Arch Jap Chir 49 (5), 555～571, Sept., 1980.

原　　著

Epidemiology and Etiology of Gallstones

YORINORI HIKASA, MASAO NAGASE, HIROSHI TANIMURA, RYUZO SHIODA, MOTOICHI SETOYAMA, NOBUAKI KOBAYASHI, SUMIO MUKAIHARA, TOSHIO KAMATA, KEISUKE MARUYAMA, HITOSHI KATO and KEIICHIRO MORI

Second Department of Surgery, Faculty of Medicine, Kyoto University
(Director : Prof. Dr. YORINORI HIKASA)

Roger D. Soloway

Hospital of the University of Pennsylvania, U. S. A.

Received for Publication, July 1, 1980.

Before and shortly after the Second World War gallstones found in Japanese people were mostly bilirubin stones, and the people in general used to eat larger amounts of crude carbohydrates rich in indigestible fibers and smaller amounts of protein, fat and sugar (a highly refined and easily absorbable carbohydrate) than Europe-American people whose gallstones are mostly cholesterol stones. However, in parallel with the increasing national wealth and the improved sanitary condition in recent Japan, the dietary habits of Japanese people have become westernized. Daily intake of protein and fat has increased, and quality of protein and fat has also changed. Daily intake of sugar has increased and that of crude and indigestible carbohydrates has decreased. With a significant correlation to these changes in dietary habits, patients either with cholesterol stones or with black stones have increased while those with bilirubin stones have decreased in recent Japan, especially in its urban areas.

Our epidemiological studies done during the last four years have shown that cholesterol stone patients and black stone patients have such similarity and difference as shown in Table 1. Among the cholesterol stones found in Japanese people, mixed or combination stones are more prevalent and pure cholesterol stones are still rare.

Age distribution of the patients having cholesterol stones in the gallbladder alone at the initial surgery are shown in Fig. 1 and those having black stones in Fig. 2. Cholesterol stones are most frequently seen in the 5th and 6th decades of life and become fewer in

Key words : Gallstone forming diets, Dilatation of the bile duct, Intrahepatic gallstones, Hepaticojejunostomy with external jejunostomy, Gallstone dissolving agents.
索引語：胆石形成食，胆管の拡張，肝内結石症，肝管空腸吻合術兼外腸瘻造設術，胆石溶解剤.
Present Address　Second Department of Surgery, Faculty of Medicine, Kyoto Uniuersity, Sakyo-ku, Kyoto 606, Japan.

Table 1 Similarity and difference between cholesterol stones and black stones viewed from epidemiological studies

Similarity : -

1) Usually found in the gallbladder.
2) Increasing in recent Japan.
3) Having similar sex ratio of incidence.
4) Showing similarity in compositions of conjugated bile acids, in ratio of glycine to taurine, and in total volume of bile acids in bile.
5) Showing no abnormal dilatation of common bile duct before the formation of stones.

Difference : -

Being different in age distribution.

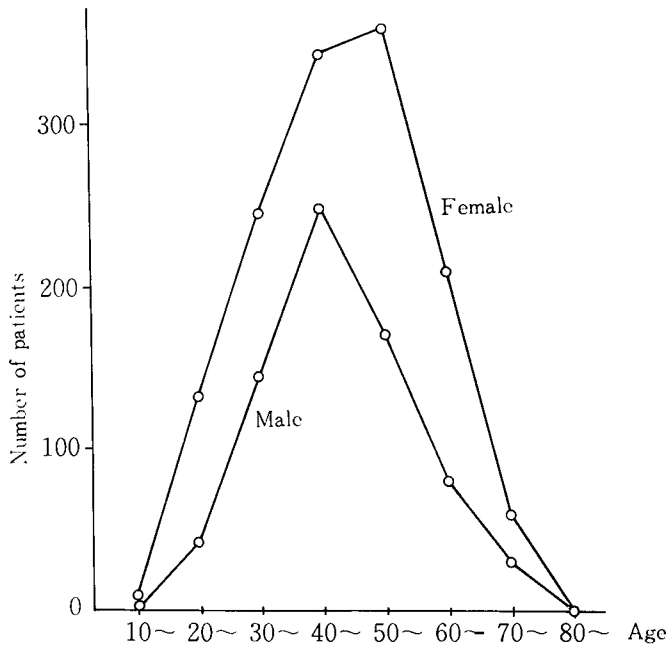


Fig. 1 Age distribution of patients with cholesterol stones in the gallbladder (1975. 6 - 1978. 7)

older patients. On the contrary, black stones increases with the ageing of the patients. As shown in Fig. 3, bilirubin stones increases markedly in patients older than 40 to 50 years.

Whole patients whose common bile duct dilated more than 1cm in diameter were analyzed according to their age and kinds of stones (Fig. 4). Among the cholesterol patients, who were mostly in the 5th or 6th decade of life, only few patients had abnormal dilatation of the common bile duct. Moreover, fewer patients with black stones showed common bile duct dilatation. On the contrary, about 60 to 70 per cent of bilirubin stone patients had common bile duct dilatation even at the 4th decade of life, although bilirubin stones were infrequently seen in these ages. The frequency of abnormal dilatation of the common bile

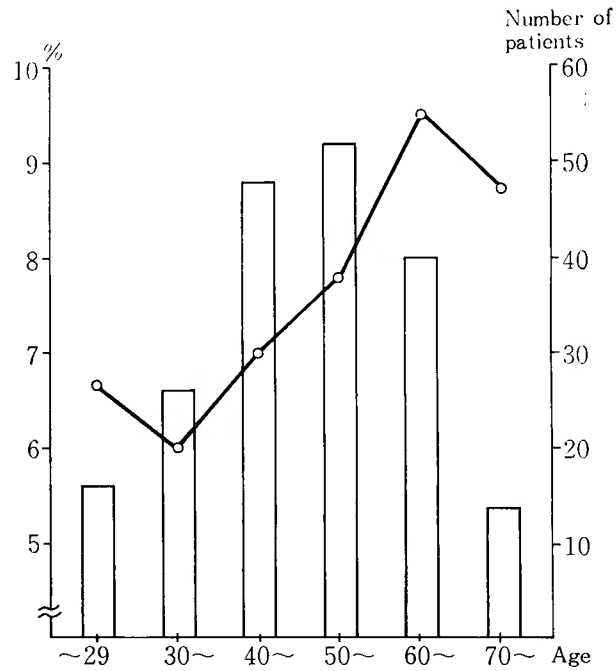


Fig. 2 Age distribution of the patients with black stones. 196 cases. (1975. 6 - 1978. 7)

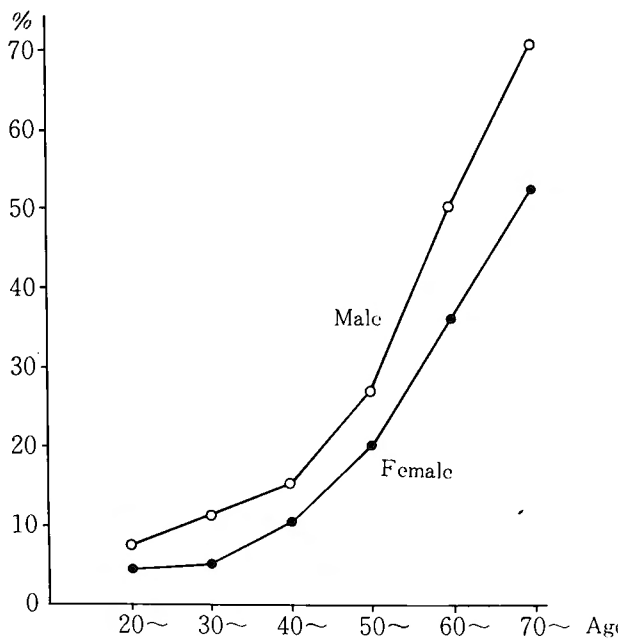


Fig. 3 Age distribution of patients with bilirubin stones. Primary operation 856 cases (1975, 6 - 1978, 7)

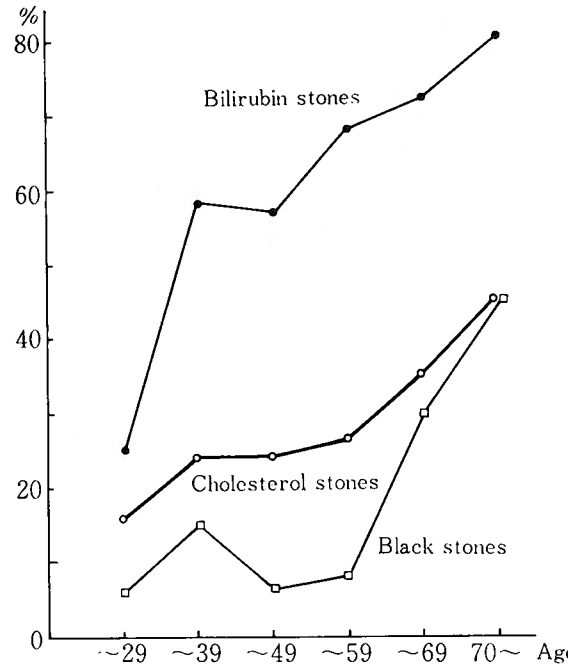


Fig. 4 Incidence of common bile duct dilatation

duct correlated well to the incidence of each kind of stones in the common bile duct.

Most patients older than 70 years had the abnormally dilated common bile duct regardless of kind of stones. This dilation is considered as one of senile phenomena.

The above mentioned phenomena were also observed among the patients having any kinds of stones in the gallbladder alone.

Recently by progress of high pressure liquid chromatography, measurements of each kind of conjugated bile acids in the bile have become possible. Glycochenodeoxycholic acid, which is contained in the bile in the largest amount among glycine conjugated bile acids, showed abnormally low level in the bile of bilirubin stone patients. KAN-JEY HO et al. have already demonstrated that glycochenodeoxycholic acid has the strongest inhibitory effect on β-glucuronidase activity among any kinds of conjugated bile acids.

As mentioned above, old Japanese people had taken smaller amounts of protein and fat. Low intake of protein may induce structural defects of bile duct wall. Release of cholecystokinin, which is elicited by ingestion of protein and fat, can not be achieved effectively by intake of such diets and may induce stasis of bile and dilatation of the common bile duct. These changes may facilitate ascending infection of intestinal bacteria into the biliary tracts. A very low intake of animal proteins rich in glycine apparently induces decrease of glycine conjugated bile acids in the bile. Therefore, it seems that the processes shown in Fig. 5 clarify the reasons why bilirubin stones were found so frequently in old Japanese

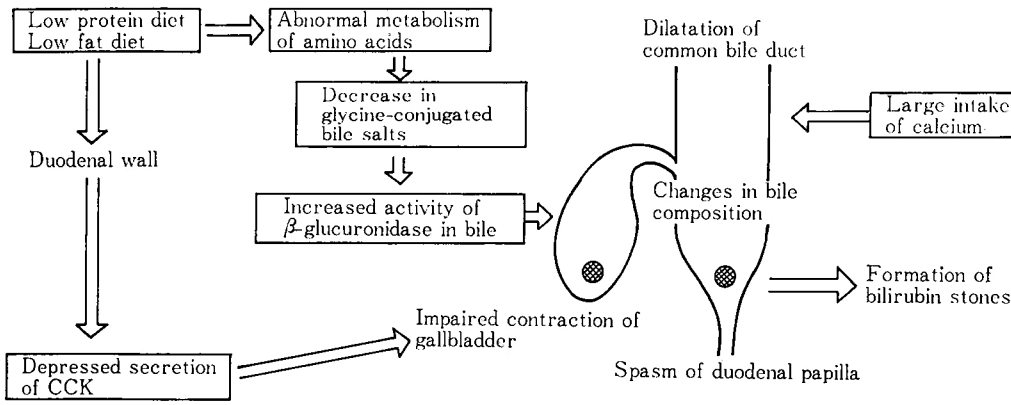


Fig. 5 Hypothesis on etiology of bilirubin stones

Table 2 Frequency of reoperation for gallstones

	Whole stones	Bilirubin stones	Cholesterol stones
Cholecystolithiasis	0.5%	0.2%	0.3%
Cholecysto- and choledocho-lithiasis	3.0	1.5	0.4
Choledocholithiasis	27.2	19.8	7.4
Intrahepatic gallstones	29.2	28.4	0.7

$$\text{Frequency of reoperation}(\%) = \frac{\text{Number of patients reoperated}}{\text{Number of whole patients operated}} \times 100$$

people. In other words, it appears that the initiating factors of bilirubin stones are whole body factor due to dietary habits.

Among the whole 4,676 patients operated on for gallstone diseases during the last 4 years, about 4 per cent of the patients had bilirubin stones in their intrahepatic ducts and their reoperation ratio was 28.4 per cent. This high ratio exceeded far those in patients with bilirubin stones either in the gallbladder alone or in the gallbladder and common bile duct, but was approximate to that in patients having bilirubin stones in the common bile duct alone (Table 2). These facts suggest that mechanism of formation of intrahepatic stones are same as that of bilirubin stones present in the common bile duct alone.

In view of the above mentioned characteristics of intrahepatic stones, the authors have endeavored to remove intrahepatic stones as far as possible by using a choledochoscope or a soft steerable catheter during surgery, and then constructed hepaticojejunostomy (Roux-Y) in order to prevent bile stasis and stone recurrence. Therewith we have prepared external jejunostomy using the proximal end of the jejunal loop, as shown in Fig. 6. When any stones are retained or reformed in the intrahepatic bile ducts, the prepared external jejunostomy is opened without laparotomy, and the retained or recurrent stones can be ex-

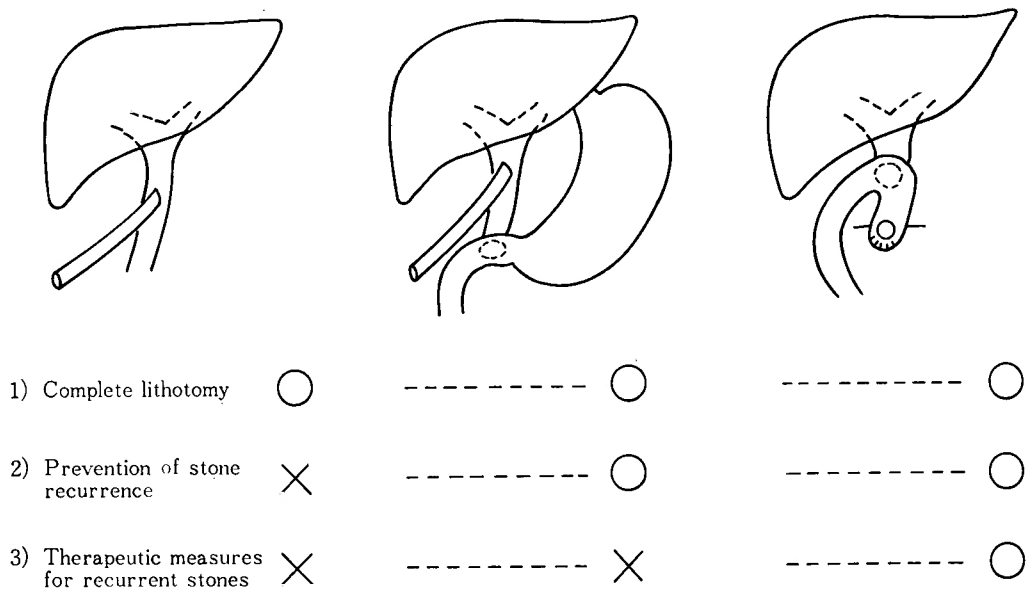


Fig. 6 Choledochal drainage, choledochal drainage and choledochoenterostomy, and hepaticojejunostomy and external jejunostomy (Hikasa et al. 1974).

tracted by a choledochoscope or a soft steerable catheter introduced into the intrahepatic ducts through the jejunal stoma. By using this technique developed by us, we have been able to obtain good results and to avoid to do hepatectomy on patients with intrahepatic stones; since the disease is not malignant in itself, the authors confine hepatectomy to the strictly indicated patients alone.

The results of above mentioned epidemiological studies have suggested that gallstones are formed by dietary factors. In order to verify the suggestion, experimental studies have been done using hamsters, which have similar anatomy of the hepatobiliary system and similar composition of bile acids to those of human being, and of which bile composition is plotted in the Small's triangular coordinate in similar pattern to that of human being.

First, according to the results of our epidemiological studies, young hamsters were fed with fat free diet containing either glucose or sucurose as a source of carbohydrates. These animals formed pure cholesterol stones in their gallbladders in very high incidences (Fig. 7).

Both rats having no gallbladder congenitally and hamsters cholecystectomized beforehand did not form gallstones. Experimental mixed stone or combination stone too were not formed in these animals having no gallbladder. These facts clearly indicate that the site of formation of gallstones of cholesterol moiety is the gallbladder.*

* If there are any anomalies in the intrahepatic bile ducts, not only bilirubin stones but also cholesterol stones and fatty acid calcium stones can be formed in the intrahepatic ducts. The cholesterol stones thus formed are different from typical stones formed in the gallbladder in their concentric cut surfaces and chemical compositions (cholesterol being contained in more than 50 per cent and bilirubin about in 10～20 per cent).

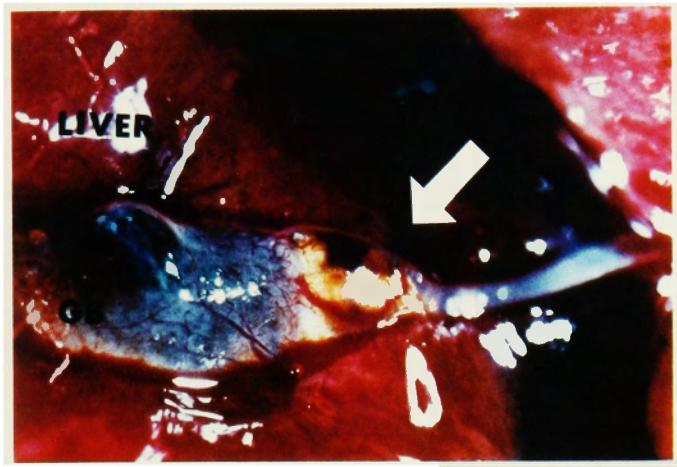
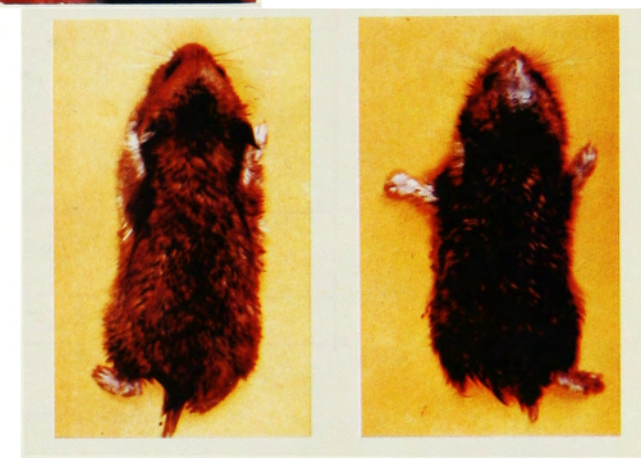


Fig. 7 Experimentally produced pure cholesterol stone (hamster)



after 3 weeks after 6 weeks

Fig. 8 Gallstone formation by fat free diet containing either glucose or sucrose as a source of carbohydrates (hamster)

Fig. 12 Hamster fed with our lithogenic diet.

However, fat and α-starch which human being intakes daily are not contained in these diets. Earlier than our experimental studies, DAM et al. of Denmark have found that young hamsters fed with the same diet form pure cholesterol stones in their gallbladder. However, the animals fed with the diet, though they form pure cholesterol stones, develop liver cirrhosis, dermatitis, epilation, anal prolapse, anal bleeding, loss of body weight etc. and finally die (Fig. 8). Since these pathological changes are never seen in cholesterol stone patients, these animal experiments can not be regarded as a real model of cholesterol cholelithiasis.

In accordance with the results of experimental study on rate of biosynthesis of cholesterol from acetate in the liver (Fig. 9), both replacement of glucose or sucurose by α-starch and addition of carboxymethyl cellulose (CMC) or agar-agar to the diet inhibited the formation of pure cholesterol stones in hamsters.

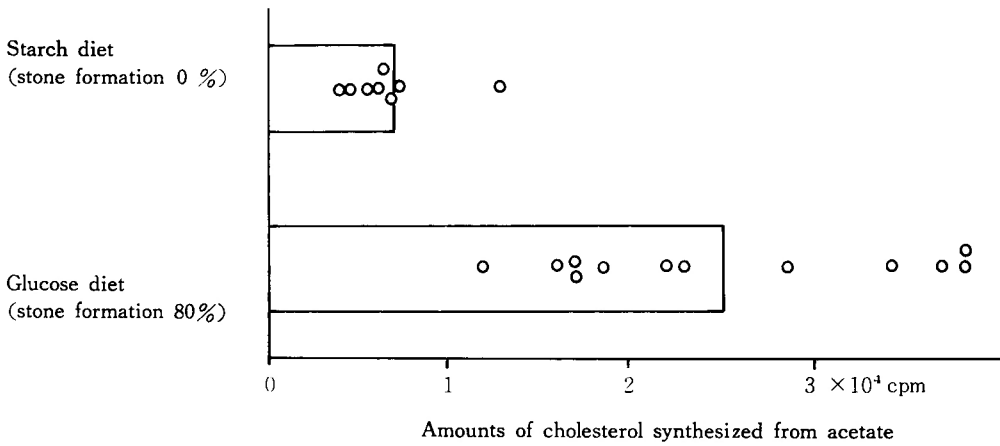


Fig. 9 Gallstone formation and acceleration of cholesterol biosynthesis in the liver

When various kinds of fats were added to the pure cholesterol stone forming diet, the fats with higher ratio of essential fatty acids to saturated fatty acids plus oleic acid inhibited formation of pure cholesterol stones more effectively (Fig. 10).

HMG • CoA reductase (Hydroxymethylglutaryl CoA reductase), a rate limiting enzyme of biosynthesis of cholesterol in the liver, is present in the hepatic microsomal membrane, of which phospholipids contain a large amount of essential fatty acids. And the activity of HMG • CoA reductase of the liver tissue was elevated by addition of saturated fatty acids to the diet and was maintained in normal range by addition of essential fatty acids (Fig. 11).

In daily life, human being eats carbohydrates in the form of easily digestible α-starch after cooking β-starch. The hamsters fed with fat free diet containing α-starch did not form pure cholesterol stones. Therefore, on the basis of the above mentioned results regarding the kinds of fats in the diet, either butter fat rich in saturated fatty acids or pure

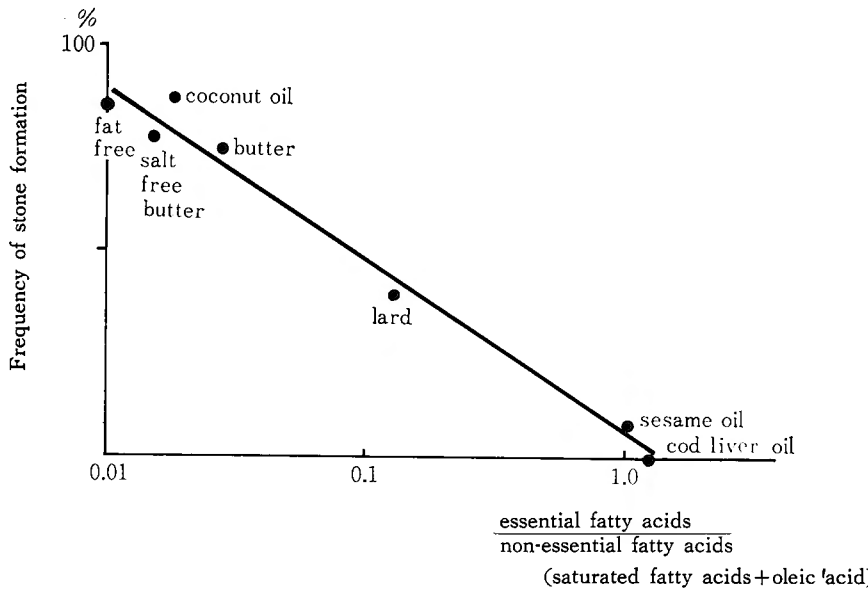


Fig. 10 Essential fatty acid contents in dietary fats and frequency of cholesterol stone formation

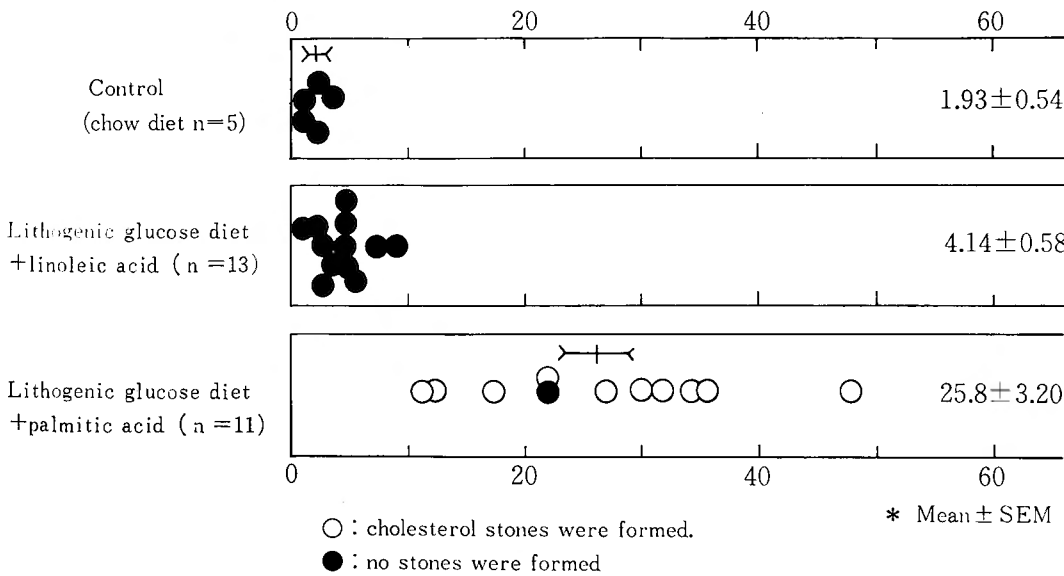


Fig. 11 Effects of dietary fats on activity of HMG・CoA reductase.
〔Activity of HMG・CoA reductase (nmol/hr/mg)〕

medium chain triglycerides (MCT) lacking essential fatty acids were added to the diet and were fed to the young hamstars, which formed pure cholesterol stones without showing the above mentioned pathological change (Fig. 12). Thus we have succeeded to induce the formation of pure cholesterol stones by feeding the animals with natural diets, which human being intakes daily. The stones thus formed had same fine structures as those of human being.

From the experimental results thus obtained, we have formulated the pure cholesterol stone forming diet which can be easily made of simple materials (Table 3), and the diet has been exclusively used in the following experiments.

Table 3 Experimental gallstone forming diet

Pure cholesterol stone forming diet		Mixed stone·Combination stone forming diet	
Glucose	60.0%	Glucose	50.0%
		α-Starch	20.0
Casein	20.0	Casein	8.5
Butter	10.0	Butter	5.0
Vitamins	1.5	Vitamins	1.5
Minerals	5.0	Minerals	5.0
Cellulose	3.5	Cellulose	10.0

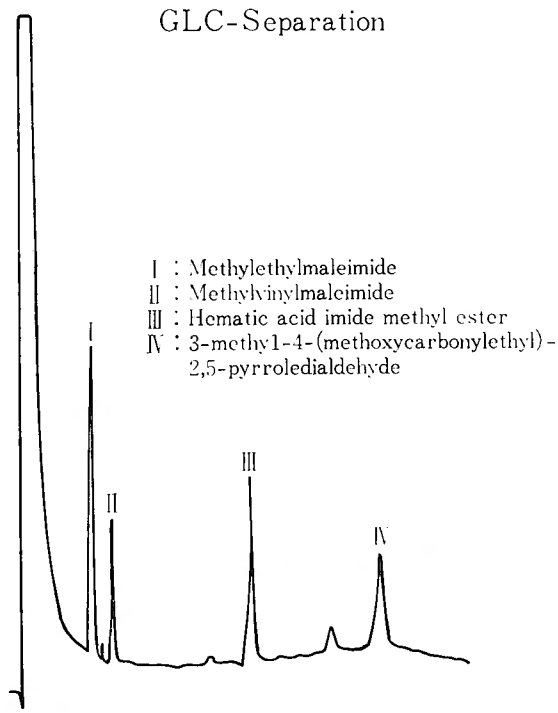
It has been reported that there are syntropisms both between diabetes mellitus and cholesterol stones and between cholelithiasis of Europe-Americans and their pancreatitis. The animals fed with our lithogenic diet had a disturbed metabolism of glucose and had a predisposition to develop pancreatitis. Our experimental studies on these subjects will be presented elsewhere. These syntropisms also have indicated that our experimental procedure to induce the formation of pure cholesterol stones is a very proper model of human cholesterol cholelithiasis.

Daily diet of Japanese people, who form mixed stones or combination stones more frequently than pure cholesterol stones, are characteristically, as mentioned above, rich in crude α-starch containing indigestible fibers and poor in protein and fat. Therefore, we fed hamsters with a low protein diet, in which protein and glucose were reduced and α-starch and CMC were increased (Table 3). The young hamsters fed with this diet formed stones which could be classified as mixed stones or combination stones. The fine structures of these mixed stones were same as those of human being ; hemispherical granules of bilirubin calcium being disseminated among columnar or laminar crystals of cholesterol. Some of the animals fed with the mixed stone forming diet formed combination stones. Hence, it was concluded that mixed stones and combination stones were formed by same dietary factors. Thus formed combination stones had same fine structures as those of human combination stones ; the parts of stones other than pure cholesterol being composed of either mixed stones or calcium phosphate and calcium carbonate.

It has been clinically reported that the bile of patients with mixed stones is more

frequently contaminated by bacteria than the bile of patients with other cholesterol stones. Therefore, the bile was obtained from the gallbladder of the hamsters fed with mixed stone forming diet for 40 days and was cultured, but no bacteria were detected. The fact indicates clearly that hydrolysis of bilirubin glucuronide by bacterial β-glucuronidase plays no role in formation of experimental mixed stones. Moreover, it has been demonstrated that the β-glucuronidase present in the bile of these animals are not bacterial origin but of tissue origin viewed from its pH profile and Km value. These facts suggest that bacterial infection in patients with mixed stones is a secondary phenomenon due to presence of the gallstones.

Black stones or so-called black colored stones which are found occasionally in the human gallbladder are of two types ; the one being like a coke or a coal with metalic luster and the other being like a comfit or a ball. Both types contain more or less bilirubin calcium. The former shows coexistence of calcium and sulfur and contains copper too, and the latter is mainly composed of calcium phosphate and calcium carbonate and contains sulfur too. WOSIEWITZ has already demonstrated that black element of black stones is degenerated tetrapyrrolic bile pigment (Fig. 13). We have dissolved black stones as far as possible and analyzed by 5 % SDS polyacrylamide gelelectrophoresis. We have detected protein in the place of high molecular (more than one million) substances. Moreover, this



Chromate degradation products of black stones

Fig. 13 Proof that black components of black stones are tetrapyrrolic bile pigment. (by U. Wosiewitz, 1978)

protein being rich in isoleucine, leucine and valine (hydrophobic amino acids) has similar amino acid composition to the protein constructing bodily membrane and is supposedly derived from the latter. And the fact that the non-hydrolyzed black derivatives, so-called humin, are formed during the process of amino acid hydrolysis means that the materials contain carbohydrate (probably glycosaminoglycan). These suggest that proteoglycan may participate in formation of black stones.

Our epidemiological studies have indicated, as mentioned above, that etiology of black stones is similar to that of cholesterol stones, though they are different in their patient's age distribution. SOLOWAY et al. have reported that "pigment stones" are found in about 29 per cent of cholelithic patients in U.S.A.; being not so rare as has been hitherto reported, and that the "pigment stones" are mostly found in elderly persons (Fig. 14). DR. SOLOWAY worked in our department in 1978. And it has been clarified that their "pigment stones" are not equal to the stones classified as bilirubin stones by us, but are equal to our black stones. Then, we fed old hamsters with our pure cholesterol stone forming diet, which is

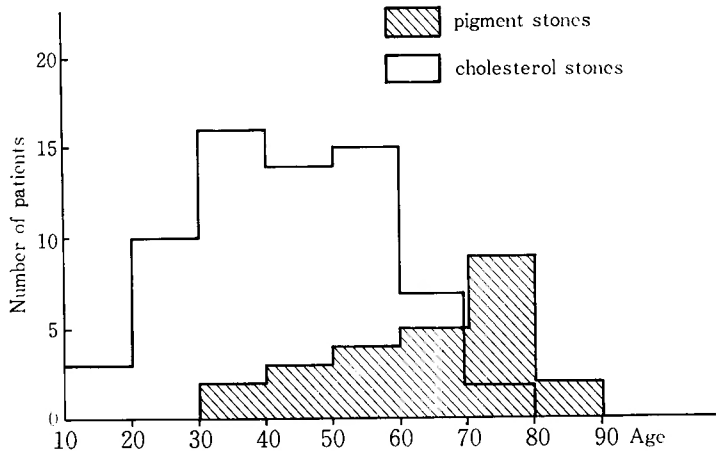


Fig. 14 Incidence of pigment or cholesterol gallstones according to age of patients at cholecystectomy. (B. W. Trotman et al., Philadelphia, 1975)

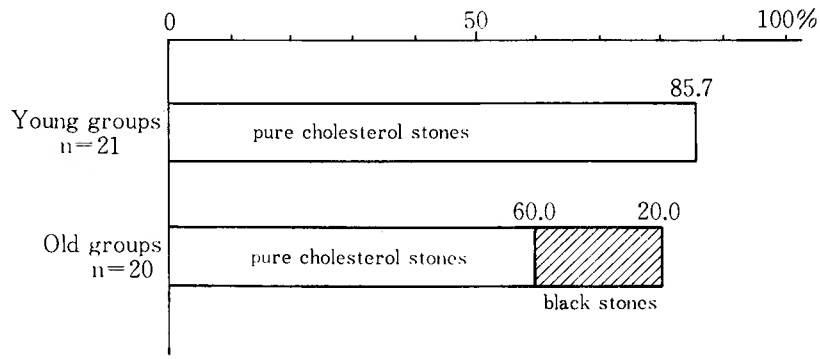


Fig. 15 Experimental gallstone formation (hamster)

similar to diets of Europe-American people. In contrast to the results obtained in young hamsters, 60 per cent of the old hamsters formed pure cholesterol stones and 20 per cent formed black stones in their gallbladder (Fig. 15). The amorphous structure and chemical composition of the experimentally produced gallstones were same as those of human black stones.

We have done experiments to induce the formation of various kinds of gallstones. Each kind of gallstones experimentally produced had fine structure and chemical composition quite similar to those of the corresponding kind of human gallstones. It has been clarified that pure cholesterol stones are produced by whole body factors, especially by dietary factors alone. Mixed stones or occasionally combination stones are formed when a condition of low protein is added to the lithogenic diet. And black stones are formed when a condition of senility is added to the lithogenic diet.

In view of the effects of dietary factors on HMG·CoA reductase (a rate limiting enzyme of cholesterol biosynthesis) and on the experimentally produced pure cholesterol stone itself, dietary therapy for pure cholesterol stones, especially for those of small. size and of floating type, is largely expected to be effective. Nowadays, chenodeoxycholic acid (CDCA) and its stereoisomer ursodeoxycholic acid (UDCA) is being utilized clinically to dissolve cholesterol stones. Therapeutic effect of CDCA is rationally expected, since CDCA inhibits HMG·CoA reductase activity with well corresponding lowering of lithogenic index of the bile. Inspired by fine crystalline structure of pure cholesterol stones, the following experiments have been done. Pellets of cholesterol labelled with ^{14}C were prepared and were incubated in the bile obtained from the patients treated preoperatively either with CDCA or with UDCA. The pellets dissolved far rapidly in the bile obtained from the patients

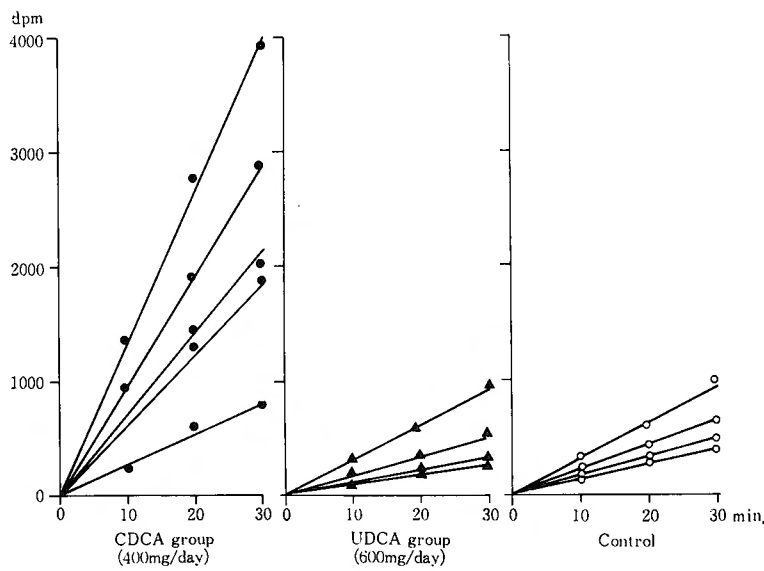


Fig. 16 Solubility of ^{14}C-cholesterol pellet in the bile of patients given CDCA or UDCA

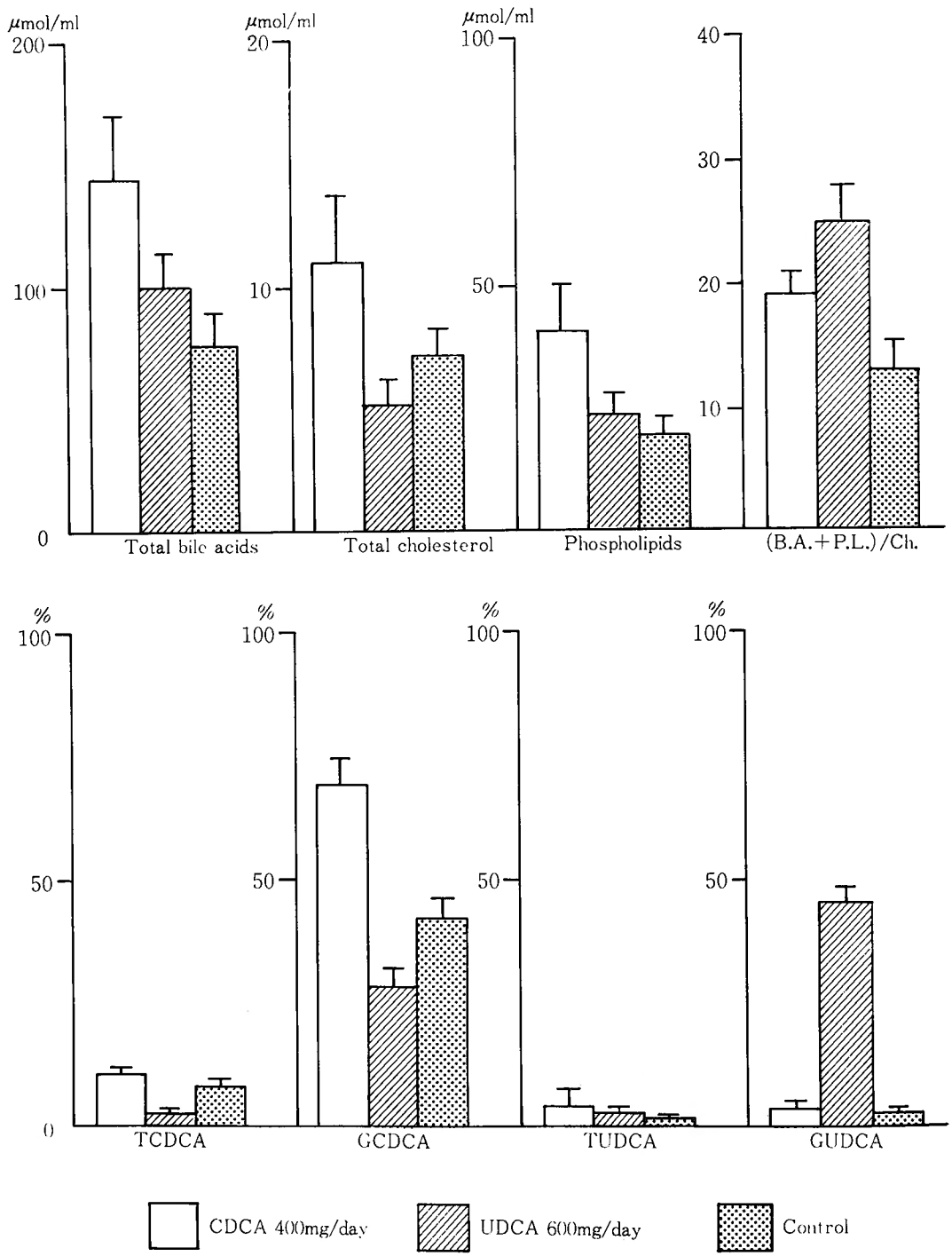


Fig. 17 Changes in bile lipid composition by administration of CDCA or UDCA (gallbladder bile, Mean ± SE)

treated with CDCA (Fig. 16). This fact suggests that dissolving mechanism of CDCA on cholesterol crystal is different from that of UDCA.

Among the conjugated bile acids increasing in the bile by CDCA administration, the one which increases mostly is glycochenodoxycholic acid (Fig. 17). In view of these facts, it seems that not only the inhibitory effect of CDCA on HMG·CoA reductase activity but also the direct dissolving effect of CDCA, especially of its glycine conjugate, participate in the dissolving effect of orally administered CDCA on pure cholesterol stones.

However, in case of its clinical application, circadian rhythm of activity of HMG·CoA reductase and that of cholesterol biosynthesis should be considered. By this consideration, its effect will be intensified and its adverse effects will be avoided.

There are some kinds of stones other than the above mentioned stones : Bilirubin calcium stone which has always sulfur in its center and is exclusively composed of bilirubin calcium having fine structure of semispherical granules ; Bilirubin fatty acid calcium stone which shows on its cut plane stratified structures with fatty acid calcium looking like white slate ; and fatty acid calcium stone which can not be included in bilirubin stone group is composed mainly of fatty acid calcium, contains more or less cholesterol and few bilirubin, and is of waxy luster and feeling, and its cut plane is white yellow and its stratified structure is not concentric but imbricate. We have still not succeeded in experimental formation of these stones. Although local factors has been hitherto attached importance to the formation of bilirubin stones, our epidemiological studies have demonstrated that formation of bilirubin stones is initiated by whole body factor, that is by dietary factors. It is expected that this hypothesis will be proved by future experimental studies.

References

1) Bouchier IAD : Recent Advances In Gastroenterology, No. 3, pp 199, Churchill Levingstone, Edinburgh London and New York, 1976.
2) Berk JE . Developments In Digestive Diseases, pp 111, Lea and Febiger, Philadelphia, 1977.
3) Baron DN, Comprton N, et al Recent Advances In Medicine, No. 17, pp 323, Churchill Livingstone, Edinburgh London and New York, 1977.
4) Been JM, Bills RM, et al : Microstructure of gallstones. Gastroenterology **76** 548, 1979.
5) Campbell CB, Cowlcy DJ, et al : Dietary factors affecting biliary lipid secretion in the rhesus monkey. A mechanism for hypocholesterolaemic action of polyunsaturated fat. Europ J Clin Invest **2** : 332, 1972.
6) Carulli N, De Leon MP, et al : Hepatic cholesterol and bile acid metabolism in subjects with gallstones . Comparative effects of short term feeding of chenodeoxycholic and ursodeoxycholic acid. J Lipid Res **21** : 35, 1980.
7) Edwards PA, Muroya H, et al : In vivo demonstration of the circadian rhythm of cholesterol biosynthesis in the liver and intestine of the rat. J Lipid Res **13** : 396, 1972.
8) Einarsson K and Grundy SM : Effects of feeding cholic acid and chenodeoxycholic acid on cholesterol absorption and hepatic secretion of biliary lipids in man. J Lipid Res **21** : 23, 1980.
9) Ginsberg RL, Duane W, et al : Hepatic 3-hydroxy-3-methylglutaryl CoA reductase activity in hamsters on a lithogenic diet. J Lab Clin Med **89** : 928, 1977.
10) Hashimoto K : Experimental studies on gallstones in hamsters. Arch Jap Chir **35** : 981, 1966.
11) Heaton KW : Bile Salts In Health And Disease, Churchill Livingstone, Edinburgh and London, 1972.
12) Hikasa Y, Kuyama T, et al : Initiating factors of gallstones, especially cholesterol stones (II). Arch Jap Chir **34** : 1430, 1965.

13) Hikasa Y, Matsuda S, et al : Initiating factors of gallstones, especially cholesterol stones (III). Arch Jap Chir **38** : 107, 1969.
14) Iijima Y, Yamazaki M, et al : Effects of dietary fatty acids on hepatic 3-hydroxy-3-methylglutaryl CoA reductase activity in hamsters on high-glucose diet. Arch Biochem Biophys **196** : 265, 1979.
15) Kang-Jey Ho, Le-Hong C Ho, et al : Characterization and determination of the activity of biliary β-glucuronidase in rats. J Lab Clin Med **93** : 916, 1979.
16) Kritchevsky D and Story JA : Binding of bile salts in vitro by nonnutritive fiber. J Nutr **104** : 458, 1974.
17) Muroya H, Suzue R and Hikasa Y : Stimulation of hepatic cholesterol biosynthesis by dietary glucose, and its relation to cholesterol gallstone formation in the hamster. Arch Biochem Biophys **124**: 12, 1968.
18) Maki T : Pathogenesis of calcium bilirubinate gallstones : role of E. coli, β-glucuronidase and coagulation by inorganic ions, polyelectrolytes and agitation. Ann Surg **164** : 90, 1966.
19) Maruyama K, Tanimura H, et al : Analysis of conjugated bile acids in bile by high-pressure liquid chromatography. Clin Chim Acta **100** : 47, 1980.
20) Normann PT and Norum KR : Newly synthesized hepatic cholesterol as precursor for cholesterol and bile acids in rat bile. Scand J Gastroent **11** : 427, 1976.
21) Nilsson S : Synthesis and secretion of biliary phospholipids in man. Acta Chir Scand Supplementum 405, 1970.
22) Nagase M, Hikasa Y, et al : Etiology of cholesterol gallstones. Gastroent Jpn **14** : 40, 1979.
23) Nagase M, Tanimura H, et al : Present features of gallstones in Japan. A collective review of 2144 cases. Am J Surg **135** : 788, 1978.
24) Nagase M, Tanimura H, et al : Treatment of intrahepatic gallstones. Arch Jap Chir **47** : 467, 1978.
25) Nair PP and Kritchevsky D : The Bile Acids, Chemistry, Physiology and Metabolism, Vol. 2, Plenum Press, New York-London, 1973.
26) Nagase M, Hikasa Y, et al : Gallstones in Western Japan. Factors affecting the prevalence of intrahepatic gallstones. Gastroenterology **78** : 684, 1980.
27) Robins SJ and Fasulo J : Mechanism of lithogenic bile production : Studies in the hamster fed an essential fatty acid-deficient diet. Gastroenterology **65** : 104, 1973.
28) Schoenfield LJ, Bonorris GG, et al : Induced alterations in the rate-limiting enzymes of hepatic cholesterol and bile acid synthesis in the hamster. J Lab Clin Med **82** : 858, 1973.
29) Schneeman BO and Gallaher D : Changes in small intestinal digestive enzyme activity and bile acids with dietary cellulose in rats. J Nutr **110** : 584, 1980.
30) Shioda R, Wood PDS, et al : Determination of individual conjugated bile acids in human bile. J Lipid Res **10** : 546, 1969.
31) Soloway RD, Trotman BW, et al : Pigment gallstones. Gastroenterology **72** : 167, 1977.
32) Small DM : The formation of gallstones. Advanced Intern Med **16** : 243, 1970.
33) Tanimura H, Shioda R, et al : Initiating factors in formation of cholesterol gallstones. Arch Jap Chir **47** : 427, 1978.
34) Tanimura H : Experimental studies on the etiology of cholelithiasis. Arch Jap Chir **34** : 1160, 1965.
35) Tanimura H, Takenaka M, et al : Pathogenesis and treatment of pancreatitis due to essential fatty acid deficiency. Gastroent Jpn **12** : 483, 1977.
36) Tanimura H, Shioda R, et al : Initiating factors of cholesterol gallstones and pancreatitis. Arch Jap Chir **45** : 3, 1976.
37) Vlahacevic ZR, Bell CC, et al : Significance of the liver in the production of lithogenic bile in man. Gastroenterology **59** : 62, 1970.
38) Wood PDS, Shioda R, et al : Dietary regulation of cholesterol metabolism. Lancet (Sept. 17, 1966) 604, 1966.
39) Wheeler HO : Biliary excretion of bile acids, lecithin and cholesterol in hamsters with gallstones. Gastroenterology **65** : 92, 1973.

和文抄録

胆石の疫学と成因

京都大学第2外科学教室（主任：日笠頼則教授）

日笠　頼則，長瀬　正夫，谷村　　弘，
塩田　隆三，瀬戸山元一，小林　展章，
向原　純雄，鎌田　寿夫，丸山　啓介，
加藤　仁司，森　敬一郎

Ⅰ．過去3ケ年間に京大第2外科及び関連病院40施設において手術を行った胆石症4,676例を集計検討した結果と，これ迄に教室で行ってきた胆石形成実験の結果から次の様な結論を得た．

1) 純コレステロール石は精製せる糖質（砂糖，ブドウ糖），動物性脂肪を多く含み，植物性線維の乏しい食生活によってその形成が誘発される。

2) 上記の様な食生活を高齢者がすると黒色石（純色素石）が形成される。

3) 上記の食餌にα澱粉，線維類を加えると共に蛋白質含有量を少なくすると，混合石または混成石が形成される．

4) ビリルビン系石の形成の第一歩にも食餌性因子が関与している．即ち，低蛋白・低脂肪食殊に低動物性蛋白質食は胆汁酸中のグリシン抱合型胆汁酸特にglycochenodeoxycholic acidの減少を招き胆汁の有するβ-グルクロニダーゼ活性抑制効果は低下する．また同時にそれによって，胆管壁の脆弱化，コレシストキニンの分泌不足よる胆汁鬱滞ももたらされ，相乗的にビ系石の形成が誘発されるものと考えられる．

Ⅱ．肝内結石症の治療法として，著者らの創案した肝管空腸吻合術兼外腸瘻造設術を紹介すると同時に，肝内結石の成因も胆汁組成の変化，ひいては食生活の面から検討すべきであることを述べた．

Ⅲ．純コレステロール石溶解剤としては，CDCAの方がUDCAより有効であることを示唆するデータが得られた．