixed with dark, greenish, thick bile. Some stones may not be discovered unless the entire length of the common duct is carefully dissected.

Choledocholithiasis is a potentially lethal condition. While the triad of Charcot's intermittent biliary fever is the usual presentation, other forms of clinical manifestations are by no means uncommon. Accurate diagnosis though essential, may be extremely difficult because of the absence of jaundice, the rapidity of the course, and the atypical site of the disease.

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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;