OBSERVATIONS ON THE AETIOLOGY
OF CHOLELITHIASIS

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It is generally taught that cholelithiasis occurs characteristically in females who are "fat, forty, and fertile." This description implies that obese multiparous women who are approaching the climacteric are especially prone to gall-stone formation; if valid, therefore, it may lead to a more precise definition of the aetiology of gall-stones—for example, in terms of endocrine disturbances affecting this group of the population.

There have been several investigations into the incidence of biliary calculi among post-mortem specimens (Gross, 1929; Cleland, 1953; Joske *et al.*, 1954), but the results have little significance to the clinician who is concerned with the occurrence of stones in living patients. Nor do such studies in themselves throw much light on the aetiology of gall-stones. Griffin and Smith (1954) carried out a limited survey of the age and sex distribution of patients with cholecystitis. Their conclusions, however, are not necessarily applicable to patients suffering from cholelithiasis.

The present investigation was undertaken as a preliminary attempt to test the validity of the above-mentioned aphorism by comparing the age, sex, fertility, height, and weight distributions of a number of patients presenting with symptoms of cholelithiasis (subsequently confirmed radiologically or at operation) with the supposed distributions in the population at risk. It was found possible to collect complete and accurate data on only a limited number (783) of patients, but it is evident that if the "fair, fat, and forty" epigram is valid, either as a diagnostic aid or for heuristic purposes, it should be suggestively demonstrated by such a sample of unselected cases. An analysis was also made of the incidence of gall-stones among a group of post-mortem cases.

Data were derived from the records of patients suffering from cholelithiasis who entered the Queen Elizabeth and General Hospitals, Birmingham, between August, 1950, and December, 1954. It was not possible to delineate the exact population at risk, since some patients entering the hospitals live outside Birmingham, and some Birmingham patients are treated in other hospitals. We have therefore defined the *related incidence* in each age and sex group as the ratio of the number of cases in

each group to the population of Great Britain in the corresponding group (Census 1951, 1% sample). Our related incidence is therefore expressed as the number of cases in each group per million of the population of Great Britain of corresponding age group and sex. The Census gives no information concerning the parity distribution of women beyond the age of 49. This information was extracted from the *Report on the Family Census of 1946* (1954); the related incidence of married women with gall-stones in each age and parity group is thus expressed per 100 of the estimated population of married women in Great Britain in the corresponding group.

Records of all post-mortem examinations conducted at the hospitals between 1946 and 1954, inclusive, were also scrutinized and all cases noted in which calculi were found in the biliary tract. These data were related to the age and sex distribution of the total population examined after death at the two hospitals during the same period.

Clinical Material

1. Influence of Age and Sex on Related Incidence of Cholelithiasis

A total of 822 patients (163 male, and 659 female) suffering from cholelithiasis were admitted during the period. Of these, 39 were not included in the analysis because the age was not known (6), the marital status was not known (14), or because they were divorced or living apart (19). This left 783 cases (150 male, 633 female).

It may be seen from Table I and Fig. 1 that the disease occurred earlier and had a higher frequency in females than in males for all age groups. The related incidence was highest among females in the age group 50-59 and in males of the 70-79 group. The interval between the date of onset of symptoms and the date at which medical aid is sought is not known, but may be appreciable. It is possible, therefore, that Fig. 1 will describe the age and sex distribution of a population older than they were at the time they first experienced symptoms.

FIG. 1.—Related incidence of gall-stones by age and sex.

TABLE I.—Hospital Cases with Cholelithiasis

Age	Numbers								Related Incidence							
	Males				Females				Males				Females			
	Total	Single	Married	Widowed	Total	Single	Married	Widowed	Total	Single	Married	Widowed	Total	Single	Married	Widowed
0-19 ..	—	—	—	—	2	2	—	—	0.3	—	0.7	—	0.6	0.7	—	—
20-29 ..	1	—	1	—	26	3	23	—	7.4	—	2.3	—	7.4	2.3	—	—
30-39 ..	12	1	11	—	69	4	62	3	3.4	1.8	3.8	—	19.0	7.8	20.6	44.6
40-49 ..	29	—	29	—	138	9	126	3	8.1	—	9.3	—	37.3	16.1	43.1	16.9
50-59 ..	42	2	39	1	201	20	156	25	15.7	8.5	16.8	9.3	63.6	40.7	70.0	59.0
60-69 ..	41	4	35	2	135	13	78	44	21.4	24.1	23.1	8.9	54.4	32.2	60.5	56.4
70-79 ..	23	1	15	7	57	6	22	29	21.6	10.4	22.4	23.7	37.4	23.9	44.9	37.1
80-89 ..	2	—	2	—	5	—	1	4	8.6	—	21.5	—	12.0	—	18.5	13.7
All ages	150	8	132	10	633	57	468	108	7.7	1.2	10.9	1.2	29.3	8.5	38.2	42.2

Biliary calculi were found with consistently greater frequency in single females than males. These findings lend support to the view (Robertson and Dochat, 1944) that factors related to child-bearing are insufficient to account for the sex differences in the incidence of the disease.

2. Fertility

The fertility—that is, number of live-born children—of married women with cholelithiasis was calculated and related to a sample of the population of Great Britain described in the *Report on the Family Census of 1946*. Up to the age of 40 women with gall-stones had rather more children and beyond this age rather fewer children than in the sample (Fig. 2). The period 40–49 appears to be a time of transition. Cholelithiasis occurred more often in married women with children than in nulliparae up to the age of 50 (Fig. 3). After this age gall-stones occurred with greater frequency among the childless than among parous women. The fifth decade is the period during which most women experience the menopause, so that the years before 50 may be designated “pre-menopausal” and those beyond

FIG. 2.—Married women according to age and average number of live-born children.

FIG. 3.—Related incidence of cholelithiasis among married nulliparae and married parous women according to age.

FIG. 4.—Related incidence of cholelithiasis among married women according to age and parity.

50, “post-menopausal.” There is a marked difference in the distribution of gall-stones among married women of the post-menopausal years compared with married women of the pre-menopausal years. These differences are also shown in Fig. 4, where data for married women are broken down according to age and number of live-born children. Up to the age of 50 the frequency of gall-stones increases with parity. Among older age groups a reversal takes place, so that cholelithiasis decreases in frequency with parity. Once again the period of 40–49 (the menopausal years) appears to be a time of transition.

Gall-stones occurred with consistently greater frequency in married than in single women (Table I). The related incidence of the disease in widows, who for some part of their lives will have lived with their spouse, lies closer to that of married than to that of single women. The question arises whether the difference between married and single women is wholly accounted for by factors related to child-bearing, for among married women there is a definite relationship between parity and the incidence of biliary calculi. The related incidence of the disease among single women was thus compared with that for married nulliparae (Table II). Since the Family Census data did not include

TABLE II.—Related Incidence of Cholelithiasis in Single Women and in Married Nulliparae

Age	Numbers		Related Incidence	
	Single	Married Nulliparae	Single	Married Nulliparae
20-29	3	2	2.3	2.9
30-39	4	5	7.8	11.5
40-49	9	13	16.1	24.9
Ages 20-49 ..	16	20	6.9	12.1

single women, numbers were related to the distribution by age and marital state of the female population of Great Britain according to the Census of 1951. Unfortunately, the Census gives data on married nulliparae to the age of 49 only. Up to this age, though numbers are small, the direction of trends is constant and shows that gall-stones occurred with greater frequency in married nulliparae than in single women.

The results enumerated above suggest that among women both the marital state alone and the factors related to or consequent upon child-bearing may be of aetiological significance in the development of gall-stones.

Data for males are very few and there is no unequivocal relationship between the incidence of gall-stones and the marital state (Table I).

3. Weight and Height

A two-months sample of women entering hospital with cholelithiasis was reviewed for height and weight measurements, since these data were not recorded in the main group of clinical material. Measurements taken from the 20 patients in the sample were compared with those of a sample of the general population measured by Kemsley (1950). Since the subjects of Kemsley's survey were measured fully dressed, 6 lb. (2.7 kg.) in weight and 1½ in. (3.8 cm.) in height were added, as suggested by Kemsley, to the clinical data, which had been recorded from women who wore no footwear and were clad only in night attire.

The linear regression of height on age was calculated by the method of least squares for our own sample and compared with Kemsley's data (Fig. 5). The curves run closely together. There is no reason to suppose, therefore, that the heights of the patients differ from those of the general population.

The curve of quadratic type fitted to the age/weight data by Kemsley is shown in Fig. 6. The scatter of weight against age was plotted for our data, and a curve of the same order was fitted. It is evident from Fig. 6: (a) that below the age of 50 the women in our sample were almost without exception

heavier, and an average of approximately 25 lb. (11.3 kg.) heavier, than the average for women of comparable age in Kemsley's population; (b) that over the age of 50 there was no preponderance of heavier-than-average women in our population. These findings are also expressed by the curve fitted to our data, which is widely separate from that for Kemsley's data for ages below 50 and close at ages above 50.

Since the distributions of heights of the two populations are closely similar, the generalization which follows is that it seems probable that, below the age of approximately 50,

FIG. 5.—Cholelithiasis. Age/height curve of 20 female patients.

FIG. 6.—Cholelithiasis. Age/weight curve of 20 female patients.

women with biliary calculi are on the average more obese than women of comparable age in a sample of the general population. It would of course be desirable to verify this by examination of the weight/age distribution of a larger sample of cholelithiasis patients; but our results are particularly suggestive (a) in that they show a marked difference in the weight/age distribution before and after 50 years as compared with the estimated distribution for the

population; and (b) in the magnitude of the apparent difference for earlier age groups.

Lowe and Gibson (1955) have shown that at corresponding ages married women with children are heavier than those without. Before the sixth decade gall-stones were more frequent among married women with children than among married nulliparae (Fig. 3). After the menopause the reverse is true. The weight curves thus follow the direction which might have been anticipated on the basis of Lowe and Gibson's report.

Post-mortem Material

The records of all post-mortem examinations (3,523 males, 2,176 females) performed at the Queen Elizabeth and General Hospitals, Birmingham, during 1946-54, inclusive were examined. All specimens in which gall-stones were discovered (492) were recorded according to age and sex and related to the distribution by age and sex of all necropsy cases examined at the two hospitals during the same period (Table III). The bias introduced by the preponderance of

TABLE III.—Incidence of Gall-stones Among Necropsy Specimens

Age	Numbers		Incidence	
	Males	Females	Males	Females
20-29	—	4	—	31.0
30-39	7	10	23.7	50.0
40-49	15	23	26.8	67.9
50-59	46	77	50.9	153.1
60-69	56	83	56.6	143.6
70-79	66	75	116.4	206.0
80-89	15	15	217.4	238.1
All ages ..	205	287	58.2	131.9

FIG. 7.—Post-mortem material. Incidence of gall-stones by age and sex.

necropsies on male subjects was therefore eliminated. No information was available concerning marital state or parity.

Gall-stones were divided into two groups. Those cases in which the stones were found impacted, or in which other pathological features were noted in the biliary tract, were referred to as "symptomatic" stones, since symptoms referable to the gall-bladder were likely to have been present during life (Table IV). The term "asymptomatic" was used to refer to those calculi found in biliary tracts in which no coexisting pathology was apparent and which were unlikely, therefore, to have given rise to symptoms during life (Table V).

It was found (Fig. 7) that in both sexes the incidence of biliary calculi increases with age and is highest in the oldest age group (80-89). In this group stones occur almost as frequently in men as in women, but below this age among women consistently more than men. Fig. 8 shows that in both sexes gall-stones of the asymptomatic variety are more frequent in each age group than those of the symptomatic variety.

If the information derived from post-mortem material be combined with that from the clinical material, a more

accurate description of the distribution of gall-stones among a living population may be obtained than from consideration of either set of data alone. Thus gall-stones which occur in hospital patients produce symptoms, and in this sense are symptomatic. They do not, however, contribute to the symptomatic post-mortem group, since symptom-producing cholelithiasis is usually treated by cholecystectomy. If such patients come to the post-mortem room at all they are without a gall-bladder. Thus a case that certainly had symptoms will not be included among the post-mortem symptomatic group. The latter will therefore be inordinately small, and would be an inaccurate index of the frequency of cholelithiasis among a living population. This is particularly true of the younger age groups, when

TABLE IV.—Incidence of Symptomatic Gall-stones Among Necropsy Specimens

Age	Numbers		Incidence	
	Males	Females	Males	Females
20-29	—	1	—	7.8
30-39	1	3	3.4	15.0
40-49	5	11	9.0	32.5
50-59	23	29	25.4	57.7
60-69	26	33	26.3	57.1
70-79	31	34	54.7	93.4
80-89	5	7	72.5	111.1
All ages ..	91	118	25.8	54.2

TABLE V.—Incidence of Asymptomatic Gall-stones Among Necropsy Specimens

Age	Numbers		Incidence	
	Males	Females	Males	Females
20-29	—	3	—	23.3
30-39	6	7	20.3	35.0
40-49	10	12	17.9	35.4
50-59	23	48	25.4	95.4
60-69	30	50	30.3	86.5
70-79	35	41	61.7	112.6
80-89	10	8	144.9	127.0
All ages ..	114	169	32.4	77.7

FIG. 8.—Necropsy specimens with symptomatic and asymptomatic gall-stones.

the number of gall-bladders removed for cholelithiasis increase with age to the sixth decade in females and to the eighth decade in males (Fig. 1). After these ages the frequency of symptom-producing stones in the hospital population decreases so that data derived from post-mortem specimens becomes an increasingly accurate index of the incidence of the condition among the older age groups of a living population.

If symptom-producing gall-stones remained as frequent after the peak periods in the two sexes as before, the diminished frequency of cholecystectomy might be expected to lead to a marked increase in the number of necropsy specimens with stones of the symptomatic type. Though not pronounced in men of the ninth decade, there is a substantial increase in the incidence of symptomatic stones in women of the 70-79 age group (Fig. 8). These findings would be consistent with the view that the incidence of symptom-producing gall-stones increases to a certain age (sixth decade in females and eighth decade in males), but does not decrease in frequency thereafter. Beyond these ages, either because cholelithiasis is not diagnosed so widely or for some other reason, patients with symptomatic stones tend to retain their gall-bladders and tolerate their symptoms until death.

All the points mentioned in the preceding paragraph suggest that the incidence of symptom-producing gall-stones increases to a maximum at certain ages in the two sexes and does not decline thereafter. The older age groups have an increasing number of cases with asymptomatic, or silent, stones. The overall picture derived from the clinical and post-mortem material indicates that there is a steady increase in the frequency of cholelithiasis with age.

In the post-mortem material the percentage of males with gall-stones decreases to the sixth decade (Fig. 9). After this time the percentage increases, indicating that sex differences in the frequency of gall-stones diminish. Among the 80-89 groups gall-stones were found almost as frequently in men as in women, and in the asymptomatic groups (Fig. 8) actually exceeded them. The percentage of males among hospital patients with cholelithiasis (Fig. 10) increases with age. The rate of increase, as indicated by the slope of the curve, is accelerated in the age groups beyond the sixth decade.

These findings suggest that in the years following the female climacteric sex differences in the incidence of cholelithiasis diminish and virtually disappear in the oldest age group (80-89).

It may not be entirely coincidental that a similar pattern emerges concerning the frequency of another condition also related to cholesterol metabolism—namely, atherosclerosis. Oliver and Boyd's (1953) data show that the incidence of coronary artery disease in men and women also converges in the post-menopausal years. In the younger age groups coronary artery disease, unlike cholelithiasis, occurs more often in men than women. It may not be too far-fetched to suggest that in the younger age group there is a sex difference in the metabolism of cholesterol, one aspect of which is that women tend to excrete the sterol into the gall-bladder. This state of affairs might account for the high incidence of stones and low incidence of atherosclerosis in women.

TABLE VI.—Variety of Stones found in Gall-bladders of Necropsy Specimens

Variety of Stone	All Cases				Symptomatic				Asymptomatic			
	Males		Females		Males		Females		Males		Females	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Mixed ..	71	45.2	122	53.8	32	48.5	53	65.4	39	42.8	69	47.3
Pigment ..	59	37.6	70	30.8	24	36.4	17	21.0	35	38.5	53	36.3
Cholesterol ..	27	17.2	35	15.4	10	15.1	11	13.6	17	18.7	24	16.4
Total ..	157	100.0	227	100.0	66	100.0	81	100.0	91	100.0	146	100.0
Other ..	7		5		5		2		2		3	
Not known ..	41		55		20		35		21		20	

On the other hand, excretion may not occur so effectively in men, as a consequence of which there is a low frequency of gall-stones and a high incidence of atherosclerosis. After the menopause sex differences in cholesterol metabolism may gradually diminish. At this time the frequency of gall-stones and that of atherosclerosis in the two sexes converge. Consistent with this view is the finding that in females the concentration of serum cholesterol increases slowly to equal that of the males by the seventh decade (Jones *et al.*, 1951).

The types of stones found in the biliary tract of post-mortem specimens are classified in Table VI into mixed,

FIG. 9.—Post-mortem material. Percentage of males in each age group.

FIG. 10.—Hospital patients with cholelithiasis. Percentage of males in each age group.

pigment, and cholesterol. In each sex the mixed type of stone occurred with greatest frequency, the pigment type next, and the cholesterol stone least. The proportion of mixed stones in gall-bladders showing additional pathology ("symptomatic") was higher than in gall-bladders without additional pathology ("asymptomatic"). These findings suggest that an infected biliary tract is associated with an increased incidence of biliary calculi of the mixed variety. Furthermore, amongst the symptomatic group the proportion of mixed stones in females is substantially higher than in males. This state of affairs may be due to a higher frequency of gall-bladder infection in women than men.

Unfortunately no information is available concerning the frequency of the various types of stones present in diseased gall-bladders of living patients.

Discussion

The aphorism "fat, forty, fertile, and female" may describe a certain patient, but it does not describe the "typical" patient suffering from cholelithiasis. The use of the dictum is thus undesirable, since it tends to focus attention on a small group of those affected by the condition.

Some of the findings of the present study warrant further comment. First, however, it is necessary to remark briefly on two of the factors contributing to the formation of gall-stones, factors which appear to be of particular significance to the discussion which follows. It is generally accepted that biliary calculi may be produced (1) consequent on an increased excretion into the gall-bladder of cholesterol, and its subsequent precipitation out of solution; and (2) following infection of the gall-bladder (Cappell, 1951).

During the years of the menopause and immediately following it, great changes take place in the endocrine system. The ovaries gradually become atrophic (Engle, 1955), ovulation ceases, and the cyclic production of oestrogens and progesterone no longer takes place. These hormones appear to exert some influence on the blood cholesterol (Okey and Boyden, 1927); both are steroid compounds, the basic structure of which is the cholesterol molecule (Pincus *et al.*, 1955). Andrews *et al.* (1932) state that cholesterol-containing stones make up a large majority of all human gall-stones. It is not impossible, therefore, that the changing endocrine balance expresses a modification of cholesterol metabolism which is related in some way to the high incidence of biliary calculi in women during the immediately post-menopausal years. Furthermore, Pincus *et al.* have shown that the average androgen outputs of men and women converge in the later decades, when the output of oestrogens in women is actually lower than in men. Thus in the older age groups hormonal differences between the sexes become less clearly defined. These changes may be one of the factors responsible for the diminishing sex differences in the frequency of stones in the older age groups, and may also account for the relationship which has been suggested between gall-stone formation and atherosclerosis.

There are other factors, however, which must be considered in the possible relationship between endocrine metabolism and gall-stone formation. During pregnancy the ureters dilate. One of the causes of this dilatation is ascribed by Stuermer (1947) to the relaxing effect of the follicular and corpus luteum hormones on the smooth-muscle component of the wall of the ureters. The muscle of the bile ducts and gall-bladder are involuntary. Under the influence of the female sex hormones the muscle may relax, the biliary passages dilate, and the duodenal contents or pancreatic secretions regurgitate into the gall-bladder and there promote conditions favourable to the formation of calculi. In this connexion it may be significant that there is a higher proportion of mixed stones and hence, probably, a higher proportion of infection in the gall-bladders of women than of men.

It is difficult to account for the change in the incidence of gall-stones which occurs among married women after the menopausal years. The fact that the change occurs so abruptly is strongly suggestive of a relation with the climacteric, though the nature of this relation, if any, is by no means obvious.

It is concluded that the frequency of gall-stones increases with age in both sexes, but that among women these trends are modified by factors operating in and related to the child-bearing period.

Summary

An investigation was made into the incidence of gall-stones among hospital patients and post-mortem material.

Among hospital patients the related incidence was highest in females of the 50-59 age group and in males

of the 70-79 age group. The frequency was higher in women than in men for all ages, though the differences were very small in the 80-89 group. At ages below 50 gall-stones were more frequent in married women without children than in single women, and more frequent in married women with children than in married nulliparae. Beyond the age of 49 the related incidence was higher in married nulliparae than in married women with children.

It was argued that by combining data from clinical and post-mortem material a more accurate description of the distribution of gall-stones in the living population could be obtained than from consideration of either set of data alone. It was found that gall-stones increase in frequency with age, but that in females after the sixth decade and males after the eighth there is a high proportion of "silent" stones.

It is concluded that, in women, age changes in the incidence of cholelithiasis are modified by factors operating in and related to the child-bearing period.

In the years following the female climacteric, sex differences in the incidence of cholelithiasis appear to diminish until there are virtually no differences in the oldest age group.

At ages under 50, women with gall-stones were heavier than normal women of a comparable age and height. After 50, differences in weight were no longer apparent.

Analysis of stones found at necropsy showed the mixed type to be most frequent, the pigment type next, and the cholesterol type least frequent in both sexes.

Comparisons were drawn between the incidence of gall-stones and of atherosclerosis. Prior to the menopause there is a sex difference in cholesterol metabolism. It is suggested that this difference is expressed in women by a high frequency of cholelithiasis and a low frequency of atherosclerosis, whilst the reverse occurs in men. After the menopause, when hormonal differences between the two sexes become less clearly defined, the pathways of cholesterol metabolism may converge and so account for the diminishing sex differences in the related incidence of gall-stones and atherosclerosis among the older age groups.

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AETIOLOGY OF GRAVES'S DISEASE IN RELATION TO RECENT EXPERIMENTAL FINDINGS

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Emotional Trauma and Graves's Disease

The occurrence of hyperthyroidism following a severe fright was first reported by Parry in 1825, when he described the condition that was later to be called Graves's disease. Ever since this first account innumerable papers describing the condition have confirmed the frequency with which emotional or psychological upsets precede the onset of thyrotoxicosis. The French school of Charcot (1859), Trousseau (1867), and others believed the disease to be nervous in origin, either a form of hysteria or associated with a definite but undetermined lesion. Such further publications as those of Crawford (1897), Marañón (1921), Deutsch (1923), Lewis (1925), Bram (1927), Moschcowitz (1930), Goodall and Rogers (1933), and many others afford evidence of the relation between psychic trauma and the onset of the hyperthyroid state.

More recent work has been devoted to the type of individual and type of disturbance likely to be associated with thyrotoxicosis. Lidz and Whitehorn (1950) have described the type of patient in whom Graves's disease occurs as one highly dependent on interpersonal relationships for his security. This relationship is often familial, such as that of a daughter to mother or a mother to child. There is little latitude for adaptability, and the patient feels abject and helpless without such symbiotic relationship. These patients react in a highly emotional or exaggerated fashion to the disruption, or threat of disruption, of such a relationship. It is this type of emotional stress which threatens their security that is apt to precipitate Graves's disease.

It has been stated that the incidence of Graves's disease declines in times of economic depression, and it is possible that such social conditions bind families into closer-knit units. On the other hand, however, it is clear that emotional stress does not result in Graves's disease in a high proportion of the population. The aerial bombardment of large towns and cities during the last war did not appear to increase the incidence of thyrotoxicosis, though in some Scandinavian countries subject to occupation thyrotoxicosis is said to have reached epidemic proportions (see discussion following the paper of Lidz and Whitehorn, 1950). If emotional stress is an aetiological factor of importance, as seems likely, it is not the sole factor underlying the onset of the disease.

In view of the possible relationship between the central nervous system and thyroid activity, it became of interest to see the effect of prolonged (one to seven days) electrical stimulation of the hypothalamus on thyroid activity.