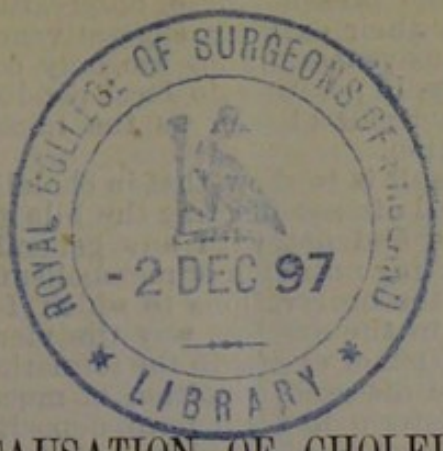
On the causation of cholelithiasis : an introduction to a discussion in the Section of Medicine at the Annual Meeting of the British Medical Association, Montreal, 1897 / by William Hunter.

Reprinted for the Author from the BRITISH MEDICAL JOURNAL,
October 30th, 1897.



ON THE CAUSATION OF CHOLELITHIASIS:

An Introduction to a Discussion in the Section of Medicine at the Annual Meeting of the British Medical Association, Montreal, 1897.

BY WILLIAM HUNTER, M.D., F.R.C.P.,

Curator and Pathologist, Charing Cross Hospital; Senior Assistant Physician, London Fever Hospital.

THE subject of cholelithiasis, which it is my privilege to bring before this Section, is one well fitted for discussion: A common disease affecting no fewer than 7 to 10 per cent. of cases, and yet in its mode of origin still exceedingly obscure; running a very varying clinical course, sometimes without symptoms, at other times the cause of the most intense suffering: presenting in its course problems in diagnosis and treatment baffling at times physician and surgeon alike. No portion of the subject presents greater difficulties than that of causation. And it is with this portion I am deputed by our President specially to deal.

What are the conditions, general or local, that determine the formation of biliary concretions within the bile passages? At the outset I would remark how slowly our knowledge of this subject has advanced; how limited it still is; how little, except in one or two particulars presently to be noted, it differs from that possessed 50 or even 150 years ago.

Stagnation and inspissation of bile contributed to by advancing age, sedentary habits, inactive life, slowing of circulation, interference with movements of chest and abdomen by such causes as lacing and pregnancy, consequent greater liability of women to suffer than men (five times greater)—all these were recognised and pointed out so long ago as 1757 by Thomas Coe.[1] In great part they represent the amount of the knowledge we have till recently possessed. Yet the inadequacy of these various factors to account for the formation of gall stones was then, as now, fully recognised, the presence of gall stones in the young and active, their absence in the old and inactive.

Did this represent all the knowledge we at present possess regarding the causation of cholelithiasis I confess I should have little satisfaction in discharging my present task.

Fortunately it does not, thanks to observations of the last few years which have introduced to our notice a new class of facts. Up to the present these observations are chiefly interesting from their extreme suggestiveness rather than from their conclusiveness. They are only conclusive in one direction, namely, in pointing to local conditions within the bile passages and gall bladder as the immediate cause of gall stone formation.

The general result is to show that in cholelithiasis we have to do with a local disease affecting the bile passages or gall bladder, or both, and not with any general constitutional disturbance affecting nutrition or metabolism.

The result of the observations to which I refer has thus been to confirm in the amplest way the view held by Budd (1857). The relation of events in the formation of gall stones Budd held to be diseased condition of mucous membrane, increase of cholesterin in solid form, deposit of this around any small particle of inspissated bile that may be present. A similar view was held by Bristowe. But the observer, to whom more than other we are indebted for establishing this on a basis of facts, is Professor Naunyn of Strassburg, whose elaborate and valuable monograph on *Cholelithiasis*, published in 1892, gives the fullest and clearest account of the subject we possess.

Physiological Considerations.

Before passing to consider what these local conditions are let me preface with a few remarks as to the bile itself and the conditions which in health determine its quantity, quality, and secretion.

We have to do with a watery secretion of low specific gravity, excreted in quantity of about two to three pints daily, containing some 1 to 2 per cent. of solids; these consisting of certain specific constituents—the bile pigments and bile acids—formed by the liver cell itself; certain inorganic salts, the most important of which in the present relation is calcium; a constant percentage of the insoluble body, cholesterin, held in solution by the salts of the bile acids and by the traces of fats and fatty acids present; and, lastly, a considerable amount of mucoid material formerly regarded as mucin, now shown to be of more complex character—a mucoid nucleo-albumin—which is added to the bile during its passage along the bile passsges, and especially during its sojourn in the gall bladder.

This fluid is secreted constantly—more abundantly four to five hours after food under the direct stimulus of the food products conveyed to the liver during digestion; less actively and more concentrated during the night when digestion is in abeyance. During active digestion and secretion it flows into the duodenum, expelled in a series of jerks by peristaltic action of the muscular fibres in the walls of the larger bile ducts. In the intervals between digestion its passage is temporarily arrested by the sphincter-like contraction of the wall of the duodenum through which the common bile duct obliquely passes; and it then collects in the gall bladder, where it lies till the next period of active digestion to be again expelled, partly by the peristaltic movements of the intestines pressing upon it, but probably in great part by peristaltic movements of the walls of the gall bladder itself.

The pressure at which the bile is secreted is very low, so that the rapidity with which it flows is greatly influenced by

outside influences, notably two:—1. The amount of resistance it meets with in the long line of narrow bile passages through which it passes. So that an increase of mucus hardly appreciable in itself may nevertheless considerably retard the flow of bile. 2. The freedom of movement of the diaphragm. Free movement of the diaphragm by compressing the liver is probably one of the most important factors in promoting expulsion of bile from the bile passages and from the gall bladder, and any cause which interferes with such movement, for example, tight lacing, pregnancy, sluggish habits of life, will correspondingly tend to retard proper expulsion of bile from the gall bladder.

General Etiology.

Age.—The most recent information is that given by Schröeder of Strassburg, 1,150 cases examined, of which 141 (12.25 per cent.) showed gall stones, and Brockbank of Manchester, 742 cases, 49 of which (6.6 per cent.) showed gall stones.

Table Showing Influence of Age.

Age.	Schröeder.	Brockbank.
0—20	2.4	2.9
21—30	3.2	5.3
31—40	11.5	3.3
41—50	11.1	7.4
51—60	9.9	9.3
61 and over	25.2	13.6

The increase with advancing years, especially after the age of 60 is well seen in both tables, especially those of Schröeder (over 25 per cent. of cases).

The relatively larger percentage of cases (over 8 per cent.) observed by Brockbank below the age of 30 is probably connected with the fact noted by him that all his cases below 30 were the subject of heart disease; in which condition there seems to be a special tendency to the formation of gall stones.

Sex.—The female sex is about five times more subject than the male, for example, 4.4 per cent. in men, 20.6 per cent. in women (Schröeder).

Pregnancy.—Out of 115 women in whom gall stones were found, no fewer than 90 per cent. had borne children (Schröeder).

Tight-lacing.—The same observer found gall stones in more than one-half of women whose livers showed any evidences of tight-lacing transverse furrows.

Laxity of Abdominal Walls.—By allowing the liver to fall down, so that the fundus of the gall bladder is considerably below the level of the junction of the cystic duct with the hepatic duct, this condition favours the retention of bile in the gall bladder.

Diminished Movements of Diaphragm.—The expulsion of bile is at all times greatly influenced by movements of diaphragm, and any restriction in the range of its movements correspondingly favours its retention. This is probably the way

in which pregnancy operates in favouring the production of gall stones ; as also tight-lacing, and sedentary habits.

Sedentary Habits.—It is this factor which probably induces the liability to gall stones seen with advancing age, also seen in inmates of lunatic asylums.

Heredity is regarded as a factor by some ; on insufficient evidence, however, I consider. Out of 165 cases, Bouchard found a parental history of gall stone in 36.

Gout is also regarded as favouring cholelithiasis. In 95 out of 166 cases Senac found a history of hereditary or acquired gout (1895). On the other hand Bouchard only found it in 13 out of 165 cases.

Influence of Food.—Habits of life as regards character of food and water have been regarded as factors in producing gall stones ; also as serving to explain the greater frequency of cholelithiasis in different countries and in different parts of the same country. On this point no definite data are, I consider, forthcoming. We are dealing with impressions rather than with facts. As a matter of fact cholelithiasis occurs in every rank and class of society ; in the poor and sparely nourished as much as in the obese and over-fed.

Influence of Disease.

Insanity.—Inmates of asylums are prone to gall stones : doubtless in consequence of the sluggish apathetic habits so characteristics of many forms of insanity.

Heart Disease seems to favour occurrence of gall stones. Out of 49 cases, no fewer than 27 were found to suffer from cardiac lesions (Brockbank).

Chronic Rheumatism.—29 out of 165 cases.

Diabetes.—16 out of 165 cases observed by Bouchard.

Renal Lithiasis.—A relation has been said to exist between occurrence of gall stones and renal calculi. Thus Kraus found the two associated in 42 cases. On the other hand the statistics of others lend no support to this view. Thus Naunyn has only observed the association once.

Conclusion.

General etiology thus throws but little light on the causes underlying the disease. It only brings out one fact—that anything which favours stagnation of bile in the gall bladder favours the occurrence of cholelithiasis.

Special Etiology.

Biliary Concretions.—In cholelithiasis we have to do with a precipitation of certain of the biliary constituents in insoluble form. (1) Cholesterin normally held in solution in normal bile by the bile salts and the traces of fats and fatty acids present in the bile. (2) Bile pigment normally in solution, now thrown down as an insoluble compound in combination with another normal constituent of the bile calcium.

The problem of the causation of cholelithiasis thus narrows itself to the question—What are the conditions, general or local, that determine the formation and precipitation of these normal biliary constituents in the mass, and in the form they are met with in gall stones ?

Characters of Gall Stones.

On the characters of these gall stones I need not dwell : their variation in shape, number, and size ; their peculiarities

in shape from pressure against each other; their amorphous or crystalline character.

They have been variously classified according as one or other constituent—cholesterin, bilirubin, calcium, carbonate of lime—predominates; according to the relation of the constituents to each other, the cholesterin surrounding a nucleus of bilirubin calcium, or itself forming a nucleus, or both intermixed; or according to the crystalline or amorphous character of the cholesterin present.

The following classification of Naunyn will illustrate the various forms met with:

VARIETIES OF GALL STONES.

1. *Pure Cholesterin.*—Oval or round, rarely facetted, crystalline consisting of almost pure cholesterin.

2. *Laminated Cholesterin*, resembling the foregoing in form and size, but more often facetted, on section more or less distinctly laminated; outer layers amorphous, becoming more and more crystalline towards the centre, consisting chiefly (90 per cent. or more) of cholesterin with a constant trace of bilirubin calcium and calcium carbonate.

3. *Common Gall Stones* from gall bladder, comprising the great bulk of gall stones of the most varying size, shape, and colour, usually facetted with a central nucleus of bilirubin calcium, surrounded by amorphous cholesterin and bilirubin calcium in varying proportions.

4. *Mixed Bilirubin Calcium.*—Size of a cherry or larger, met with singly or at most two or three in number, in gall bladder or larger bile ducts, dark in colour, the greater mass formed of layers of a dark or rusty brown colour, made up in great part (75 per cent. or more) of bilirubin calcium, the remainder cholesterin.

5. *Pure Bilirubin Calcium.*—Small, black, irregular, size of a pea, non-facetted, found in gall bladder, but frequently also in intrahepatic bile ducts, consisting almost entirely of bilirubin calcium with a constant trace of humin substances.

6. *Rarer Forms.*—(*a*) Amorphous and imperfectly crystalline stones of cholesterin, often of pearl-like colour, seldom laminated, with a central nucleus of bilirubin calcium; with this exception consisting of pure cholestrin.

(*b*) Chalk stones, composed of calcium carbonate recognisable by their extreme hardness.

(*c*) Conglomerate stones, the body consisting of mixed bilirubin calcium stone, the nucleus of pure cholesterin, in many cases two or more nuclei surrounded by a common body; or the nucleus formed by a foreign body—for example, a needle, plumstone, piece of round worm, of a distoma, or cast of intrahepatic bile duct.

(*d*) Stones having the shape of the larger bile ducts, consisting of bilirubin calcium, not seldom in cattle, very rare in man.

From the point of view of causation, I prefer a simpler classification. From that point of view, it appears to me to be of relatively little importance in what proportions the constituents are present, or in what form, crystalline or amorphous, or the degree and character of the lamination or stratification.

What impresses me is—

1. In the vast proportion of gall stones the two chief constituents are cholesterin and bilirubin calcium.

2. While in exceptional cases cholesterin may form the nucleus of the stone, in the vast majority the nucleus is made up of bilirubin calcium. This latter must therefore have been the earlier formed, and around this the cholesterin is deposited pure, or intermixed with more bilirubin calcium, as the case may be.

3. Almost equal in frequency to this mixed gall stone is the biliary concretion formed of bilirubin calcium alone, without any cholesterin; the small dark brittle concretions one so frequently finds, not only in the gall bladder, but also not infrequently within the intrahepatic bile ducts themselves. These characters I can demonstrate to you in the lantern slides I now show.

These two facts—the frequency of concretions of pure bilirubin calcium without any cholesterin, and of nuclei formed of this material, denote that the conditions underlying the formation of gall stones are, in the large majority of cases, primarily such as favour the precipitation of bilirubin with calcium.

Seat of Formation of Gall Stones.

In this connection there appear to me to be three outstanding facts:

1. Within the intrahepatic bile ducts the concretions have nearly always the character of pure bilirubin calcium. The conditions, whatever they be, which lead to the precipitations of bile pigment and calcium in insoluble form, must thus occasionally exist high up within the liver, and be entirely independent of anything prevailing in the gall bladder, or common bile duct. We can conceive of such small concretions, for they are always of small size, being carried down with the bile into the hepatic duct, and thence into the gall bladder (and this is probably the source in many cases when present in the gall bladder); but we cannot conceive the reverse, namely, such concretions having been formed low down and carried up in the absence of obstruction into the liver against the direction of the bile flow.

2. In the common bile duct and hepatic duct the stones usually met with have a special character of their own—such as I now show you. They are usually large, round, or oval, dark in colour, and either single or at most in groups of two or three. They are found in cases of obstruction of the common duct, in which the duct become widely dilated, its walls thickened and inflamed. On section the bilirubin calcium element is found to predominate. It forms the nucleus and the greater mass of the stone, only a small proportion of cholesterin surrounding the central mass. The original source of this kind of gall stone is doubtless in most cases the gall bladder, a smaller stone derived from the gall bladder having become impacted on its way down. But there can be hardly any doubt that the large size which such stones attain to is due to further formation and deposition of its constituents within the walls of the inflamed common duct. And it is interesting to note that just as in the case of the concretions formed higher up within the intrahepatic ducts, the bilirubin calcium element is here the prevailing constituent. Cholesterin is in relatively small quantity.

3. It is, however, the gall bladder that is the chief seat of formation of gall stones, and it is in this situation—a sort of *cul-de-sac* or back eddy where the bile can lie for varying

periods of time undisturbed—that the chief conditions are to be sought favouring the formation of gall stones. The stones here formed have in general this distinction: that, differing from the two classes just considered, the chief constituent is cholesterin, albeit that, as I have already pointed out, in the vast majoritythere is a darker central nucleus of bilirubin calcium.

Source of the Constituents of Gall Stones.

We are now in a position to approach more closely the problem which cholelithiasis presents us, namely, What is the source and mode of origin of the cholesterin and bilirubin calcium which make up the great bulk of gall stones?

1. With regard to cholesterin. Is it formed *in situ*, the product of a diseased mucous membrane of gall bladder or bile passages; or is it precipitated from the bile by deficiency of its chief solvent agent, the bile salts; or, lastly, is it due to an increased excretion by the liver?

The evidence on this point although not conclusive is, I think, all in one direction, namely, in favour of it being entirely of local origin—a product of secretion or disintegration of the epithelium of mucous membrane and glands of gall bladder, and of larger bile ducts. It is a product widely distributed throughout the body. It occurs not only in bile, but also in nervous tissues, blood corpuscles, spleen, seminal fluid, testes, ovary, yolk of egg. Hence it has been thought that its presence in the bile is solely due to its excretion by the liver from the blood. There is, however, no actual evidence, in my opinion, that such is the case.

On the other hand, there is conclusive evidence that it is a frequent product of degenerative conditions, being found in atheromatous, cancerous, tuberculous products; in ovarian less frequently in ascitic and pleuritic fluids; in pus; thyroid cysts, and more especially in the secretions of mucous membranes, for example, sputum of bronchitis, phthisis, etc. This latter fact appears to me to be one of great significance in relation to our present subject—strongly suggesting that if it can be formed in quantity by mucous membranes elsewhere, it probably has a similar origin in cholelithiasis. In bile it is present in the small proportion of about 0.7 per 1,000; in the bile from gall bladder in much higher amount, namely, 3½ to 11 per 1,000.

In the sputum of catarrhal bronchitis it has been found in proportion of 0.9 per 1,000; in the sputum of bronchiectasis in even higher proportion—1.5 per 1,000 (Naunyn)—2.2 and 2 per cent. of the solid constituents respectively. In pus it has been found in still higher proportion, namely, 7 per cent. of the solid constituents. Cholesterin then appears to be pre-eminently a product of cellular degeneration, especially of epithelium degeneration. And such appears to be its source in the bile. The evidence appears to me to point to its local origin in the bile passages, both in health and disease.

Naunyn indeed has been able to trace the origin of this product from the degenerating epithelium. It is formed as viscous myelin globules within the degenerating epithelial cell. It escapes in this viscous condition and can be seen floating about, and on the addition of a few drops of acetic acid it can be seen solidifying into a mass of cholesterin crystals. Conversely, similar myelin masses can be produced by the action of a solution of soap on cholesterin as described

by Brockbank. The formation of viscous masses by the mucous membrane of gall bladder, consisting almost solely of pure cholesterin, I have also been able to observe; these viscous masses by pressure against one another and adjacent gall stones already possessing the characteristic shape of gall stones. The important conclusion is thus led up to, that the cholesterin which goes to form gall stones has never really been in solution in the bile, but has been in a more or less solid viscous form from the beginning, formed as a product of degeneration of the epithelium of bile passages.

2. With regard to the insoluble compound, bilirubin calcium. In normal bile these two constituents are not combined. Nor can they be made to combine by any mere concentration of bile. Bilirubin itself may deposit under such circumstances, but not in combination with calcium. Nor can the two be made to combine by any mere excess of lime, at least in the first instance. But if further excess be added a deposit of bilirubin calcium finally takes place, till finally the whole of the bilirubin is thus precipitated. There appear then to be substances in the bile which prevent the precipitation of bilirubin calcium, even when the amount of lime is considerably increased (Naunyn). The bile salts seem to exercise some such function. Thus it only requires the addition of a few drops of limewater to a weak ammoniacal solution of bilirubin to precipitate the whole of the latter as bilirubin calcium (Naunyn). But if such a solution contains 2½ per cent. of glychocolate of soda, precipitation only begins when five times the quantity of limewater is added. The lime is seized upon by the bile acid. It is probable then that a certain reaction of bile is necessary for the formation of this bilirubin calcium compound.

Apart from mere reaction, or proportion of bile salts present, there is another observation of interest in this relation, namely, that just as egg albumen favours the precipitation of calcium carbonate from solutions of bile salts, so also egg albumen favours the precipitation of bilirubin calcium (Naunyn). This suggests, then, that the presence of albumen in the bile passages and gall bladder may favour the formation of bilirubin calcium concretions. Albumen derived from the disintegration of epithelium, that is catarrh which promotes such disintegration, is thus in all probability the factor which determines the precipitation of bilirubin calcium within the bile passages and gall bladder.

Catarrh of Gall Bladder and Bile Ducts as the Immediate Cause of Cholelithiasis.

It thus appears that the conditions leading to increased formation and deposition of cholesterin in solid form, and to the precipitation of the insoluble body—bilirubin calcium—are essentially local; and are of the kind—increased epithelial degeneration and presence of albumen—that prevail in a special degree in catarrhal and inflammatory conditions of the lining membrane of gall bladder and bile ducts. I have now to consider what it is that sets up this catarrh.

Among the various factors which have been held responsible for the formation of gall stones—the influence of age, sex, heredity, gout, rheumatism, etc., the only one whose influence is undoubted is stagnation of bile. In the list of conditions I have noted under "general etiology" it will be seen that the degree to which any one of them favours the inci-

dence of cholelithiasis may safely be regarded as in direct proportion to their liability to favour stagnation of bile in the gall bladder. Hence the greater frequency of the condition in advancing age, in women, especially in pregnant women; in those of inactive habits of body from gout, rheumatism, etc.

Frerichs taught that stagnation of bile alone might of itself in time excite a catarrhal condition of the mucous membrane by favouring decomposition of the bile itself. With the knowledge we now possess this view cannot be accepted. It may, I think, be taken as certain that such a decomposition does not occur in the absence of micro-organisms. Stagnant bile, if kept sterile, does not deposit bilirubin calcium, or cholesterin. Normal bile is aseptic, as shown by Netter for rabbits (1884); by Naunyn for dogs and rabbits. Human bile is also sterile. Gilbert and Girode found it so in 6 out of 8 cases even as long as twenty-four hours after death; Naunyn in 2 cases examined one, and five hours after death, and in 2 cases punctured during life; and myself in 2 cases examined fourteen hours after death. In a third case examined by me twenty-two hours after death, *post-mortem* infection had already occurred. the bile contained a gelatine liquifying organism.

Causes of Catarrh.

As causes of catarrh there are, I consider, two possible factors to be considered.

Infection as a Cause of Catarrh.—As one of the commonest causes of catarrh and inflammatory conditions of gall bladder and bile ducts, we have now to recognise infection of the bile and bile passages with organisms; and in favouring such infection no single factor is more important than stagnation of bile. This is very well brought out by certain experiments made by Naunyn. In five cases of gall stones he obtained the bacillus coli communis by puncture of the gall bladder during life. The injection of this organism into the gall bladder of the dog excited no trouble; but if the common bile duct were previously ligatured so as to bring about a stagnation of bile, then the injection set up the most violent inflammation (cholecystitis and cholangitis).

The organisms which have been found as causes of inflammation of the gall bladder in individual cases include the pyogenic organisms: staphylococcus and streptococcus; the common bacillus of the intestine—B. coli communis—and the typhoid bacillus.

The observations in this relation are so far but few. But they are likely to be rapidly added to now that attention has been drawn to the subject, and especially now that opportunities are afforded by the surgeon for more frequent examination of the gall bladder. For the present chief interest attaches to the B. coli communis and the B. typhosus. The former is the organism that has been found in the majority of cases of cholecystitis and cholangitis. The connection between the latter organism and inflammatory conditions of gall bladder is of peculiar interest. Dufort (1893) has described a case of cholecystitis and gall stone following at a few months' interval an attack of typhoid fever, and he found the typhoid bacillus in the gall bladder. Up to 1876 18 such cases were collected by Hagenmüller from the literature. In a recent case I found a marked inflammatory con-

dition of the whole mucous membrane of the gall bladder in a case of typhoid fever. On microscopic examination the mucous membrane showed thickening and recent acute inflammatory changes.

The question as to the connection between such an infection and cholelithiasis is of still more interest. In a certain number of cases the first attack of gall stones has followed at an interval of two or three months an attack of enteric fever, as in Dufort's case above noted. A similar case has been described by Gilbert and Girode (1893). In no fewer than 19 out of 22 cases of enteric fever the presence of the typhoid organism has been demonstrated in the contents of the gall bladder by Chiari (1893); in 15 of these cases in pure culture. In all these cases the common bile duct and cystic duct suggest themselves as the channel of infection by which the organism has found its way upward from the duodenum. This would be in accordance with Sherrington's results. Sherrington has shown for a large number of organisms investigated by him that it is the exception for them to pass into the bile after their injection into the general circulation. So that this source of infection may in general be excluded. And yet certain interesting observations made by Professor Welch, of Baltimore, and published in the *Bulletin* of the Johns Hopkins Hospital in 1891, would indicate not only that infection of the gall bladder with the typhoid organism may incur from the blood, but that this infection may persist there after it has disappeared from every other organ of the body. He found the typhoid bacillus in the gall bladder of rabbits as long as three to four months after its intravenous injection at a time when it could not be found in any other organ of the body, even in the spleen and intestine.

Such, briefly, are the chief facts. Here I must caution against any too hasty generalisation from them as to the frequency of the connection between cholelithiasis and typhoid fever. That remains a problem still to be worked out.

At the present time the facts are, I think, chiefly interesting from their suggestiveness. In whatever way the infection occurs, whether through the bile passages, as is probably the most common, or through the blood, the important fact I wish to bring out is that infection of the bile and gall bladder with organisms is of no infrequent occurrence; that under favourable circumstances, the chief of which is stagnation of bile, such infection can set up catarrhal and subacute inflammatory conditions of the lining membrane of the gall bladder and bile ducts, in certain cases even intense suppurative conditions.

In the etiology of gall stones, where, as I have shown, catarrhal inflammation plays such an important part, infection thus comes to rank as a possible and most important factor. I do not speak here of the part it plays in producing the symptoms of acute attacks—the fever, the swelling, and tenderness over the gall bladder, possibly the ague-like attacks—from which the subjects of gall stones suffer, or the suppurative conditions of gall bladder and bile ducts met with in severer cases. I am only concerned with the earlier and gentler *rôle* played by infection as a catarrh-producing factor, setting up a catarrhal inflammation sufficient to lead to a largely increased formation of cholesterin and to the precipitation of bilirubin calcium.

A temporary infection of this kind, whether the organism

be the colon bacillus, or the bacillus of typhoid fever, or other organism extending over a few months, may, without causing any symptoms, excite a catarrhal inflammation of gall bladder sufficient to produce a crop of gall stones, and then pass off completely, leaving the latter as a permanent legacy to the patient. It is probably in this way that gall stones usually arise and why they are met in such numbers. If the infection passes off the stones may remain quiescent for years without causing any symptoms, probably undergoing but little increase in size. But even so they are always liable to excite trouble. Their mere presence may serve mechanically to keep a certain moderate degree of congestion of the mucous membrane of the gall bladder. But a more important danger is that a subsequent infection may occur and induce a cholangitis or a cholecystitis, or one of the stones may pass down and become impacted.

Excretion through the Liver as a Cause of Catarrh.—So far the only factor I have spoken of as a possible catarrh-producing agent has been infection. And in speaking of it, I have had specially in mind the gall bladder as the chief seat of formation of gall stones. In general it may be stated that what applies to the gall bladder in this relation applies also to the cystic and common bile ducts. Stones found in the latter situation have originally come from the gall bladder, although they attain the large size so commonly met with in stones in this situation by subsequent increase. I have, however, now to refer to another class of stone, the seat of whose formation is not necessarily the gall bladder or the common bile duct, but higher up within the intrahepatic ducts. In speaking of the possible seats of formation of gall stones, I pointed out that small dark calculi consisting of bilirubin calcium are not infrequently met with high up within the liver, lying within the smaller intrahepatic ducts. The presence of these calculi in this situation appears to me to be of particular interest. They consist usually of bilirubin calcium—the insoluble body for whose formation catarrh of the bile passages is as important as for that of cholesterin itself.

How is this intrahepatic catarrh set up? Infection may, I consider, here be set aside. It is highly improbable that an infection may travel up along the bile duct and excite catarrh in the higher intrahepatic ducts without affecting the lower. The more probable cause of such intrahepatic catarrh appears to me to be one pointed to by certain observations of my own, namely, the excretion of products through the bile, exerting an irritant action on the bile passages.

That the bile has an excretory function for substances injected into the blood or administered by the mouth or intestine has been shown for quite a number of drugs and medicinal substances, for example, ferrocyanide of potassium (Claude Bernard); iodide of potassium, cane and grape sugar, sulphate of copper, oil of turpentine (Mosler); iodide of potassium, bromide of potassium, iron, lead, nickel, arsenic, silver, bismuth, and antimony (Wichert); iodide of potassium, salicylate of soda, carbolic acid (Peiper); oil of turpentine, salicylic acid (also after administration of salol) bromide of potassium, iodide of potassium, chlorate of potash, arsenic, iron, lead, mercury (Prevost and Binet).

The excretion through the bile may begin very early;

for example, salicylate of soda is detected in the course of half an hour after administration, iodide of potassium after some six to eight hours (Peiper).

In the case of the above substances there is no evidence that in the course of their excretion they exert any injurious action. On the contrary, the action of some of them is beneficial, causing an increased secretion and flow of bile.

Very different, I find, is the result with another class of substances, of which toluylenediamine may be taken as a type. This body has the power of producing intense jaundice in dogs, the jaundice being obstructive and caused by intense concentration and viscidity of the bile.

When the jaundice is at its height, the smaller bile ducts are found plugged with thick viscid bile, while lower down in the common duct only thick viscid colourless mucus is found.

The particular observation of my own I have referred to is that this change in the character and viscidity of bile is due to inflammatory catarrh of the whole system of bile ducts extending from above downwards, set up by the excretion of the poison itself (or derivatives of it) through the bile. I found the drug in the bile as early as half an hour after its injection into the blood. In large doses it exerted an intense irritant action, not only on the bile passages, but also on the duodenum in cases.

From the opening of the bile duct downward the most intense inflammatory condition was produced, the mucous membrane, as determined by actual measurement, being swollen to 3½ times its normal thickness, reddened and inflamed, and covered with tenacious colourless, inflammatory mucus, and similar mucus was seen exuding from the opening of the common bile duct.

The intrahepatic catarrh, I would ask you to note, is not secondary to the duodenal catarrh, but precedes it. It is produced even when the common bile duct is ligatured, and the bile is allowed to flow out through a fistula.

It is thus no question of a catarrh of bile ducts secondary to a duodenal catarrh. The relation is the other way: the catarrh has spread down the bile ducts from their origin.

The significance of these observations in relation to the pathology of jaundice caused by poisons, and in relation to catarrh of the intrahepatic bile ducts, I have discussed in full elsewhere.[2] Tney establish to my mind the great importance of this excretory function of the liver in relation to intrahepatic catarrh. The liver is constantly being called on to deal with products more or less harmful carried to it in the portal blood from the intestines. It deals with them in two ways, either by destroying them, or by excreting them—most usually by both.

If these products possess any irritant qualities, this continuous excretion will tend to set up and maintain a certain degree of intrahepatic catarrh in direct proportion to any irritant qualities they possess.

And this is precisely the state of things favoured in the chronic dyspeptic, in those who lead a sedentary life, in the "bilious" subject generally.

I consider it possible, then, that under the conditions just referred to, a state of intrahepatic catarrh of excretory origin may be induced, and that in certain cases this may suffice to lead to the precipitation of the bile pigment and lime of

the bile in the form of the insoluble bilirubin calcium compound.

In this way small biliary concretions may, I think, be produced independent altogether of infection. It is conceivable even that in certain cases, such intrahepatic concretions, carried downwards and lodging in the gall bladder, may form the starting-point of a moderate and non-infective stone formation in the gall bladder itself.

Such, I conceive, may well be the mode of origin of the gall stones so often met with in the gall bladder of old people that have never caused any symptoms. Such also I consider to be the nature of the cholelithiasis met with in the subjects of heart disease. Here the catarrh of bile passages and gall bladder is set up and maintained by the passive congestion prevailing in the liver generally. In a recent case of this kind I found the mucous membrane of gall bladder chronically congested and thickened, producing thick viscous clumps of material which lay between the individual stones, many of the clumps already showing the shape of stones. On the addition of a few drops of acetic acid they threw down cholesterin crystals in abundance. I regard them as gall stones in their earliest stages.

Conclusions.

1. In cholelithiasis we have to do with a local disease affecting the bile passages or gall bladder or both, and not with any general constitutional disturbance affecting nutrition or metabolism.

2. General etiology—the influence of age, sex, pregnancy, sedentary habits, food, heredity, etc.—throws but little light on the immediate causes underlying the disease. It only brings out one important fact: that anything that favours stagnation of bile in the gall bladder favours the occurrence of cholelithiasis. Yet stagnation alone is not sufficient to cause the condition.

3. The two chief constituents of gall stones are cholesterin and bilirubin calcium.

4. The conditions that determine the presence of these constituents in insoluble form are entirely local. The cholesterin found in gall stones has never been in solution in the bile, but is formed as viscous masses as a product of degeneration of the epithelium, chiefly of the gall bladder; and the combination of bilirubin with calcium to form the insoluble compounds—bilirubin calcium– is determined by the presence of albumen, such as is derived from degenerating epithelium in the bile passages or gall bladder. The favouring conditions in both cases are thus such as specially prevail in catarrhal conditions of bile passages and gall bladder.

5. As causes of catarrh, two factors are to be recognised: (*a*) Infection of gall bladder with micro-organisms, an occurrence specially favoured by stagnating bile. The chief organisms hitherto found are B. coli communis and the typhoid bacillus. An infection of this kind is probably a common cause of the gall-stone formation so common in the gall bladder. (*b*) Excretion of irritant products through the bile. The catarrh so set up is always in the first instance intrahepatic, and may be entirely confined to the intrahepatic bile ducts; it leads to the formation of bilirubin-calcium concretions. The concretions so formed may be afterwards

carried to the gall bladder, and there form the nuclei of larger stones.

6. Whether the immediate cause of the catarrh be of an infective or a non-infective character, the indications for treatment are in the main the same: (*a*) We cannot prevent accidental infection of the gall bladder, but a certain sojourn within the gall bladder is a necessary condition for organisms to set up catarrh; and by preventing stagnation of bile (by proper exercise, avoidance of tight-lacing, etc.) we can render the conditions unfavourable to their action. (*b*) In the case of the catarrh of non-infective origin, we can hope by appropriate treatment to do away not only with the catarrh itself, but with its causes, by promoting an absolutely healthy gastric and intestinal digestion, so as to avoid the formation of any products which may possibly excite any degree of catarrh in the event of their being excreted through the bile; and, secondly, by promoting a free flow of bile by diluents given between meals by exercise, by suitable diet, of which the chief is meat, and by drugs, the chief of which is salicylate of soda.

REFERENCES.

[1] Brockbank, *On Gall Stones*, London, 1896. [2] Hunter, Jaundice and Functional Diseases of Liver, Allbutt's *System of Medicine*, vol. 4.