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Review Article

# Classification and Nomenclature of Gallstones Revisited

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Over the decades, there has been a great deal progress in the understanding of gallstones owing to the continuous efforts aimed at elucidating their pathogenesis. An optimal classification system is needed because the etiology, pathogenesis, clinical features and treatment can be different according to the classes. Currently, two systems are widely used: one from the National Institutes of Health (NIH)-International Workshop on Pigment Gallstone Disease held in 1981 and the other from Gallstone Research Committee from the Japanese Society of Gastroenterology in 1984. However, some stones cannot be classified into either of these categories. In addition, several terms have been not been clearly defined. In several aspects, both systems need to be reevaluated. This paper reviewed the classification systems and terms that are currently used for gallstones, and raises several points that need to be reconsidered. In the near future, large scaled prospective studies on gallstones need to be carried out on the basis of the external color, chemistry, cutting surface, etc. Only when these studies are completed can an ideal classification system for gallstones be expected.

**Key Words:** Cholelithiasis, classification

## INTRODUCTION

Cholelithiasis is one of the most prevalent diseases affecting the gastrointestinal tract. An optimal classification system for gallstones is needed because the etiology, pathogenesis, clinical features and treatment can be different according to the classes. Over the past several decades, there have been continuous efforts aimed at elucidating the pathogenesis of gallstones, and the rapid proliferation of novel methods for analyzing the composition and the morphology of gallstones have been reported. With progress in scientific technology, new classes of gallstones can be added to the existing classification systems. Moreover, the incidence and composition of gallstones can change over time.[1] Therefore, the classification systems need to be revised from time to time.

The best classification system for gallstones generally accepted and used widely must fulfill the following criteria: 1) it must have etiologic significance; 2) the terminology used should be simple and easily understood; 3) it must be relevant to the therapeutic procedures to be employed; and 4) it must be understood internationally.[2] Therefore, this account will review the classification systems and terms that are currently used for gallstones.

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## HISTORICAL BACKGROUND

Several suggestions have been made in classifying gallstones since early 20th century.[3]

In 1896, Naunyn proposed a classification of gallstones based on the etiologic factors (stasis vs.infection).[4] This concept was generally accepted until 1924 when Aschoff suggested an additional causative factor, a metabolic derangement (Table 1).[5] Unfortunately, the classification had not been generally accepted over the 73 years since the publication of this study.

In May 1981, the 1st National Institutes of Health (NIH)-International Workshop on Pigment Gallstone Disease was held at the University of Pennsylvania. In this workshop, gallstones were broadly classified as being cholesterol or pigment stones, and the pigment stones were further divided into black or brown stones (Table 2).[6] This

**Table 1.** Classification of Gallstones[5]

| |
|---|
| Inflammatory stone |
| Metabolic stone |
| Pure pigment |
| Calcium bilirubinate |
| Pure cholesterin (solitaire) |
| Combination stone |
| Primary metabolic and secondary inflammatory |
| Stasis stone |
| Primary in common duct (earthy) |

**Table 2.** Classification of Gallstones[6]

| |
|---|
| Cholesterol stone |
| Pigment stone |
| Black stone |
| Brown stone |

classification system is one of the most popular systems these days.

In 1986, the Gallstone Research Committee from the Japanese Society of Gastroenterology proposed a new classification system (Japanese classification), which divided gallstones into three different classes: cholesterol, pigment, and rare stones. Cholesterol stones were sub-classified into pure cholesterol, combination, and mixed stones, while pigment stones were further divided into calcium bilirubinate and black stones (Table 3).[3,7-9] The classification systems reported by Naunyn and Aschoff were based on the etiology of the gallstones, whereas the NIH and Japanese classification also considered the composition and morphology of the gallstones.[6,7,10,11]

## CLASSIFICATION OF GALLSTONES

### Classification by composition

Most investigators have agreed to classifying gallstones into two groups, cholesterol and pigment, based on their major composition. Gallstones containing cholesterol as the main constituent are classified as cholesterol stones, whereas those predominantly composed of bile pigments are called pigment stones.[6,12-14] However, in the

**Table 3.** Japanese Classification of Gallstones

| |
|---|
| Cholesterol stone |
| Pure cholesterol stone |
| Combination stone |
| Mixed stone |
| Pigment stone |
| Black stone |
| Calcium bilirubinate stone |
| Rare stone |

Japanese and NIH-classification, 'cholesterol stones' are defined as stones with cholesterol comprising more than 70% of the stone dry weight.[6,11] The stone components were weighed and expressed as a percentage of the initial weight of the stone.[15]

The dividing line between cholesterol and pigment stones is based on the facts that the proportion of cholesterol is usually more than 70% in cholesterol stones; while the cholesterol content in pigment stones is less than 25% to 30%.[6,7,9,11,16] However, the problem is that there is an intermediate group of stones containing 30% to 70% cholesterol.[17-19] Several investigators have used a threshold of 50%[20-22] or even 25%[23,24] of the dry weight of the stone to separate cholesterol stones from pigment stones. It may be reasonable to readjust the threshold of the cholesterol content for defining a 'cholesterol stone', or to introduce an additional criterion of a cholesterol stone, such as stones with morphological characteristics (for example, a radial fashion on cross section), even if the cholesterol content of those stones is less than 70%.

The principal constituent of pigment stone is calcium bilirubinate, which forms an average of 40% to 60% of dry weight. In addition, the cholesterol content is usually less than 25% to 30%.[6,19] However, pigment stones are vaguely defined as stones consisting mainly of pigment (calcium bilirubinate), in contrast to the cholesterol stones which have a threshold percentage of their constituents.[6,19] In one report, the calcium bilirubinate content of a black stone, which is a type of pigment stone, ranged from 10% to 90%.[25] However, there is some controversy as to whether extreme cases of stones containing 10% calcium bilirubinate can be classified as pigment stones. In

addition, the average cholesterol content of intrahepatic stones, which were categorized as brown pigment stones on a visual inspection and by infrared spectroscopy was 43%. This is in contrast to the concept that the cholesterol content of pigment stones is no more than 25% to 30%.[26] In this situation, a modification of the classification system may be indispensable.

Pigment stones contain minor components other than calcium bilirubinate and cholesterol such as calcium carbonate, calcium phosphate and calcium fatty acids. The composition of a black pigment stone differs from that of brown pigment stone. Calcium bilirubinate is the major component of both stones as previously mentioned. Calcium carbonate and calcium phosphates are contained in black pigment stones but are rarely found in brown stones. However, calcium fatty acids are found only in brown stones. Therefore, measuring these minor components in addition to calcium bilirubinate would be helpful for differentiating between brown and black pigment stones.[6,7]

There appears to be no objection to classifying gallstones as either cholesterol or pigment. However, the definitions should be clarified, and the dividing line between the two classes needs refinement, as some gallstones that cannot be classified into any of these two classes.

## Classification by morphology

The indexes that can be used for the morphological classification of gallstones are the external appearance (color, shape) and the internal structure (cross sectional shape).[19,27-30]

Cholesterol stones. The macroscopic classification of gallstones proposed by the Japanese Society of Gastroenterology is based on the presence of characteristic structures on their cut surface.[31] According to this classification, cholesterol stones can be divided into three subtypes; pure cholesterol stones, mixed stones and combination stones (Table 3). Cholesterol stones containing more than 70% cholesterol are further divided into three subdivisions according to their cross sectional appearance.

Pure cholesterol stones have a radial structure from the center to the periphery on cross section (Fig. 1).[32] Most cholesterol gallstones have pigment at the center and grossly visible cholesterol crystals although their pathogenetic process has not been clarified.[32,33] The stones are considered to be pure cholesterol stones when the diameter of the pigment center does not exceed one third of the stone diameter.[31] However, this classification of gallstones based on the fraction of diameter of the pigmented portion should be further supported by scientific evidence. They contain more than 95% cholesterol in most layers.[34,35] The external appearance is usually oval to round, and the color ranges from white to yellow. The typical case has a mulberry shape.[34,35]

Mixed and combination stones differ in their distribution of cholesterol and other constituents. On cross section, a combination stone is composed of two definite separate layers; an external layer with pigment constituents and an inner one with a cholesterol component or vice versa. By definition, the thickness of the external layer must be greater than 1 mm (Fig. 2).[35,36] The inner layer of these stones radiates from the center to the periphery like the cross-sectional appearance of pure cholesterol stones. The external shape of combination stones is oval or round and the color is brownish or dark brown due to the pigment component. In other words, combination stones are often referred to as combined or composite stones.[36,37]

The cut surface of a mixed stone is with a blend of a concentric and radial shape because the main components of the stone, cholesterol and pigment, are mixed throughout the layers (Fig. 3). The external layer is not definite.[35,36] The surface of the mixed stone exhibits various shapes ranging from round to faceted. The color of the surface varies; yellowish white, yellowish brown, greenish brown, or black brown.

Stewart, et al. examined combination stones using scanning electron microscopy.[37] Bacteria were noted within the pigment coats but not in the cholesterol portion of the combination stones. In addition, they could not locate any bacteria in pure cholesterol stones. Tabata and Nakayama reported a higher bacteria detection rate in combination stones, compared to pure cholesterol stone.[38] Furthermore, they observed that the outer shell of a combination stone contained abundant bacteria, suggesting that a bacterial infection may

**Fig. 1.** Cut surface of a pure cholesterol stone showing a radial structure from the center to the periphery.

**Fig. 4.** Cross sectional morphology of a brown pigment stone showing concentric layers.

**Fig. 2.** Cross sectional appearance of a combination stone. Two separated layers with a distinct outer shell of a pigment component and an inner layer of cholesterol are shown.

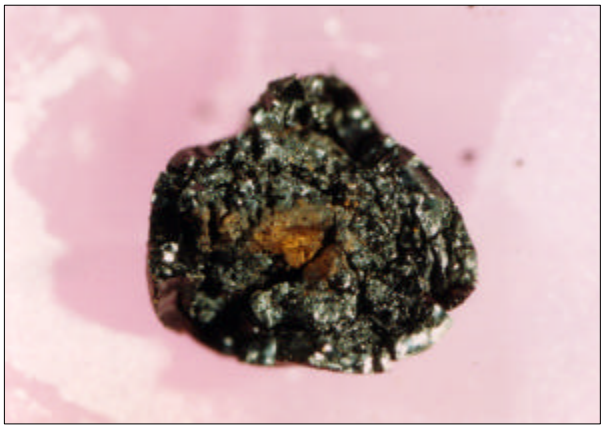

**Fig. 5.** Cross sectional finding of a black stone revealing an amorphous appearance.

**Fig. 3.** Cut surface of the mixed stone shows a concentric and radial fashion.

have contributed to the last stages of stone formation. Recently, using molecular biological techniques, a bacterial gene was identified in the cholesterol stones as well as in pigment stones. The frequency of bacterial detection using PCR (polymerase chain reaction) was much higher than the frequency obtained from the culture result because the detection rate of bacteria using this technique reflects the bacterial remains as well as living organism.[39] Swidsinski, et al. reported that most cholesterol gallstones harbor bacterial DNA by species-specific ribosomal RNA gene analysis.[39] However, no bacterial DNA was found in the gallstones with a cholesterol content of greater than 90%. Lee, et al. also detected bacterial DNA in mixed stones but not in pure

cholesterol stones.[40] Therefore, the cholesterol gallstones with a cholesterol content greater than 70% can have a different pathogenesis according to the subclasses based on their cross sectional appearance. The classification system of cholesterol stones into pure, mixed, and combination stones according to their cross sectional appearance by the Japanese Society of Gastroenterology is rational in this respect. This classification based on the cut surface (pure, mixed, combination), and has implications for treatment as well. Combination stones are resistant to oral or contact dissolution therapy due to their pigmented outer rims.[41-43]

Combination and mixed stones in the Japanese classification system are defined by their cross sectional structure as with the cholesterol stones with a cholesterol content greater than 70%.[34-36] However, some investigators are using these terms, mixed or combination stone, for stones of the intermediate group, which are difficult to classify into either cholesterol stones or pigment stones. The definition of these terms is rather confusing.[11,16,17,37,44,45]

Pigment stones. According to the classification system of the Japanese Society of Gastroenterology, pigment stones are divided into two groups, calcium bilirubinate stones and black stones, based on their cut surface (Table 3). On cross section, calcium bilirubinate stones have a concentric layer (Fig. 4), while black stones have an amorphous appearance (Fig. 5).[34-36] The primary confusion in the classification of pigment gallstones is that they all contain pigment (calcium bilirubinate) as the major component. Although calcium bilirubinate is a common constituent in both stones, evidence suggests that this pigment may be polymerized to a greater degree in black stone.[25,46]

The cut surface of pigment stones exhibit a stratified structure (lamellation) or an amorphous appearance, without a radiating crystalline structure seen in cholesterol stones.[6,31,47,48] The cross sectional appearance of a radial pattern can be an index to differentiate a cholesterol stone from a pigment stone.[24,34-36,49] The high accuracy of the correlation between the cut surface morphology and the cholesterol content in the gallstones has been reported earlier.[10,11,19,49] The validity of classifying stones by means of their cross sectional appearance was documented chemically in this laboratory as well.[47] However, the classification system based on the cross sectional appearance also has some controversial points. Some gallstones have a cholesterol content of only 40-50%, and their cut surface has a typical radial structure.[32] In contrast, there are gallstones containing more than 50% cholesterol, which can be classified as typical calcium bilirubinate stones according to their cross sectional morphology.[8,50] Accordingly, it is difficult to conclude whether or not the cross sectional morphology or composition is important.

In 1981, at the NIH-International Workshop on Pigment Gallstone Disease in Philadelphia, USA, pigment gallstones were broadly divided into brown and black stones (Table 2).[6] The Japanese Society of Gastroenterology classifies a brown stone as a calcium bilirubinate stone (Table 2 and 3). The movement to use the standardized term brown and black pigment stones arose from this meeting. Currently, the classification system of pigment stones into two types, brown and black stones, is the most widely used system. Brown stones have been referred to as various terms other than calcium bilirubinate stones, such as a bilirubin stone, a bile pigment calcium stone, an earthy stone and muddy stone.[8,24,30,48,50] Black stones are also referred to as pure pigment stones.[45,51] Brown and black stones differ in their pathogenesis and clinical features as well as in their structure and composition.[30] Brown stones are primarily formed in the bile ducts, and bacterial infections and bile stasis are the two major causes. On the other hand, black stones are commonly formed in the gallbladder and are not associated with a bacterial infection.[6,14] Brown pigment stones found in Occidental subjects are almost always de novo common bile duct stones, which develop after a cholecystectomy.[6] However, in the Orient, brown stones are commonly found in the intrahepatic and common bile duct. These intrahepatic stones have previously been referred to in the West as oriental cholangiohepatitis.[52]

The sub-classification of pigment stones into black or brown stones is simple and easily understood. However, the terms used in this classification give too much emphasis on the color of the

gallstones even though their original description was based on the stone composition, morphology, and clinical features.[6] Consequently, when placing too much emphasis on the color of the stone in the classification, a stone with a different pathogenesis and composition may be inappropriately classified in the same group.

Atypical stones with a black or brown colored surface, but with a radial fashioned cut surface and a high cholesterol content are not rare.[8,50] Malet et al. reported 44% (N=36) of 81 cholesterol gallstones had a brown or another colored surface.[53] Their average cholesterol content was 87.7%, and the bilirubin content was only 1.0%. Kim, et al. reported that black-colored intrahepatic stones which exhibited a mixed radial and concentric pattern on the cross section and a much higher cholesterol content (up to 50%).[17] These stones could not be differentiated from black pigment stones originating from the gallbladder by their external appearance. Moreover, a small amount of pigment can turn a colorless stone into a brown one, and the surface color of a gallstone can change after drying.[54] Even though a stone can be classified as being a black stone immediately after extraction, it can exhibit a brown or gray white color after drying.[36] Labeling stones visually as black or brown pigment stones appears to be a suboptimal and inadequate method of classification. Pigment gallstones may be classified in a more precise way rather than just describing color.[53] Instead, the composition and morphology of the stones as well as the clinical setting where the stones occurred may also be taken into consideration. Undoubtedly, in the NIH-International Workshop, a brown or black stone was determined not only by the color, but also by the cut surface appearance and clinical features.[6] However, there appears to be confusion when classifying pigment stones because too much emphasis is placed on the color.

## Classification by anatomical location

Gallstones can be divided into gallbladder (including cystic duct) and bile duct stones according to the anatomical location. Moreover, bile duct stones are further separated into intrahepatic and extrahepatic stones.[7,8] Intrahepatic stones are defined as stones involving the right and left hepatic ducts, and their branches, peripheral to their junction at the hepatic hilum, even though the junction is outside the liver substance.[55] This gallstones classification according to the anatomical location has an implication in that the pathogenesis, clinical features and management can differ according to the location of the gallstones.

Previously, cholesterol stones were known to form only in the gallbladder.[56] However, the presence of intrahepatic pure cholesterol stones was recently reported.[57,58] Cholesterol stones arising in the intrahepatic duct cannot be distinguished from gallbladder stones according to their external morphology and cross sectional appearance.[59-61] Gallbladder stasis is important in the formation of cholesterol stones of the gallbladder,[62,63] whereas intrahepatic bile stasis plays a major role in the formation of a cholesterol gallstone of the intrahepatic duct.[59-61]

Moreover, in case of a brown stone, intrahepatic and extrahepatic gallstones were reported to have a different composition.[11,64,65] Brown pigment stones obtained from the intrahepatic duct are qualitatively different in composition from recurrent brown stones found in the common bile duct after a cholecystectomy. Brown stones that form in the intrahepatic duct contain more cholesterol and less bilirubin than an extrahepatic brown stone.[66] In addition, discriminant analysis using the bile acid parameters modified by bacterial intervention suggested that a bacterial infection plays a less crucial role in the formation and ensuing subsequent growth of most intrahepatic brown pigment stones than in extrahepatic stones.[66] On the other hand, a brown stone can be formed not only in the bile duct, but also in the gallbladder.[48,51,55] It can be anticipated that brown stones arising from the gallbladder will have a different pathogenesis than brown stones of the bile duct.

Therefore, the stones should be discriminated according to their anatomical locations such as the gallbladder, intrahepatic duct, or extrahepatic duct, even in cholesterol or pigment stones clearly classified by their morphology and composition. This is because they may be different in the pathogenesis, clinical features, and treatment.

**Classification by original site where gallstones were formed**

Gallstones can be classified as being primary and secondary stones based on their original site. When a stone stays in its original site, it is called a primary stone. In contrast, a secondary stone means that the stone migrated from its original site.[67,68] For example, in cases of common bile duct stones, they are secondary when they formed primarily in the gallbladder and subsequently migrated through the cystic duct into the common duct. On the other hand, stones that are formed in the common bile duct and remain there are called primary common bile duct stones.[67,68] Clinically, primary common bile duct stones can form in the common duct several years after a cholecystectomy, and are mostly brown stones (calcium bilirubinate stones).[68-70] On the contrary, secondary common bile duct stones are usually associated with gallbladder stones, and cholesterol stones are the most prevalent because they migrate from the gallbladder.[71-73] Therefore, when the gallstones composition is analyzed according to the anatomical location, data concerning the concept of primary and secondary stones should be analyzed.

Intrahepatic stones can also be classified as primary and secondary stones. Secondary intrahepatic stones may originate in the gallbladder and migrate into the intrahepatic ducts. On other occasions, the stones may reach the intrahepatic duct continuously piled up from the stenotic site at the distal common bile duct.[2,17, 52,74,75] Primary intrahepatic stones are mainly associated with intrahepatic strictures, and gallstones are formed at the proximal dilated duct to a stricture.[2,17,52,75] In contrast, a definite intrahepatic stricture cannot found in secondary stones.

A distinction between primary and secondary stones is needed because the therapeutic approach as well as the pathogenesis and composition differ.[23,24] In secondary common bile duct stones, a cholecystectomy and the removal of common bile duct stones by a common duct exploration is adequate for treatment. Whereas, in primary common bile duct stones, the removal of stones without a drainage procedure may result in a recurrence because the bile stasis in the common bile duct due to the papillary stenosis is frequently associated.[23,24,67] In these cases, an additional endoscopic sphincterotomy or drainage procedure may be required to relieve the stasis.[69]

Recently, stone removal after an endoscopic papillary balloon dilatation for the removal of common bile duct stones was attempted.[76] Preserving the sphincter of the Oddi function is considered to be a major benefit of this procedure.[77,78] However, a primary common bile duct stone is commonly associated with a papillary stenosis.[67] Therefore, it is reasonable to highlight that preserving the sphincter of the Oddi function does not always mean it will be beneficial. Theoretically, common bile duct stone removal by a balloon dilatation should be applied only in cases of secondary common bile duct stones with the cause of their formation being within the gallbladder.

However, in clinical practice, an exact differentiation between primary and secondary stones can be difficult except in those with a previous cholecystectomy. Therefore, the decision as to whether or not to perform a drainage procedure or an endoscopic sphincterotomy is usually based on the clinical parameters such as the size of the stones, any dilatation of the CBD and a papillary stenosis rather than the primary or secondary stone classification.

In primary intrahepatic stones, if the stone removal is not followed by an adequate correction of the intrahepatic strictures, the recurrence rate is higher compared to secondary intrahepatic stones.[17,52] Therefore, when a gallstone is examined, the clarification as to whether it is formed de novo or migrated from the original site is vital when making a clinical decision in addition to satisfying scientific interest.

**What is the best classification system for gallstones?**

This reviewed the merits and demerits of the current gallstone classification schemes. Although these systems offer certain advantages in providing practical and readily available information on gallstones, it has become clear that several debatable problems still persist in these schemes. Therefore, the question as to what is the best clas-

sification system for gallstones still remains. Theoretically, a perfect classification system would convey data regarding the major gallstone components for the understanding of etiologic significance through its categories. However, it is impractical to measure all the gallstones components, as it requires sophisticated laboratory methods.

In addition, the classification should be easily understood for practical use and must be relevant to the therapeutic procedures. The currently used NIH classification and Japanese classification may be very attractive systems regarding these aspects. They have advantages in describing and understanding many different types of gallstones. Firstly, the NIH-International Workshop classification is based on well-defined patterns of epidemiological, etiological, clinical and radiological features associated with the different types of stones. Moreover, it is a simple scheme and only requires the measurement of cholesterol on a weight/weight basis in a typical stone. The Japanese classification system divided the cholesterol stone into a pure cholesterol, a combination or a mixed stone according to its cross-sectional appearance unlike the NIH-International Workshop classification. This scheme may be helpful when estimating the response of the dissolution therapy. Accordingly, it is evident that a newer classification system needs to be developed on the basis of these two widely used schemes, which most workers in the East and in the West are familiar with. The newer classification system should have the advantages of both systems. Moreover, the system should classify some stones that cannot be classified into any of the classes in the current systems.

Under the NIH-International classification system, the definition of a cholesterol stone is based on its chemical composition rather than its morphology. However, the cross-sectional appearance is regarded as an important factor when classifying the gallstones in the scheme under the Japanese classification system. In these schemes, some stones cannot be classified into either cholesterol or pigment stones as described earlier. Therefore, it may be useful to add the cross-sectional appearance, such as a typical radial fashion, when classifying stones that are difficult to classify based solely on their chemical composition. However, this may require further discussion.

This study outlined the problems in classification from previously established works. Finding an ideal method of classification can only be accomplished when more extensive and large scaled studies are conducted with cooperation from multi-clinical centers. In the near future, large scaled prospective studies on gallstones should be carried out on the basis of the external color, chemistry, cutting surface, etc. Only then can an ideal classification of the gallstones be proposed.

## CONCLUSION

Clinicians have become less interested in the classification of gallstone since the introduction of laparoscopic cholecystectomy. For the treatment of gallstones, it is not important as to whether or not the main component of the gallstone is cholesterol as a laparoscopic cholecystectomy can be performed regardless of the gallstone composition. Moreover, dissolution therapy has become less often used since the introduction of laparoscopic cholecystectomy. Furthermore, in cases of CBD stones, the stones can be removed by endoscopic procedures regardless of its composition.

However, establishing an appropriate classification system is still essential for understanding the pathogenesis of gallstones, which will contribute to the prevention of gallstones. In the near future, it is hoped that another international conference, such as the one held in Philadelphia, 1981, will be helpful in improving the understanding of gallstones.

## REFERENCES

1. Nakayama F, Miyaki H. Changing state of gallstone disease in Japan. Am J Surg 1970;120:794-9.
2. Nakayama F, Furusawa T, Nakama T, Miyazaki K. Clinical features and classification of hepatolithiasis. Prog Clin Biol Res 1984;152:115-27.
3. Kameda A. The history of gall stone. Nippon Naika Gakkai Zasshi 2002;91:105-9.
4. Naunyn B. A treatise on cholelithiasis, trans. by Garrod AE. London: New Sydenham Society; 1896.
5. Aschoff L. Lectures in pathology. New York: Paul B.

Hoeber Inc.; 1924.
6. Trotman BW, Soloway RD. Pigment gallstone disease: summary of the National Institute of Health-International Workshop. Hepatology 1982;2:879-84.
7. Takagi I, Toda G. Definition, classification and clinical symptoms of cholelithiasis. Jpn J Clin Med 1993;51: 1705-10.
8. Suzuki N, Takahashi W, Sato T. Types and chemical composition of intrahepatic stones. In: Intrahepatic calculi. New York: Alan R Liss, Inc.; 1984.
9. Suzuki N, Sato T. A new classification of gallstone. J Biliary Tract Pancreas 1986;7:1467-70.
10. Iida M, Okayama Y, Goto K, Shiraki S, Hoshino M, Takeuchi T. Gallstone classification and analysis of their constituents. Jpn J Clin Med 1993;51:1718-24.
11. Mukaihara S. Chemical analysis of gallstones: classification and composition of human gallstones. Arch Jpn Chir 1981;50:476-500.
12. van Erpecum KJ, van Berge Henegouwen GP, Stoelwinder B, Stolk MF, Eggink WF, Govaert WH. Cholesterol and pigment gallstone disease: comparison of the reliability of three bile tests for differentiation between the two stone types. Scand J Gatroenterol 1988;23:948-54.
13. Cetta F, Lombardo F, Giubbolini M, Baldi C, Cariati A. Classification of gallstones and epidemiologic studies. Dig Dis Sci 1995;40:2189-91.
14. Carey MC. Pathogenesis of gallstones. Am J Surg 1993; 165:410-9.
15. Malet PF, Williamson CE, Trotman BW, Soloway RD. Composition of pigmented centers of cholesterol gallstones. Hepatology 1986;6:477-81.
16. Ravnborg L, Teilum D, Pedersen LR. Gallbladder stones classified by chemical analysis of cholesterol content. Scand J Gatroenterol 1990;25:720-4.
17. Kim MH, Sekijima J, Park HZ, Lee SP. Structure and composition of primary intrahepatic stones in Korean patients. Dig Dis Sci 1995;40:2143-51.
18. Cahalane MJ, Neubrand MW, Carey MC. Physical-chemical pathogenesis of pigment gallstones. Semin Liver Dis 1988;8:317-28.
19. Trotman BW, Ostrow JD, Soloway RD. Pigment vs. cholesterol cholelithiasis: comparison of stone and bile composition. Am J Dig Dis 1974;19:585-90.
20. Donovan JM, Carey MC. Physical-chemical basis of gallstone formation. Gastroenterol. Clin North Am 1991;20:47-60.
21. Sherlock S, Dooley J. Diseases of the liver and biliary system. U.S.A.: Blackwell science; 1997. p.593-8.
22. Dolgin SM, Schwartz JS, Kressel HY, Soloway RD, Miller WT, Trotman BW, et al. Identification of patients with cholesterol or pigment gallstones by discriminant analysis of radiographic features. N Engl J Med 1981; 304:808-11.
23. Lotveit T, Foss OP, Osnes M. Biliary pigment and cholesterol calculi in patients with and without juxtapapillary duodenal diverticula. Scand J Gastroenterol 1981;16:241-4.
24. Ontiveros AG, Hinojosa JC, Extremera BG, Moral JMD. Differences in gallstone sturcture in primary common bile duct lithiasis and gallbladder lithiasis. Klin Wochenschr 1990;68:496-502.
25. Ostrow JD. The etiology of pigment gallstones. Hepatology 1984;4:215S-22S.
26. Shoda J, He BF, Tanaka N, Matsuzaki Y, Yamamori S, Osuga T. Primary dual defect of cholesterol and bile acid metabolism in liver of patients with intrahepatic calculi. Gastroenterology 1995;108:1534-46.
27. Freilich HS, Malet PF, Schwartz JS, Soloway RD. Chemical and morphologic characteristics of cholesterol gallstones that failed to dissolve on chenodiol. Gastroenterology 1986;91:713-8.
28. Been JM, Bills PM, Lewis D. Microstructure of gallstones. Gastroenterology 1979;76:548-55.
29. Bills PM, Lewis D. A structural study of gallstones. Gut 1975;16:630-7.
30. Malet PF, Takabayashi A, Trotman BW, Soloway RD. Black and brown pigment gallstones differ in microstructure and microcomposition. Hepatology 1984;4: 227-34.
31. Tsuchiya Y, Matsumoto Y. New trends in treatment for cholelithiasis, 1st ed. Tokyo: Kanehara; 1991. p.1-14.
32. Kaufman HS, Magnuson TH, Pitt HA, Frasca P, Lillemoe KD. The distribution of calcium salt precipitates in the core, periphery and shell of cholesterol, black pigment and brown pigment gallstones. Hepatology 1994;19:1124-32.
33. Malet PF, Williamson CE, Trotman BW, Soloway RD. Composition of pigmented centers of cholesterol gallstones. Hepatology 1986;6:477-81.
34. Sato T. Diseases of the biliary tract. Osaka: Nagai shoten; 1983. p.81-3.
35. Kameda H, Hanyu F. The gallstone disease, 1st ed. Tokyo: Igaku-shoin; 1980. p.304-6.
36. Ohto M. Common disease series No.13. The gallstone disease. Tokyo: Fumimaro Takaku; 1990. p.233-7.
37. Stewart L, Smith AL, Pellegrini CA, Moston RW, Way LW. Pigment gallstones form as a composite of bacterial microcolonies and pigment solids. Ann Surg 1987; 206:242-50.
38. Tabata M, Nakayama F. Bacteria and gallstones: etiological significance. Dig Dis Sci 1981;26:218-24.
39. Swidsinski A, Ludwig W, Pahlig H, Priem F. Molecular genetic evidence of bacterial colonization of cholesterol gallstones. Gastroenterology 1995;108:860-4.
40. Lee DK, Tarr PI, Haigh WG, Lee SP. Detection and identification of bacterial gene sequences in mixed cholesterol gallstone by amplification of 16S rRNA genes. Gastroenterology 1997;112:A513.
41. Freilich HS, Malet PF, Schwartz JS, Soloway RD. Chemical and morphologic characteristics of cholesterol gallstones that failed to dissolve on chenodiol. The National Cooperative Gallstone Study. Gastroenterology 1986;91:713-8.
42. Whiting JM, Jarvinen V, Watts JM. Chemical composition of gallstones resistant to dissolution therapy with

chenodeoxycholic acid. Gut 1980;21:1077-81.
43. Kim MH, Rim MK, Kim TH, Yoo BH, Seo DW, Jung HY, et al. Dissolution effect of various contact solvents on the primary intrahepatic stones. Korean J Gastroenterol 1996;28:705-13.
44. Zakim D, Boyer TD. Hepatology: a textbook of liver disease. Philadelphia: WB Saunders; 1996. p.1834-5.
45. Maki T, Matsushiro T, Suzuki N. Clarification of the nomenclature of pigment gallstones. Am J Surg 1982; 144:302-5.
46. Burnett W, Dwyer KR, Kennard CH. Black pigment or polybilirubinate gallstones: composition and formation. Ann Surg 1981;193:331-3.
47. Kim MH, Yoo BM, Jung HY, Lee MH, Park SH, Choi HS, et al. The study on the correlation between chemical composition and cross- sectional appearance of gallstones. [abstract] Korean J Gastroenterol 1995;27: A108.
48. Trotman BW. Pigment gallstone disease. Gastroenterol. Clin North Am 1991;20:111-26.
49. Nakayama F. Quantitative microanalysis of gallstones. J Lab Clin Med 1969;72:602-11.
50. Tanimura H, Kobayashi N, Yoshida K, Ozawa K. Chemical composition of intrahepatic stones in Japan. Jpn J Clin Med 1987;45:154-62.
51. Soloway RD, Trotman BW, Maddrey WC, Nakamura F. Pigment gallstone composition in patients with hemolysis or infection/stasis. Dig Dis Sci 1986;31:454-60.
52. Kim MH, Sekijima J, Lee SP. Primary intrahepatic stones. Am J Gastrenterol 1995;90:540-8.
53. Malet PF. Nomenclature for pigment stones. Letter to the editor. Hepatology 1987;7:988.
54. Peled Y, Rattan J, Gilat T, Fireman Z. The crucial role of bile infection in the pathogenesis of bild duct stones. Letter to the editor. Hepatology 1987;7:206.
55. Nakayama F, Koga A. Hepatolithiasis: present status. World J Surg 1984;8:9-14.
56. Donovan JM. Pathogenesis of gallstones. In: Feldman M, LaRusso NF, editors. Gastroenterology and hepatology: the comprehensive visual reference. Vol. 6 Gallbladder and bile ducts. Philadelphia: Churchill Livingstone; 1997. p.7.1-3.
57. Shoda J, Tanaka N, Matsuzaki Y, Honda A, Osuga T, Shigematus S, et al. Microanalysis of bile acid composition in intrahepatic calculi and its etiological significance. Gastroenterology 1991;101:821-30.
58. Ohta T, Nagekawa T, Takeda T, Fonseca L, Kanno M, Mori K, et al. Histological eveluation of the intrahepatic biliary tree in intrahepatic cholesterol stones, including immunohistochemical staining against apoprotein A-1. Hepatology 1993; 17:531-7.
59. Kondo T, Nimura Y, Hayakawa S. Cholangiographic and endoscopic finding in primary intrahepatic cholesterol stones. Jpn J Gastroenterol 1989;86:2779-89.
60. Shimada H, Nihmoto S, Matsuba A, Nakagawara G, Kobayashi M, Tsuchiya S. Primary cholesterol hepatolithiasis. Gastroenterol Jpn 1989;24:170-6.
61. Saito K, Nakanuma Y, Ohta T, Ueda N, Higashino Y, Yamamichi N, et al. Morphological study of cholesterol hepatolithiasis. J Clin Gastroenterol 1990;12:585-90.
62. Johnston DE, Kaplan MM. Pathogenesis and treatment of gallstones. N Engl J Med 1993;328:412-21.
63. Saunders KD, Cates JA, Roslyn JJ. Pathogenesis of gallstones. Surg Clin North Am 1990;70:1197-216.
64. Yamashita N, Yanagisawa J, Nakayama F. Composition of intrahepatic calculi-etiological significance. Dig Dis Sci 1988;33:449-53.
65. Kobayashi A, Tanimura H. Chemical analysis of intrahepatic gallstones. J Biliary Tract Pancreas 1984;5: 1609-13.
66. Shoda J, Tanaka N, Matsuzaki Y. Microanalysis of bile acid composition in intrahepatic calculi and its etiological significance. Gastroenterology 1991;101:821-30.
67. Madden JL, Vanderheyden L, Kandalaft S. The nature and surgical significance of common duct stones. Surg Gynecol Obstet 1968;126:3-8.
68. Malet PF, Dabezies MA, Huang G, Long WB, Soloway RD. Quantitative infrared spectroscopy of common bile duct gallstones. Gastroenterology 1988;94:1217-21.
69. Saharia PC, Zuidema GD, Cameron JL. Primary common duct stones. Ann Surg 1977;185:598-602.
70. Lygidakis NJ. Incidence and significance of primary stones of the common bile duct in choledocholithiasis. Surg Gynecol Obstet 1983;167:434-6.
71. Glenn F. Postcholecystectomy choledocholithiasis. Surg Gynecol Obstet 1972;134:249-52.
72. Trotman BW, Morris TA III, Sanchez HM, Soloway RD, Ostrow JD. Pigment versus cholesterol cholelithiasis: identification and quantitation by infrared spectroscopy. Gastroenterology 1977;72:495-8.
73. Braasch JW, Fender HR, Bonneval MM. Refractory primary common bile duct stone disease. Am J Surg 1980;139:526-30.
74. Way LW. Retained common duct stones. Surg Clin North Am 1973;53:1139-47.
75. Kimura K, Ohto M, Okuda K. Cholangiographic features in hepatolithiasis. In: Intrahepatic calculi. New York: AR Liss; 1984. p.149-62.
76. Mathuna PM, White P, Clarke E, Merriman R, Lennon JR, Crowe J. Endoscopic balloon sphincteroplasty (papillary dilation) for bile duct stones: efficacy, safety, and follow-up in 100 patients. Gastrointest Endosc 1995;42:468-74.
77. Sato H, Kodama T, Takaaki J, Tatsumi Y, Imamura Y, Maeda T, et al. Endoscopic papillary balloon dilation may preserve sphincter of Oddi function. Gastrointest Endosc 1997;45:A147.
78. Minami A, Nakatsu T, Uchida N, Hirabayashi S, Fukuma H, Ahmed Morshed S, et al. Papillary dilation vs. sphincterotomy in endoscopic removal of bile duct stones: a randomized trial with manometric function. Dig Dis Sci 1995;40:2550-4.