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Gallstones in Western Japan —Epidemiologic Factors Affecting the Type and Location of Gallstones—

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Introduction

Gallstone disease in Japan is presently distinguished from that found in western countries by the presence of a significant proportion of patients with bilirubin stones and by the high frequency with which bilirubin stones are found in the common bile duct and liver with or without concommitant disease in the gallbladder[26,35,36]. With the gradual introduction of a western-style diet since the 1950's, the proportions of gallstone types in Japan have been changing progressively to more closely resemble the western pattern of cholesterol stone predominance[26,35,36,46]. Thus, Japan presently provides a virtually unique opportunity to examine, in a genetically homogeneous people, factors affecting the incidence of the various types of gallstones with the aim of identifying mechanisms that predispose to or that cause lithogenesis. The continuation of a cooperative study with prospectively collected data[36] allowed simultaneous evaluation of a number of these factors in a group of patients large enough to give meaningful results even when they were divided into multiple subgroups.

Methods

Data Collection: Surgeons at 40 affiliated hospitals of the Second Department of Surgery, Faculty of Medicine, of the University of Kyoto, using Kameda's system[21], visually identified 90% of gallstones obtained at operation during the period July 1975 to June 1978. Surgeons in Japan are familiar with this method of classification and additional instruction was given at the inception of the study. The remainder of the stones were identified by microscopic or chemical analysis[31]. A standard form was distributed to each hospital and clinic, diagnostic and

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operative data were obtained prospectively for each patient.

Because the incidence of bilirubin stones has been said to be increased in rural populations who eat a more traditional Japanese diet[48], statistics from hospitals serving urban and rural populations were compared. The proportions of urban and rural patients in this study did not reflect the overall Japanese population, but rather indicated the numbers and sizes of participating urban and rural hospitals. The percentage of rural patients was underestimated in this study since up to one third of patients at urban hospitals were from rural areas while rural hospitals serve predominantly rural populations.

Forms identified hospitals by number and listed the age, sex, stone type, stone location and common bile duct diameter for each patient and identified this as the original or a subsequent operation.

Stone Classification: Kameda identified 9 types of gallstones visually[21] and other authors have used similar classifications[21,30,34,45,46,48]. For purposes of comparison, several subgroups have been combined into cholesterol, bilirubin calcium and black stones. Rare stones, including fatty acid stones and calcium carbonate stones account for less than 0.2% of the total number of stones collected. Cholesterol stones have a smooth or mulberry shaped surface with a white to light yellow color and a radial cross-sectional pattern with a small dark center. These stones contain more than 70% cholesterol. Black ("pure pigment") stones are dark brown or black on the surface and on cross-section have a smooth conchoidal appearance resembling the surface. Black stones constitute the vast majority of stones previously reported as "other"[36] and are referred to in the Euroepan and American Literature as "pigment" stones[10,50,53]. Bilirubin ("bile pigment calcium") stones (Figure 3) have a rough light to dark brown surface, have multiple circular layers on cross-section and exhibit multiple concentric layers of varying shades of brown. Such stones are seen uncommonly in the United States in patients who have not undergone previous biliary surgery.

Stone Location: Stones in extrahepatic locations have been divided into the following groups based on their location at operation: gallbladder alone (GB), gallbladder and common bile duct together (GB+CBD) and common bile duct alone (CBD). Intrahepatic stones have been analyzed in a separate report[38] because of the special interest in this group.

Consent: All patients agreed to have data submitted for the study and no names or chart numbers were included on the forms. Forms were identified by consecutive numbers from each hospital. The members of the study compiling the data had no knowledge of the identity of specific patients. In Japan, there are no human subjects committees.

Statistics: Difference between groups were assessed using the χ^2 test. The relative importance of each individual number (cell) to the total value for χ^2 was assessed by the size of the term: (observed number-expected number)^2/expected number[44]. The χ^2 test discriminates between smaller differences in proportions as the sample size increases and maintenance of the same proportions with increasing sample size may allow detection a difference which was no significant in a small sample to become significant. A log-linear model was fitted to all the data simultaneously[14]. The best model included all of the first-order interactions examined using

Table 1. Comparison of the distribution of cholesterol, bilirubin and black stones by location in the biliary tract for stones collected during the first two years with those collected during the third year of the study

Location	Years of study	Stone Type: Cholesterol	Bilirubin	Black	Total
GB	1 and 2	1303 81*	185 12	117 7	1605
	3	764 78	123 13	79 8	966
GB+CBD	1 and 2	179 55	140 42	11 3	330
	3	116 64	61 34	5 3	182
CBD	1 and 2	28 15	159 85	0 0	187
	3	22 23	75 77	0 0	97

* Number in the upper right hand corner of each cell represents the percent for that cell of the entire horizontal group.
GB=gallbladder, CBD=common bile duct

the individual χ^2 analysis. Differences in importance of individual interactions could not be distinguished. Use of the χ^2 technique was therefore the only feasible method for discrimination between groups.

All patients; *First and Second Years vs Third Year of Study*: Since the previous report of this study[36], 1245 cases have been added for a total of 3387. Data from the first 2 years[36] was evaluated against data from the third year to assess comparability. There was no change in the distribution of stone types (Table 1) by location in the biliary tract. The only significant change was in the distribution of patients according to stone location in the biliary tract examined by stone type (Table 2). The distribution of those with cholesterol and black stones was unchanged but the distribution of patients with bilirubin stones showed a slight decrease in the proportion of those with CBD stones (29 vs. 31%), a larger decrease in those with stones in the GB+CBD (24 vs 32%) and an increase in the proportion of patients with GB stones (47 vs 37%)

Table 2. Comparison of distribution among locations in the biliary tract of cholesterol, bilirubin and black stones collected during the first two years with those collected during the third year of the study

Stone type	Years of study	Location: GB	GB+CBD	CBD	Total
Cholesterol	1 and 2	1303 86*	179 12	28 2	1510
	3	765 85	116 12	22 2	902
Bilirubin	1 and 2	185 37	160 32	159 31	504
	3	123 47	61 24	75 29	259
Black	1 and 2	117 91	11 9	0 0	128
	3	79 94	5 6	0 0	84

* Format as in Table 1

Table 3. Age distribution of urban and rural and male and female patients

	Age					
	<30	30–39	40–49	50–59	>59	Total
Urban	154 7*	361 16	597 27	555 25	552 25	2219 66
Rural	70 7	141 12	217 19	298 26	442 38	1168 34
Male	58 5	197 15	347 27	297 23	375 29	1274 38
Female	166 8	305 14	467 22	556 26	619 29	2113 62

(χ_2^2=7.28, p<0.025).

General Characteristics: Of the patients accessed, 66% went to urban and 34% to rural hospitals. Urban and rural hospitals had a similar male to female ratio. Rural patients were significantly older (Table 3) than urban patients (χ_4^2=76.0, p<<<0.001). This was primarily accounted for by the increased number of patients above the age of 60 (38 vs 25%).

Stone Type: Among males, 67% have cholesterol, 27% bilirubin and 6% black stones while females have 74% cholesterol, 20% bilirubin and 6% black stones (χ_2^2=21.4, p<0.001) due to an increase in the proportion of male patients with bilirubin stones (Table 4 and 5, vertical totals). Among urban patients 77% had cholesterol, 17% bilirubin and 6% black stones while among rural patients 60% had cholesterol, 33% bilirubin and 7% black stones (χ_2^2=127, p<<<0.001) due to an increase in the proportion of bilirubin stones in rural patients (Tables 6 and 7, vertical totals). Seven per cent of patients were below age 30 and 87% of these had choletserol gallstones (Table 8). Patients with bilirubin stones were older at operation than patients with cholesterol or black stones (χ_4^2=450, p<<<0.001) and patients with black stones were slightly older than patients with cholesterol stones (χ_4^2=11.0, p<0.05). Patients between the ages of 30 and 49 had similar proportions of stone types (Table 8, vertical columns). In the 50–59 year age group, the proportion of bilirubin stones increased significantly (χ_2^2=27.7, p<0.001) and this was accentuated when the group above 59 years of age was compared with the 50–59 year age group (χ_3^2=124, p<<<0.001). The proportion of patients with black stones remained constant with increasing age but the number of patients increased progressively.

Table 4. Distribution by stone type of stone location in male patients

	Location			
Stone type	GB	GB+CBD	CBD	Total
Cholesterol	722 85* 77** 50	107 13 18	24 3 67	853
Bilirubin	136 40 15 17	99 29 82	106 31 27	341
Black	74 93 8 3	6 8 0	0 0 6	80
Total	932 73	212 17	130 10	1274

* Format as Table 1

** The number in the lower left hand corner of each cell represents the percent for that cell of the entire vertical group.

Table 5. Distribution by stone type of stone locations in female patients

Stone type	Location GB	GB+CBD	CBD	Total
Cholesterol	82 1345 86* 59	188 12 17	26 2 74	1559
Bilirubin	10 172 41 38	122 29 83	128 30 20	442
Black	7 122 92 3	10 8 0	0 0 6	132
Total	1639 78	320 15	154 7	2113

* Format as in Tables 1 and 4

Stone Location: There were differences between males and females in the location of stones in the biliary tract ($\chi_2^2=11.1$, $p<0.001$) due to a higher proportion of CBD stones among males (Table 4 and 5, horizontal totals). Urban patients had stones in the GB 80% of the time, 14% in the GB+CBD and 6% in the CBD while rural patients had stones in the GB 68% of the time, 19% in the GB+CBD and 13% in the CBD ($\chi_2^2=72.0$, $p<<<0.001$) (Tables 6 and 7, horizontal totals). The largest proportional difference was in those with stones in the CBD alone. Differences in stone location in the biliary tract were due more to living location than to sex. Patients with GB stones had a peak operative incidence between 40 and 49 years of age while those with CBD stones had a peak incidence above age 59 ($\chi_4^2=175$, $p<<<0.001$). Patients with stones in the GB+CBD also had a peak incidence above age 59 and were older than those with GB stones ($\chi_4^2=128$, $p<<<0.001$) and were younger than patients with CBD stones ($\chi_4^2=14.7$, $p<0.01$). Although the proportion of patients with CBD stones, with or without GB stones, increased slightly from the youngest group to the one between 40 and 49 years of age ($\chi^2{}_2=3.76$, $p<0.05$), there was a more striking increase in patients with CBD stones when the youngest group

Table 6. Distribution by stone type of stone location in urban patients

Stone type	GB	GB+CBD	CBD	Total
Cholesterol	84** 1482 86* 62	195 11 29	38 2 77	1715
Bilirubin	10 170 45 36	112 30 71	92 25 17	374
Black	7 122 94 3	8 6 0	0 0 6	130
Total	1774 79	315 14	130 6	2219

* Format as in Table 1 and 4.

Table 7. Distribution by stone type of stone location in rural patients

Stone type	GB	GB+CBD	CBD	Total
Cholesterol	73 585 84* 46	100 14 8	12 2 60	697
Bilirubin	17 138 35 50	109 28 92	142 37 33	389
Black	9 74 90 4	8 10 0	0 0 7	82
Total	797 68	217 19	154 13	1168

Table 8. Distribution of age by stone type in all patients

Stone type	Age <30	30–39	40–49	50–59	>59	Total
Cholesterol	194 (8*; 87)	437 (18; 87)	675 (28; 83)	622 (26; 73)	484 (20; 49)	2412 (71)
Bilirubin	13 (2; 6)	36 (5; 7)	88 (12; 11)	178 (23; 21)	448 (59; 45)	763 (23)
Black	17 (8; 8)	29 (14; 6)	51 (24; 6)	53 (25; 6)	62 (29; 6)	212
Total	224 (7)	502 (15)	814 (24)	853 (25)	994 (29)	3387

* Format as in Table 1 and 4

Table 9. Distribution of age by stone location in all patients

Location	Age <30	30–39	40–49	50–59	>59	Total
GB	203 (8*; 91)	431 (17; 86)	688 (27; 85)	662 (26; 78)	857 (23; 59)	2571 (76)
GB+CBD	17 (3; 8)	55 (10; 11)	89 (17; 11)	129 (24; 15)	242 (45; 24)	532 (16)
CBD	4 (1; 2)	16 (6; 3)	37 (13; 5)	62 (22; 7)	165 (58; 17)	284 (8)
Total	224 (7)	502 (15)	814 (24)	853 (25)	994 (29)	3387

* Format as in Tables 1 and 4

was compared to the one between 50 and 59 years of age ($\chi_2^2=19.9$, $p<0.001$). The difference was even more striking when this latter group was compared to the one over 59 years of age ($\chi_2^2=75$, $p\ll\ll 0.001$) (Table 8, vertical columns).

Analysis by stone type

Stone Location vs Stone Type (*Table 7*): Eight per cent of patients with black stones had stones concommitantly in the GB+CBD while patients with cholesterol stones had a 12% incidence ($\chi_2^2=8.9$, $p<0.025$). Patients with bilirubin stones had a 29% incidence which was higher than patients with cholesterol stones ($\chi_2^2=792$, $p\ll\ll 0.001$). Patients with black stones had no stones in the CBD alone. This was less frequent than for patients with cholesterol stones ($\chi_1^2=4.44$, $p<0.05$). The frequency of patients with CBD cholesterol stones alone (2%) was, in turn, less than the 28% frequency in patients with bilirubin stones ($\chi_1^2=585$, $p\ll\ll 0.001$).

Cholesterol Stones: The male to female ratio was 1 : 1.83 and the frequency of females was above 1 : 1 ($\chi_1^2=105$, $p\ll\ll 0.001$). The male : female ratio for patients less than 30 years of age was 1 : 2.89, greater than among the older patients with cholesterol stones ($\chi_4^2=8.45$, $p\ll 0.0005$). Patients with stones in the GB+CBD were older (Table 10) than patients with stones in the GB ($\chi_4^2=29.3$, $p\ll 0.001$) due to the presence of fewer patients below the age of 30 and more patients above the age of 60. Urban patients were younger than rural patients in the 40–49 year age group (23 vs 30%) and more rural patients were in the group over 59 years of age (25 vs 18%).

Table 10. Distribution of age by stone location subdivided by stone type in all patients

Stone type	Location	<30	30–39	40–49	50–59	>59	Total
Cholesterol	BG	91** 177 9* 88	385 19 88	593 28 85	529 26 79	383 18 86	2067
	GB+CBD	8 15 5 11	47 16 10	70 24 13	78 26 16	85 29 12	295
	CBD	1 2 4 1	5 10 2	12 24 2	15 30 3	16 32 2	50
Bilirubin	GB	77 10 3 56	20 6 53	47 15 46	81 27 33	150 49 40	308
	GB+CBD	8 1 1 14	5 2 18	16 7 28	50 23 33	149 67 29	221
	CBD	15 2 1 30	11 5 28	25 11 26	47 20 33	149 64 31	234
Black	GB	94 16 8 90	26 13 94	48 24 98	52 27 87	54 28 92	196
	GB+CBD	6 1 6 10	3 19 6	3 19 2	1 6 13	8 50 8	16

*, ** Format as in Tables 1 and 4, but the vertical percent for each cell is a proportion of each stone type calculated separately.

Bilirubin Stones: The male to female ratio was 1 : 1.24 and the frequency of females was just above 1 : 1 ($\chi_1^2=4.18$, $p<0.05$). Rural patients (Tables 6 and 7, bilirubin stone row) had stones in the CBD more frequently (37 vs 25%) and stones in the GB less frequently (35 vs 45%) when compared to urban patients ($\chi_2^2=14$, $p<0.001$). Patients with bilirubin stones in the GB+CBD and in the CBD alone were older (Table 10) than patients with stones in the GB alone ($\chi_4^2=29.9$, $p\ll0.001$) due to the presence of fewer patients with GB stones over 59 years of age. There was no difference in the age distribution for patients with GB+CBD and CBD stones alone.

Black Stones: The male to female ratio was 1 . 1.65 and the frequency of females was above 1 : 1 ($\chi_1^2=6.48$, $p<0.25$). No other significant differences were detected.

Analysis by stone location

Gallbladder: Males have more bilirubin and fewer cholesterol stones ($\chi_2^2=10.4$, $p\ll 0.01$) (Tables 4 and 5, GB Column). The male to female ratio for patients with cholesterol stones was 1 : 1.86 and females were greater than 1 : 1 ($\chi_1^2=93.3$, $p\ll\ll0.001$). The sex ratio for patients with bilirubin stones was 1 : 1.26, very similar to the ratio for the total bilirubin stone group, but was not significant because of the smaller sample size. The ratio for patients with black stones was 1 : 1.65 ($\chi_1^2=5.97$, $p<0.025$) and was similar to the total black stone group because 93% of the patients were in this subgroup. The male to female ratio for patients with cholesterol stones was not significantly different from that for patients with black stones (Tables 4 and 5) but was greater than for patients with bilirubin stones ($\chi_1^2=7.8$, $p<0.01$). Urban patients had more cholesterol and fewer bilirubin GB stones than rural patients ($\chi_2^2=39.2$, $p\ll 0.001$) (Tables 6 and 7, GB columns). When the age distribution of patients with GB stones was examined by stone type, patients with bilirubin stones were older than patients with cholesterol stones ($\chi_8^2=160$, $p\ll\ll0.001$), predominantly due to the large proportion of patients

with bilirubin stones more than 59 years of age (bilirubin 49% vs cholesterol 19% vs black stones 28%) (Table 10, horizontal percentages).

Gallbladder and Common Bile Duct: There was no difference in the incidence of stone types when males and females were compared (Tables 4 and 5, GB+CBD columns). The male to female ratio for patients with cholesterol stones was 1 : 1.96 (χ_1^2=12.2, $p<0.001$). The ratio for bilirubin stones was 1 : 1.23 and for black stones was 1 : 1.67, neither of which demonstrated a significant increase in females. Rural patients, compared to urban patients (Tables 6 and 7, GB+CBD columns), had more bilirubin stones (50 vs 36%) and fewer cholesterol stones (45 vs 62%), χ_2^2=7.39, $p<0.025$). When the age distribution of patients with GB+CBD stones was examined by stone type, patients with bilirubin stones were older (χ_3^2=12.8, $p<0.005$), predominantly due to the greater proportion of patients with bilirubin stones over the age of 59 (67 vs 29%).

Common Duct: There was no difference in the incidence of stone types when males and females were compared (Tables 4 and 5, CBD columns). The male to female ratio for patients with cholesterol stones was 1 : 1.08 and for bilirubin stones was 1 : 1.21, neither of which was significantly different from 1 : 1. Accentuating the effect seen in patients with GB+CBD stones, the rural group with CBD stones alone had an even smaller proportion of patients with cholesterol stones (8 vs 29%) and a larger proportion of patients with bilirubin stones (92 vs 70%) compared to the urban group (Tables 6 and 7, CBD columns) (χ_1^2=22, $p<<0.001$). Patients with bilirubin stones were older than patients with cholesterol stones (χ_3^2=16.6, $p<0.005$) predominantly due to the large proportion of patients over age 59 (64 vs 32%). When compared with patients with GB+CBD stones, fewer patients with CBD stones over age 59 had cholesterol stones (18 vs 57%) and many more patients had bilirubin stones (82 vs 43%), (Table 10) (χ_2^2=115, $p<<<0.001$).

Discussion

General Comparisons, Japan vs United States: This study dealt with the operative prevalence of gallstones and did not measure the incidence of gallstones in the general population. Prior to 1940, bilirubin stones were the predominant type of gallstone in Japan[25,35]. In this series, as in other recent studies in Japan, cholesterol stones were the most prevalent type of gallstone found at operation[35,46] and autopsy[21] and the prevalence of cholesterol stones in the United States[50] and Japan is now similar. The differences between Japanese and American patients now lie in the lower prevalence in Japan of patients with black stones, called "pigment" stones by American and European investigators[10,50,53], and the 16% prevalence of bilirubin stones. The overall male to female ratio in Japan is lower than that reported for an urban United States population[21]. However, the proportion of females in the group under 30 years of age is very similar to western studies, raising the possibility that dietary or other effects on cholesterol metabolism affect young females more than young males. It will be interesting to see whether the overall proportion of females continues to increase with time to become equal to

that in the United States. When data from the first 2 years was compared with the third year, the small decrease noted in the proportion of bilirubin stones may reflect the continuing changes noted in the first report[36]. In addition, a significant shift of bilirubin stones away from the common bile duct and into the gallbladder was demonstrated, again reflecting a trend toward a closer resemblance to western experience.

General Characteristics: Sex did not affect the differences in stone type and location noted between urban and rural populations. The rural population in Japan is said to be older than the urban population because young people migrate to the cities to obtain jobs in industry. In this study, rural patients were significantly older than urban patients in keeping with that impression.

Stone Type, All Patients: The typical patient coming to operation with cholesterol stones was an urban female between 40 and 49 years of age while the typical patient with bilirubin stones was a rural male who was more than 59 years old. Although patients with black stones could not be typified by sex or living location, when actual numbers were examined, a typical patient would most likely be between 40 and 49 years of age. In agreement with a report from the United States[34], the proportion of bilirubin plus black stones increased relative to cholesterol stones so that after age 59, these two groups accounted for 51% of all gallstones found at operation.

Stone Location, All Patients: The typical patient coming to operation with GB stones was a young urban female with cholesterol stones. If the patient had GB+CBD stones, the patient was still most likely to be urabn and female, although males and rural patients made up a significantly greater proportion of this group. Such patients were significantly older than patients with GB stones and this might be expected since GB stones may be present for years before passage into the CBD. The prevalence of 15.7% GB+CBD stones is higher than reports from western countries ($p<0.001$) of 5%[33] and 6%[32] and a compilation of 5 series with an prevalence of 11%[12]. When examined by stone type Japanese patients with bilirubin stones had a 60% prevalence of GB+CBD or CBD stones, those with cholesterol stones had a 14% prevalence and those with black stones had an 8% prevalence. Patients with bilirubin stones had a much greater prevalence than any of the western reports ($p<0.001$) and those with black stones were not significantly different. Of interest, Japanese patients with cholesterol stones had a greater prevalence of GB+CBD or CBD stones than the compiled report[12] ($\chi_1^2=18.9$, $p<0.005$), suggesting that Japanese patients with cholesterol stones have an additional factor leading to choledocholithiasis. This could be due either to an increased tendency for the passage of gallbladder stones or an increased incidence of *de novo* formation of stones in the common bile duct. Diet may also be a factor and therefore, it will be of interest to see if, the incidence of cholesterol choledocholithiasis decreases with time in the same way that bilirubin choledocholithiasis is decreasing. Stones in the CBD alone are quite uncommon in the United States where reports suggest that 98% of all gallstones originate in the gallbladder[12]. Twenty-four per cent of the patients in this study have stones in the CBD with or without gallbladder involvement. When patients from this study with intrahepatic stones[38] are added to the total, the prevalence of CBD

stones was 27%. This rate is much higher than western reports[12,32,33] and thus, in addition to differences in stone type, there are differences in stone location between Japan and western countries. This is supported by our finding of an increased prevalence of intrahepatic stones in Japan[38] and by the significantly increased prevalence of common duct stones in this study in patients with bilirubin stones compared to those with cholesterol and black stones.

Analysis by Stone Type: Repetition of the analysis by specific stone type highlighted differences in epidemiology and clarified characteristics identified when the group was analyzed as a whole.

Stone Location vs Stone Type: Both cholesterol and black stones are believed to form only in the gallbladder[12]. The lack of recurrent black stones after the original operation in patients with intrahepatic stones[38] and the absence of black stones in the common duct alone in this series strongly supports this theory for the latter group. It is widely believed that bilirubin stones form throughout the biliary tree and quite frequently form in multiple locations independently. The increased incidence of patients with cholesterol stones in the CBD alone and in the GB+CBD together compared to Japanese patients with black stones and patients from the United States who have predominantly cholesterol stones[49] made us evaluate the possibility that some proportion of cholesterol CBD stones in patients with GB+CBD stones formed in the common bile duct *de novo*. Table 11 outlines this possibility. Since black stones were absent from the bile ducts if no stones were present in the gallbladder, we assumed that all black stones in the CBD originated the GB (an prevalence of 7.55%). Then, assuming an equal probability that gallbladder stones of different types would pass into the common duct, the number of patients with stones of each type who would have stones present in the CBD through this mechanism was calculated (Table 11, column d). This number was then subtracted from the total number of patients with stones found in the GB+CBD (column b), giving the numbers in column e. This column indicates the number of patients who may have formed stones in the gallbladder and common duct independently. Of interest, 39.7% of patients with cholesterol and 81.9% of patients with bilirubin GB+CBD stones may have formed their CBD stones in the common bile duct rather than passing them from the gallbladder. In addition, although there were no patients with black stones in the CBD alone (Table 11, column f) there were 50 patients with cholesterol and 234 patients with bilirubin stones in this location. Since physicians believe that bilirubin stones can form directly in the CBD[37,41], these calculations suggest that they should also consider that a proportion of cholesterol stones found in the CBD at operation can also originate in this manner. Cholesterol stones can uncommonly form in the common duct primarily since one of the authors (R.S.) is aware of 4 patients who have had documented recurrence of cholesterol stones in the common bile duct on multiple occasions following normal cholangiography after cholecystectomy at the original operation. Also, western articles have reported a small incidence of this type of stone[20,43]. There may be a low incidence of recurrent common duct stones after cholecystectomy because post-prandial bile flow may carry the vast majority of stone nidi formed in the common duct during the interdigestive period into the intestine. A widened and/or irregular bile duct may provide the opportunity for such nidi to grow with the

Table 11. Estimate of the incidence of concomittant formation of stones in the gallbladder and common bile duct

Stone type	GB (a)	GB+CBD (b)	Total (c)	Total×7.55% (d)	(GB+CBD) (e) Total×7.55%	CBD (f)
Cholesterol	2086	295 12·5*	2362	178	117 39·7**	50
Bilirubin	308	221 41·8*	529	40 81·9	181 81·9**	234
Black	196	16 7·55*	212	16	0	0

* Number indicates the percent of all patients with gallbladder stones (total) who have stone concomittently in the gallbladder and common bile duct.

** Number indicates the theoretical percent of patients with stones in the gallbladder and common bile duct who developed these stones in both locations independently.

Column a=stones in gallbladder, column b=stones in the gallbladder and common bile duct, column c=a+b, column d=c×7.55%, the minium number of patients who passed stones from the gallbladder into the common bile duct, column e=b−d, the number of patients with stones which could form in the common bile duct *de novo*, column f=the number of patients with CBD stones in the absence of gallbladder stones.

duct and occasionally reach clinical significance. Some have observed that black stones are generally smaller than cholesterol and bilirubin stones. This may mean that such stones can pass into the duodenum without obstructing the ampulla as frequently as larger stones. This possibility cannot be excluded, but the size of the cystic duct in patients with GB stones is relatively small and should limit the range of stone sizes which can pass from the GB to the CBD.

Individual Stone Types: Rural living increased the prevalence of stones which may form in the common bile duct but did not change the prevalence of black stones which form only in the gallbladder. A possible mechanism for this may be the different composition of the traditional Japanese and western diets leading to differential effects on bile flow. The traditional Japanese diet contains large quantities of starch and is low in saturated fats and protein[48], the substances that stimulate the release of cholecystokinin[27], which in turn, causes relaxation of the sphincter of Oddi and contraction of the gallbladder[1]. Less stimulation of cholecystokinin release could decrease bile flow in response to a meal and lead to relative stasis, allowing more chance for formation of common duct stones. A life-long increase in pressure could predispose to duct dilatation, especially in a duct weakened by the aging process. In addition, a low protein diet is associated with a reduction of the β-glucuronidase inhibitor, glucaric acid, with a consequent increased opportunity for hydrolysis of bilirubin glucuronide to free bilirubin and glucaric acid [26,28]. Free bilirubin is sparingly soluble in bile and easily combines with calcium to form calcium bilirubinate. This is a major component of bilirubin stones. An alternative hypothesis is that rural patients are more susceptible to Odditis than urban patients, but there is no evidence for this and it doesn't explain why bilirubin stones are presently decreasing in incidence in Japan and do not occur in people of Japanese origin living in other countries[26]. Since the preponderance of patients with CBD stones are over 30 years of age, we cannot exclude long term effects secondary to Odditis caused by Ascaris[25], since as recently as 1958, the general population had

a 25% rate of infestation[54]. Since 1965 the rate has been at or below 5%[54] perhaps explaining the decreasing incidence of bilirubin stones. The question of why western countries have a low prevalence of CBD stones in the absence of gallbladder stones cannot be fully answered[24]. Is there a genetic defect[54] among asian people rendering them more susceptible to this condition?[29] The high incidence of similar stones from Brazil[7] makes diet and/or parasitism a much more likely cause than a genetic defect. Although the influence of sex is less important than living location, it is striking that for each stone type there is an increased prevalence of females. This has been noted previously for patients with cholesterol stones[49] but has not been clear for patients with bilirubin or black stones[49]. In the United States, the report of a male to female ratio of 3 : 5 among patients with black stones was corrected, because of the small sample size, by the number of hospital admissions for each sex, and of another study in Japan[46] confirm that there is an increased tendency for females to form black stones. Interestingly, an animal model for black stones, developed in the mouse by Trotman and co-workers[51] also demonstrates female predominance. The finding of an increased proportion of females among each stone type, despite the very different patterns of incidence and postulated difference in pathogenesis, suggests that being female increases susceptibility to gallstones of any type by a common mechanism. Estrogens are known to cause cholestasis[15,22] and during pregnancy the gallbladder and CBD relaxes excessively[11,40] as do other muscles[9,52]. These factors could influence stone formation by promoting stasis or could influence stone formation much later in life if the biliary tract never fully regained its tone. If the decrease in muscle tone and the stretching of connective tissue and elastic fibers that occurs with aging is superimposed, the decrease in the male to female ratio toward 1 : 1 with advancing age may be partially explained. Within each stone type, the average age of patients with GB+CBD stones was greater than that of patients with GB stones and the average age of patients with CBD stones was greater than that of those with GB+CBD stones. These data indicate that aging is also associated with an increased incidence of common duct stones, irrespective of stone type and that one or more of the following may occur with increasing age: (A) increasing relaxation of the wall of the common bile duct, (B) increasing stenosis of the spincter of Oddi or (C) decreasing ability of the common bile duct to contract after dilatation secondary to the passage of GB stones. An alternative hypothesis is that the cystic duct may also dilate with advancing age leading to an increased prevalence of passage of larger stones into the common duct.

Analysis by Stone Location: Among patients with GB stones, males have more bilirubin and fewer cholesterol stones than females but this difference was not present in the groups with GB+CBD together and CBD stones alone. When the male: female ratio was examined by stone type, subdivided into stone location, the differences became more explicable. In the gallbladder the male: : female ratios for cholesterol and for black stones were significant but the ratio for bilirubin stones was not, suggesting that differential stasis between the sexes was important for the first two groups but at the time when bilirubin stones formed there was stasis in the gallbladder in both sexes because of the aging process. In patients with GB+CBD stones, the sex difference was smaller but still present in patients with cholesterol stones and was not

present for patients with bilirubin stones, again reflecting the differences in age of the two groups. Neither patients with cholesterol or bilirubin CBD stones demonstrated a significant difference in the ratio of males to females, reflecting the fact that these patients had the oldest average age and thus the aging process may have obliterated the male: female difference.

Etiology: The reciprocal trends in the prevalence of bilirubin and cholesterol stones in Japan suggested that epidemiologic studies might help define factors important in the pathogenesis of both of these stone types. A number of studies[47,48] and experimental data[16,17,18] have suggested that formation of cholesterol stones is enhanced by diets high in saturated fat, refined sugar and animal protein, the antithesis of the traditional Japanese diet. Since the early 1950's, there has been a concommitant increase in cholesterol gallstones in Japan and a shift to a western-style diet[35,48]. Westernization has taken place more rapidly in urban than in rural areas. We suggest that this mechanism is most likely to explain the continuing prevalence of bilirubin stones, the differences between Japanese urban and rural populations and the changing prevalences of bilirubin and cholesterol stones. The focus concerning the etiology of bilirubin stones has been concerned with the frequent association with different parasites in various countries in Asia[19,25,30,39]. Parasites have become progressively less frequent in Japan for the past 15 to 20 years[54], but bilirubin stones still continue to be detected in relatively young people. This does not rule out a significant etiologic role in the past or a long term effect of previous parasitic infestation, especially ascariasis[26], but indicates that parasites are unlikely to be responsible for newly formed bilirubin stones, especially in patients less than 30 years of age. In Japan, there continues to be a high prevalence of concommitant bacterial infection in patients with bilirubin stones. Some feel that infection is a primary and others believe that it is a secondary factor in the formation of these stones because of inefficient clearing of bacteria due to dilatation and stasis in the biliary system. In contrast, infection is much less frequent in Japanese patients having cholesterol stones in the same locations. In the United States, in contrast to Japan, infection is an infrequent occurrence with asymptomatic gallstones and does not appear to be important in gallstone pathogenesis[13] probably because bilirubin stones are rarely seen in United States patients.

Hypothesis: This study has enabled identification of a number of factors affecting the type and location of gallstone formation making it possible to construct a theoretical natural history of gallstone disease interrelating these factors. Gallstones are very infrequent before puberty, perhaps because adult hormone levels and other conditions causing stasis have not been achieved. Thereafter, females outnumber males in all types of gallstones, but especially in cholesterol gallstones, perhaps due to the relationships between estrogens, cholesterol supersaturation of bile[11,22], and gallstone formation[9,16,17,47,52]. Concommitantly, western-style urban diets in Japan may lead to increased biliary cholesterol secretion[3,8,42,48]. For these reasons, cholesterol stones predominate in young urban adult females. Cholesterol stones may be more frequent in patients with disease limited to the gallbladder compared with patients with common bile duct involvement alone or in combination with the gallbladder, because female hormones may act on cholesterol metabolism[4,22] and gallbladder motility[11,40] rather than on the bile ducts. Black

stones may also be related to a western-style diet, but the additional relationship to the aging process cannot be explained at present. Bilirubin stones begin later in life and then increase in frequency with a much smaller female predominence because sex differences in serum hormone levels have decreased following menopause and may not be as important in the production of biliary stasis so often associated with this type of stone. The increasing prevalence of gallstones with advancing age may reflect a progressive relaxation and dilatation of the gallbladder and biliary tract. This process may not be uniform throughout the biliary tract, there by leading to formation of bilirubin stones in the gallbladder, common bile duct or intrahepatic ducts separately or together. This process is more likely to occur among rural patients, both because they are older and possibly as a result of the static effects of the traditional Japanese diet. Alternatively, the relationship with increasing age may reflect the increased chance for inflammation of the sphincter of Oddi by parasites in the past or by bacterial or viral diseases with the development of fibrosis or malfunction of the sphincter. The long term effects of past Odditis cannot be eliminated and a genetic susceptibility to duct dilatation is difficult to identify. Chronic relative biliary stasis may follow and, after a period of years, dilatation of the biliary tree may occur. This presupposes that the gallbladder in patients with gallstones does not act as an efficient pressure reducer through distention and fluid reabsorption. After stasis occurs, the normal rapid clearing of bacteria from bile may become inefficient and bacterial infection with resultant cholangitis may develop. Whether bilirubin stones form secondary to stasis or infection or both cannot be determined at present. Thus, in the oldest patients, after a lifetime of increasing biliary stasis, first more prevalent in females, but later equally common in males, there is increased formation of bilirubin stones with increased localization to the biliary ductal system.

Summary

Epidemiologic data, prospectively collected on 3387 patients operated upon for biliary tract disease at 40 hospitals in western Japan were analyzed to identify factors affecting gallstone type and location. Stones were classified visually as cholesterol (75%), bilirubin (16%) or black (9%) stones. Males and rural patients had more bilirubin and fewer cholesterol stones than females and urban patients. Patients with bilirubin stones were older than patients with cholesterol stones and the operative proportion of patients with bilirubin stones increased with advancing age. Patients with black stones were intermediate in age and did not show a proportional increase with advancing age. Males and rural patients had an increased incidence of common bile duct stones with or without gallbladder stones; living location was more important than sex. Patients with gallbladder stones were operated upon at a younger age than those with gallbladder and common bile duct stones alone. Stones in both the gallbladder and common bile duct were present in 29% of patients with bilirubin stones, 12% of those with cholesterol stones and in 8% of those with black stones. Stones in the common bile duct in the absence of gallbladder stones were present in 28% of patients with bilirubin stones, 2% of those with cholesterol stones and in none of those with black stones. Females more frequently had stones than males in all three stone types, but especially among those with cholesterol stones. The male : female ratio (1 : 1.83)

was less than that reported for U. S. patients, but patients under age 30 had a 1 : 2.89 ratio, comparable to western estimates. When patients with gallbladder stones were examined separately, males and rural patients still had more bilirubin and fewer cholesterol stones compared to female and urban patients. Among patients with gallbladder and common bile duct stones, there was less female predominance for each stone type. Among patients with common bile duct stones, the sex difference was no longer present. At present, the differences between Japanese and western gallstone disease lie in the increased incidence of bilirubin and decreased incidence of black stones. In keeping with this, there was an increased incidence of common bile duct stones among Japanese patients. In addition, there was a significant increase in the incidence of cholesterol common bile duct stones compared to United States patients. All black stones and the vast majority of cholesterol stones form in the gallbladder but bilirubin stones can originate anywhere in the biliary tree. We postulate that the increased incidence of common duct cholesterol stones may arise from *de novo* formation in the common bile duct in a small proportion of cases.

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和文抄録

西日本における胆石症
—胆石の種類及び所在部位に関する疫学的研究—

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西日本における当教室及び関連病院40施設で施行された3,387例の胆石症例について，疫学的分析を行ない，以下の結論を得た．

主たる胆石により症例を分析すると，コレステロール系石症例は75%，ビリルビン系石症例16%，黒色石症例9%であった．男性が女性より，また非都市地域に住む症例は，都市地域に住む症例より，ビ系石例が多く，コ系石例が少ないことが判明した．

一方，結石の種類から，その特徴を検討してみると，ビ系石例はコ系石例に比較し，高齢者が多い．すなわちビ系石対コ系石の比は，高齢者になるほど増加していた．

胆嚢及び総胆管ともに胆石が存在したものは，ビ系石例の29%，コ系石例の12%，黒色石例の8%で，総胆管内のみに存在した例はビ系石例の28%であるが，コ系石例では2%であり，黒色石例にはなかった．

胆石症全体の男女比は1：1.83で，米国の報告より女性例が少なかったが，30歳以下では男女比1：2.89と米国における比率とほぼ同一であった．

現在の本邦と米国との胆石症の主たる相異点は，ビ系石が多く，黒色石が少ないこと，さらに総胆管結石が多いこと，特に総胆管内に落下したと思われるコ系石が発見される率が多いことであるといえる．

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