

CHRONIC CHOLECYSTITIS

A review of the subject with a follow-up
of 247 cases treated by operation.

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INTRODUCTION.

Historical.

Chronic cholecystitis, with or without gall stones, is not a product of this civilisation, as is borne out by the fact that gall stones have been discovered in Egyptian mummies. Whether their existence was recognised in these early days is not known, but no reference to them has been found before the 14th century when they were first described by Gentile de Foligno of Padua.

Hoppe-Seyler (1903) thinks that the absence of comment on gall stones by the early European anatomists must mean that gall stones were much less common in these days than they are now, and suggests that the different modes of living in the ancients as compared with the ways of modern civilisation may have some bearing on the subject.

In 1554 Fernelius gave a description of gall stones along with the symptoms which they may produce. He realised that obstruction of the common bile duct may lead to swelling of the gall-bladder, together with light coloured faeces and dark urine, and also that when the hepatic duct is obstructed the gall-bladder is empty. About that time also Forestus held the opinion that gall stones are formed under the/

the conditions in which the gall-bladder is not properly emptied and the cystic duct is occluded.

Gradually it became realised that gall stones were associated sometimes with colic and jaundice, and pain which radiated upwards to the region of the shoulder. Such a case is described by Glisson in 1654.

Little treatment seems to have been suggested in these early days, and the whole subject of gall-bladder disease appears to have advanced very slowly until about the middle of the 19th century when the advent of general anaesthesia made modern surgery possible. Although ether was first used as a general anaesthetic in 1844, a considerable time was to elapse before the commencement of operative surgery on the gall-bladder, and it was not until 1868 that John Bobbs of Pennsylvania first performed the operation of cholecystostomy, to be followed by many others soon afterwards.

Frequency of Chronic Cholecystitis.

The real importance of the diseased gall-bladder now began to be recognised owing to the fact that it was being found possible to treat the condition. Since that time rapid strides have been made in the fields/

fields of diagnostic and operative technique, and the interest in the condition of chronic cholecystitis has become greater. The disease is much commoner than at one time was thought, but even at the present day the extreme frequency of the disease, with or without apparent symptoms, is probably not fully appreciated. In recent years some light has been thrown on the subject by the study of large series of cases from the post mortem room, which in the course of routine examination have been found to suffer from some degree of chronic change in the gall-bladder.

The results of large numbers of consecutive autopsies examined from this point of view have been published by many people. Barclay (1933) describes how, in 4616 consecutive autopsies carried out at St. George's Hospital, gall stones were recorded in 268 cases, that is, 5.8%. Rolleston and McNee (1929) record a series in Germany combining the figures of Roth, Schloth and Schroder, where gall stones were found in 1,029 out of 10,866 consecutive cases giving 9.4%. Other large series of cases quoted by Mentzer (1926) give the following results:-

	Number of <u>cases.</u>	Percentage of cases with <u>gall stones.</u>
Mitchell (Munich & Erlanger)	19,974	7.8%
Mitchell (Basel)	16,025	10.7%
Rovsing (Copenhagen)	7,447	8-25%

It/

It would appear from these results that the frequency of gall stones is somewhere in the region of 5-10% of all persons at death. Mentzer (1926), working at the Mayo Clinic, has published his results in a series of 612 consecutive autopsies. The number of cases is much smaller than those quoted above, but his results are very striking. He found that of the 612 cases there were 123 (20%) in which gall stones were present. When he has excluded those autopsies performed under the age of 21, the final result was that there were 21% found to have gall stones at the time of death. He found that 17% of the males had stones and 28% of the females. These findings are considerably higher than the others quoted. Mentzer comments on this high comparative figure and explains that possibly this may be due to the relatively high percentage of patients with gall-bladder trouble who come to the Mayo Clinic, saying that in 1922 5% of the total cases registered complained of gall-bladder trouble.

All the above figures relate only to the finding of gall stones at death, and make no mention of the state of the gall-bladder itself, with the exception of the series recorded by Mentzer. He also examined the state of the gall-bladder wall and found that, omitting/

omitting all the cases under 21 years of age, there were altogether 66% which showed "grossly visible disease" of the gall-bladder. In another 9% he found that pathological changes were seen microscopically. This is particularly striking in view of the fact that of all the cases only 8% had a primary diagnosis of gall-bladder trouble.

It seems feasible, therefore, to assume from all the above results that gall-bladder disease must be a great deal commoner than is usually thought, and also that there must be a great many people with diseased gall-bladders who suffer symptoms which have never been connected with the possibility of the gall-bladder being the source of the trouble.

Wilkie (1928) considers that infection of the gall-bladder is probably the commonest of all abdominal maladies, particularly amongst those of sedentary habits.

With increasing knowledge and the great assistance which is now lent by radiology, there is no doubt that by a correlation of symptoms, clinical findings and the pathological findings at operation, more and more knowledge is accumulating which is to act as a guide in deciding whether the gall-bladder is/
is/

is at fault.

METHODS OF TREATMENT.

It is necessary at this point to mention briefly the methods of treatment used in chronic gall-bladder disease before starting the discussion of the 247 cases reviewed in this thesis.

There are two methods of treating chronic cholecystitis:-

(1) Medical Treatment. In discussing the treatment of chronic cholecystitis Beaumont (1935) states that if gall stones are present, then the gall-bladder should be removed, but that in other cases an attempt should be made to disinfect the contents of the gall-bladder by hexamine and alkali. The difficulty which immediately arises here is that it may not be possible to know if the gall-bladder contains stones. Radiological examination may disclose the presence of stones in the gall-bladder, but it is a far more difficult thing to say that stones are not present. As will be seen later, a negative radiological report, either by straight X-ray or by cholecystography, does not mean that stones are not present.

There seems to be little doubt that medical treatment may be of great value in some cases.

Douthwaite/

Douthwaite (1935) recommends the use of thirty or more grains of potassium citrate thrice daily, accompanying this after a few days with hexamine, up to 80 grains daily. He also recommends the use of olive oil which encourages the drainage of the biliary tract. He considers that encouraging results are obtained in mild cases of cholecystitis in this way.

The disadvantages of medical treatment are:-

(a) It is difficult to gauge the extent of disease present in the gall-bladder. Thus medical treatment is always rather a doubtful quantity.

(b) If stones are present, it is unlikely that medical treatment will help the condition permanently. Even though the gall-bladder in such a case empties itself of stones, it is likely that they will form again at a later period.

(c) It is doubtful if medical treatment is of great value in cases where the damage to the gall-bladder wall is of a permanent nature and has decreased its functioning powers.

Thus it is probably only in the very early cases, which are difficult to diagnose, that medical treatment is of permanent value. In these cases where no permanent damage has been done, then medical treatment may prevent it. Medical treatment is also indicated in/

in those cases which are considered a bad operative risk.

(2) Surgical Treatment. Until recent years the common practice in dealing with chronic gall-bladder disease surgically was the operation of cholecystostomy. Here the gall-bladder was drained and stones removed if present. It was found, however, that many of the cases had recurrent symptoms in later years owing to the fresh formation of stones.

This earlier method has now been almost entirely replaced by cholecystectomy, where the gall-bladder is removed.

It is with cases dealt with surgically that this thesis deals.

SCOPE OF THE THESIS.

The subject of chronic cholecystitis will be dealt with in two parts.

Part I. A series of 247 consecutive cases operated on for chronic cholecystitis, with or without stones, has been analysed. These cases are viewed from various angles, and in particular an attempt is made to correlate the findings at operation with etiological factors observed, symptoms and radiological findings.

These/

These cases will be dealt with under the following headings:-

Sex incidence
 Age incidence
 Age and sex incidence
 Pathological findings at operation
 Etiology
 Symptomatology
 Radiological findings
 Operative mortality
 Summary

Part II. This consists of a follow-up of patients after operation. All the 247 cases were operated on from one to ten years previously, and an attempt was made to get into touch with each of these cases. This was successful in 162 cases.

An attempt is made in these cases to assess the degree of success which has followed operation. In particular an attempt is made to show which types of case were most benefitted by operation by correlating the operation results with the findings at operation.

These cases will be dealt with under the following headings:-

Method of follow-up
 Classification of results
 Object of follow-up
 Results in chronic cholecystitis with or without stones
 Results in different groups
 (1) Multiple mixed stones
 (2) Single cholesterol stones
 (3) Single cholesterol plus multiple mixed stones
 (4) Pigment stones
 (5) Stoneless gall-bladder
 (6) Cholesterosis.
 Symptoms which persist after operation
 Summary.

PART I.

PART I.Sex Incidence.

It is generally agreed that the disease occurs more frequently in females than in males. In the present series it was found that there ^{were} 212 females and 35 males. This gives a proportion of approximately six females to one male. This is a higher proportion than has been found in some groups of cases, especially those in America.

Graham (1926) finds the proportion of females to males to be two and a half to one. Blalock (1924), in an analysis of 888 cases at the Johns Hopkins Hospital between 1889 and 1924, shows the proportion to be two females to one male. Wakeley (1935), working in this country, found in a series of 467 cases of chronic cholecystitis that there were 386 females and 81 males, giving a ratio of about 4.8 to 1. The possible reasons for the greater frequency of the disease in the female will be discussed under the heading of the etiology of the disease.

Age Incidence.

Chronic cholecystitis is principally a disease of middle life. It may occur in the young and the aged, but it is most common in the fifth decade of life. Blalock, in his series mentioned, finds that most/

most of his cases fall into the fifth decade. Only one case in the present series was found to be under the age of 20 at the time of operation, and there were three other cases where the operation was performed at a later age but where symptoms developed before the age of 20 years. It is probable that the disease of cholecystitis in its chronic form is comparatively rare before that age, but in the acute form it is more common. Graham (1929) mentions that during ten years at the St. Louis Children's Hospital there were 8 cases of acute cholecystitis in children from $1\frac{1}{2}$ to 15 years of age, in all of which the gall-bladder was found to be reddened, swollen and distended. It may be that the occurrence of the disease in the acute form in the very young may be missed at the time, and that it may be the forerunner in some cases of the more chronic state which develops in later life, when other factors become superimposed. It is undoubtedly a disease which does not enter into the differential diagnosis to any great extent in children, and Snyder (1925) can find only 80 cases of gall-bladder disease under the age of 10 years recorded between 1722 and 1922. Farr (1922) sums up this state of things by saying that cholecystitis in children is probably not very rare, but usually unrecognised.

There/

There were 15 cases in the series of 247 cases in which the age of the patient is not known. In the remaining 232 cases the figures found were:-

Grouping according to age at operation.

	Number of cases	Percentage
Under 20 years - -	1	.4
20-29 - - - - -	11	4.8
30-39 - - - - -	33	14.2
40-49 - - - - -	58	24.9
50-59 - - - - -	83	35.9
60-69 - - - - -	36	15.5
70 onwards - - - -	10	4.3
	<u>232</u>	

It is seen that the majority of cases came for operation in the sixth decade of life. There were 83 cases (35.9%) out of the total of 232, in which the age was known, occurring between the ages of 50 and 59, after which the numbers decrease in the ensuing decades. It would appear from this that the disease reaches a peak in the sixth decade and is less commonly met with after the age of 59.

These figures may to some extent be deceptive for two reasons. (1) They do not allow for the fact that the number of persons alive in the sixth decade of life is greater than in the seventh decade. Thus the decrease in incidence after the sixth decade may to some extent be due to the fact that there are fewer people alive to suffer from the disease. (2) A greater fallacy in the above age grouping occurs when it/

it is remembered that the above table was based on the age of the patients when they came for operation. A great number of these, however, developed symptoms many years before, and therefore a more accurate method of estimating the age incidence is from the appearance of the first symptoms. When the cases are grouped according to the age at which symptoms first appeared the following are the results.

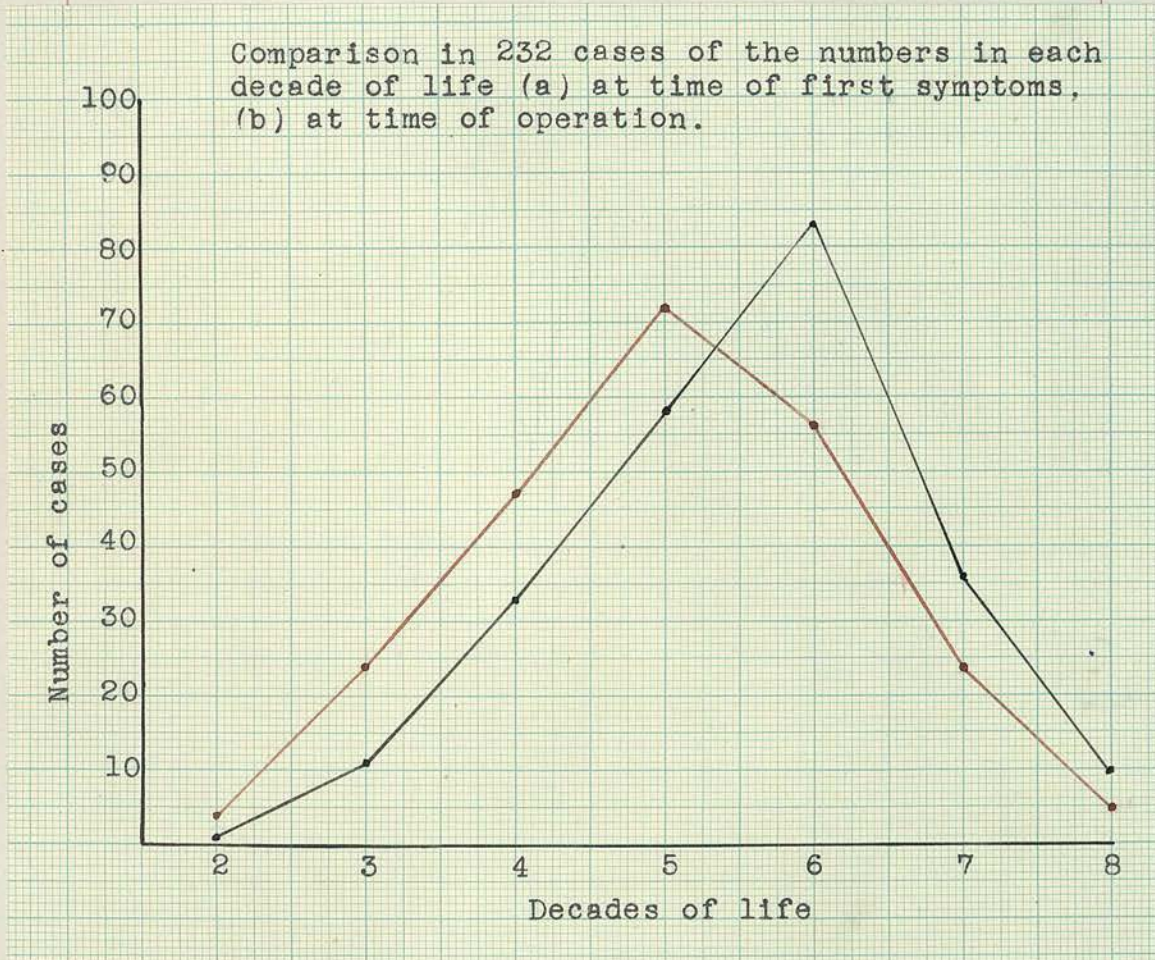
Grouping according to age at appearance
of first symptoms.

	Number of cases	Percentage
Under 20 years - - -	4	1.7
20-29 - - - - -	24	10.4
30-39 - - - - -	47	20.3
40-49 - - - - -	72	31.
50-59 - - - - -	56	24.
60-69 - - - - -	24	10.4
70 onwards - - - - -	5	2.2
	<u>232</u>	

It is seen that there are considerable differences occurring when this table is compared with the previous one (age at time of operation). At the time of operation the greatest number of cases, 83 (35.9%), was in the sixth decade of life. When considered from the time when symptoms first occurred, the number in the sixth decade falls to 56 (24%). On the other hand there were 58 (24.9%) cases in the fifth decade at the time of operation, which is increased to 72 (31%) when related to the first symptoms.

The/

The differences in the two tables is represented in the following graph:-



From the 232 cases under consideration the following conclusions may be drawn. (1) At the time of operation the age grouping shows a minimum of cases in the earlier years gradually rising to a peak (35.9%) in the sixth decade. The numbers decrease rapidly thereafter. (2) At the time of first symptoms the age/

age grouping shows an even increase from early years to a peak (31%) in the fifth decade, and an even decline thereafter. (3) Chronic cholecystitis most frequently shows itself between the ages of 30 and 59 (75.3% of cases). The commonest years are between the ages of $\frac{4}{50}$ and $\frac{4}{59}$ (31%).

Age and Sex Incidence.

When the age and sex of the patients are considered together, the age being that at which the patient came for operation, the following were the results:-

Proportion of females to males in each decade of life.

<u>Age</u>	<u>Number of Cases</u>		<u>Proportion of Females to Males</u>
	<u>Females</u>	<u>Males</u>	
Under 20 - - -	1	0	1 to 0
20-29 - - - -	8	3	3 to 1
30-39 - - - -	31	2	15 to 1
40-49 - - - -	52	6	9 to 1
50-59 - - - -	70	13	6 to 1
60-69 - - - -	29	7	4 to 1
70 onwards - -	7	3	2 to 1

It is very noticeable here how the proportion of females is much higher between the ages of 30 and 39, and how it shows a decrease from that time onwards. This may be due to the influence of pregnancy as an etiological factor, as it is seen that the highest proportion of females to males is during the years when/

when pregnancy most frequently occurs, and the years succeeding. This will be dealt with subsequently in discussing the etiology.

Pathological Findings at Operation.

Following on an examination of the operative findings the cases are divided into groups. It is essential to divide the cases into groups at this early stage as they will be used as a basis for discussing the cases under the succeeding headings.

All of the 247 cases under consideration have been summed up under the heading of chronic cholecystitis, irrespective of the different groups into which they will be divided and which will be discussed later. The majority (241) came to operation with a primary diagnosis of chronic cholecystitis. The remaining six cases were found to be suffering from chronic cholecystitis, and their previous symptoms were then put down to the condition of the gall-bladder.

These six cases were originally diagnosed as

Possible malignant disease of the stomach	- 3
Peptic ulcer	- - - - - 2
Chronic appendicitis	- - - - - 1.

All these showed a pathological gall-bladder with multiple stones at operation, and, as nothing else was found, they are included in the series.

The findings at operation in the 247 cases will be/

be discussed under two heads: (a) The pathological condition of the gall-bladder wall; (b) The contents of the gall-bladder.

(a) The pathological condition of the gall-bladder wall. The pathological state of the gall-bladder has been based on the naked eye appearance as presented to the surgeon at the time of operation in the majority of cases. In a certain number of cases the gall-bladder was examined later by a pathologist, and the findings on microscopic examination were found to correspond very closely with those described by the surgeon. As a result, it has been possible to divide up the cases as follows:-

Grouping of 247 cases according to the state of the gall-bladder wall.

Normal	- - - - -	5
Moderately pathological	-	124
Markedly pathological	- -	106
Cholesterosis	- - - - -	12

The division into moderately and markedly pathological is somewhat vague, but the criteria have been based as follows. By a moderately pathological gall-bladder has been meant when the gall-bladder has lost its transparent appearance and there has been some increased fibrosis, with the result that it appears somewhat white in colour and thickened. There may/

may have been some increase in subserous fat, and the liver in some cases showed some subcapsular fibrosis in the region of the gall-bladder bed. There may also in some cases be some enlargement of the cystic gland lying in the region of the cystic duct. Microscopically the mucosa was either somewhat desquamated or had a degree of proliferation present. There was in some cases some round cell infiltration of the deeper layers, and the muscle layer was to some extent replaced by fibrous tissue (Figs. 1 and 2).

By a markedly pathological gall-bladder has been meant one where there is marked thickening of the wall with a pearly white colour, where it is either markedly contracted in size or else extremely distended owing to the presence of a stone in Hartman's pouch blocking the outlet, or distended by a large mass of multiple gall stones. There were usually marked adhesions round the outside of the gall-bladder. Microscopically the mucosa showed a marked degree of desquamation and was in some cases totally absent. The muscle layer was to a great extent replaced by fibrous tissue, and in many cases there was marked round cell infiltration and congestion (Figs. 3, 4, 5)

It/

Moderately pathological gall-bladder



Fig.1. × 85 diam. Gall-bladder showing partial desquamation of the mucosa. There is some round cell infiltration and some fibrous proliferation in the muscle layer.



Fig.2. × 60 diam. Gall-bladder wall showing some proliferation of the mucosa. There is marked round cell infiltration of the submucosa, and considerable replacement of the muscular layer by fibrous tissue.

Markedly pathological gall-bladder.



Fig.3. $\times 75$ diam. Gall-bladder wall showing complete absence of the mucosa. The muscular layer is almost completely replaced by well formed fibrous tissue.

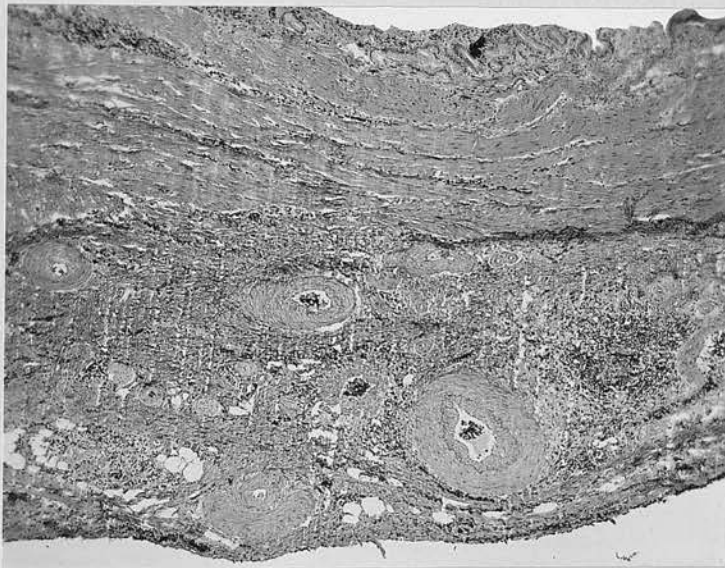


Fig.4. $\times 35$ diam. Gall-bladder showing only fragments of the mucosa remaining. The muscular layer is to a great extent replaced by fibrous tissue. In the outer layer there is marked round cell infiltration, and the vessels show degenerative changes.

Markedly pathological gall-bladder.

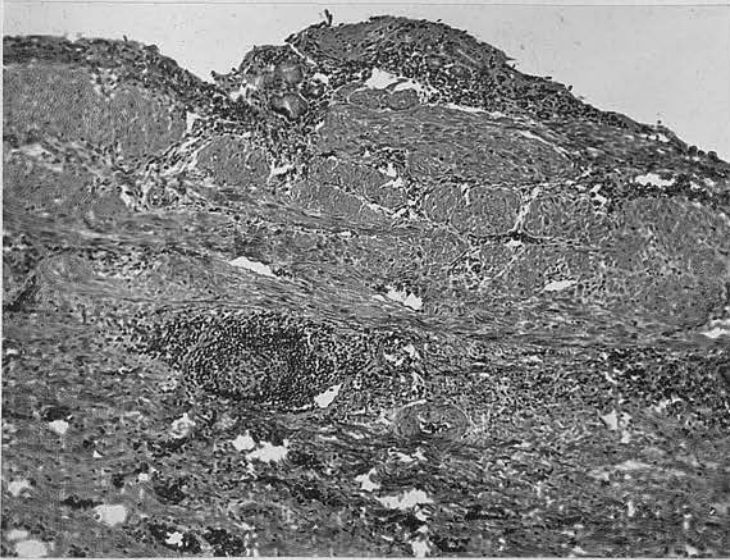


Fig.5. x70 diam. Gall-bladder wall showing almost complete absence of the mucosa and some round cell infiltration of the submucosa. The muscular layer is to some extent replaced by fibrous tissue. In the outer layer there is marked congestion and patchy round cell infiltration.

Cholesterosis.



Fig.6. xl50 diam. Gall-bladder wall showing lipid deposit in the mucosa.

It is seen that at operation five cases were found to have a normal gall-bladder. Of these three were found to contain pigment stones. In the other two no stone was found, the one being found to have a considerable degree of peri-hepatitis present and the other a pathological appendix and a large mass of tubercular glands in the region of the gall-bladder.

In the cases of cholesterosis the appearance was that of the typical "strawberry" gall-bladder. In these cases the mucous membrane, instead of being thin and tenuous, was found to be swollen and distended, due to an overloading by yellow lipid masses. The lipid is contained in large cells which lie for the most part in the stroma of the villi, but to some extent in the basal parts of the epithelial cells (Fig. 6).

(b) The contents of the gall-bladder. Having discussed the condition of the gall-bladder, it remains to discuss the findings within the gall-bladder. The grouping resorted to here does not correspond exactly to some other series of cases, but has been done according to the data available and is as accurate as possible under the headings used.

Grouping/

Relation of the state of the gall-bladder wall to the contents of the gall-bladder in 247 cases.

Gall-bladder wall	Total cases	Multiple mixed stone	Single cholesterol stone	Single cholesterol + multiple stones	Pigment stone	No stone
Normal	5	0	0	0	3	2
Moderately pathological	124	73	15	2	1	33
Markedly pathological	106	58	24	9	2	13
Cholesterosis	12	3	0	0	0	9
	247	134	39	11	6	57

Grouping of 247 cases according to the contents
of the gall-bladder.

Multiple stones of mixed composition - - - -	134
Single cholesterol stone - - - - - - - - -	39
Single cholesterol + multiple mixed stones -	11
Pigment stones - - - - - - - - - - - - -	6
No stone present - - - - - - - - - - - - -	57

These groups will be discussed in detail when dealing with their etiology.

The correlation of the pathological findings in the gall-bladder wall with the contents of the gall-bladder is seen in the table facing this page.

For the purpose of discussion under succeeding headings the cases will be considered primarily in the grouping according to the gall-bladder contents.

Etiology.

A great deal has been written regarding the etiology of chronic cholecystitis and gall stones, and it is intended here to consider the etiology more from the point of view of the findings in the present series than a consideration of all the various views which have been put forward. Some of these only will be considered, in so far as they lead up to the various factors in etiology being discussed.

In dealing with the pathological findings at operation in the 247 cases in the series, the cases were/

were divided into groups in two ways. Firstly, the cases were grouped according to the condition of the gall-bladder wall. Secondly, the cases were grouped according to the contents of the gall-bladder.

For the purpose of discussing the etiology, the cases are considered under the second grouping and will be dealt with individually under the following heads:-

(1) Multiple mixed stones - - - - -	134 cases
(2) Single cholesterol stone - - - - -	39
(3) Single cholesterol + multiple mixed stones - - - - -	11
(4) Pigment stones - - - - -	6
(5) No stone - - - - -	57
	<u>247</u>

There were 12 cases in which cholesterosis was noted. In three of these multiple stones were found, and in the remaining nine cases no stone was found. This group will be dealt with after considering the above.

(1) Multiple stones of mixed composition. Of the 247 cases there were 134 in which multiple stones of this type were found. Thus it may be said that 54% of the cases of chronic cholecystitis showed multiple stones at operation. This excludes the cases in which multiple stones were found in company with a single cholesterol stone.

It is also noted that out of the total of 190 cases/

Multiple stones of mixed composition.



Fig.7. Gall-bladder containing multiple faceted stones of mixed composition.

cases in this series in which stones were found at operation, 134 cases (70.5%) were of the multiple mixed type. This compares with 63.3% found by Illingworth (1936) in a series of 300 cases reviewed. It is clear that this is the most prevalent type of stone found. (Fig.7).

In discussing the etiology of this type of stone it is necessary to trace it back to the time when it was the custom to consider all the different types of stone together.

Naunyn (1892) was the first to submit any valuable theories as regards the causation of gall stones and maintained that the only definitely established cause of gall stone formation was bile stasis. He could not, however, explain by this means how in many cases there were hundreds of gall stones all of the same size and apparently formed at the same time. It seemed impossible to him that bile stasis alone could explain the fact that they were all formed at the same time, especially as bile stasis was a condition of long duration. He therefore came to the conclusion that a second factor, namely an ascending infection of the biliary passages coming from the intestine, came into play and by this means a stone forming catarrh was set up. As a result of this catarrh an abundance of cholesterol was secreted by the gall-bladder and so led/

led to the formation of multiple stones. The calcium was also produced in this way to help in stone formation. He considered that the start of actual stone formation was the catarrhal debris or precipitated bile pigment and calcium, and that the cholesterol was deposited on the nucleus so formed.

These views remained unchallenged until Aschoff (1924) brought forth the theory that gall stones were of two kinds, the one being of non-inflammatory or metabolic origin, and the other of inflammatory origin, and this view has been generally maintained since.

The multiple stones of mixed composition which are now being considered are of inflammatory origin, and in their etiology three factors have to be considered:-

- (1) Stasis as a predisposing factor;
- (2) Modes of infection of the gall-bladder;
- (3) Formation of the stones.

(1) Stasis - a predisposing factor. The importance of stasis in the production of gall stones is a point over which there is some dispute nowadays. When first explanations were sought to explain the formation of gall stones, stasis acted as a conveniently vague term which was used to gloss over points which were not properly understood.

As has been said above, Naunyn thought originally that stasis in the gall-bladder predisposed to infection/

infection by the formation of a stone forming catarrh. Although some doubt has been cast upon this, there is now evidence to show that there was a good deal of truth in what Naunyn said.

In the present series there is everything to suggest that the type of person involved is the type in which stasis is most wont to occur. An attempt will therefore be made first of all to show the possible ways in which stasis may affect the gall-bladder, and then to show that the present cases were the type in which it would be expected that stasis would exist.

Stasis may influence the formation of stones in two ways: a) It may act as a predisposing cause to infection; b) It may help the actual formation of the stone.

a) Stasis - a predisposing cause to infection.

There is general agreement that infection plays a large part in the formation of multiple mixed stones. If, then, it can be shown that stasis may predispose to infection of the gall-bladder, it follows that it is of importance in stone formation. This is apparently so, at any rate, in some cases.

Aschoff (1924) describes a condition of chronic stasis in the gall-bladder associated with microscopic changes/

changes. These changes occur independently of either infection or stone formation, although in his view are liable to be complicated by one or both of these.

This is borne out in a series of cases recorded by Schmieden and Rohde (1921) in which at operation no calculi or evidence of infection were present, but which presented symptoms of biliary colic. This they attributed to a congenital malformation causing kinking at the neck of the gall-bladder and so stasis. These persons were relieved by operation, and the important fact is that the gall-bladder in these cases, although free from evidence of stone or infection, was found to be pathological. Three definite stages of pathological change were recorded. 1) The wall showed venous congestion, lymphoid hyperplasia, and slight muscular hypertrophy. 2) The muscular hypertrophy was more pronounced and there was increase in connective tissue. 3) The muscle was to a large extent replaced by fibrous tissue.

These findings seem to show clearly that stasis is an important factor in producing changes in the gall-bladder wall which may predispose to infection.

b) Stasis and the formation of stones. The importance of stasis here is that it leads to a condition of stagnation in the gall-bladder with increased/

increased precipitation of the contents of the bile. There is some doubt if this can really take place. Newman (1933), in dealing with this, considers stasis a vague term and maintains that the condition in the gall-bladder must be one either of "standstill" where the cystic duct is blocked and the distension is continuous, or else one of "distension" where the outflow is reduced in relation to the inflow. He maintains that "distension" can have no relation to stone formation because any precipitation which may have taken place in this condition is resolvable in any further bile which may enter the gall-bladder, and is as a result washed away in the bile. If this is true, it would appear to follow that stones could only form where there is a state of "standstill" present, which would mean that the gall-bladder is not functioning. This, however, does not seem to fit in with the fact that a gall-bladder which contains stones may on radiological examination be found to be still functioning. This being so, it would result in their being washed away in the bile which enters and leaves the gall-bladder.

Whittaker (1927) has worked on the subject of stasis in the gall-bladder in experiments on cats and considers it of importance in the formation of stones. He/

He observed how the bile becomes darker and more viscid, and apparently more concentrated as the gall-bladder empties. He has noticed this when feeding cats and killing them at various intervals of time afterwards. As the gall-bladder empties, the mucosa is thrown into folds somewhat resembling those of the small intestine. The gall-bladder thus decreases in size, and the ratio of surface to cubic content increases, making a partially collapsed gall-bladder a more efficient concentrator than a full one. He maintains the possibility that in any condition in which the gall-bladder is maintained in partial collapse and refilling prevented, concentration might go on to precipitation. He has demonstrated this as occurring in cats where the sphincter of the common bile duct was cut and dilated and the gall-bladder containing some bile was filled with iodized oil. After nine hours a meal of egg yolk was given and the result was expulsion of some of the bile and most of the iodized oil. The gall-bladder did not refill with bile owing to the common duct sphincter being damaged. There remained a residue of bile in the gall-bladder, and when the animal was killed three days later, the gall-bladder was found to be shrunken and filled with a hard cast resembling a gall stone. He considers that this was produced/

produced by inspissation of the bile left in the gall-bladder.

He concludes from this that any condition which keeps the gall-bladder in a state of partial collapse over a long period will favour concentration and precipitation and so the formation of gall stones.

In human beings he maintains that this is most likely to happen with frequent meals when the stimulus to emptying of the gall-bladder is repeated too often. The organ is thus in a state of partial collapse, which favours increased concentration and precipitation, and produces in fact a condition of stasis of the gall-bladder. In such persons, also, he maintains that with very frequent meals the efficiency of the musculature of the alimentary tract as a whole may be decreased and with it that of the gall-bladder, and a resulting stasis of bile occur. Tone may be lost in the common duct sphincter and prevent complete refilling of the organ, with further promotion of concentration.

To sum up what has been said about the part played by stasis in stone formation:-

(a) According to Aschoff and Schmieden and Rohde, stasis can produce definite changes in the gall-bladder wall which may predispose to infection and so to stone formation/

formation.

(b) According to Whittaker, stasis produces increased precipitation in the gall-bladder. If the mechanism of the biliary tract is such as to prevent the gall-bladder from filling and emptying freely, then this precipitation is continuous and will tend to bring about the formation of stones.

It would seem that the subject of stasis has to some extent been laboured. This was felt to be necessary before discussing the various factors which, in the present series of cases, may lead to the production of stasis.

The factors which are commonly held to bring about stasis and their relation to the cases in the present series will now be considered.

(1) Lack of exercise. In the 134 cases of multiple stone under consideration, the general trend is that they were of the type who led a sedentary life and took little exercise. There were 111 females and 23 males in the group, a proportion of nearly 5 to 1. These women were of the working classes where for the most part the life of the woman was at home doing the house-work with little opportunity of getting out and getting healthy exercise. Of the males in this group it cannot be said that stasis/

stasis arose from want of exercise, as they were of the labouring class and for the most part did a hard day of manual labour. Some other factor must be looked for in these cases.

The age incidence in this group tends to show that the cases occurred mostly in middle or later life and this again might have something to do with the fact that exercise becomes less as life goes on.

Age grouping in 134 cases of multiple stones.

<u>Age</u>	<u>Number of cases</u>	<u>Percentage</u>
Below 20 - - - -	1	.7
20-29 - - - -	3	2.3
30-39 - - - -	20	14.9
40-49 - - - -	35	26.1
50-59 - - - -	45	33.6
60-69 - - - -	18	13.4
70 onwards - -	6	4.5
Age not known -	<u>6</u>	4.5
	134	

From this it is seen that about 78% of the cases occurred after the age of 40, and that therefore it is comparatively uncommon before the fifth decade of life.

Thus, if lack of exercise is a factor in producing stasis of the gall-bladder, it is borne out by the findings in the 134 cases here, firstly on account of the occupation of most of the cases, and secondly according to the age incidence.

The question now arises why should lack of exercise produce stasis, and does it really do so?

It/

It has been said that the important predisposing cause of stasis in these people is due to the fact that by lack of exercise the abdominal muscles and diaphragm are not so freely used, and so do not aid in the emptying of the gall-bladder as they should do. This point is open to argument, as Whittaker (1926) has done work to show that extrinsic factors such as respiration play little part in the emptying of the gall-bladder. Thus, although this type of person appears to be more susceptible to gall stones, the question whether this is due to stasis produced by lack of use of the abdominal muscles and diaphragm, on account of sedentary habits, is an open one.

It seems that the question whether lack of exercise produces stasis of the gall-bladder hinges on the problem of how the gall-bladder empties. If the emptying of the gall-bladder depends to some extent upon the movements of the abdominal muscles and diaphragm, then it would appear to be important. This view is supported by Graham (1926) who considers that emptying seems to depend very little on the muscle of the gall-bladder wall but is rather of a passive nature. He thinks it is very greatly influenced by an increase in intra-abdominal pressure. On the other hand it has been found that the gall-bladder/
bladder/

gall-bladder tends to empty as the result of a physiological stimulus from food, particularly fats, passing into the duodenum. Newman (1933) describes how as a result of this stimulus the gall-bladder rears up, becomes stiff and contracts. And although the mechanism of the emptying of the gall-bladder is one which is by no means settled, there is little evidence to show that it depends on the abdominal muscles and the diaphragm. Lack of exercise in itself, therefore, appears to have a very doubtful bearing on the production of stasis in the gall-bladder.

Possibly a more important factor in the most prevalent type of person dealt with here - the housewife of the lower classes - is that they tend to be the type of person who is continually taking small quantities of food at frequent intervals. In this way the gall-bladder never gets the chance to fill properly and so loses its capacity for healthy contraction and proper emptying. In later life when the continued abuse of the alimentary tract in this way has gone on over a long period, the condition begins to show itself by the production of stasis, possibly leading to gall stone formation.

(2) Obesity. Obesity and the common wearing of tight corsets by obese women has been held to be of importance in producing stasis of the gall-bladder. In the 134 cases under consideration, of the 111 females the weight was noted in 96 cases. 76 persons were of the obese type, their weights varying from 10 st. to 15 st. 3 lbs. 20 were normal or thin, the lightest being 5 st. 11 lbs. Thus, 79% of those whose weights were known were of the obese type. It is seen from this that multiple gall stones does seem to predominate in the obese type. Mentzer (1927) verified that gall stones predominate in the heavy type. He found in a post mortem study that 90% of patients weighing 15 st. 10 lbs. had gall-bladder diseases, and that in patients under 8 st. the incidence was only 30%.

In those cases which came for follow-up it was found that in almost all cases the obese person was in the habit of wearing tight corsets.

Thus if, as has been shown, gall stones occur commonly in the obese type of person, the reason for this must be sought. The question arises whether or not obesity and the wearing of tight corsets by obese persons produces stasis by preventing the proper mechanical/

mechanical emptying of the gall-bladder. The same objectives may be raised to this theory as were raised when discussing lack of exercise. It is more likely that stasis is found in these persons on account of the dietetic errors which have produced the obesity. By this it is meant that the alimentary abuse which has brought about the stasis has also brought about the obesity. It is doubtful, therefore, if obesity itself produces stasis.

(3) Pregnancy. An important factor in the production of stasis has been ^lalleged to be the upward pressure of the gravid uterus. Of the 111 females in this group the history obtained was as follows:-

Grouping of 111 female cases according to sex history.

Unmarried - - - - -	10
Married:	
No children - - - - -	3
Borne children - - - - -	71
Not known - - - - -	<u>27</u>
	111

Thus in the 74 married women whose history is known in regard to their having produced children, the large number of 71 out of 74, or about 96%, have had pregnancies, and only 10 unmarried women are found in the total of 111. This is very much in favour/

favour of the possibility of pregnancy playing a part in the formation of multiple gall stones. But whether this is due to the upward pressure of the gravid uterus producing stasis, or whether it is due to metabolic changes is not so clear.

Gross (1929) has published an analysis of 802 cases of gall stones from the post mortem room of the Leeds General Infirmary, and found that the proportion of females to males was about 2 to 1. But she found that when the proportion of married to single women admitted to the hospital was considered, the proportion of married women with gall stones was very little greater than unmarried, finding 27.5% of married women with stones, as opposed to 21.5% of unmarried women.

This is contrary to usual opinions, and to the findings in this series, and it is felt that pregnancy must influence gall stone formation to some extent. There is, however, some doubt as to whether this is the result of the stasis produced. Crossen and Moore (1928) have produced evidence on radiological examination of normal filling and emptying of the gall-bladder at the fortieth week of pregnancy, and question the importance of pregnancy producing stasis.

It may therefore be on account of other factors, such as the tendency to constipation in pregnant women/

women, and thus a tendency to infection of the gall-bladder, and probably the high blood cholesterol may have an influence upon it. On the other hand, it is probable that the upward pressure of the gravid uterus may produce stasis in some cases by dislocating the upper abdominal viscera and thus making it more difficult for the gall-bladder to empty freely.

To sum up what has been said about stasis and the relation it has to the formation of multiple gall stones:-

(a) There seems to be evidence that stasis can exist and that it may produce changes in the wall of the gall-bladder which predisposes it to infection.

(b) Stasis would appear to play a part in increasing the amount of concentration and precipitation which may take place in the gall bladder. Thus it may help in the formation of stones.

(c) Lack of exercise and obesity are said to produce stasis because they inhibit the free use of the abdominal muscles and diaphragm in aiding the gall-bladder to empty. This is disputed. It is considered more probable that stasis occurs in these subjects as a result of abuse of the alimentary tract, resulting in the gradual deterioration in the emptying function/

function of the gall-bladder. As a result of this long continued abuse stasis is brought about.

(d) From the frequency of pregnancy in these cases it seems feasible that a certain dislocation of the abdominal viscera by the gravid uterus may lead to stasis in some cases.

(e) Stasis therefore may be a factor, at any rate in some cases, predisposing to gall stone formation.

(2) Modes of infection of the gall-bladder.

There is little dispute that infection plays a very important part in the formation of multiple gall stones. The work of Rovsing (1924), who attempted to show that infection was by no means always present in gall stones, failed to observe the bacteriology of the gall-bladder wall, and as this has been a common source of organisms, his work is not convincing. Gordon-Taylor and Whitby (1930) found that in gall stones the gall-bladder wall was infected in 67% of cases, whereas the fluid was infected in only 39% and the stones in 33% of cases.

Infection may reach the gall-bladder in four ways.

1) Portal blood. Amongst the most common organisms found in the gall-bladder are those whose natural habitat is in the bowel - *B. coli*, *B. Welchii*, *Streptococcus faecalis* and *B. typhosus*. Williams and McLachlan/

McLachlan (1930) investigated the bacteriological findings in 93 cases of chronic cholecystitis and found *B. coli* and streptococci the most common. The streptococci isolated were largely of the type normally found in the bowel.

Probably if typhoid was more common in this country these organisms would be found more frequently, because Blalock (1924), reviewing 888 cases of gall-bladder disease, found that 28% of 712 cases gave a history of typhoid fever.

It is believed that organisms from the bowel reach the gall-bladder by means of the portal blood which conveys the organisms from the bowel to the liver. From there they are excreted along with the bile and so reach the gall-bladder. For this abnormal absorption of organisms to take place, the normal healthy condition of the bowel must be upset. The appendix may be at fault. In 19 cases in this group the appendix was found to be definitely pathological, with either marked thickening or in several cases with stricture and concretions.

Constipation is very commonly found in these cases and in the present series was a frequent finding. The hold up in the bowel causes putrefaction and the multiplication of organisms, and when after long duration/

duration the friction of the hard faeces has caused damage to the intestinal wall, then absorption takes place, and so organisms reach the portal blood stream and later the gall-bladder.

In this way the bile may be a possible source of infection to the gall-bladder, but the presence of organisms does not necessarily mean inflammatory changes. Graham (1926) injected large amounts of *B. coli* into the gall-bladder of 10 dogs, and found that in only one case was cholecystitis the result. But he found that if the outflow of bile was obstructed, then cholecystitis did arise. Thus the portal route may be one of the causes of cholecystitis where a condition of stasis also exists in the gall-bladder.

2) Systemic blood. A focus elsewhere in the body may release organisms into the systemic blood stream which may settle in the gall-bladder. The teeth are a common source of such a focus. In this series there were 91 persons with bad teeth, or who had had their teeth already removed, presumably in many cases on account of their septic state. The remaining 20 cases out of the total 111 had good teeth. This common finding of bad teeth in these cases points to them as a possible source of infection.

The state of the tonsils and sinuses is another possible source, but this was not noted in this series.

Rosenow/

Rosenow (1916) has worked on the relation of streptococci to infection of the gall-bladder. He believes that streptococci are responsible for cholecystitis in a large number of cases, and that certain types of these organisms bear an "elective affinity" to the gall-bladder. Thus, when freed into the blood stream, they tend to settle selectively in the gall-bladder wall. He came to these conclusions after experiments where he injected various strains of streptococci intravenously into the blood stream of rabbits. He considers the *B. coli* found in chronic cholecystitis as being frequently only a secondary invader.

(A.L.)

Wilkie (1928) has followed up the work of Rosenow. He examined bacteriologically 50 consecutive cases of gall-bladder disease submitted to operation. Later he injected into rabbits streptococci isolated from the cystic gland in these cases. He found that when cultures are made from the whole thickness of the gall-bladder wall a growth is infrequently obtained. But if the culture is made from the submucous and outer coats, leaving the mucosa intact, then a growth is obtained in 42% of cases. He attributes this to the fact that bile inhibits the growth of streptococci. His conclusions from this work are that cholecystitis appears to be a blood-borne streptococcal intramural infection/

infection.

The work of Wilkie created great interest at the time, but his experiments have not been confirmed. The view that cholecystitis is chiefly due to blood-borne streptococci with an "elective affinity" for the gall-bladder is by no means universally held. It is probable, however, that blood-borne streptococcal infection plays a part in a number of cases.

3) Ascending infection. The spread of infection to the gall-bladder from the duodenum via the common bile duct is now considered unimportant as a source of infection of the gall-bladder. It is considered that a healthy duct system does not allow infection to spread upwards, and in most cases with the gall-bladder even grossly diseased the ducts are healthy.

4) Lymphatic infection. The theory that many infections of the gall-bladder arise as a result of lymphatic spread from the liver is strongly upheld by Graham and Peterman (1922). By the injection of Prussian Blue into the portal vein they have demonstrated the close interrelation of the lymphatics of the liver and gall-bladder, and believe that a great many cases of cholecystitis arise as a result of hepatitis. They have found in animal experiments that injections of/

of organisms in large numbers into the portal vein produced simultaneously a hepatitis and a cholecystitis. Conversely they produced hepatitis by injecting organisms into the gall-bladder of animals. They believe, therefore, in a two-way infection from liver to gall-bladder or from gall-bladder to liver by means of lymphatics, and consider this a much more important source of cholecystitis than infection by means of the bile. They explain the finding of chronic appendicitis along with cholecystitis by this means, as a spread of organisms to the portal blood from the appendix, and thereafter a hepatitis is set up which spreads by lymphatics to the gall-bladder.

The finding of hepatitis in the region of the gall-bladder along with cholecystitis has been frequently noted, but in spite of Graham's work it is a commoner view that the hepatitis is a result of the cholecystitis rather than a forerunner of it. In this series there were 7 cases where a definite hepatitis was seen with the naked eye. Sections of the liver were not taken and possibly a degree of inflammation would have been found more frequently on microscopical examination. All the 7 cases in which peri-hepatitis was noted were found with adhesions round/

round the gall-bladder, and there seems no reason to suppose that they did not arise from the gall-bladder as much as from the liver.

(3) Formation of the stone. The various means by which the gall-bladder may become infected have now been discussed, and the theory upheld that stasis may in some cases predispose to this infection taking place. It now remains to discuss the means by which stones may be formed as a result of this infection.

Moynihan has described this type of stone as "tombstones erected to the organisms dead within them". The dead organisms or debris in an infected gall-bladder form a nucleus upon which calcium, bile pigment and cholesterol are precipitated as a result of upset in gall-bladder function. In the healthy gall-bladder the hepatic bile is changed into gall-bladder bile in a consistent fashion. The main function of the gall-bladder is the concentration of the bile so that a supply of concentrated bile is ready for discharge into the duodenum when a meal is taken. Newman (1933) states that the gall-bladder is capable of concentrating 49.8 c.c. of bile to 4.6 c.c. in $22\frac{1}{2}$ hours. He also states that bile, by merely/

merely passing through the gall-bladder, as occurs when a tube is brought to the surface after cholecystostomy, is concentrated from 2.3 to 4.8 times.

In the healthy gall-bladder this concentration takes place in a constant manner. Riegel, Johnston and Morrison (1936) consider that calcium, bile pigment, bile salts and cholesterol are all concentrated in the gall-bladder. Small quantities of calcium and bile salts are absorbed along with the water from the bile, but the balance is one of concentration. They believe that bile pigment and cholesterol are concentrated only, with no absorption in the gall-bladder.

As a result of infection the gall-bladder loses its selective function and so absorption and concentration become abnormal. The most important disturbance of function is the decrease in bile salt concentration. Normally the ratio of bile salt to cholesterol is about 18 to 1 according to Newman. Now as a result of inflammation, the bile salts are absorbed abnormally with the result that the ratio may become lowered to about 2.5 to 1.

The important point is that cholesterol depends upon the bile salts for holding it in solution and the/

the ratio in the normal gall-bladder does this, but now with a lowered ratio the result is that the cholesterol is precipitated.

The common stone of mixed type is composed predominantly of cholesterol. Peel (1927) in his analysis of the contents of these stones found that approximately 95% of the calculus was made up of cholesterol. And the formation of the stone probably takes place upon a nucleus made up of organisms, desquamated debris from the gall-bladder wall and inflammatory exudate. Upon this nucleus the cholesterol is precipitated along with a certain amount of bile pigment and calcium. The result is the formation of multiple mixed stones.

On this assumption it would appear that for the formation of the common mixed stone a hypercholesterolaemia is not necessary. In papers on the formation of gall stones much has been written on the subject of the part played by cholesterol in the formation of gall stones. Some have maintained that a hypercholesterolaemia is a very important factor, and others have pointed out that it is by no means invariably found. The fallacy would appear to lie in the tendency to discuss the causes of all types of gall/

gall stones together. Instead it should be realised that gall stones are of different types, and so that their origin is different. In the case of the multiple stone a hypercholesterolaemia may increase the chance of gall stone formation by decreasing the bile salt - cholesterol ratio and thus aid in bringing about its precipitation. It has been shown, however, that this is not an essential factor, since sufficient explanation of precipitation of cholesterol is found in the decreased bile salt concentration as a result of upset of gall-bladder function. This upsets the bile salt - cholesterol ratio in the gall-bladder, thus leading to precipitation without a hypercholesterolaemia in the first place.

To sum up the etiology of the multiple mixed stone:-

(a) It would appear that an adequate explanation of their formation is to be found as a result of an infection of the gall-bladder.

(b) In, at any rate, some cases, it would seem that stasis plays a part in producing a condition which predisposes to infection.

(c) Infection may reach the gall-bladder by various/

various routes, the more important being 1) by means of the systemic blood from a focus elsewhere in the body; 2) by means of the portal blood which bears organisms from the bowel and excretes them in the bile. The other sources are by direct spread from the duodenum up the biliary tract and lymphatic spread.

(d) As a result of infection the normal function of the gall-bladder is upset. In particular the bile salt - cholesterol ratio is upset, and the result is precipitation of cholesterol.

(e) A nucleus of debris or bacteria in the gall-bladder, resulting from the infection, acts as a nucleus upon which cholesterol, bile pigment and calcium are precipitated to form a stone. Stasis may in some cases aid in this precipitation.

(2) Single cholesterol stone. In discussing the etiology of the multiple mixed stone it has been shown that it probably arises as a result of infection of the gall-bladder. The single cholesterol stone, in contrast, has a different origin, and although it may be complicated by infection, it appears to arise primarily as a result of upset in metabolism. Gross (1929)/

(1929) has found in a series of autopsies at Leeds General Infirmary, that in 93 cases in which a single cholesterol stone was found, only 3 were accompanied by cholecystitis. This is strong evidence in favour of the stone being aseptic and metabolic in origin.

This type of stone is composed almost entirely of pure cholesterol, the crystals being formed radially from the centre of the stone outwards. Illingworth (1936) found up to 95% pure cholesterol in these stones.

Cholesterol circulates in the blood, derived on the one hand from synthesis within the body and on the other as a result of absorption from various foods ingested. It depends for its excretion upon the liver. It is found as a constituent of bile in loose combination mainly with bile salts, and in small quantities with fatty acids. As mentioned earlier, (Newman, 1933), the normal proportion of bile salts to cholesterol is in the region of 18 to 1. This is sufficient to hold the cholesterol in solution. Should an upset occur in this ratio, either by a decrease in bile salts or an increase in cholesterol, then precipitation will take place. The first of these alternatives is what occurs in the precipitation of cholesterol in the multiple mixed stone, as there is an abnormal absorption/

absorption of bile salt owing to the infected state of the gall-bladder wall. There is no evidence to show, however, that bile salts are to any extent absorbed in the healthy gall-bladder, and so in the aseptic cholesterol stone precipitation is unlikely to arise in this manner. It seems more probable that an actual increase in the cholesterol content of the bile brings about the upset of the bile salt - cholesterol ratio and resultant precipitation of cholesterol.

From this it would follow that any condition which leads to a hypercholesterolaemia and a consequent increase in the bile cholesterol would favour the formation of the cholesterol stone. It would seem that hypercholesterolaemia is certainly closely related to gall stones, for Moynihan (1925) found in 101 cases of all types of stones that there were 65% with a hypercholesterolaemia, these patients having a blood cholesterol of over .192% (He considers the normal range to be between .133% and .16%). This is, however, a point on which there is not general agreement. Campbell (1924) found the blood cholesterol in patients with cholelithiasis to be within normal limits. His conclusions, however, are based on 10 cases in which gall stones were found, all of the multiple/

multiple mixed type except one, and thus have little bearing on the subject of the single cholesterol stone.

Gardner and Gainsborough (1930) found that the marked hypercholesterolaemia found in some forms of nephritis did not seem to lead to an increased incidence of cholelithiasis. These authorities are considering cholelithiasis as a whole and not the single cholesterol stone. And it would seem that although possibly a high blood cholesterol may not necessarily mean cholesterol stone formation, yet when it is accompanied by an increased cholesterol content in the bile, conditions are certainly favourable for such precipitation. Another point about which there is dispute is the relation between the cholesterol content of the diet and stone formation. Gardner and Gainsborough (1930) think that there is no evidence that the cholesterol content of the food influences the cholesterol content of the bile and has any relation to the formation of gall stones. McMaster (1924), on the other hand, found that a diet rich in cholesterol increases the total quantity and concentration of cholesterol in the bile.

Doubt still exists as to the exact relation of a high/

Single cholesterol stone



Fig.8. Gall-bladder grossly distended with a large cholesterol stone impacted in the neck.

high blood cholesterol to the formation of the single stone, but it is generally held that it plays an important part, and it seems more than likely that an overloading of the bile with cholesterol will tend towards precipitation.

Investigation on this subject is made more difficult on account of the fact that the single stone so frequently gives rise to no symptoms. Gross (1929) found that in 100 cases found with a single stone at autopsy, only 8 had had symptoms of disease of the gall-bladder. It is therefore by nature a "silent stone", and it is probable that unless it becomes impacted in the neck of the gall-bladder or infection becomes superimposed, it will give rise to no trouble and remain undiagnosed (Fig.8). If some simple method is found of diagnosing the presence of a single stone, then estimation of the cholesterol content of the blood in such cases may throw some light on the subject.

There is little doubt, however, that the single stone arises from the upset in the condition of the bile which the liver secretes and that it does not arise primarily as a result of conditions within the gall-bladder. The cholesterol is in such a state that/



that it is easily precipitated to form a stone and the only part played by the gall-bladder itself is in providing some nucleus upon which precipitation may take place. This nucleus may be found in a clump of bacteria, some desquamated cells or possibly bile pigment, all of which can be found in the healthy gall-bladder. Mentzer (1927) suggests that the nucleus may be found in portions of cholesterol-laden mucous membrane lying free in the gall-bladder cavity, this applying to the cases in which cholesterosis exists.

In the present series there were 39 cases in which a single stone was found, and in all of these the gall-bladder was found to be pathological. It can be assumed therefore that although the stone may have been aseptic to start with, conditions have arisen which have led to superimposed infection giving rise to symptoms. Either that, or else symptoms have arisen as a result of the stone being impacted in the gall-bladder neck with the result that infection followed.

The type of person who in this series was found to suffer from the single cholesterol stone will now be discussed.

Sex./

Sex. The relation of hypercholesterolaemia to pregnancy and menstruation leads to an expectation of a greater proportion of the patients being female. Moynihan (1925), quoting work by Dr. Cecilia Shirkin, states that the blood cholesterol just preceding and during the first day or two of menstruation reaches about .26%. During pregnancy she also found that blood cholesterol gradually rises until in the ninth month it is in the region of about .26%. The female is therefore prone to hypercholesterolaemia in all cases, and more so if pregnancy occurs.

In this series the findings as regards sex and sex history were:-

Males - - - - -	2
Females	
Unmarried - - - - -	4
Married	
No children - - - - -	2
Borne children - - - - -	17
Not known - - - - -	14
	37

This indicates the infrequency of the condition in males, 5.4% of the 39 cases. It shows also that it appears much more commonly in married females who have had children, since of the 19 females whose married history was known, 17 had children and only two had no children.

This/

This appears to show that the temporary hypercholesterolaemia of menstruation and the more prolonged type found in pregnancy have some close relation with this type of stone.

This has been generally agreed, but Gross (1929) in her 100 autopsies with single stone found evidence implying that it did not have the importance generally thought. She found that there were 53 females and 47 males. Also taken as a percentage of the total autopsies performed there were 3.9% of the single women, 5.4% of the married women and 2.1% of the men who showed the presence of a single stone. It has to be remembered, however, that the majority of her cases (92%) had no symptoms of gall-bladder disease, and therefore had a "silent stone". Thus her results are not altogether irreconcilable with those generally found and those in this series. An explanation may be found in the fact that in the pregnant woman stasis may occur. Potter (1936), in investigating the relation of pregnancy to gall stones, found that stasis in the gall-bladder at term is common. He found that in 390 Caesarean sections the gall-bladder was distended in 75% of cases. With this stasis there is an increased liability to infection, and thus a "silent stone" may easily be changed into one which produces/

produces symptoms.

Age. The age grouping of the 37 females was:-

<u>Age</u>	<u>Number of cases</u>
20-29	3
30-39	4
40-49	9
50-59	12
60-69	6
70	0
Unknown	<u>3</u>
	37

It is seen that most cases were in the 5th and 6th decades of life, 21 cases out of a total of 37. This brings the majority somewhat over the child bearing age. But 19 out of the 37 cases had symptoms for periods varying from 5 to 23 years, which brings them more within that age period.

Weight. Of 33 cases in which the weight was known, 29 patients were of the obese type, the heaviest being $15\frac{1}{2}$ stones. There were 4 patients normal or underweight. Obesity, therefore, seems to play a part in this type of stone also, probably on account of the tendency to stasis and infection in such persons.

To sum up the etiology of the single cholesterol stone:-

(a) It would seem that it is by nature a silent stone, not producing symptoms unless infection becomes superimposed or the cystic duct becomes blocked.

(b)/

(b) It appears to form as a result of precipitation of cholesterol in the gall-bladder, where the bile is over-loaded with cholesterol.

(c) The exact relation between this type of stone and hypercholesterolaemia is not yet known.

(d) The hypercholesterolaemia occurring in menstruation and pregnancy may increase the liability of the female to develop this type of stone.

(e) In the present series the woman who has borne children appears to be the commonest victim. This may be due to stasis in these persons and their increased liability to infections which changes a silent stone into one which produces symptoms.

(3) Single cholesterol stone and multiple mixed stones. There are 11 cases in this group. The etiology of the condition would seem to arise out of a combination of the etiological factors in the formation of multiple mixed stones and the single cholesterol stone. It appears to be a further stage of the single cholesterol stone formation.

The single stone is first formed in the gall-bladder as an aseptic stone. Later it may bring about infection of the gall-bladder either by friction upon/

Single cholesterol + multiple mixed
stones.



Fig.9. Gall-bladder containing a large stone impacted in the neck with multiple mixed stones filling the gall-bladder. The large stone here is irregular and although originally probably pure cholesterol has a deposit of calcium upon it.

upon its walls damaging the mucous membrane, or by helping to bring about a condition of stasis in the gall-bladder. As a result conditions arise which lend themselves to the formation of multiple mixed stones in the way described previously (Fig.9).

The majority of patients in this group had had symptoms of long duration. The age incidence was found somewhat later in life, 3 of the 11 cases being between 50 and 59, and 5 between 60 and 69.

(4) Pigment stones. Of the 190 cases in which stones were found in the gall-bladder, only 6 were found to be pigment stones, just over 3%. This compares with 5.6% found by Illingworth (1936) in 300 cases. It is thus a rare condition in this country, although according to Miyake (1913) it is the commonest type of stone found in Japan. In discussing the etiology of gall stones he mentions that in 191 cases in Tokio where gall stones were found, there were 99 (52.3%) with pigment stones.

They appear to form as a result of excess of bilirubin and are made up of bilirubin in combination with calcium. They have been found as a frequent accompaniment of haemolytic jaundice, where there is excess/

excess of bilirubin in the bile due to the increased destruction of red cells in the blood.

In the 6 cases in this series, 2 were males. The remaining 4 were females, all of whom had borne children. The age varied from 20 to 60 years. The only noticeable feature in these cases was the fact that none were of the obese type.

(5) No stone. There were 57 cases in which no stone was found in the gall-bladder at operation. Two of these had a normal gall-bladder, and no other lesion was found. This leaves 55 patients in whom a pathological gall-bladder was found with no stones.

The etiology of this condition appears to be somewhat similar to that in which multiple mixed stones are found, and the same factors are brought into play.

The gall-bladder becomes infected by one of the roots mentioned in discussing the multiple stone.

(a) It may be by the systemic blood from some focus in another part of the body, very often streptococcal in nature. (b) It may be by means of the bile which derives organisms from the portal blood, which in turn derives them from the bowel. (c) It may be as a result/

result of lymphatic spread from neighbouring organs.

(d) In a few cases it may be a spread upwards from the duodenum.

By whichever of these routes infection arrives, the result is that pathological changes are brought about in the gall-bladder wall. This may arise as a legacy of an acute cholecystitis or may arise insidiously as a chronic condition from the start until a point is reached where symptoms are produced.

If the etiology in chronic cholecystitis without stones is similar to that in which multiple stones are found, the problem arises why should stones form in the one case and not in the other. Conditions in the infected gall-bladder seem to be suitable for stone formation, for, as mentioned earlier (Newman, 1933), there is increased bile salt absorption through the gall-bladder wall and so cholesterol is precipitated.

There are several possible explanations why stones are not always found accompanying a pathological gall-bladder at operation.

(1) It is possible that in some cases where no stone is found at operation, stones may actually have been present at one time and been expelled from the gall-bladder/

gall-bladder. There is evidence to support this view by the fact that in 3 patients in this series where no stone was found in the gall-bladder there were stones found at operation in the common bile duct. Further evidence is found in a case which shows clearly the powers of the gall-bladder in ridding itself of stones. A woman aged 56, who had been troubled with pain in the right iliac fossa off and on for about 5 years, and in whom tenderness was elicited in the appendicular region, came for operation as a case of chronic appendicitis. At operation the appendix was found to be congested and adherent and was removed; also in the course of examining within the abdomen the gall-bladder was found to be filled with stones, but as it appeared inflamed it was not removed. Five weeks later she underwent a second operation to deal with the gall-bladder. When removed it was found to be moderately inflamed but contained no stones. Again, the incidence of jaundice occurring in the history of cases where no stone was found at operation suggests that a stone may have been present at one time, sufficient to block the common duct. There were 20 cases of the 55 (35%) with no stone/

stone who gave a history of jaundice.

(2) Another explanation may be that the condition may not in some cases have gone on long enough for the formation of stones. In the 55 patients here the duration of symptoms was found to be shorter than in the other groups. 27% had symptoms of less than 1 year duration and another 42% from 1 to 5 years. This,

however, may not be of very great importance, as it appears that gall stones do not necessarily require a long time in which to form. Harries (1934) reports a case in which he operated and removed two gall stones from the gall-bladder, there being no more present. A year later the patient was operated on again after attacks of biliary colic and over a dozen stones were found. These must have formed in less than a year.

(3) Lastly it may be that if the gall-bladder can still function in respect of its emptying powers, then any precipitate which forms may continue to be washed away in the bile and never get the length of actual stone formation.

There is some evidence here to show that the pathological changes in the gall-bladder found at operation were not in such an advanced state in the cases with no stone as those in which multiple mixed stones/

stones were found.

	<u>State of gall-bladder.</u>		
	<u>Moderately pathological</u>	<u>Markedly pathological</u>	<u>Choles-terosis</u>
No stone (55 cases)	33 (60%)	13 (24%)	9
Multiple stones (134 cases)	73 (54.5%)	58 (43%)	3

It is seen in the above table that whereas 43% of the cases with multiple stones had a markedly pathological gall-bladder, only 24% of these with no stone came under this heading. It may be, therefore, that the more gross the pathology of the gall-bladder, the more tendency there is to stone formation. And if this is the case, it is probably because this type of gall-bladder is less able to empty itself of debris or stones which have been formed.

Other findings in this group according to sex, age, obesity and pregnancy, were of a somewhat similar type to the group with multiple mixed stones. The following tables show the corresponding results.

No/

No stone.

Sex 47 females, 8 males.
Proportion of females
to males is 6 to 1.

Multiple stones.

111 females, 23 males.
Proportion of females
to males is 5 to 1.

<u>Age</u>	<u>Number of cases</u>	<u>Percen- tage</u>	<u>Number of cases</u>	<u>Percentage</u>
Below 20	0		1	.7
20-29	5	9	3	2.3
30-39	8	14.3	20	14.9
40-49	12	21.7	35	26.1
50-59	20	36.4	45	33.6
60-69	6	11.2	18	13.4
70	3	5.6	6	4.5
Not known	1	1.8	6	4.5

Obesity. In these cases in which the weight was
known the comparative figures are:

No stone (46 cases)

Obese 38 (83%)
Thin 8 (17%)

Multiple stone (111 cases)

Obese 76 (79%)
Thin 20 (21%)

Sex history.No stone.

Males 8
Females
Unmarried 4
Married
No children 1
Borne children 27
Not known 15

Multiple stone

Males 23
Females
Unmarried 10
Married
No children 3
Borne children 71
Not known 27

It is thus seen that these factors present some-
what similar findings in the cases with multiple stone
and those with no stone.

To/

To sum up the etiology of the pathological gall-bladder which is found at operation to contain no stones:

(a) There seems to be a certain similarity in the etiological factors involved between the cases where multiple stones were found and where no stone was found at operation.

(b) The absence of stone in the 55 patients in this group may be due to several factors:-

(i) It may be due to the gall^{bladder} having sufficient emptying power to rid itself of stones. Evidence is produced that at one time some of these cases had stones present. (ii) It may be due to the gall-bladder condition being of fairly recent origin, and stones have not yet formed. (iii) It may be due to the fact that the pathological change is not sufficiently advanced and the gall-bladder still retains its emptying powers. It may thus rid itself of any precipitate which forms. There is evidence in the 55 patients that this is to some extent true when compared with the degree of pathological change found in the 134 patients with multiple mixed stones.

Cholesterosis. Finally, in dealing with the etiology/

Cholesterosis.

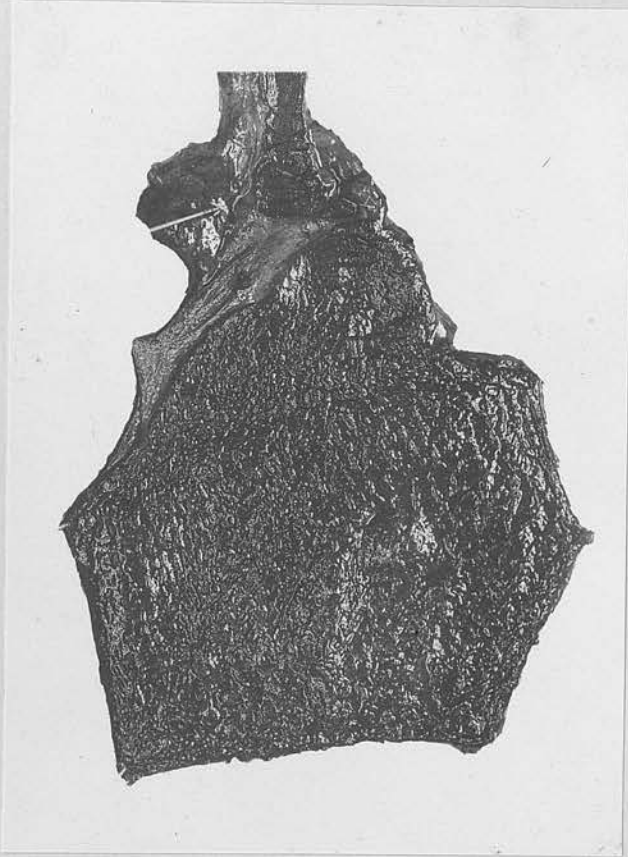


Fig.10. Gall-bladder showing typical "strawberry" appearance of cholesterosis.

etiology, a brief mention will be made of cholesterosis. There were 12 cases in this series in which cholesterosis was noted at operation. These cases have already been included in the previous groups in accordance with whether they contained stones or not.

The fact that there were only 12 cases found with cholesterosis in a series of 247 consecutive cholecystectomies is at once striking. According to Illingworth (1929) it is by no means an uncommon condition, and he found in 100 consecutive cholecystectomies that cholesterosis was present in 21 cases. It may be that in the present series this condition was not being looked for with any special attention and was noted only in the very marked cases (Fig.10).

The etiology of cholesterosis has been a much disputed subject. Even to-day it is not fully understood. According to Illingworth there are two primary changes essential to the production of cholesterosis:

(1) The cholesterol content of the bile must be increased. The result of this is that a certain amount/

amount of absorption of cholesterol takes place into the mucous membrane of the gall-bladder. In some cases this high bile cholesterol is associated with a high blood cholesterol. This being so, it might be expected that the condition would occur more commonly in females, particularly those who have borne children. These persons, as has been mentioned in discussing the single cholesterol stone, have been subject to a hypercholesterolaemia at times. In the present series the distribution of the 12 cases occurred as follows:-

Males	1	
Females		
Unmarried	1)
Married) 11
Borne children	9)
Not known	1)

Thus, although the numbers are too small from which to draw any real conclusion, it is noticeable that at least 75% of the 12 cases were married women who had borne children. Pregnancy therefore may play a part in the production of cholesterosis in view of the hypercholesterolaemia produced.

(2) A physical and chemical change of the cholesterol takes place in such a way that the cholesterol/

cholesterol absorbed is rendered visible, and also is prevented from being absorbed beyond the mucous membrane. This leads to an accumulation of visible cholesterol in the gall-bladder wall.

It is maintained that cholecystitis plays an important part in rendering the cholesterol visible on account of the interference with the absorption process in the gall-bladder which takes place in cholecystitis. This is borne out by the 12 cases here, where in every case the gall-bladder was found at operation to be pathological.

To sum up the etiology of cholesterosis:

(a) The condition is closely allied to conditions where there is an increase of cholesterol in the bile. It is found most commonly in women who have had children, and therefore may be associated with the hypercholesterolaemia found in these cases.

(b) It is closely allied to infection of the gall-bladder where the absorption of the gall-bladder is upset. The result is a deposit of visible cholesterol in the mucous membrane.

Symptomatology./

Symptomatology.

The symptomatology will be discussed under the following headings:-

- (1) Pain in the upper abdomen;
- (2) Pain radiating to the right shoulder;
- (3) Flatulence and distension;
- (4) Intolerance to certain foods;
- (5) Nausea and vomiting;
- (6) Jaundice;
- (7) Initial symptoms in chronic cholecystitis.

In each case an attempt will be made to correlate these with the findings at operation.

(1) Pain in the upper abdomen. Pain or discomfort in the upper abdomen, in one form or another, is the commonest symptom found in chronic cholecystitis. Pain also is the most important symptom in that it is the one from which people most desire relief.

In the 247 cases under consideration pain was found as a symptom in 243 cases (98.4%). It was found to be about equally common in each different group.

The occurrence of pain as a symptom in the different groups.

	<u>Number of cases</u>	<u>Having pain</u>	<u>Percentage with pain</u>
Multiple stone	134	131	98
Single cholesterol stone	39	39	100
Single cholesterol stone and multiple stones	11	11	100
Pigment stone	6	6	100
No stone	57	56	99

Morley/

Morley (1931) divides the pain occurring in cholecystitis into three main types:-

(a) Gastric in origin. This type varies from a feeling of discomfort to a condition of actual pain in the epigastrium or gall-bladder region. He considers that this is due to a reflex spasm of the pylorus, with consequent increased tension in the pyloric antrum. This spasm is the result of the changes which have taken place in the gall-bladder.

(b) Biliary colic. This type of pain is much more severe and is usually sufficient to double the person up in agony. It lasts for a matter of hours, and is followed by tenderness and a less acute pain which tends to radiate through to the scapula. Morley attributes the initial intense pain of the colic to the fact that the bile duct, which is a fibro-muscular tube, goes into violent peristaltic waves in an attempt to get rid of a stone. It is thus a true visceral pain.

The tenderness and pain of a lesser degree which come on later he considers are the result of the congestion and oedema produced in the bile duct by the colic. This causes a stimulation of the adjacent cerebro-spinal sensory fibres of parietal peritoneum, and/

>
Why not in
full blood

>

and then, by a process of radiation to more superficial branches, gives rise to the right-sided pain and tenderness.

(c) Obstructive cholecystitis. The pain in this case occurs when a small stone becomes impacted in the cystic duct, or else a large stone becomes impacted in the neck of the gall-bladder. To start with the pain is of the intense nature of true biliary colic, and the mechanism is the same - the attempt to get rid of a foreign body, with violent peristaltic waves. The pain does not pass off in a matter of hours, as is the case with true biliary colic. It may last for several days and is followed by extreme deep tenderness and rigidity. Morley attributes this extreme deep tenderness to radiation from the sensory nerves of the parietal peritoneum through the centres in the cord. The rigidity he considers a definite reflex with the afferent limb in the sensory cerebro-spinal nerves of the parietal peritoneum.

It may be said, therefore, that the upper abdominal pain found in cholecystitis is due to three causes: (i) reflex spasm of the pylorus; (ii) true visceral pain from violent peristaltic waves in the biliary tract; and (iii) stimulation of the parietal peritoneum/

peritoneum as a result of changes brought about by (ii).

If the type of pain present in an individual case can be accurately classified, it should help greatly in making an accurate diagnosis of the actual condition present. The great difficulty, however, is in obtaining a history which will allow this. In each case the individual threshold of pain, and the different ways each tells his story, make a classification exceedingly difficult.

Of the 243 patients in this series in whom pain in the upper abdomen was a symptom, an approximate division may be made as follows:-

(a) 33 cases in which the pain was not severe and was described as soreness or intense discomfort. These may be considered as the cases where the pain was gastric in origin, the condition in the gall-bladder having produced a reflex pyloric spasm. In these cases no stone had become impacted in the neck of the gall-bladder, the cystic duct, or the common bile duct.

(b) 210 cases in which the description of the pain resembled that of colic. It was most frequently described/

Relation of types of pain in the different groups of gall-bladder disease.

	<u>Total cases with pain</u>	<u>No. of cases with colic</u>	<u>Percentage with colic</u>	<u>Percentage with pain but no colic</u>
Multiple stone	134	117	87	13
Single cholesterol stone	39	37	95	5
Single cholesterol + multiple stones	11	11	100	0
Pigment stones	6	4	66	34
No stone	57	45	79	21

described as a pain which doubled the patient up. Here the pain is initially of visceral origin. Later the pain, tenderness and rigidity found as the intense pain passed off were probably due to stimulation of the parietal peritoneum.

The table facing this page shows the relation of these two types of pain in the different groups of gall-bladder disease. The most striking feature is the large percentage in all groups in which colicky pain was a symptom.

It is seen that in the case of the single cholesterol stone complicated by multiple stones, all cases gave a history of colic. This is the group where the largest percentage would be expected, as there are two predisposing causes to colic. Either one of the multiple stones may pass into the cystic or common duct, or else the large cholesterol stone may become impacted in the neck of the gall-bladder.

In the case of the single cholesterol stone, 95% gave a history of colic. This high percentage fits in with the view that such a stone is essentially a "silent stone", and seldom gives rise to symptoms until it becomes impacted in the gall-bladder neck.

In the case of the multiple mixed stones, there were/

were 87% with a history of colic. It would seem, therefore, that there is a great tendency in these cases for the gall-bladder to attempt to get rid of the stones with the result that colic ensues.

In the case of the pigment stone, there were only 6 cases, and although they show the lowest percentage in which colic occurred, this cannot be considered of any significance.

In the cases with no stone, the large percentage of 79 gave a history of colic. If the above explanation of the mechanism of this type of pain is correct, this is a very striking finding. It means that there must have been stone present at one time in these cases and that during the attacks of colic these have all been expelled from the gall-bladder. The alternative explanation of this type of pain in these patients may be that it was due to dyskinesia, where there is a functional disturbance of the sphincter of Oddi. According to McNee (1936), the spastic variety can produce distension of the gall-bladder and give rise to pain simulating gall stone colic.

It is probable that a certain fallacy has crept in in these cases on account of the difficulty in obtaining/

obtaining a really accurate history from the patient. Thus a number of these patients may not have had true colicky pain. There is, however, some evidence, as shown in discussing the etiology of this condition, to indicate that stones have been present in a gall-bladder at one time, although not found at operation. Thus it may be that the stoneless gall-bladder in many cases may be one which has temporarily relieved itself of stones. This point will be dealt with again in discussing jaundice.

So far, then, the cases have been discussed in two groups, (a) the 33 cases where the only pain recorded has been attributed to a reflex condition in the pylorus; (b) the 210 cases where the pain has been attributed to a definite colic, succeeded by a pain of lesser degree due to stimulation of the parietal peritoneum.

There is reason to believe, however, that in many of the 210 cases in which colic is recorded there was also present pain which was gastric in origin. This is borne out by the fact that there were 44 cases out of the 210 in which the initial pain experienced suggested gastric origin, and it was only later in the history that true colic appeared. These 42 cases fall/

Cases with colic who had pain of gastric origin earlier in the history.

	<u>Number of cases with colic</u>	<u>Cases with gastric pain preceding colic</u>	<u>Percentage with gastric pain preceding colic</u>
Multiple stones	117	23	19
Single cholesterol stone	37	8	22
Single cholesterol + multiple stones	11	3	27
Pigment stone	6	0	0
No stone	<u>45</u>	<u>10</u>	<u>22</u>
	210	44	

fall into the groups shown in the table facing this page.

This seems sufficient to show that in all groups (except that of pigment stones which may be dismissed owing to the small number of cases) abdominal pain of gastric origin may co-exist along with the colic pain of visceral origin. In the above cases, the changes in the gall-bladder have at first been sufficient to initiate pyloric spasm, and later the movement of a stone has started colic.

To sum up the findings in regard to the symptom of upper abdominal pain:-

(a) Upper abdominal pain occurred in 243 out of the 247 cases (98.4%).

(b) Of the 243 patients with pain, there were 33 (13.6%) in whom the pain appears to be gastric in origin due to reflex pyloric spasm.

(c) Of the 243 patients with pain, there were 210 (86.4%) in whom colicky pain is recorded. This is attributed to true visceral pain caused by a stone in the neck of the gall-bladder, cystic or common bile duct. This was followed by pain of a lesser degree due to stimulation of the parietal peritoneum.

(d)/

(d) There is reason to believe that many of the 210 patients with colicky pain also had pain of gastric origin. This conclusion is arrived at because there were 44 (21%) of these patients where pain of gastric origin was followed later in the history by true colic pain.

(2) Pain radiating to the right shoulder. Most general text-books deal with the close association of pain in the right shoulder with disease of the gall-bladder. In many it is considered a diagnostic feature in gall-bladder disease. This would appear to some extent to be a fallacy.

Pain in the shoulder is of two kinds:-

(a) Pain felt on the top of the shoulder. This is caused by stimulation of the sensory terminals of the phrenic nerve in or near the diaphragm. As a result, pain is felt in some part of the segmental areas corresponding to the 3rd and 4th and sometimes the 5th cervical segments of the spinal cord. According to Morley (1931) this occurs in about 5% of cases of biliary colic.

Cope (1922) agrees that it is not so common as usually thought and also maintains that it is by no means a symptom exclusive to gall-bladder disease, saying/

saying that it is more commonly found in perforated pyloric or duodenal ulcer than in gall stones and gall-bladder disease. He enumerates various abdominal and chest conditions in which it occurs. Cope maintains that neither cholecystitis nor impaction of a stone in the cystic duct causes this type of pain unless accompanied by local peritonitis. Also that stone impacted in the common duct gives no shoulder pain of this type unless accompanied by congestion and oedema of adjacent parts.

(b) Pain felt in the scapular region. Pain in this region has been referred to in discussing upper abdominal pain. It is attributed by Morley to stimulation of sensory fibres in the parietal peritoneum as a result of congestion and oedema produced in the ducts by colic. It radiates to the region of the scapula. This is the type of shoulder pain which occurs most frequently in gall-bladder disease. But again, it is not exclusive to it, and may occur in any upper abdominal lesion which produces stimulation of the parietal peritoneum. Blalock (1924) in a series of 735 cases of gall-bladder disease found that in 51% pain radiated to the shoulder. Millet (1925) in 200 cases of various types of gall-bladder disease found/

found that 45% had shoulder pain. Both these presumably include both the types of pain considered above.

In the present series of 247 cases, shoulder pain occurred in 106 cases (43%). It has been difficult to decide which type of pain this was. In the follow-up an attempt was made to clarify this, but unfortunately the significance of this point was not realised until the follow-up was partly completed, and no figures are available. It can, however, be said that a large proportion of the cases did not have the true pain on the top of the shoulder.

To sum up:-

(a) Pain in the shoulder in gall-bladder disease is of two kinds: that which is on the top of the shoulder, caused by stimulation of the phrenic nerve; and that which is in the scapular region and is caused by stimulation of sensory nerves in the parietal peritoneum.

(b) In the present series of 247 cases, shoulder pain, which includes both the above types, occurred in 106 cases (43%).

(c) Neither type of pain is exclusive to gall-bladder disease, and occurs frequently in other conditions/

conditions. It is therefore doubtful if it is of great diagnostic significance.

(3) Flatulence and distension. Flatulence and distension are common symptoms in chronic gall-bladder disease. Rehfuss and Nelson (1936) found that in 908 cases there were 88.2% who complained of upper abdominal flatulence.

It would appear that the flatulence present here is due to aerophagia in the majority of cases. This is borne out by the fact that the symptom comes on most commonly immediately or shortly after a meal. It is accompanied by a feeling of distension in the upper abdomen which frequently requires the corsets or belt to be loosened. Since the tendency is for the symptom to come on so soon after food it is not due to fermentation which requires some considerable time to take place. Also the accompanying distension suggests the swallowing of air. Rehfuss and Nelson believe that this aerophagia is due to some incoordination between the two sides of the autonomic nervous system. They also consider that in cases where flatulence and distension occur like this immediately after a meal, before fermentation takes place, and is sufficient for the sufferer to loosen his clothes, gall-bladder/

gall-bladder disease is probably present.

A condition of atony of the stomach may be the cause of flatulence in some of these cases. According to Graham, Cole, Copher and Moore (1929), however, there is a comparatively low percentage of those with gall-bladder disease of the asthenic type, most of them being of the sthenic type. They came to this conclusion as a result of their radiological studies.

In the present series of 247 cases, there were 180 patients (73%) who complained of flatulence as a prominent symptom and it was invariably accompanied by a feeling of distension in the stomach. Although it appeared frequently during fasting intervals, there was a great tendency for it to be most marked shortly after a meal.

In considering the frequency of this symptom in the different groups of the disease, the figures in the three main groups are given in the following table:

Flatulence and distension as a symptom in the three main groups.

	<u>Number of cases</u>	<u>Cases with flatulence & distension</u>	<u>Percentage with flatulence & distension</u>
Multiple stones	134	97	72
Single cholesterol stone	39	29	74
No stone	57	45	80

It/

It is seen that it is a symptom common to all these groups. The fact that, in this series, the percentage is higher in the group with no stones is probably of no significance.

To sum up what has been said about these symptoms:

(a) Flatulence and distension are common symptoms in chronic cholecystitis. They occur in 180 (73%) of the 247 cases under consideration.

(b) In most cases it seems probable that it is due to a nervous upset in the autonomic system causing aerophagia.

(4) Intolerance to certain foods. It is a common finding that many cases of chronic cholecystitis show an intolerance to various foodstuffs. In the present series there were 126 (51%) of the 247 cases who complained that they were unable to take or were upset by various foods. It was found that the principal foods which were not tolerated were in order of frequency:- 1) fats and greasy foods (This was found in 108 of the 126 cases); 2) soups; 3) potatoes and vegetables; 4) eggs. It was found that this symptom occurred almost equally commonly in all the groups of gall-bladder disease. It seems probable that/

that this symptom is due either to an accompanying chronic gastritis, or to the inability of the bile to help in the digestion of fats.

(5) Nausea and Vomiting. Nausea and vomiting are symptoms frequently met with in gall-bladder disease. There are two main causes of vomiting here:

(a) Vomiting which occurs during or just after an attack of biliary colic. Here the condition is a reflex from the strong peristaltic waves set up in the biliary tract.

(b) Vomiting which occurs intermittently, and which is due to associated chronic gastritis. This type of vomiting is frequently found along with nausea.

In the 247 cases there were 183 patients (74%) who had a history of vomiting. This includes both the types referred to above, as it has not been found possible to distinguish them clearly in many histories. From the follow-up cases, many of whom were questioned on this point, it would seem that both types are common.

There were a further 16 patients who complained of nausea as a symptom, but where there had been no vomiting. This is probably due to a lesser degree of chronic gastritis.

The/

The symptom of vomiting in the three main groups was found as follows:-

Vomiting as a symptom in the three main groups.

	<u>Number of cases</u>	<u>Vomiting</u>	<u>Percentage with vomiting</u>
Multiple stone	134	98	73
Single cholesterol stone	39	33	85
No stone	57	37	65

It is seen that the highest percentage occurs in those cases with a single cholesterol stone. This may be on account of the tendency of the single stone to become impacted in the gall-bladder neck and so setting up a severe colic which brings about a reflex condition in the stomach. It is seen to be a symptom common in all groups.

To sum up what has been said about vomiting and nausea;

(a) Vomiting was found to be present in 74% of the 247 cases under consideration.

(b) It may be due to a reflex condition in the stomach caused by biliary colic. On the other hand, it may be due to chronic gastritis, in which case it is usually accompanied by nausea.

(c) There were 14 cases in which nausea was a symptom/

symptom without vomiting. This is assumed to be due to a condition of chronic gastritis present which is insufficient to bring about vomiting.

(6) Jaundice. Jaundice occurs most commonly in chronic cholecystitis when a stone passes into the common bile duct and blocks it to such an extent that the bile cannot flow. The result is that all the biliary constituents are retained in the blood.

The bile salts are the most toxic constituents of the bile as they have properties of haemolysis and of reducing surface tension. They cause little disturbance, however, owing to the fact that they disappear in the course of a few days owing to some compensating mechanism. Cholesterol accumulates but appears to produce no ill effects. The bile pigments, however, when retained produce jaundice. This is a common symptom in gall-bladder disease and was found by Blalock (1924) to occur in 55% of all his 735 cases. Of the cases in which he found jaundice on physical examination 80% were found at operation to have stone in the common duct.

In the present series jaundice was found in the history of 104 patients (42%). The distribution of these/

these cases is seen in the following table:-

The frequency of jaundice as a symptom.

	<u>Total cases</u>	<u>Jaundice</u>	<u>Percentage with jaundice</u>
Multiple stones	134	60	45
Single cholesterol stone	39	17	44
Single cholesterol and multiple stones	11	5	45
Pigment stones	6	2	33
No stones	57	20	35

It is seen that 45% of cases with multiple stones and single cholesterol plus multiple stones had a history of jaundice. These are the groups where the largest number would be expected, since stones must frequently pass into the bile duct.

The cases of single cholesterol stone show 44% with a history of jaundice and those with no stone 35%.

Thus it is seen that a history of jaundice is almost as common in these groups as in those referred to in the previous paragraph. This at once suggests that there may be causes of jaundice in chronic cholecystitis other than the blocking of the common bile duct by a stone.

In the cases with a single cholesterol stone it is possible that jaundice was produced in a proportion of cases when the stone was in Hartman's pouch and was associated with acute inflammatory changes in and around/

around the gall-bladder. This could produce oedema and partial obstruction of the common bile duct.

In the cases with no stone there may in some instances have been a catarrh of the common bile duct producing obstruction and so catarrhal jaundice. It does not seem likely, however, that this was so in all these cases, as the common bile duct is usually found to be healthy in chronic cholecystitis.

The explanation may be that the gall-bladder contained stones which, although not found at operation, must at some time have been passed from the gall-bladder and produced obstruction. If so, this is further evidence that the stoneless gall-bladder is frequently one which has at one time contained stones.

Relation of jaundice to the finding at operation of stone in the common bile duct. Of the 104 patients with a history of jaundice there were 25 (24%) in whom stone or stones were found in the common duct at operation. A further 4 cases were found to have stones in the common duct at operation where there was no history of jaundice, showing that stones in the common duct need not bring about complete obstruction and so jaundice.

There were 46 patients in whom there was a degree of jaundice present at the time of operation, and of these/

these 14 (30%) were found to have stones in the duct. Operation was carried out as the jaundice was dying away, and presumably by that time the stone had passed down the duct into the duodenum in the other 32 cases.

Relation of jaundice to colic. All of the 104 cases with a history of jaundice had a history of biliary colic. This is the finding expected, as in these cases the bile duct would produce violent peristaltic waves in an attempt to get rid of the stone, and so produce colic.

To sum up the main findings in regard to jaundice:

(a) Of the 247 cases there were 104 (42%) with a history of jaundice. It is thus a fairly common finding.

(b) In 35% of the cases, where no stone was found at operation, there was a history of jaundice, which suggests that stones were present at some previous time.

(c) Of the 104 cases with a history of jaundice 25 (24%) were found to contain stones in the common duct at operation.

(d) All the 104 cases with a history of jaundice also had a history of biliary colic.

(7) Initial symptoms in gall-bladder disease.

Finally, before leaving the symptomatology, it was thought that the cases should be considered from the point of view of what was the first symptom to appear.

For this purpose the cases have been divided into two groups:-

(a) Those whose first symptom was pain;

(b) Those whose first symptom was indigestion which includes flatulence, distension, intolerance to certain foods, vomiting and nausea.

Flint (1934) discusses the findings from this point of view in 100 cases. He found that colic was the first symptom in 45 cases, indigestion in 40 cases and 15 were uncertain. He concludes from this that in approximately 50% of cases stone antedates colic.

These findings are not in accordance with those in the present series, where, as far as could be made out, there were only 29 of the 247 cases (11.7%) in which indigestion preceded pain. In the remaining 218 cases pain was a first symptom.

There is no reason, however, to doubt the conclusion that the appearance of stone may antedate that of colic. This is borne out by the fact that in/

in the present series there were 44 patients in whom pain was a first symptom, but it was not of a colicky nature. In these patients the original pain was probably of the reflex gastric type due to the presence of stones in the gall-bladder. At a later date in these 44 patients true colic developed.

Radiological/

Radiological findings.

The radiology of the biliary tract is a subject in itself and it is intended only to deal briefly with it here. There were a considerable number of the cases in this series who underwent radiological examination of the gall-bladder, and the radiological findings in these cases will be discussed in relation to the findings at operation. They will be discussed under two heads:

- (1) straight X-ray;
- (2) cholecystography.

(1) Straight X-ray. Gall stones were first demonstrated in the living subject by Carl Beck of New York who published his results in 1900. He examined 28 cases. At operation 9 were found to have stones, and of these he managed to demonstrate stones in 2 cases.

Apart from the technique employed, the success of demonstrating gall stones by the direct method of X-ray depends on the nature of the stone or stones present. From a radiological point of view there are two types of stone.

(a) The opaque stone which contains sufficient inorganic material, chiefly calcium, to absorb the X-rays and thus produce a shadow. The common multiple mixed/

mixed stone being of inflammatory origin usually contains a fair amount of calcium and thus may be opaque to X-rays (Fig.11).

(b) The non-opaque stone, where the stone is composed almost entirely of organic material, chiefly cholesterol. This type of stone is permeable to X-rays. The single cholesterol stone in its pure form is of this type. If, however, it has ceased to be a silent stone as a result of superimposed infection, then a crust containing calcium may form on the outside of the stone and thus render it opaque to X-rays, giving a "ring shadow" (Fig.12).

There were in the 247 cases in the series, 65 cases in which a straight X-ray and a radiological diagnosis of a stone visible or not visible were made. Of these 65 cases there were 36 cases in which at radiological examination a stone was diagnosed as present. When compared with the findings at operation the results were as follows:

Diagnosis of stone visible at radiological examination.

<u>Number of cases</u>	<u>Stone found at operation</u>	<u>No stone found at operation</u>	<u>Percentage correct</u>
36	35	1	97.2

It is seen that a wrong diagnosis was made in only/

Straight X-ray.



Fig.11. X-ray showing presence of multiple mixed stones in the gall-bladder.

Straight X-ray.



Fig.12. X-ray showing the typical "ring shadow".

only one case. At operation in this case calcified tuberculous glands were found in the region of the gall-bladder.

Of the 65 cases, there were 29 in which no stone was reported visible at X-ray examination. The findings at operation were as followed:-

No stone visible at radiological examination.

<u>Number of cases</u>	<u>Stone found at operation</u>	<u>No stone found at operation</u>	<u>Percentage correct</u>
29	19	10	34

It may be assumed from this second table that in the 19 cases in which stones were found at operation and undiagnosed at radiological examination, the stones were of the non-opaque variety.

It may be concluded from this that (1) if a suggestive of shadow/stone is seen at radiological examination, it is almost certainly present; (2) if no stone is seen at radiological examination, it does not mean that there is no stone present.

(2) Cholecystography. This was first introduced by Graham and Cole (1924) who injected tetrabromphenolphthalein intravenously. This dye was concentrated within the gall-bladder, and, being opaque/

opaque to X-rays, gave a shadow of the gall-bladder.

For a satisfactory filling of the gall-bladder with this substances there are three important factors.

(a) The dye must circulate in the blood in sufficient quantity.

(b) The liver must function actively and excrete the dye.

(c) The substance must be able to enter the gall-bladder and the mucous membrane of the gall-bladder must be sufficiently healthy to concentrate its contents.

Various other substances introduced by the intravenous route have been used to give a shadow of the gall-bladder in this way. In the present series the substance was sodium-tetraiodophenolphthalein.

Although at first the dye was invariably introduced by the intravenous route, it was later given orally, and this has to a great extent superseded the earlier method. The advantage of the oral method is that it avoids the necessity of an intravenous injection and the possibility of some of the dye getting into tissues surrounding the vein and doing damage. On the other hand the intravenous method is still useful in those cases where a gastric condition may prevent the substance being tolerated orally.

It/

It has been found that the oral method is as satisfactory as the intravenous method. Mather and Williams (1927) found that in 125 cases the oral method was as useful as the intravenous method. Operation in 35 cases confirmed the radiological diagnosis in 94.3% of cases. Later Hauser (1933) confirmed this and found that when administered by the oral route results were correct in 94.9% of cases, compared with 92.5% by the intravenous route.

In the present series there were 68 cases in which the patient was examined by cholecystography. These cases dated from the years 1928 to 1936. At first the intravenous route was invariably employed. This was displaced by the oral method which was the one used in all the cases occurring in more recent years. No distinction is made in the two methods of administering the dye in considering the results. The three essential conditions which must be fulfilled in order that a shadow of the gall-bladder may be obtained in this way have been mentioned above.

If the dye is circulating in sufficient quantity in the blood, and if the liver is functioning actively in excreting the dye, then a satisfactory shadow depends on the condition of the gall-bladder. There are/

are two ways in which the gall-bladder may be involved so that a shadow is not seen.

(1) The gall-bladder fails to concentrate the dye.
This will occur when the wall of the gall-bladder is not functioning properly, which is due in many cases to some inflammatory change. This therefore depends on the pathological state of the gall-bladder wall.

(2) The dye may not enter the gall-bladder.
This will occur if one of the following conditions exists:- (a) A stone blocks the cystic duct. (b) A single cholesterol stone blocks the entrance to the gall-bladder. (c) The gall-bladder is packed full of stones.

The cases will be discussed from these two points of view.

Firstly, as regards the state of the gall-bladder wall, it is seen in the following table how this condition was related to the radiological findings.

<u>Radiological report</u>	<u>Total cases</u>	<u>Findings in gall-bladder at operation</u>		
		<u>Markedly pathological</u>	<u>Moderately pathological</u>	<u>Normal</u>
No shadow	35	17	18	0
Poor shadow	17	6	10	1
Normal shadow	16	<u>3</u>	<u>13</u>	<u>0</u>
		26	41	1

It is seen that there are 35 cases in which no shadow was visible, and that in all these cases a pathological/

pathological gall-bladder was found at operation. In almost half the cases the gall-bladder was found to be markedly diseased.

In the 17 cases in which there was a poor shadow, only one case showed a normal gall-bladder at operation. This case was the one where tuberculous glands were found in the region of the gall-bladder, and it is probable that their presence may have prevented the proper filling of the gall-bladder. The remaining 16 cases were all found to have pathological gall-bladders, the majority coming under the heading of moderately pathological.

It may be deduced from these results that if the gall-bladder shows no shadow or a poor shadow, it is very probable that it is pathological. The findings in the 52 cases including both these groups give only 1 error, and thus there is a correct result in about 98% of cases.

In the 16 cases where a normal shadow was found, it is seen that all cases proved to have a pathological gall-bladder, although in most instances the gall-bladder was only moderately diseased. It is seen from this that a normal shadow does not mean that the gall-bladder is normal. It does mean, however, that the/
the/

the gall-bladder is still functioning to some extent.

These findings are in line with other statistics which have been produced. Carter (1933) enumerates 54 cases in which there was a positive radiological finding and the gall-bladder was found to be pathological in 95% of cases. On the other hand, he enumerates 16 cases in which the radiological finding was negative and of these 13 had a pathological gall-bladder at operation. He concludes from this that a negative finding has no value in deciding whether the gall-bladder is pathological.

Wilkie and Illingworth (1927) enumerate 50 cases in which no shadow was seen, and in 44 of these the gall-bladder was found at operation to be grossly diseased. There were also 10 cases in which a poor shadow was seen, and in all of these chronic cholecystitis was found in the gall-bladder.

As has been said above, the findings in this series suggest that a normal shadow does not rule out the existence of a pathological gall-bladder. This finding is at variance with that of McWhirter (1935), describing 735 cases which were examined by cholecystography and later operated upon at the Mayo Clinic in 1932. He finds that in 287 cases where the shadow was normal, the gall-bladder was proved to be normal
in/

in 89.5% of cases. The explanation of this difference may be either that in the present series there were no normal controls, or that the technique was not very good. A good many of the patients underwent cholecystography during the years 1928 to 1930, and in these days probably it had not reached the state of efficiency now existing.

Secondly, as regards the contents of the gall-bladder, and the possibility of their preventing the dye entering the gall-bladder, the following table shows the relation of the gall-bladder contents to the radiological findings.

<u>Radiological report</u>	<u>Findings in gall-bladder at operation</u>			
	<u>Multiple stone</u>	<u>Single cholesterol stone</u>	<u>Single cholesterol + multiple stones</u>	<u>No stone</u>
No shadow	22	2	3	8
Poor shadow	9	2	1	5
Normal shadow	<u>8</u>	<u>3</u>	<u>0</u>	<u>5</u>
	39	7	4	18

There are 39 cases where multiple mixed stones were found in the gall-bladder. 22 cases gave no shadow and it is probable that the stones filled the gall-bladder to such an extent that the dye could not enter. In the 9 cases where a poor shadow was obtained, dye was evidently able to enter the gall-bladder to some extent. In the 8 cases where a normal shadow/

Cholecystography



Fig.13. Shadow of the gall-bladder showing the presence of ~~very~~-opaque multiple stones which cause a denser shadow than that of the dye.

Cholecystography.



Fig.14. Shadow of the gall-bladder showing a negative shadow cast by single large ^{NON-}opaque stone.
A

shadow was obtained, the dye must have been able to enter the gall-bladder freely.

In the 7 cases with a single cholesterol stone, the two cases with no shadow were due to complete blocking of the entrance to the gall-bladder. In the two cases where a poor shadow was obtained, the blocking was apparently not complete. Whereas in the three cases with a normal shadow, the stone must have been in such a position as to allow free access of dye into the gall-bladder.

In the 18 cases in which no stone was found, the 8 cases where no shadow was seen and the 5 cases with a poor shadow may be attributed to the lack of concentrating power of the gall-bladder. In the 5 cases with no stone and a normal shadow, the gall-bladder wall still possessed the power of concentrating the dye.

In some cases a stone may be seen in cholecystography. This will occur when the dye casts a shadow of the gall-bladder but where it contains a stone or stones of different density. An ~~opaque~~ opaque stone may show as a denser shadow (Fig.13) and a ~~non~~opaque stone, by displacing the dye, as a clear shadow (Fig.14).

To sum up the findings in the examination of the gall-bladder by means of cholecystography:

(a)/

(a) In 35 cases in which no shadow was found and 17 cases in which the shadow was poor, all were found at operation to have a pathological gall-bladder except one case (98% correct). This indicates that a positive radiological result is strong evidence of disease of the gall-bladder.

(b) In 16 cases a normal shadow was found, and in all of these a pathological gall-bladder was revealed at operation. This indicates that a negative radiological result does not mean that the gall-bladder is normal.

(c) The conditions in the gall-bladder which can produce no shadow or a poor shadow on cholecystography are attributed either to the inability of the gall-bladder to concentrate the dye properly, or else to stone or stones preventing the gall-bladder filling with the dye.

Mortality as a result of operation. In the total of 247 cases there were 19 deaths occurring shortly after operation, 9 of which occurred on the second or third day, and the rest before the patient left hospital. This gives a mortality rate of 7.7%. In all the 19 cases/

cases the operation performed was that of cholecystectomy. The causes of death were as follows:-

Heart failure	10	cases
Pulmonary embolism	2	"
Pulmonary congestion	2	"
Peritonitis	1	case
Paratyphoid B.	1	"
Acute bronchitis	1	"
Acute pancreatitis	1	"
Cause not known	1	"
	<u>19</u>	

A percentage of 7.7 is high compared with other series recorded. Wakeley (1935) found in his series of 467 cases a mortality rate of 5.5%. This may be accounted for by the fact that some of the subjects in this series were not of a good operative risk. One death occurred in a patient, aged 45, with a diagnosis of gastric ulcer, after frequent haematemesis, who, in spite of blood transfusion after operation, died of heart failure. Another patient, aged 55, was found post mortem to have very marked atheroma of the coronary vessels and aorta. Another patient, aged 47, was found to have a gastric ulcer as well as the gall-bladder lesion, and the ulcer was removed at operation. This evidently produced too much shock, as he died of heart failure. Another patient, aged 58, was an old case of myxoedema, with a tendency to chronic bronchitis/

bronchitis. Also one patient, aged 74, required a choledocotomy, with the removal of several stones from the common bile duct, resulting in death afterwards from shock and heart failure.

If these cases which proved to be a poor operative risk be excluded, the percentage is reduced to 5.7%. If it is considered that at the time of operation there were 36 patients between 60 and 69 years of age, and 10 over 70 years of age, it does not appear that an over-all mortality rate of 7.7% is excessive.

As regards sex, in the 212 female cases there were 16 deaths (7.5%), and in the 35 male cases 3 deaths (8.6%). This shows a slightly higher percentage in the male cases. Wakeley in his series also found this, the mortality rate being 6.2% in males as opposed to 5.4% in females. In these series the difference in mortality rate in the two sexes is not very marked, but Graham, Cole, Copher and Moore (1929) maintained that women are the better operative risk. They found that in their series of operations of all kinds on the biliary tract, 51.4% of all deaths were males, although there were two and a half times as many females in the series.

As/

As regards the age of the patients who succumbed to operation, there were 3 cases over 70, and 5 cases between 60 and 69. The youngest was aged 36 and died of acute pancreatitis. Three deaths occurring between the ages of 40 and 49 were in obese women and were all due to shock and heart failure. The percentage mortality at the varying ages, in 18 of the 19 patients in whom the age is known is shown in the following table:-

<u>Age</u>	<u>No. of cases</u>	<u>Deaths</u>	<u>Percentage</u>
Below 20	1	0	0
20-29	14	0	0
30-39	33	1	3
40-49	58	3	5
50-59	85	6	7
60-69	36	5	14
70 onwards	10	<u>3</u>	30
		18	

and as would be expected, the operative mortality increases with age.

Wilkie (1928) found a mortality of 6.7% in 74 patients over 60 years of age as opposed to approximately 4% in his whole series of 452 cases, and considers that old people stand operations well, and that operative risk depends more on the age and severity of the disease than the age of the patient.

To sum up the findings in operative mortality:

(a) /

(a) In the total of 247 cases there were 19 deaths, giving an operative mortality of 7.7%.

(b) The commonest cause of death was found to be heart failure (10 out of the 19 deaths).

(c) A mortality rate of 7.7% is high compared with the findings of others. This may be attributable to the fact that a number of the cases were a poor operative risk.

(d) The mortality rate in males (8.6%) was found to be slightly higher than in females (7.5%).

(e) The mortality rate was found to increase with advancing years. No death occurred before the fourth decade where the mortality rate was one out of 33 cases. Thereafter there was a steady increase, and in the 10 patients over 70 years there were 3 deaths.

(f) Although the operative mortality is high in this series, the risk of operation in a person of reasonable age and with no complications is small enough not to enter greatly into a decision whether operation should be performed or not.

SUMMARY/

SUMMARY OF PART I.

1. 247 cases of chronic cholecystitis treated by operation have been reviewed.
2. It was found that the disease was commoner in the female, in the proportion of 6 to 1.
3. The age grouping according to the time at which symptoms first appeared showed the largest number (31%) in the fifth decade of life.
4. The cases are grouped according to the findings at operation.
5. Multiple mixed stones were found in 134 patients (54%) in this series. They are therefore the commonest lesion. It is maintained that infection of the gall-bladder is the important point in their etiology. Infection plays its part by upsetting the function of the gall-bladder and providing a nucleus upon which bile contents are precipitated. Infection in many cases is preceded by stasis. It is argued that lack of exercise and obesity are not so much the causes of stasis but are concomitant with it - all the result of alimentary abuse.
6. A single cholesterol stone was found in 39 patients and is considered to be metabolic and aseptic in origin/

origin. It ceases to be a silent stone when it is complicated by infection. It has been found most commonly in women who have had children, and it is considered that it is closely associated with the hypercholesterolaemia of pregnancy.

7. There were 55 patients with a diseased gall-bladder where no stone was found at operation. Evidence is produced which indicates that the stoneless gall-bladder may be one which has temporarily ridded itself of stones.
8. The symptoms and their causes are discussed. It is found that upper abdominal pain is the commonest symptom, occurring in 98.4% of cases. It is argued that pain in the shoulder is of little diagnostic significance.
9. Other symptoms found were vomiting (74%), flatulence (73%), and intolerance to certain foods (51%). It is maintained that vomiting is due either to a reflex from colic or a coexisting chronic gastritis. Flatulence is attributed mostly to a nervous unbalance producing aerophagia. Intolerance to certain foods is due either to the inability of the bile to digest fats or to chronic gastritis.

10. Jaundice was found as a symptom in 104 patients (42%). The main cause of this symptom is blocking of the common bile duct by a stone. In 25 out of the 104 patients stones were found in the common duct at operation.
 11. 65 patients underwent examination by straight X-ray. A shadow suggestive of stone proved to be correct in 97.2% of cases. If no shadow is seen, it does not mean that no stone is present.
 12. 68 patients underwent examination by cholecystography. In the 35 patients with no shadow and the 17 with a poor shadow, the gall-bladder was pathological in 98% of cases. The fact that in 16 patients a normal shadow was seen and a diseased gall-bladder found is attributed to the gall-bladder still functioning.
 13. The operative mortality was found to be 7.7%.
-

PART II.

FOLLOW-UP OF 162 CASES.Method used in the follow-up.

All the cases under consideration were operated on from one to 10 years previously. Before considering the actual results of the follow-up, the method by which it was carried out will first be explained.

Of the total number of cases, 247, there were 19 deaths occurring after operation at varying periods before the patient left hospital. There was one further death occurring two months after operation when the patient collapsed suddenly and died of heart failure. An attempt has been made to get into touch with the remaining 227.

It was considered that the most satisfactory method was to see and examine personally as many patients as possible. Consequently a letter was sent to as many as lived within reasonable distance, and whose cases gave no indication, such as excessive age, why they should not appear for examination, asking them to attend. To the remainder who lived far away, or who were old, a questionnaire was sent with the following questions:-

1./

1. Do you have pain in the stomach?
2. Is the pain as bad as before your operation?
3. Are you able to do your work?
4. Do you have to avoid certain foods?
5. Which foods have you to avoid?
6. Do you suffer from vomiting?
7. Do you suffer from a feeling of sickness?
8. Do you suffer from wind on the stomach?
9. Do you have a feeling of fulness in the stomach?
10. Have you had any jaundice since your operation?
11. Is there any weakness of your operation wound?
12. Do you think the operation has done you good?

Also a request was made to add any notes about their own particular case not included in the above questions.

In the majority of cases where these lines of investigation failed, an attempt was made to find out about the patient by communicating with the patient's own doctor.

The results were that information was gained in a good proportion of cases as follows:-

Patients seen and examined.....	89
Answered questionnaire.....	54
Information from doctor.....	<u>19</u>
	162

This left 65 patients with whom it was not found possible to get into touch. In a number of these cases information was received that the patient had since died, and in the rest the patients did not answer or were not to be found.

Classification/

Classification of results.

(1) Cured. Those cases to whom the operation had brought complete relief from previous symptoms. There was no pain, no vomiting or nausea, and only occasionally a little flatulence or distension. They had usually no trouble with diet and were quite able to work. Many of them described themselves as "feeling a new person" since operation.

(2) Very much improved. This group includes those cases which showed marked improvement as a result of operation. Pain as a rule was absent or else very slight. Vomiting did not occur. Occasionally a little nausea was found, and quite frequently there was some discomfort from flatulence and distension. They were able to work. Trouble with diet was present in some cases. In their own opinion they felt very greatly improved. No hernia was present.

(3) Improved. Those cases which had apparently been benefitted to some extent by operation, but who still suffered from moderate symptoms. Pain in the right hypochondrium was often present, but not so severe as previously. Vomiting and nausea were often present but not so severe as before operation, and flatulence and distension often persisted. They were/

were generally able to do some work. Trouble with diet was frequently present, and in a few cases there was a ventral hernia. In their own opinion they had benefitted from operation, the reason being in most cases that the pain was gone or less severe.

(4) In statu quo. Including those cases in which no improvement had occurred as a result of operation. They still suffered from pain in the gall-bladder region which was as bad as before operation. Digestive troubles, along with vomiting, nausea, flatulence and distension persisted in many of these patients. They were often unable to do their work. In some cases a ventral hernia was present and in a small number jaundice had occurred since operation.

In assigning a patient to one of these groups, consideration was given in each individual case, not only to the symptoms or absence of symptoms present at the time of follow-up, but also as to how their present condition compared with that prior to operation. For example, two cases whose present condition appeared to be the same, would sometimes be put into different groups, such as Improved or Very much Improved, if the change which had taken place in the two/

two cases as a result of operation seemed to warrant it.

The object of the follow-up.

(1) The establishment of a prognosis. As mentioned at the beginning, the object of the follow-up is to consider the ultimate results of operative treatment in chronic cholecystitis. It is hoped that in doing this a prognosis may be established in these cases. A prognosis may be based on (a) the findings before operation; (b) the findings at operation.

(a) Findings before operation. The time when an accurate prognosis is most desired is before operation has taken place. A patient complains of certain symptoms, presents certain physical signs, and shows certain findings at radiological examination. The question arises whether operation is justified in view of the results that may be expected.

As will be shown later, the prognosis differs to some extent in the various types of gall-bladder trouble present. It is often not possible to say exactly what the findings in the gall-bladder will be. This can frequently be known definitely only at operation. Therefore it has been felt that it would be/

be useful to try and establish a prognosis based purely on symptoms which suggest chronic cholecystitis. In order to do this, all the cases in the follow-up which came for operation with a primary diagnosis of chronic cholecystitis will be reviewed together, and the results of operation classified. These were all cases which presented symptoms of chronic cholecystitis, and although in some cases it was possible to forecast what the findings at operation would be, the majority were such that only a diagnosis of chronic cholecystitis with or without stones could be made. For this purpose the cases will be reviewed under the heading: (1) Chronic cholecystitis with or without stones..... 157 cases.

(b) The findings at operation. When the gall-bladder has been removed and inspected after operation, it is then possible to assign the case to a definite group. To reach a more exact prognosis, the results of operation are reviewed in each group according to the contents of the gall-bladder at operation. In this way it is hoped that a prognosis may be established in the different types of chronic gall-bladder disease either before operation when it is possible to/

to forecast accurately what the condition is, or after operation when the gall-bladder has been inspected.

This part of the follow-up will therefore be discussed under the following heads:-

(2) Multiple stones of mixed composition....	87	cases
(3) Single cholesterol stone	25	"
(4) Single cholesterol + multiple mixed stones	9	"
(5) Pigment stones	4	"
(6) Stoneless gall-bladder	37	"
(7) Cholesterosis	9	"

A point which has to be remembered in arriving at a prognosis is the importance of the individual factors which come into play in each case. Although in two cases the pathological findings may be similar, the individual factors such as the age of the patient, sex, build, and the duration of symptoms may differ to such an extent that the prognosis in the two cases is different. An attempt will therefore be made to take these things into consideration and assess what bearing they seem to have on the prognosis.

(2) A consideration of symptoms persisting after operation. After the cases have been reviewed in the above manner, the symptoms which persist after operation will be considered. An attempt will be made to show which symptoms are most commonly found to be relieved/

relieved by operation, and also to explain the persistence of certain symptoms after the gall-bladder has been removed.

(1) Chronic cholecystitis with or without stones.

There were 162 patients with whom it was possible to get into touch and follow up. Of these there were 5 patients who came for operation with a diagnosis other than chronic cholecystitis; three of these were operated on for possible malignant disease of the stomach, one for peptic ulcer and the other for chronic appendicitis. In these 5 cases all were found to have multiple gall stones at operation, but their histories were not typical. Since the object of this part of the follow-up is to consider the prognosis in all cases diagnosed as chronic cholecystitis with or without stones, these five cases will be left out.

There remain 157 patients who came for operation with a primary diagnosis of chronic cholecystitis with or without stones. The results of operation in these cases are seen in the following table:-

Results of operation in 157 cases of chronic cholecystitis with or without stones.

Number of cases	<u>In statu quo</u>	<u>Improved</u>	<u>Very much improved</u>	<u>Cured</u>
157	15	29	40	73

In/

In order to interpret these figures as percentages and obtain a true idea of the success of the operative treatment, it is necessary to add the number which would be expected to succumb in operative mortality (shown previously to be about 7.7% in the total series of 247 cases). This represents the addition of approximately 12 patients to the above number of 157, giving a total of 169 cases. Taking this into consideration, the results of operation are interpreted as percentages in the following table:-

Results of operation in 169 cases expressed as percentages.

<u>Operative mortality</u>	<u>In statu quo</u>	<u>Improved</u>	<u>Very much improved</u>	<u>Cured</u>
7.7	9	17	24	43

If those cases coming under the classification of "operative mortality", "in statu quo" and "improved" be reckoned as unsuccessful cases, and those "very much improved" and "cured" as successful cases, then they may be grouped as follows:-

The success or otherwise of operative treatment in 169 cases.

Operative mortality... 7.7%)	
In statu quo 9%)	33% unsuccessful
Improved 17%)	
Very much improved ... 24%)	
Cured 43%)	67% successful.

From/

From the above results it is seen that in two thirds of the cases operative treatment may be considered to have been successful, and the fairly satisfactory number of 43% represents those patients who were completely relieved of all their symptoms. To the 67% in which operation was definitely successful might be added the 17% which, although not completely relieved by operation, may be looked upon as cases where the operation was at any rate worth while, giving a total of 84% in which benefit was derived from operative treatment.

It would appear, therefore, that in view of the pain and discomfort suffered by these people prior to operation, they have a good chance of being cured, or at least a very good chance of being improved if they submit to operation.

Comparison of the above results with those of others. When the results found in this series are compared with those of others they are a little disappointing. Wilkie (1934) in a follow-up found that 70% of patients were relieved of symptoms. This may be compared with the 67% successful results found in this series and is very similar. On the other hand, Davis (1928) in a series of 144 cases which he followed up/

up by means of a questionnaire found that 69.4% were cured and 21.5% relatively cured. Sanders (1930) had even better results in his series of 352 cases followed up, finding complete relief in 84% of patients. Comparisons, however, are difficult in view of the difference in classification in each series. In this series a great effort was made to try to assign each patient into a group without prejudice, and if ever there was doubt then the case was placed in the lower group. The exceptionally good results found in the series by Sanders are very striking, particularly as there were found to be 8.5% with hernia after operation, and it may be that his classification was a little optimistic.

Cholecystectomy and cholecystostomy. As was mentioned at the beginning, the type of operation employed in this series was as a rule cholecystectomy. Cholecystostomy was carried out in 10 cases where it was not considered advisable to perform a cholecystectomy because of the existence of the following conditions:-

Poor general condition	3	cases
Excessive age	2	"
Pancreatitis	2	"
Localised peritonitis	1	case
Adhesions	1	"
Anaesthetic difficulty	1	"
		<u>10</u>	

The/

The results of operation in these 10 patients were very satisfactory as it was found that 7 of them considered themselves cured. It is not possible here to compare the results of cholecystectomy with those of cholecystostomy, as the numbers in the latter group are too small. It would seem, however, that in view of the other complications which existed in the 10 cases of cholecystostomy, the results of operation were satisfactory.

It is usually considered that cholecystectomy is more satisfactory than cholecystostomy. Rowlands (1932) found that cholecystectomy afforded permanent relief in 86% of cases, whereas with cholecystostomy it was only in 45%. Black (1935), in a follow-up of 25 cases of cholecystostomy found that 24% required a further operation at a later date. The findings in this series bear out the view that cholecystostomy may require further surgical intervention. There were 6 patients in the 162 followed up who had a cholecystostomy performed in earlier years and whose symptoms necessitated their return to undergo cholecystectomy.

Individual/

Individual factors affecting the prognosis. It has now been shown in this follow-up of 154 patients who had a diagnosis of chronic cholecystitis taken without any consideration of individual factors, good results can be expected in 67% of cases.

The individual factors which may play a part in estimating the prognosis in a single case will now be considered.

(a) Age. The following table shows how the results of operation in the 157 cases were related to the age of the patient.

Results of operation in 157 cases according to age.

<u>Age</u>	<u>In statu quo</u>	<u>Improved</u>	<u>Very much improved</u>	<u>Cured</u>
20-29	2	-	2	6
30-39	2	5	4	11
40-49	5	10	9	17
50-59	5	11	17	21
60-69	1	3	7	16
70 onwards	-	-	1	2
Total	15	29	40	73

When these results are expressed as successful and unsuccessful, the percentage of successful results are seen to be as follows:-

The success or otherwise of operation according to age.

<u>Age</u>	<u>Unsuccessful</u>	<u>Successful</u>
20-29	2	8 (80%)
30-39	7	15 (68%)
40-49	15	26 (63.5%)
50-59	16	38 (70%)
60-69	4	23 (85%)
70	-	3 (100%)

It/

It is seen from this that after the decade between 20 and 29 where 80% of cases were successful, there is a drop and then a gradual increase in the percentage of successful results as age increases. It would seem then that although one would hesitate to say that the chances of success are more likely to increase along with age, there is little or no indication that age decreases the likelihood of a good prognosis. In fact as the percentage of good results, neglecting the very small number over 70 years where all were successful, varied from 63.5% at the lowest to 85% at the highest, it would seem that age does not appear to play a large part in influencing the prognosis.

These figures indicate that good results may be expected in elderly patients undergoing operation. It has to be remembered, however, that as age increases the operative mortality is found to be higher.

(b) Sex. In regard to the relation of the sex of the patient to the results obtained, the following were the findings:

	<u>Results of operation according to sex.</u>			
	<u>In statu quo</u>	<u>Improved</u>	<u>Very much improved</u>	<u>Cured</u>
Females	15	22	39	61
Males	--	7	1	12

Considering/

Considering these as a percentage of the 137 females and 20 males who were followed up, it is found that the results are:-

Results of operation according to sex expressed as percentages.

	<u>In statu quo</u>	<u>Improved</u>	<u>Very much improved</u>	<u>Cured</u>
Females	11	16	29	44
Males	--	35	5	60

Owing to the small number of males involved, it is not possible to conclude very much from these findings. It is seen that 60% of the males are cured compared with 44% of females, and that in the unsuccessful cases 35% of the males were to some extent improved compared with 16% of females. This may perhaps indicate that really good results are more frequent in males, and that males are likely to be benefitted by operation.

(c) Build of the patient. There were 130 of the patients followed up where it was possible to class the person as definitely either of the obese type or of the thin or normal type. The results in these classes may be classified as follows:

Results of operation according to the build of the patient.

	<u>In statu quo</u>	<u>Improved</u>	<u>Very much improved</u>	<u>Cured</u>
Obese	10	23	27	45
Thin	2	3	7	13

Considered/

Considered as approximate percentages these figures give:-

Results of operation according to build expressed as percentages.

	<u>In statu quo</u>	<u>Improved</u>	<u>Very much improved</u>	<u>Cured</u>
Obese	10	22	25	43
Thin	8	12	28	52

It seems from these figures that the results are slightly better in the thin than the obese type, showing a comparative figure of 52% cured in the thin type of patient as opposed to 43% in the obese type. Also grouping those very much improved and cured as successful cases, and the remainder as unsuccessful, it is found that in the obese type 68% are successful and 32% unsuccessful, compared in the thin type with 80% successful and 20% unsuccessful. The balance, therefore, appears to be in favour of the patient who is not of the obese type.

Duration of symptoms. It has been felt that the duration of symptoms might show a difference in the end results of treatment, on the grounds that the longer a patient has had disease of the gall-bladder the more damage will have been done to surrounding organs and the body as a whole. This, however, does not seem to be borne out/

out when considering the results in this series.

These are seen in the following table:-

Results of operation according to duration of symptoms.

<u>Duration of symptoms</u>	<u>In statu quo</u>	<u>Improved</u>	<u>Very much improved</u>	<u>Cured</u>
Up to 1 year (46 cases)	5	7	10	24
1-5 years (54 cases)	5	11	10	28
More than 5 years (57 cases)	5	11	20	21
	15	29	40	73

From this it would appear that the duration of symptoms is of little importance in the prognosis of the case. The only fallacy that may arise here is that those who have had symptoms over a long period may appreciate the relief of operation more than those in whom the symptoms are of short duration, and so have been classified too favourably.

To sum up the findings in 157 patients treated by operation and with a primary diagnosis of chronic cholecystitis with or without stones:-

(a) Operation proved to be successful in 67% of cases. In 43% patients were entirely relieved of symptoms. In only 9% was operation of no benefit.

(b)/

(b) 147 patients underwent cholecystectomy, the remaining 10 patients having a cholecystostomy. Cholecystostomy was performed only when some complication existed and the results were satisfactory.

(c) The age of the patient appears to have little bearing on the ultimate result; in fact the results appear to be slightly better as age increases, but age increases the operation risk.

(d) The sex of the patient shows a slightly better result in male cases.

(e) As regards the build of the patient, better results are obtained in patients who are not of the obese type.

(f) Duration of symptoms appears to play no part in influencing the prognosis.

(2) Multiple mixed stones. Having discussed the follow-up of cases as a whole with the object of ascertaining the likely prognosis in chronic cholecystitis, irrespective of the type, it is now necessary to discuss the results in the light of the findings at operation.

As the greatest number of cases fell into the group where multiple mixed stones were found, they will be taken first. It will be possible in this way to/

to arrive at a more accurate prognosis either before operation where multiple stones can be definitely diagnosed, or, failing that, at operation where the gall-bladder is found to contain multiple stones.

In this group there were 87 patients followed up and the results were as follows:

Results of operation in 87 cases with multiple stones.

	<u>Number of cases</u>	<u>Expressed as percentages</u>	
In statu quo	9	10.4)) 28.8% unsuccessful
Improved	16	18.4)	
Very much improved	21	24.1)) 71.2% successful
Cured	41	47.1)	

The results here are found to be better than in the whole group of chronic cholecystitis with or without stones. 71.2% are successful compared with 67%. 47.1% are completely relieved compared with 43%. Later on the results in cases with stone and without stone will be compared.

It is now necessary to examine the results in their relation to the degree of pathology found in the gall-bladder wall at operation. In the 87 cases here/

here the findings were as follows:-

Results of operation in 87 cases with multiple stones in relation to the pathology of the gall-bladder.

<u>Gall-bladder wall</u>	<u>In statu quo</u>	<u>Improved</u>	<u>Very much improved</u>	<u>Cured</u>
Moderately pathological	7	10	12	21
Markedly pathological	2	6	9	20

These results expressed as percentages give:

Moderately pathological	14	20	24	42
Markedly pathological	5.4	16.2	24.4	54

It is noted that there is a difference in the results obtained according to the state of the gall-bladder wall. The noticeable factors are that a lower percentage (5.4% as opposed to 14%) of those with a marked pathological condition of the wall remained in statu quo, and also that a large percentage (54% as opposed to 42%) of those with a marked pathological gall-bladder were cured. This would appear to suggest that the grosser the pathological condition of the wall,, the better the result of the removal of the gall-bladder. This is a usual finding, and it is the view of Wilkie (1934) and Weir and Snell (1935) that less favourable results are obtained with the lesser degrees of pathology/

pathology present in the gall-bladder wall. To illustrate this point more clearly, the corresponding findings in all the cases previously referred to under the heading of chronic cholecystitis with or without stones are shown in the following table. This includes the 150 cases in which the gall-bladder was found to be moderately or markedly pathological, and excludes the three cases in which the gall-bladder was normal, and the 9 cases in which cholesterosis was found.

Results of operation in 150 cases of chronic cholecystitis with or without stones in relation to the pathology of the gall-bladder.

Gall-bladder wall	In statu quo	Improved	Very much improved	Cured	Total
Moderately pathological	10	21	20	33	84
Markedly pathological	2	8	14	42	<u>66</u> 150

These results considered as percentages give:

Moderately pathological	12	25	24	39
Markedly pathological	3	12	21	64

From this it is seen that the findings in favour of the markedly pathological gall-bladder are even more noticeable in the cases in the whole follow-up than/

than in the cases of multiple stones considered above. It is seen that 64% are cured where the degree of pathology is marked as opposed to 39% where it is moderate. Also 12% remain in statu quo with a moderate degree of pathology compared with only 3% where it is marked. This suggests that better results are obtained in the more grossly pathological organ. This finding may be explained in two ways. Firstly, it may be that the more extensive pathological lesion has given rise to severer symptoms and thus the relief from its removal is correspondingly greater. Secondly, a much more likely explanation is to be found in the fact that the more grossly affected gall-bladder is often a non-functioning gall-bladder. If the gall-bladder is non-functioning, then the biliary tract has already adapted itself to work in such a way that the gall-bladder is not necessary. If such a state exists, as it does with a marked pathological lesion, then the actual removal of the organ will not alter the function of the biliary tract. On the other hand, when the pathological condition is only moderate, the gall-bladder may still be functioning, and so with its removal the whole biliary tract is upset and has to adapt itself to work under new conditions. It is possible/

possible that this gives rise to symptoms and so the success of removal is diminished.

The individual factors will now be considered in the cases with multiple stones.

Age. The results found at varying ages are shown in the following table:-

Results according to age in 87 patients with multiple mixed stones.

<u>Age</u>	<u>In statu quo</u>	<u>Improved</u>	<u>Very much improved</u>	<u>Cured</u>
20-29	1	-	-	3
30-39	2	2	2	6
40-49	3	5	7	7
50-59	3	6	9	16
60-69	-	3	3	7
70 onwards	-	-	-	2
	9	16	21	41

Considered as successful or unsuccessful the following are the results obtained:-

Success or otherwise in 87 patients with multiple mixed stones.

<u>Age</u>	<u>unsuccessful</u>	<u>Successful</u>
20-29	1	3 (75%)
30-39	4	8 (67%)
40-49	8	14 (64%)
50-59	9	25 (74%)
60-69	3	10 (77%)
70	-	2 (100%)

From this it would seem that age has little bearing on the results of operation in this group. The only notable fact is that the results in later years/

years are especially good, 77% being successful between 60 and 69 years, and both the cases over 70 years being cured by operation.

Sex. The sex incidence in this group was 72 females and 15 males, with the following results:-

Results according to sex in 87 patients with multiple mixed stones.

	<u>In statu quo</u>	<u>Improved</u>	<u>Very much improved</u>	<u>Cured</u>
Females	9	12	20	31
Males	-	4	1	10

These results expressed as percentages give:-

Females	12.5	16.5	28	43
Males	-	26	7	67

As is seen in reviewing the whole follow-up there is a larger percentage of males "cured" by operation and none remain in the group "In statu quo" where there are 12.5% of the females. It would therefore seem that the results in males are more satisfactory. Again the small number of males makes any definite conclusion unconvincing.

Build of the patient. In this respect the results appear to show little difference in relation to the build of the patient.

Results in 87 patients with multiple mixed stones according to the build of the patient.

	<u>Unsuccessful</u>	<u>Successful</u>
Obese	15	45 (75%)
Thin	4	13 (77%)

Duration of symptoms. In this respect the findings are of a similar type to those found in the series of all the follow-up cases.

Results/

Results in 87 patients with multiple mixed stones according to duration of symptoms

<u>Duration of symptoms</u>	<u>In statu quo</u>	<u>Improved</u>	<u>Very much improved</u>	<u>Cured</u>
Up to 1 year (28 cases)	4	4	4	16
1-5 years (24 cases)	2	5	5	12
More than 5 years (30 cases)	3	5	11	11

The only point which is at all noticeable in the above table is the fact that a larger proportion were cured when the symptoms were of less than 5 years' duration compared with cases where symptoms had existed longer than that. But again these results may be confusing owing to the small number of cases.

To sum up the results of operation in 87 patients where multiple mixed stones were found:-

(a) Operation proved successful in 71.2% of cases. In 47.1% patients were entirely relieved of symptoms. Only 10.4% derived no benefit from operation.

(b) Better results were found where the gall-bladder was found to be grossly pathological. 78.4% were successful where the gall-bladder was markedly pathological compared with 66% where the disease was moderate.

(c)/

(c) Age appears to have little bearing on the prognosis, and good results were obtained in the elderly.

(d) Sex shows slightly better results in the male.

(e) The build of the patient seemed to bear no relation to the results in this group.

(f) As regards duration of symptoms, better results were obtained where symptoms had existed less than five years.

(3) Single cholesterol stone. There were 25 patients followed up in whom a single cholesterol stone was found at operation. The results of operation were found to be as follows:-

Results of operation in 25 patients with single cholesterol stone.

<u>In statu quo</u>	<u>Improved</u>	<u>Very much improved</u>	<u>Cured</u>
1	5	6	13
4%	20%	24%	52%

From this it is seen that the results are very good in this type of case. Only 4% remain in statu quo, and 76% of the cases show definitely successful results, whereas 52% are cured by operation. These results compare favourably with the group in which multiple/

multiple stones were found, a smaller proportion remaining in statu quo and a larger proportion cured. Again in this group the grosser lesions of the gall-bladder would appear to give better results.

Results of operation in 25 cases with single cholesterol stone in relation to the pathology of the gall-bladder.

Gall-bladder wall	In statu quo	Improved	Very much improved	Cured
Moderately pathological (10 cases)	1 (10%)	4 (40%)	2 (20%)	3 (30%)
Markedly pathological (15 cases)	-	1 (7%)	4 (27%)	10 (66%)

The numbers are very small from which to draw a certain conclusion, but the fact that 93% of the cases with a markedly pathological gall-bladder were successful compared with 50% of those where the gall-bladder was only moderately pathological is very suggestive that a better result is obtained in the more advanced lesion.

In considering the individual factors in this group, it is not intended to draw out tables in full as the numbers are so small (25 cases) that any conclusions come to in this was are very apt to be fallacious. Therefore in this group and the succeeding groups where the number of cases is small also, the individual/

individual factors will be dealt with briefly, noting only those points which appear to warrant discussion.

The age incidence in this group showed that good results were obtained in the elderly. All four of the cases over 60 years gave successful results and of those between 40 and 60 years about 75% were successful. The age of the patient would therefore seem to be of little importance.

The sex factor in this group does not arise here as all the cases were females.

As regards the build of the patient, nearly all the cases in this group were of the obese type - 22 cases out of 24 in which this factor was known. No conclusion can therefore be come to in this respect as regards prognosis.

The duration of symptoms in this group showed 3 cases with symptoms of less than 1 year's duration, 10 from 1 to 5 years, and 12 over 5 years. In the 3 cases under 1 year, all were successful, whereas in those over 1 year about 75% were successful. No conclusion can be drawn from this.

To sum up the results in 25 patients where a single cholesterol stone was found:-

(a) Operation proved successful in 76% of cases.

In/

In 52% patients were entirely relieved of symptoms. Only 4% derived no benefit from operation.

(b) Better results were found where the gall-bladder was found to be grossly pathological. 93% were successful where the pathology was marked, compared with 50% where it was moderate.

(c) Age, sex, build, and duration of symptoms did not throw any light upon the results to be expected. It is noted that all the cases were females, mostly of the obese type.

(4) Single cholesterol stone and multiple mixed stones. As mentioned earlier in discussing the etiology of this condition, it follows as a complication of the single stone where conditions have developed in the gall-bladder in such a way that multiple stones are formed. The results to be expected in this group are therefore a sort of compromise between the single cholesterol stone group and the group with multiple mixed stones.

Only 9 cases in this group were successfully followed up, and the results were as follows:

	<u>Very much improved</u>	<u>Cured</u>
Total cases 9	3	6

From/

From this it is seen that all were successful, and that two thirds of the cases were completely relieved by operation. It would seem, therefore, that the only conclusion that can be drawn from this is that cases of single cholesterol stone which are complicated by the formation of multiple infected stones are suitable cases for operative treatment and that good results may be expected. Individual factors will not be considered in this group owing to the small number concerned.

(5) Pigment stones. There were only 4 cases in which pigment stones occurred which were followed up. Of these two cases remained in statu quo as a result of operation, whereas the other two were completely relieved.

(6) The stoneless gall-bladder. There were 37 cases followed up where at operation no stones were found, and the gall-bladder was found to be pathological. The end results in these cases were as follows:-

Results/

Results of operation in 37 patients with no stone

	<u>In statu quo</u>	<u>Improved</u>	<u>Very much improved</u>	<u>Cured</u>
Number of cases	3	10	11	13
Percentages	8	27	30	35

From these results it may be said that in the cases with no stone a successful result is obtained in 65% of cases, and unsuccessful in 35%. These findings are similar to those of Graham and Mackay (1934), who found in a series of 105 cases of stoneless gall-bladder that 65% were well or greatly improved as a result of operation. Mackay (1936), in another series of 243 cases found 60% relieved or greatly improved.

It is immediately clear that the results in this group are not so satisfactory as in the other two main groups - those with multiple mixed stones and those with a single cholesterol stone. For the sake of comparison the results in the three main groups are set out in the following table, expressed as percentages:-

Results of operation in the three main groups.

	<u>In statu quo</u>	<u>Improved</u>	<u>Very much improved</u>	<u>Cured</u>
Multiple mixed stones	10.4	18.4	24.1	47.1
Single cholesterol stone	4	20	24	52
No stone	8	27	30	35

When/

When these results are compared it is seen that the number of those with no stone completely relieved by operation (35%) was smaller compared with the 47.1% in multiple stones and 52% in the single stone. When considering those who were "cured" and those who were "very much improved" as successful cases, it is seen that the difference is less in the three groups:-

Multiple stones ...	71.2%	successful
Single stone	76%	"
No stone	65%	"

It would seem, therefore, that the removal of a pathological gall-bladder which contains no stones gives a large percentage of good results, but not so large as when stones exist.

These findings are in accordance with general opinion on this subject. Several persons have compared the results of operation in cases with or without stones, and agree that better results are obtained when stones are present. Wilson, Lehman and Goodwin (1936), in a follow-up of 447 cases, found that ^a satisfactory result was obtained in 79% of cases with stone compared with 64% with no stone. Davis (1928) in his series of 144 cases followed up by questionnaire found 79.7% of cases with stones cured, compared with 60% without stone.

The/

The reason why a definitely smaller percentage of the stoneless cases come under the heading of those completely relieved may be found in the fact, mentioned previously when discussing the results in relation to the degree of pathological change present in the gall-bladder wall, that in the stoneless case the gall-bladder may be still functioning when removed. When the biliary tract has to adapt itself to new conditions after removal, a dyskinesia may be caused and may give rise to symptoms which detract from the results obtained. If this be so, it would be expected in the stoneless case to get a better result in the cases where the pathological condition is more advanced, as in these cases the function of the gall-bladder is not likely to be so good. This is apparently confirmed in this group, if the small number of cases may be taken as a guide.

Success or otherwise of operation in 37 patients with no stone, in relation to the pathology of the gall-bladder.

<u>Gall-bladder wall</u>	<u>Unsuccessful</u>	<u>Successful</u>
Moderately pathological	11	20
Markedly pathological	1	5

Here it is seen that about two thirds of the cases are successful where the pathological condition is moderate, whereas five out of six cases are successful in those where/

where the pathological condition is advanced. The individual factors seem to indicate little in this group. The same findings approximately as regards age, sex, build, and duration of symptoms occur in this group as those previously dealt with.

To sum up the results of operation in 37 patients where no stone was found at operation:-

(a) Operation was successful in 65% of cases. In 35% there was complete relief of symptoms. 8% remained in statu quo.

(b) When compared with the groups with multiple mixed stones and single cholesterol stone, the results are found to be less favourable in the cases with no stone.

(c) The results appear to be better when the gall-bladder is found to be grossly diseased.

Cholesterosis. It is necessary to mention briefly the results found in the 9 cases of cholesterosis which were followed up. Four of these cases were completely relieved by operation, two very much improved, and the remaining three improved. Of the three cases in this group where stones were present, two cases were cured and the other one very much improved. No conclusions can, however, be drawn from this/

this small number.

Symptoms persisting after operation.

So far, in discussing the results of operation on the 162 patients who were followed up, the cases have been classified according to the general success of the operation. An attempt has been made to show what percentage of these cases benefitted from operation, and in assessing a prognosis the individual factors have been taken into consideration.

It now remains to discuss the cases in more detail, and find out what symptoms persisted after operation, and how these compared, in severity and frequency, with the symptoms prior to operation. It is also necessary to discuss the cause of these persisting symptoms.

If symptoms are present in a patient who has undergone cholecystectomy, they may be due to two causes:-

- (1) a lesion which is present in some organ other than the gall-bladder;
- (2) a lesion produced by operation
 - (a) functional lesion,
 - (b) organic lesion.

(1) A lesion present in some organ other than the gall-bladder. As has been pointed out when discussing the etiology, there is reason to believe that the person/

person who commonly suffers from chronic cholecystitis is the person who has over a long period abused the alimentary tract. It has been argued, for example, that obese persons, who are the common victims of gall-bladder disease, owe their gall stones not so much to their obesity as to a general alimentary abuse which has caused both the gall stones and the obesity to come into being. It is not surprising, therefore, that in such persons other lesions will co-exist along with that of the gall-bladder, and that these may give rise to symptoms even after the removal of a pathological gall-bladder.

The argument is that etiological factors which have brought about chronic cholecystitis have also produced other lesions which may continue to give trouble after cholecystectomy.

Lesions may also be caused in other organs as a direct result of the condition of the gall-bladder. Weir and Snell (1936) consider that pathological changes may occur in the bile ducts, liver and pancreas as a direct result of cholecystitis and cholelithiasis. Judd and Mentzer (1927), reviewing 1000 cases, found that 14% of cases with gall stones had hepatic lesions, and 16% had pancreatic lesions.

It seems clear, therefore, that some of the symptoms/

symptoms that persist after cholecystitis are attributable to a lesion in another organ. Such a lesion may be brought about either by the same etiological factors which brought about the gall-bladder disease, or may be a direct result of the gall-bladder disease.

(2) A lesion produced by operation. (a) Functional. If the gall-bladder is filled with stones or is in such a pathological state at operation that it is non-functioning, then its removal is unlikely to give rise to any great change in the function of the biliary tract. The tract has already adapted itself to function without the gall-bladder.

On the other hand, if at the time of operation the gall-bladder is still functioning, then its removal is going to necessitate a reorganisation of function of the biliary tracts. Up to the time of removal the gall-bladder has acted as a concentrator of bile and as a tension bulb. When it is no longer there the biliary tract has to adapt itself to function without the gall-bladder, and it is probable that inability to do this successfully accounts for post-operation symptoms in some cases.

According to Newman (1933), the gall-bladder and biliary/

biliary tract fill and empty under the influence of a carefully balanced nervous control by the sympathetic and parasympathetic nerves, supplemented by the hormone cholecystikinin. under normal conditions this control acts in such a way that bile is stored and concentrated when not required, and when a meal has been taken, is poured out into the duodenum.

After cholecystectomy this carefully balanced control is upset. There is at first an incompetence of the sphincter of Oddi and the result is that unconcentrated liver bile trickles continually into the duodenum. As time elapses the sphincter may again regain its tone, and the biliary tract adapt itself to new circumstances. If it does not do so, symptoms may arise, principally on account of the fact that a continuous flow of dilute bile cannot fulfil the demands of proper digestion.

What may be the result of this?

Bergh and Sandblom (1936) maintain that this incompetence of the sphincter of Oddi may persist and that the result is a back pressure from the duodenum and a consequent dilatation of the ducts. They studied this subject on dogs and found that there was evidence that the pressure within the ducts rose when the sphincter was destroyed. This may give rise to symptoms owing to distension of the ducts.

Another/

Another cause of distension of the ducts is when the sphincter of Oddi recovers its function too far and tends to go into spasm. This form of dyskinesia also will cause a dilatation and may give rise to symptoms.

It is seen, therefore, that the removal of a functioning gall-bladder requires a readjustment of the biliary tract. If this does not take place successfully, then symptoms may occur. If the gall-bladder at the time of operation is non-functioning, then this adjustment has already taken place, probably in gradual stages, and this may account for the fact that the results of cholecystectomy are more successful when the disease is gross, as has been found earlier in this series.

(b) Organic. At the time of operation there may be some damage to surrounding parts which later give rise to symptoms. Beye (1936) enumerates some of the conditions which may necessitate further operation. He mentions damage to the ducts causing some degree of kinking or stenosis. He also observes the part played by adhesions in the gall-bladder bed which may produce obstruction of the common duct, the pylorus or duodenum. These conditions are probably not very common/

common, and do not account for many of the symptoms which persist.

Having discussed broadly the various factors which may come into play in producing symptoms which exist after operation, the symptoms which were found in the 162 patients at the time of the follow-up will now be considered under the following heads:-

- (1) Pain in upper abdomen
- (2) Flatulence and distension
- (3) Intolerance to certain foods
- (4) Nausea and vomiting
- (5) Jaundice
- (6) Hernia.

(1) Pain in the upper abdomen. As was mentioned earlier, when discussing the symptomatology, pain or discomfort in the upper abdomen was the commonest symptom found prior to operation. It was found in 98.4% of all cases. The various mechanisms by which pain may be produced in gall-bladder disease were discussed.

In the follow-up it was found that a large percentage were now free from pain, and in the majority of cases where pain was still a symptom it was of a lesser degree. There were 24.7% of patients who still complained of pain, but in only 8.6% was this pain/

pain as bad as before operation.

The persistence of pain as a symptom in the various groups is shown in the following table:

Persistence of pain as a symptom in the 162 cases after operation.

	<u>Total cases</u>	<u>Pain still present</u>	<u>Pain as bad as before operation</u>
Multiple stones	87	22	8
Single cholesterol stone	25	5	1
Single cholesterol multiple stones	9	1	0
Pigment stones	4	2	2
No stone	<u>37</u>	<u>10</u>	<u>3</u>
	162	40 (24.7%)	14 (8.6%)

When considered as percentages and compared with the whole series prior to operation the findings in the three main groups are:-

Comparison of pain as a symptom before and after operation.

	<u>Percentage with pain before operation</u>	<u>Percentage with pain after operation</u>
Multiple stones	98	25
Single cholesterol stone	100	20
No stone	99	27

It is therefore seen that operation is to a great extent/

extent successful in relieving pain. Only about a quarter of those who originally suffered pain continue to do so after operation. Of that quarter only about a third still have pain which is as severe as it was before operation.

These results are fairly satisfactory, but the fact remains that there are still 24.7% who complain of pain after operation and the possible causes of this must be considered.

There were 14 patients (8.6%) in whom the pain was as bad as it was before operation. These cases were investigated carefully and the following conditions were found to exist.

	cases
Duodenal ulcer established by X-ray	2
Acidity, ? ulcer	2
? adhesions	1
? stone in duct	1
Chronic pancreatitis (verified by operation) .	1
Died 2 years after operation of acute infection of liver and bile ducts	1
Anaemia and chronic nephritis	1
Diabetes and high blood pressure	1
No apparent explanation	4

It is seen from this that an explanation of the persistent pain is to be found in some of these 14 cases in a lesion other than that of the gall-bladder, and apparently in these cases the removal of the gall-bladder in no way relieved the condition.

There/

There are 4 cases where there were no means of explaining the persisting pain. Possibly in these cases it might be attributed to a form of dyskinesia existing. In the patient with anaemia and chronic nephritis and the patient with diabetes and high blood pressure the explanation of the persisting pain is also obscure.

There were 26 patients who still had pain after operation, but of a lesser degree. These cases all gave a history of colic pain prior to operation. After operation the symptoms varied from a discomfort in the epigastrium to actual pain. The pain, however, did not persist as a true colic. The explanation in many of these cases may be in pyloric spasm due to a reflex upset. It may find its explanation in a degree of dyskinesia present, and may in some cases be due to a definite gastric or duodenal lesion. It was impossible in investigating these cases to say definitely what the commonest cause might be, but it is probably to be found in one or more of the conditions just mentioned.

To sum up what has been said in relation to pain existing after operation:-

(a) As a result of operation the symptom of pain is relieved completely in about three quarters of the cases/

cases.

(b) Pain persists in 24.7% of cases, but only in 8.6% is the pain as bad as before operation.

(c) The possible causes of pain persisting after operation have been considered.

(2) Flatulence and distension. In dealing with the symptomatology it was found that flatulence and distension was a common finding in chronic cholecystitis. It has been attributed mainly to aerophagia. It was found to be present in 73% of cases prior to operation.

In the follow-up, flatulence and distension persisted in a fairly large number of cases after operation.

Persistence of flatulence and distension as a symptom in the 162 cases after operation.

	<u>Total cases</u>	<u>Flatulence and distension still present</u>	<u>Percentage</u>
Multiple stones	87	44	50
Single cholesterol stone	25	10	40
Single cholesterol + multiple stones	9	2	22
Pigment stones	4	2	50
No stone	37	26	70.3
	<u>162</u>	<u>84</u>	<u>51.9</u>

It/

It is seen that 51.9% of patients still complained of flatulence and distension after operation, compared with 73% before. In the table it is seen that a considerable difference in the percentages exists in the different groups. It is very doubtful if any significance can be attached to this owing to the fairly small number of cases concerned in some of the groups. Possibly the high percentage in the cases with no stone may be due to the fact that a dyskinesia accounted for some of their symptoms prior to operation and continued to persist afterwards.

The results from operation as regards this symptom of flatulence and distension are disappointing. A little less than a third of the patients were relieved. The symptoms have been ascribed mainly to a nervous unbalance bringing about aerophagia. The explanation of their persistence in so many cases is probably to be found in the continuance of the nervous upset even after a pathological gall-bladder has been removed.

(3) Intolerance to certain foods. Before operation it was found in the series that 51% of patients suffered/

suffered from some degree of intolerance to certain foods. As mentioned in dealing with the symptomatology, these were mostly of the fat and greasy type.

The effects of operation in relieving this symptom were found in the follow-up to be disappointing. The number of patients who still complained of this symptom amounted to 46%. Thus there is seen to be a drop of only 5% before and after operation.

Obviously then, the removal of a pathological gall-bladder does not go far in helping to restore a normal digestion. The cause is probably that the symptoms are due either to a degree of chronic gastritis, or the inability of the bile to digest the fats properly, both of which conditions have continued after the removal of the gall-bladder.

(4) Nausea and vomiting. The causes of nausea and vomiting have been dealt with earlier in discussing the symptomatology. Vomiting has been ascribed as due either to a reflex condition brought about by biliary colic, or to chronic gastritis.

In the follow-up an attempt was made to distinguish which type of vomiting had been a symptom prior to operation. Whether it was the type which occurred in/
in/

in association with an attack of colic, or whether it was of the intermittent type, the histories given by the patients were of such a vague nature in many cases that it is impossible to produce any figures on this point. All that can be said is that both types of vomiting were commonly present before operation.

Vomiting which is due to the reflex set up by biliary colic is a symptom which will be to a great extent relieved by operation. The cause of the colic is removed and so also is the cause of this type of vomiting. In those cases where the vomiting was of the intermittent type associated with chronic gastritis the relief from operation is not so great.

It was found that in the 162 patients followed up there were still 30 (19%) who complained of vomiting. This compares with a figure of 74% who were found to suffer from vomiting in the series considered before operation.

When the symptom of vomiting is compared in this way before and after operation, the following are the results in the three main groups:-

Comparison/

Comparison of vomiting as a symptom before and after operation.

	<u>Vomiting before operation</u>	<u>Vomiting after operation</u>
Multiple stones	73%	18%
Single cholesterol stone	85%	24%
No stone	65%	16%

From this it is seen that in each of these groups approximately three quarters of the cases were relieved of vomiting as a symptom. It will be remembered that when discussing pain as a symptom persisting after operation it was found that approximately three quarters were relieved by operation. There may therefore be a close relation between these two, namely that the cause of the pain having been removed, the cause of reflex vomiting is removed also.

There were still 19% of the cases followed up who continued to suffer from vomiting. The explanation of this may be that in these cases the vomiting is due to a co-existing chronic gastritis.

Besides the 30 patients who complained of vomiting as a persistent symptom there were a further 18 (11%) who complained of nausea. This may be ascribed also to the existence of chronic gastritis where the condition was presumably not sufficiently severe/

severe to produce vomiting.

To sum up what has been said:-

(a) Vomiting as a symptom is relieved by operation in about three quarters of the cases.

(b) In many cases this relief is probably due to the removal of the cause of biliary colic which brought about reflex vomiting.

(c) This is borne out by the fact that approximately the same percentage were relieved of pain as were relieved of vomiting.

(d) In 19% of cases vomiting was a persistent symptom after operation. In a further 11% nausea persisted. This is attributed to the existence of an associated chronic gastritis.

(5) Jaundice. As has been found earlier, jaundice was a fairly common symptom prior to operation. The commonest cause has been ascribed to the blocking of the common bile duct by a stone. It would be expected, therefore, that this symptom would be relieved by operation.

In the 162 patients followed up there were only three who gave a history of recurrent jaundice. These cases were all cases in which multiple mixed stones were found. Of the cases in this group/

group, there were 41 who gave a history of jaundice prior to operation, and who were found in all but 3 cases to be relieved by operation.

Of the 3 cases where jaundice recurred, one died three years after operation with carcinoma of the head of the pancreas. A second died two years after operation with an acute yellow atrophy of the liver. In the third no apparent cause was found for the recurrent jaundice. It was unlikely to be due to a stone remaining in the bile duct as there was no pain after operation, and thus may have been due to a catarrhal jaundice.

It is clear, therefore, that jaundice is a symptom which is practically always relieved by operation.

(6) Hernia. Finally, the complication of post-operative ventral hernia will be considered. It is not to be wondered at that a hernia should be found in some of these cases after operation in view of the fact that they are commonly of the obese type with a large amount of superfluous fat on the abdomen. This makes operation more difficult, and also the muscular wall/

wall is probably not very strong in many of these cases owing to the tendency to wear tight corsets.

In the 162 patients followed up a ventral hernia was found in 9 patients (5.5%). In one patient a further operation was performed successfully with the relief of the hernia. In three others considerable discomfort arose from the hernia until a supporting belt was worn. In the remaining 5 patients the hernia did not give rise to trouble but a belt was worn.

SUMMARY/

SUMMARY OF PART II.

1. 162 patients operated on for chronic cholecystitis with or without stone have been followed up. The period which had elapsed since operation ranged from 1 to 10 years.
2. In 157 patients who came for operation with a primary diagnosis of chronic cholecystitis, with or without stones, it was found that operation was successful in 67%, and that 43% were completely relieved of symptoms.
3. When the results were considered in the light of the findings at operation, it was found that better results were obtained when stones were present. In 25 patients with a single cholesterol stone 76% were found to be successful. In 87 patients with multiple mixed stones 71.2% were successful. In 37 patients with no stone 65% were successful.
4. Complete relief from symptoms was found in 52% of patients with a single cholesterol stone, 47.1% with multiple stones and 35% with no stone.
5. Results of operation are more successful where the gall-bladder wall is grossly diseased. This is attributed to the fact that the more grossly diseased/

diseased gall-bladder is probably non-functioning. In 150 patients in all groups it was found that results were successful in 85% of cases with a markedly diseased gall-bladder compared with 63% successful where the degree of pathology was moderate.

6. Individual factors such as age, sex, build of the patient and duration of symptoms were considered. No very striking facts were observed, except that the prognosis is good in elderly people.
7. Consideration was given to symptoms persisting after operation. It was found that operation gave relief particularly in the symptoms of pain (75% relieved), vomiting (75% relieved), and jaundice (98% relieved). It is concluded that these symptoms are usually caused directly by the condition of the gall-bladder.
8. The symptoms of flatulence and intolerance of certain foods have been found to persist frequently after operation. Their persistence in many cases is ascribed to the existence of chronic gastritis or dyskinesia.
9. Post-operative hernia was found in 5.5% of all cases.

10./

10. It may be concluded that cholecystectomy performed in persons presenting symptoms of chronic cholecystitis is successful in a large number of cases. If it can be ascertained that stones are present and that the gall-bladder is grossly diseased, then very good results may be expected. The difficulty in deciding whether operative interference is indicated in many cases is because it is frequently difficult to assess exactly the condition of the gall-bladder and its contents.
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