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THE ORIGIN OF GALL STONES

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HISTORICAL SUMMARY

The occurrence today of gall stones is so frequent that it is astonishing that in the writings of medical writers of antiquity there is so little mention of the condition. Very little data is given in the writings of the early authors that allow us to infer with certainty that the physicians of that day knew of this disease.

(1). In the works of Hippocrates and Galen there are found a few brief communications on pain in the hepatic region, and on icterus as a result of constipation without fever; but these descriptions as compared with the precise and exact communications on renal colic, convey only a very inadequate idea of gall bladder colic. Nowhere do we find further mention of concretions in the bile passages or in the gall bladder.

In view of the fact that the old Greek physicians were very good clinical observers and at the same time thorough students of anatomy, we are forced to the conclusion that gall stones were less frequent in those days than they are in modern times. An explanation for this difference might be sought in the mode of life then as compared to now. The people of Greece ate other food than we do, and their whole regime was different. Food was prepared in a different manner, meals were simpler, and exercise was a part of the curriculum of every youth and also of the older men and women.

(2). Hoppe-Seyler's historical summary is concerned only with the knowledge of the gall bladder disease which was occurrent among Europeans. He makes no mention of the early Jewish writings on the subject of gall stones, which was here quoted by (3) Boyden from Joseph Caro's 16th Century "Shulhan' Aruch", the final and authoritative codification of the Talmudic law.

"If hard things are found in the gall bladder, which are like the pits of dates, without sharp edges, the animal is kosher. But if the edges are sharp as in pits of olives, the animal is terefah, it being assumed that the pit has perforated the gall bladder in entering; the reason why the perforation is not visible is because it is healed over with skin".

The first mention of gall stones by a European writer was by (1). Antonius Benivenius who died around 1592. The stones he described were seen in the liver and gall bladder of a woman who had suffered from abdominal pain. Fernelius in 1554 gave not only a description of gall stones but also the symptoms which they may produce. He knew that occlusion of the common duct may lead to a swelling of the gall bladder; passing of dark urine, a discoloration of the feces and also that when there is an obstruction of the hepatic duct the gall bladder is empty.

(1). Columbus, who died in 1557, stated that a post-mortem examination made on the body of the Jesuit General Ignatius de Loyola, showed numerous concretions in the liver, portal vein, kidneys and lungs. This anatomist probably confused the portal vein with branches of the bile ducts, the stones being in them instead of the portal vein.

(1). Johann Kentmann in 1565 described gall stones of different sizes and shapes. He noted that when multiple, they were more likely to have an angular shape and that the broken surface of a stone showed it to have a circular structure.

(1). Forestus held the opinion that gall stones are formed under conditions in which the gall bladder is not properly emptied and the cystic duct is occluded.

(4). Glisson, after whom the capsule surrounding the portal vein hepatic artery and ducts is named, in 1654 in his book, described gall stones in cattle, and also gave a very interesting description of his own case, in which he describes an attack of colic, associated with jaundice, and pain radiating to the region of the clavicle. Since he could not demonstrate the presence of nerves in any other parts than in the hepatic capsule and walls of the bile ducts, he concluded the pain must originate in the bile ducts.

(4). Wepler 1658-by making use of Glisson's studies, concluded that bile is formed in the liver and conveyed through the bile passages and the common duct into the small intestine. He also believed that jaundice could never occur as the result merely of occlusion of the cystic duct, unless at some time there is occlusion of the common duct.

(2). Sydenham 1624-1689 according to Hoppe-Seyler is frequently credited with discoveries that have thrown light on the pathology of gall stones. As a matter of fact, however, he considered gall stones colic as a symptom of hysteria, and described its occurrence in female subjects who were suffering from other forms of hysterical seizures.

(1). Vater (1722) attributed the fever which often occurs after gall stones are passed to an irritation of the nervous system caused by the impaction and the passage of the stone through the narrow lumen of the bile passages.

(1) Fredrick Hoffman attributed the formation of gall stones to the stagnation of the bile.

(2). Morgagni (1662-1781) concluded that occlusion of the bile passages is the result of a simple contraction of the ducts, a thickening of their mucus lining, and compression of the passages by swollen glands, etc. This occlusion is always followed by jaundice. If the cystic duct alone is occluded, jaundice will not occur. He mentions as predisposing causes - the age of the subject, sedentary habits, and other factors. He also had the opinion that irritation of the glands of Malpighi, in the wall of the gall bladder is another predisposing factor in the formation of stones.

Pouillettier de la Salle, according to Hoppe-Seyler, was the first to isolate cholesterin. This occurred about the middle of the 18th century.

PHYSIOLOGY OF THE GALL BLADDER

(5). Bile leaves the liver by way of the hepatic ducts which come together and form the common hepatic duct, which in turn joins the cystic duct, and through this the bile enters the gall bladder. Filling of the gall bladder depends on closure of the duodenal end of the common duct. By inserting a canula in the intramural portion of the common duct, the gall bladder will not fill. The regulation of flow into the duodenum is by the sphincter of Oddi and tonus of duodenum. (2). Burget, Carlson, Copher and Kodama believe that tonus of the duodenum has more to do in keeping a continuous flow of bile from entering duodenum than has the sphincter of Oddi.

(6). The regulation of the outflow is accomplished by the wall of the duodenum, due to the fact that the common bile duct passes through the muscular coats of the duodenum in an oblique manner. The anatomical arrangement of the muscle fibers of the duodenal wall about the intramural portion of the common duct, constitutes a sphincter-like mechanism which is dependent on the tonicity of the duodenum, and makes it possible for peristalsis to be a factor in emptying the duct.

Normal tonus of the duodenum is sufficient to prevent a continuous flow into it. When the intra-ductal pressure becomes high enough, it overcomes this resistance and bile flows intermittently into the lumen of the duoden.

(7). A column of bile exerting a pressure of from 60 to 100 mm

pressure is sufficient to distend the gall bladder. The sphincter of Oddi will stand more pressure than this. It is probable that tributary ducts receive a portion of this pressure.

(8). However, after removal of the gall bladder, in time there is a giving away of the sphincter, due to the result of increased pressure in the dilated tributary ducts.

Discharge of bile into the duodenum occurs especially at a relaxation stage in peristalsis of the intestine.

In all probability the function of the sphincter of Oddi has been over-emphasized.

Bile during its stay in the gall bladder is concentrated by loss of water, and addition of mucin from the lining cells of the vesicle mucosa.

Bile from the gall bladder contains many more solids than bile that does not enter it. There may be ten times the amount of pigment in gall bladder bile, as compared to hepatic bile.

The extra hepatic ducts have no concentrating power and may even dilute the bile with a thin secretion of their own.

Some investigators - (9) Sweet - Halpert - Demel, formerly believed that gall bladder bile left the gall bladder mainly by absorption, and not through the cystic duct, due to the presence of the valves of Keister. It has been proved though that practically all of the bile leaves by way of the cystic duct.

According to Mentzer, on a series of normal gall bladders removed

at autopsies, the valves of Heister are not very important - they probably merely check bile flow, and do not entirely prevent it.

Elasticity of wall of gall bladder is a big factor in its emptying.

The movements observed in the gall bladder are an active contraction and passive reaction to varying pressures in the hepatic and common bile ducts.

(10). TYPES OF GALL STONES:

I. Cholesterin Stones

II. Bilirubin Calcium Stones

All other types can be grouped under these two headings.

TYPE I. Cholesterin Stones:

(a) Pure cholesterin stones - those which contain free or conglomerate cholesterin crystals.

(b) Radial cholesterin stones - essentially a cholesterin rich stone, composed of cholesterin crystals arranged in a radial manner about a nucleus and containing little other substance.

(c) The "common stone" - which some have classified separately, but which is essentially a cholesterin stone, composed of varying proportions of cholesterin and bile pigments, with very small amounts of such elements as Sodium, Potassium, Calcium, Iron, Copper, Sulphur and Zinc.

TYPE II. Bilirubin Calcium Stones:

Generally but not always of intra-hepatic origin, as multiple calculi have been found in the gall bladder lumen many times. They are small, dark in color, and spicular, and are composed of bile pigments mixed with mucus, and with traces of calcium, they rarely contain cholesterin.

The calcium carbonate stone is grouped by Mentzer with the bilirubin calcium stone, because it contains little cholesterin. It is also a non-inflammatory stone and is rare in man, but common in animals.

THEORIES OF GALL STONE FORMATION

I. Stasis Theory:

This has long been considered as a primary factor in the etiology of biliary calculi. Stasis has been attributed to sedentary lives, decreased muscular movements of the diaphragm, the abdominal wall and enclosed organs. In this connection the rarity of finding stones in animals and the comparative frequency in which they are found in man is interesting. (11). Fox reported in an extensive zoo series only six animals affected. (10). Mentzer examined the gall bladders of 9000 cattle and found only .4 per cent had gall stones, and in 600 consecutive autopsies at the Mayo Clinic 21 per cent had gall stones.

There have been, however, a number of cases reported in which undoubtedly there was stasis, even in the presence of marked infection - with no signs of the formation of biliary calculi.

II. Infection Theory:

This theory was started by (10). Gallipe in 1886, and affirmed by Naunyn in 1892. Ascholff and Bacmeister regard it as the cause of most gall stone formation with the exception of the occasional pure cholesterin stone.

It is denied by some but there is ample proof that this is a factor in the production of gall stones.

The gall bladder may become infected by passage of organisms through the circulation into the wall of the gall bladder.

Contrary to the usual conception of the origin of bilirubin calcium stones, is that of Rous and his co-workers, who found floccules of

bilirubin and calcium carbonate, deposited on glass tubing, inserted in gall bladder lumen in experimental work on dogs, with no evidence of inflammatory change in the bile ducts. (12). Aschoff contends that this is not a true crystallization, but a sedimentation.

III. Nucleus Theory:

According to Mentzer in an examination of several thousand gall stones, a nucleus of some sort was invariably found, and is probably a necessary adjunct in stone formation. According to him, no gall stone is without a grossly demonstrable nucleus. A foreign substance that is introduced into the gall bladder will not alone cause stone formation however.

There are a number of instances in which the round worm *Ascaris* has formed the nucleus of a biliary calculus. DeGorce reports a case of 40 cholesterin stones, each of which contained as a nucleus an ascaris. The usual nuclei are, however, masses of bile pigment. Nuclei, composed of masses of bacteria, mucus plugs, blood coagulum, epithelial cells, portions of sutures or needles have been reported. Often, also, a gall stone of one type has formed the nucleus of totally different type of stone.

Mentzer suggests that without a nucleus, that the ingredients of stones pass out of the gall bladder.

IV. Hypercholesteremia Theory:

(2). This theory was brought forward in 1909 by Aschoff and Bacmeister. Their views of a dysfunction of cholesterin metabolism as a contributing factor in gall stone formation has had wide acceptance. (12). Wilensky is of the opinion that infection is associated with an increase of cholesterin in the blood and bile in

the pathogenesis of gall stones.

Rothschild and Wilensky believe that a saturation of the gall bladder bile with cholesterin alone will precipitate stones and Dewey has produced them by feeding animals an excessive amount of fat.

Huchard in 1882 first noted the relation of pregnancy to gall bladder disease - due to the increased cholesterin content of the blood during pregnancy.

V. Lichtwitz's Theory:

According to this theory published in 1907, bile is a colloid held in suspension by ions of like charges. With a change in the H ion concentration of the bile, these charges are altered - resulting in a precipitation of cholesterin. The bile salts probably hold the cholesterin in suspension and when a change occurs in these salts and a consequent variation in the acidity of gall bladder bile, this equilibrium is disturbed. Cholesterin content of bile varies from hour to hour and probably also the bile salt content changes. The conditions, therefore, for a change in the charges of the cholesterin ions are present.

THE ORIGIN OF GALL STONES

Modern investigation pertaining to the etiology of biliary calculi, according to (13). Aschoff, began in the fundamental work of Naunyn in his book "Die Klinik der Cholelithiasis", in which he contends that the only proven general cause for the origin of biliary calculi is the stasis of bile. Naunyn's idea, however, is that stasis alone cannot accomplish the formation of calculi. There has to be added a second cause which has only a transitory action. Accordingly, he views ascending infection of the bile passages, and the gall bladder in particular, as the second cause. The organism most often playing the main role in this ascending infection is the *B. coli communis*.

(14). The bacterial origin of biliary calculi was first suggested by Gallipe in 1886. Hanot and Milan discovered the bacillus typhosus in the center of gall stone in 1896. For many years before the present preventative method of controlling typhoid fever, the bacillus typhosus played an important part in forming the nuclei or precipitation centers around which were built various types of biliary stones. However, today, the part played by this organism as an etiological factor in biliary calculi formation is practically nil.

(13). Naunyn maintains that following infection of the gall bladder with *B coli communis*, there is produced a stone forming catarrh of the vesicle mucus membrane. As a direct result of the inflammatory change in the epithelial lining of the gall bladder, there is produced an abundance of cholesterin, which furnishes the cholesterin for the pure and also the mixed stones. The calcium is also looked

upon by Naunyn as a secretory product of the inflamed gall bladder epithelium.

In his opinion, the cholesterin and calcium are not as a general rule dissolved in the hepatic bile, but are first formed under certain conditions, as a decomposition product or direct secretion of the gall bladder epithelium, which has been stimulated to secrete them. Accordingly, there arises partly from precipitates, disintegrated epithelial cells and mucus, the beginning of a calculus. The growth of these calculi according to Naunyn's concept, is by the absorption of the stone forming substances, now present in the static bile. Very often a hard shell is formed, while in the center, which is semi-fluid in character, crystals are being formed. There is a gradual transformation of the entire stone including the nucleus by an infiltration with cholesterin -- the so-called cholesterinization of the calculus. He does not admit any influence which can be demonstrated, of the constitution or diet of an individual on the formation of biliary calculi.

Aschoff differentiates two fundamentally different forms of gall stones, the metabolic and the inflammatory calculi. There are two different types of stones whose formation is due, primarily, to disturbances in metabolism. The first is the radially built or pure cholesterin stone, and the second is a type of bilirubin calcium stone.

The pure cholesterin stone is the more important, and shows the following general characteristics:

- (1). Composed of between 95 to 97 per cent of cholesterin traces of calcium and protein.

- (2). The cholesterin is in columns, is coarsely crystalline, and lacks the lamellation of most other stones.
- (3). Never occur except singly.
- (4). No evidence of inflammation, generally in the gall bladders in which they are found.
- (5). These stones occur at any time during life, even in childhood. In many women it is probable that they are formed during or after a pregnancy.

A type of calculus to have so many distinguishing characteristics from other stones, must have a rather special origin. Ziegler Naunyn is very positively of the opinion that stagnation of bile in the biliary passages is the universal cause of their formation, that this condition along with an existing infection of the bile, causes a precipitation of cholesterin without leaving any apparent histological changes in the gall bladder. Rolleston is of the opinion that the cholesterin that goes into the formation of these stones is not derived from the bile itself, but from the disintegration of the lining cells of the gall bladder, and is the result of a perverted metabolism preceded by a catarrh.

If according to Naunyn's views, the infection of the bile, did nothing more than decompose it, this view would be acceptable.

(13). In this event, decomposition of the bile by microorganisms would have as a sole consequence the precipitation of cholesterin, however, such action of microorganisms has so far not been recorded. Naunyn has explained it on a basis of stimulation of the gall bladder epithelium by the bacteria. If such were the case, there would be evidence in the form of histological changes of some sort in the

lining of the gall bladder epithelium. According to Aschoff's extensive studies, there are not to be found any such changes, at least not in the pure cases.

Cholesterin according to him is not secreted by the epithelial cells of the gall bladder or bile ducts, at least not to any appreciable extent, but is secreted by cells of the liver, which do not disintegrate in the process. (17). A proof of the excretory part played by the liver is the dependence of cholesterin content of rabbit's bile, upon the cholesterin level maintained by the blood. Normally the bile of a rabbit does not contain very much cholesterin. By feeding cholesterin to a rabbit, the cholesterin content of the blood is increased, and there occurs an increase of the cholesterin content of the bile, which is excreted by the liver cells. Any participation of the epithelial cells of the gall bladder cannot be demonstrated.

As Naunyn maintains that the epithelium of the bile passages, especially the gall bladder, are responsible for the normal secretion of cholesterin, it can be reasonably expected, according to his views, that they are responsible for the pathologically increased excretion of cholesterin.

Aschoff ran a series of experiments on dogs, where the gall bladder was ligated, the contents aspirated, and half of the contents reinjected. The portion of the bile that was removed was quantitatively analyzed to determine the amount of cholesterin present. Several weeks later the gall bladders were removed, and the contents again analyzed. A few of the gall bladders showed an increase in cholesterin content, and the others did not. The ones that showed

an increase, also bore evidence of inflammatory changes in the lining epithelium. A few of the gall bladders showed a decrease of cholesterin content, but no evidence of an inflammation. He concluded that the gall bladders which showed an increase in cholesterin content, was due to no physiological secretion by the epithelium, but to the inflammatory exudate. When the portion of contents was first removed, it was replaced with physiologic saline, which he believes caused the inflammatory changes. Another series was then run through, and this time no salt solution replaced that portion of the contents which was removed. At the end of several weeks the gall bladders were removed and showed no increase of cholesterin content, but most of them bore evidence of a decrease. He proved by this that in the dog's gall bladder, there is no increase in cholesterin from the lining epithelium, but a resorption, and this not to a very marked degree.

Conceding that there is cholesterin excretion by the epithelium of the gall bladder, according to all observations made upon man and the results of experimental study on animals, especially rabbits and dogs, this excretion depends in the last analysis upon the cholesterin content in the blood.

The rabbit excretes very little cholesterin in the bile, and (18). Dewey by feeding cholesterin to rabbits was able to bring about so marked an excretion of cholesterin by the liver, and bile passages, that small cholesterin calculi were formed.

The chief analogy according to Dewey of the value between experimentally produced gall stones, and those occurring in man, lies in the association of biliary calculi formation with hypercholesteremia. The frequent occurrence of gall stones in women, has often been

attributed to mechanical factors, among them the pressure effects of pregnancy. Hypercholesteremia is always associated with this condition, and probably plays the leading role.

(19). In experimental hypercholesteremia, the effects vary not only to the size and number of doses, but also to the general condition of the animal - be it a dog or rabbit. Constitutional integrity and functional activity of the cell prior to the injection are more essential it seems than the amount of cholesterin.

(18). The ready infiltration of the liver of the rabbit, contraster to that of the carnivora, is an expression of insufficiency on the part of an organ which has normally a rather light task to perform, as regards the metabolism of cholesterin. Dewey as a result of producing a condition of hypercholesteremia in rabbits was able to produce calculi in sterile bile, without injury or infection of the gall bladder. Preceding their formation there was some epithelial desquamation, due to an irritating action of an excess of cholesterin.

This disturbance in cholesterin metabolism consists of a transitorily increased excretion, and this is no better shown than the increased cholesterin excretion during a pregnancy. Aschoff is also of the opinion that pure cholesterin stones may be quite quickly formed during a period where there is a rapid loss of fat, be it in the course of treatment for obesity, following infections or otherwise. From the experimental researches of (16) Mignot, he believes that it takes about six months to form a well stratified biliary calculus.

(13). Okuneff doing experimental work on the morphology of the lipoid substance in hunger, confirms the statements of (Landau), that cholesterin esters of the adrenal cortex are increased during

hunger. Okuneff went further to establish the fact that these esters occur in increased quantities in the epithelial cells of the bile passages, and are abundantly stored in the reticulo endothelial system. Accordingly, we may assume that there may be some increased cholesterin excretion by way of the hepatic bile.

The more quickly emaciation or removal of fat occurs, the more marked must be the excretion in the bile of cholesterin, which has become superfluous for the wasting body. In this way the cholesterin in the bile, even in colloidal solution can be greatly increased, until precipitation occurs. Therefore, the general condition and nutrition of the body is of great importance for the cholesterin excretion, and the possible precipitation of cholesterin and formation of calculi in the gall bladder.

The relation of bodily constitution with such calculi formations can also be pointed out in another way. Disturbances in the metabolism of other constituents of the bile, especially of the bile acids, is of importance in the precipitation of cholesterin.

(13) Dr. Rosin in Freiburg has carried out experiments on the solvent power of desoxycholic acid on gall stones. There have been many attempts to dissolve biliary calculi in man. The starting point was the results of experiments carried out in vivo in dogs or in vitro, with bovine bile. It is to be understood that the results obtained from such experiments cannot be at once applied to man. In the first place, biliary calculi from a human gall bladder react quite differently, whether brought into contact with human or animal bile. (20). Wieland through his experimental work on the bile acid and cholesterin content, of various varieties of animals, and human bile, has shown that the variability in these relations are quite marked in the individual species. It can be readily understood that

calculi from a human gall bladder, that are rich in cholesterin, dissolve when brought in contact with bovine bile. But it would be erroneous to assume that the same thing happened in human bile.

Dr. Aoyana working in Aschoff's laboratory, carried out a series of comparative experiments, by putting calculi from a human gall bladder, first in direct contact with bovine bile, and then in contact with human bile. These stones were accurately weighed after being in one type of bile, before being put in the other. The results showed that while the stones were in the bovine bile they lost in weight, but upon being added to the human bile they gained weight. A reasonable assumption for the increase in weight, was a direct result of infiltration of the calculus by the cholesterin present in the human bile. Biliary calculi from human gall bladders are acted upon similarly by bile from the gall bladder of a dog, moreover, if the calculi are put into the gall bladder of a living dog. In that the body heat of a dog is normally about three degrees higher than the body heat of man, it has been thought that this may be the deciding factor. However, this has been proved to not be the deciding factor, because, if the same stones are put in human bile at a similar temperature - there is a gain in weight. The bile of a dog's gall bladder normally possesses a comparatively large amount of cholesterin. Accordingly, the deciding factor in the solution by bovine bile, cannot very well be the lack of cholesterin in the bile. Other conditions which are as important as the cholesterin content also play a part. These conditions are the content of the bile acids. The bile salts (2). Morse are composed of sodium and organic acids, of which there are two, glycolic and taurocholic acid. These occur in equal quantities in human bile. Experimental studies by Dr. Rosin have shown that sodium desoxycholate,

which is formed by reduction of cholic acid, has three to four times the solvent power as either taurocholate or glycholate mentioned above.

(22). Therefore, the solvent power existant in human bile, depends upon not only the total amount of bile acid that is present, but to a large extent upon the proportions in which they appear. There will be a greater solvent power the more desoxycholate that is present in bile, and the solvent power will recede proportionately as there is less present. Being as the production of the bile acids is dependent upon the diet, and the functional activity of the liver, it may well be that there are variable mixtures that occur in which there are present too little of the solvent bile acid. The above assumption is all the more justifiable, the more it can be shown that the bile acids are formed by the liver, at the sacrifice of a certain amount of cholesterin.

(13). Windaus in experimental study has to a large degree determined the relations of the bile acids to cholesterin, and according to him we are here dealing with a rather special variety of cholesterin metabolism. Assuming that such a disturbance is the cause of the production of the pure radially built cholesterin stone, explains to us the in part the properties of this calculus, namely the single occurrence, lack of an infectious gall bladder catarrh and the coarsely crystalline structure of the stone.

of one-third of the different types of calculi that are formed in the human gall bladder. They do not present themselves as pure cholesterin stones, but in the form of mixed or combination calculi.

Inflammation of the gall bladder neck, caused by impaction of and irritation by a pure cholesterin stone, or by a pressure increase, can very easily lead to dysfunction in the region of the sphincter, to reflex disturbances in bile secretion, and to ascending infections of the bile and gall bladder. A deposition of microorganisms in the gall bladder brought there by the blood can be responsible for an inflammation of the gall bladder wall, resulting in an increased pressure and impaction of the calculus in the vesicle neck. No matter how the infection may have had its origin, the inflammatory reaction in the stagnant bile can develop to a dangerous degree. The disease up until now has run its course without fever, and only occasional local spasms in the gall bladder neck region, or reflex spasm in the sphincter area. Now that it is a true inflammatory gall bladder disease, all the symptoms common to cholecystitis may become very apparent. If the impacted stone remains in the neck of the gall bladder, there will occur a collection of pus behind it, which will lead to an empyema of the gall bladder. In the course of time there develops the well known hydrops of the gall bladder (23) which is generally characterized by its particular type of closing stone - the radially built or pure cholesterin calculus. In case the calculus does not remain impacted it returns to the lumen of the now inflamed gall bladder. The fluid content of the gall bladder is no longer bile. Some of the bile has been forced out, due to pressure of the inflammatory exudate, and the

There occurs in bile which is not infected, and is free of foreign materials, sedimentation and crystallization, and this is on a single center because other centers are not present. According to Aschoff's observations, if there is an attack of hypercholesterinosis, there will occur further precipitation of cholesterol upon the previously formed calculus without changing its structure. He has been unable to ever find present more than one coarsely crystalline stone in a gall bladder.

By the demonstration of small brownish tinged nuclear-like masses in the central portion of pure cholesterol stones, Naunyn contends the inflammatory origin of them. These are attributed to small particles of pigment calcium which had their origin in the bile passages, following a cholangitis. Rovsing also believes that these concrements originate in this manner. Aschoff is of the opinion that they are bilirubin and bilirubin particles that are present in the bile and are deposited on the crystallization center of the pure cholesterol calculus. It is not a question of the material colored throughout, as is demonstrable in the case of pigment calcium. Therefore, quite a difference is present in the make-up of the nucleus of the cholesterol pigment calcium stone, and that of the pure cholesterol stone. The nuclear portion of the pure calculus is constructed similar to the rest of it, and it may be stated that in reality there is no nucleus present, but there may be slight coloring in the center, due to absorption of pigment material that is present. In the mixed calculus, a true nuclear and cortical portion can be seen.

On the basis of an extensively studied collection of biliary calculi, Aschoff believes that the pure cholesterol stones, are precursors

portion that is retained by the blocking calculus, is badly decomposed, due to the existence of the inflammatory condition in the gall bladder wall.

Thus the fresh bile that now flows in, comes in contact with an amorphous mass of finely divided material that it mixes with and forms a new colloidal system in which the colloidal precipitation products (proteins), leucocytes, and lining cells, etc. furnish the necessary conditions for new precipitation phenomena in the incoming bile. A precipitation takes place of bilirubin cholesterol in the form of granular-like semi-crystalline masses, that which in the presence of the protein rich environment, form rosettes, that have a heavy crystalline-like structure. As long as the original cholesterol stone that is in this colloidal mixture has added to it that which crystallizes out, no precipitation will occur except on this primary cholesterol stone. It becomes in reality a nucleus and a cortex is built around it and the resulting stone is that which is known as a combination stone.

The inflammatory exudate of the mucus membrane of the gall bladder wall, is rich in calcium--partly under its influence and that of the decomposition of the bile -- there are precipitations of pigment calcium masses which have a great deal of cholesterol -- and a layer or layers of cholesterol and pigment calcium around the pure cholesterol stone which serves as a nucleus. So, the combination stone has a nucleus of non-inflammatory origin and an outer shell or cortex of inflammatory origin.

The true combination stones can be easily recognized from the false,

because in a gall bladder even with several hundred stones there will only be one true combination stone, while the false or so-called secondary nuclei may be contained in many of the stones. Of course, the reason for this is that the true combination stone presupposes a radial cholesterin stone which is formed only singly. This cholesterin stone is usually the largest in the gall bladder. Besides the cortex or shell around the radial cholesterin stone there may arise from the precipitating cholesterin pigment calcium masses, numerous independent concretions, which are lacking in a radial cholesterin stone as a nucleus. These are the faceted cholesterin pigment calcium stones which show a lamellation on the cut surface. These lamellations are entirely like the layers of the cortex of the combination stones - and according to Aschoff have, therefore, been laid down when this cortex was.

As a rule along with the combination stone are found - sometimes a great many - laminated cholesterin pigment calcium stones. These are the stones that have an infectious origin. It is understood that a gall bladder infection or a bile passage infection can occur, without a preexisting blocking stone - then, of course, the infectious stone formation can and does occur and the only type of stone found in the gall bladders of these cases are the infectious stones.

These stones, according to our knowledge, are closely hooked up in their formation with an inflammation of the gall bladder. The size, shape and number of the stones of this type vary greatly. The stones referred to can be divided into several groups. The first are the faceted cholesterin pigment calcium stones which generally occur in goodly numbers. The second are the cylindrical cholesterin pigment calcium stones.

Of the first group, their shape seems to depend to quite an extent on their number. Where there is a medium number, the shape of the stones is usually that of a tetrad. These stones are movably suspended in the bile of the gall bladder. The color of the stone surface and the surfaces seen when they are sectioned, also vary. However, every section or layer has a structure which is characteristic. A nucleus is in the center which is composed of plain, rather coarse rosettes, outside of which is cortex composed of finer and coarser systems of lamellae. The change from the nucleus to the cortex is not sharply marked off. The nucleus and cortex are built of the same components and blend into one another. The central portions of these stones are rather soft, and the hardness progresses out through the cortex. All the stones in the gall bladder may vary considerably in size, appear in section - including both cortex and nucleus - to be of like make up. The nuclear portion is generally darker yellow or a brownish color and the cortex a lighter shade.

How are they formed and why do no new stones arise? The microscopic structure must be studied to understand this.

In the laminated cholesterol pigment calcium stones the structure is quite different from that of the pure cholesterol stones. The latter are made of practically a pure material and the former of a mixture of cholesterol and pigment calcium. The laminated cholesterol pigment calcium stones contain a framework of protein which can be demonstrated by removing the crystalline structure by ether or chloroform - a protein frame work will be left that shows the same radial and concentric lamellation as the stone. This protein framework is not present in the pure stones. From this it may be stated concerning the origin of the cholesterol pigment calcium stones, that they are formed only in a medium rich in

protein and the coarsely columned pure cholesterin stones - only in a medium poor in protein content.

In every inflammation of the gall bladder there is an exudate poured into it, which is rich in protein and in calcium. The conditions that are necessary for the crystallization from the bile are furnished by the changes in the colloidal solubility relations, by the more marked admixture of calcium, and the presence of crystallization centers in the form of leucocytes, (24). disintegrated epithelial cells, bacteria, etc.

According to (13) Aschoff in the development of every cholesterin pigment calcium stone, there are three periods:

- (1). Period of crystallizing out-i.e. the peculiar formation of rosettes.
- (2). Period of agglutination-i.e. accumulation of the rosettes into a nucleus.
- (3). Period of apposition-i.e. formation of the cortex.

The above periods are governed by the colloidal state, and also the concentration of the bile. Concerning the shapes of the stones, the facettes do not originate through more pressure at a given point. On observing a section of a stone the laminae are not broken through, as, of course, would be the result had they robbed against another stone. At the angles of the cube there is evidence of a more pronounced development of the layers, which is evidence of greater growth at the projecting portions. When there are a number of stones together in a gall bladder, the growth is going to be greater at the angles, as these portions are washed more by the fluid contents than the surfaces are.

The second type of infectious stone - the cylindrical or barrel shaped ones present two surfaces, a faceted one where they are in contact with one another, and a surface which is not faceted, but is nodular, and is in contact with the mucus membrane lining of the gall bladder. The faceted stones are to a large degree freely movable and the cylindrical stones more or less immobile. In the cylindrical stone the nucleus is made up of a mass of many small rosettes and in the faceted stones, made up of a few large quarter or half rosettes. The lamellation around the nucleus in the cylindrical stones is clear only at the poles and in the faceted ones the lamellation is more even and well marked throughout. Where the stone is in contact with the mucus membrane, the lamellation is absent. From this it can be seen that here, in contradistinction to the other instance, that the bile is not the only source of the stone forming substance. It is the inflamed, ulcerated mucus membrane of the wall, where the chronic pus formation is found. From this pus comes the protein, part of the cholesterin, and some of the calcium, and along with the cholesterin of the bile makes the substance for building the cortex. The processes of crystallization and agglutination do not come to an end, because new material is being constantly furnished, so the nucleus grown irregularly, without receiving a real cortex. The different composition of the nucleus will not allow for the formation of a real cavity in the center. Under these conditions a quite different type of stone development is observed.

The question as to why there are generally no new stones formed may be answered by assuming, that in the presence of an already finished stone, when new inflammatory periods again become evident, the

previous formed stone acts as a precipitating center. The layers of the cortex may present a changed structure, but there have been no crystallization and agglutination processes occur. However, this does not always take place, and then there will arise a second or possibly a third generation of calculi.

(13). The infectious and metabolic stone formation has been covered, but there still remains a third type which we will refer to as stasis stones. These differ from the above named two mainly in where they are formed. The metabolic and infectious types of stones, except very rarely, develop within the gall bladder, and the stasis stones form only in the bile passages, except when the gall bladder has lost its protecting valve in the cystic duct.

The stasis stones make up the second variety of bilirubin calcium stones and are sometimes referred to as earthy stones.

They are a rather soft, uniformly colored reddish brown, and are plainly laminated. Their shape is varied, and they may be oval, or elongated. The condition that brings about their formation is stasis of bile in the bile passages. They are generally found formed around a foreign body. The usual one is a small gall stone that has wandered out of the gall bladder, so it may be referred to as a combination stone. It can form around any of the previously discussed gall stones. The cortex is of bilirubin calcium, which is also rich in cholesterin.

This ends the discussion of the various types of calculi found in the human gall bladder. We see that there are three distinct and different processes that are the basis of formation of gall stones

in the human, disturbances in metabolism, infection of the biliary tract, and thirdly the stasis of bile. Accordingly, whichever of the above named conditions is predominant in the extra hepatic system, entirely different stones will be formed. So, we are justified in saying, that there is no one cause for gall stone formation in man. I believe that Aschoff is right when he says that he does not consider it justifiable on the basis of experiments of one definite kind, to draw conclusions as to the origin of human gall stones, which occur in so great a variety.

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