Epidemiology of Gallbladder Disease in an Appalachian Community

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GALLBLADDER disease is a major cause of morbidity and mortality in this country. Glenn has emphasized the burden placed on hospital facilities by the 300,000 cholecystectomies performed annually in the United States (*1*), and Ingelfinger has estimated that in this country alone 15 million persons have cholelithiasis (*2*). Although the medical literature contains many articles dealing with the clinical aspects of gallbladder disease, only a few deal with its epidemiology (*3, 4*).

In this paper, we describe the population of an Appalachian community which has an abnormally high incidence of gallbladder disease and examine epidemiologic factors that may contribute to occurrence of the disease.

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Community Setting

The community chosen for study was Rowan County, in the foothills of the Cumberland Mountains of northeastern Kentucky. The population of the county is roughly 14,000 with one-third living in the city of Morehead, the only urban area in this county. The residents are 99.8 percent white and primarily of Anglo-Saxon descent. Four general practitioners, two internists, and two surgeons staff the fully accredited local hospital, which is affiliated with the University of Kentucky College of Medicine. In 1969, cholecystitis accounted for 3.5 percent of this hospital's 2,484 admissions.

Methods and Materials

We designed a random household survey to interview 2.5 percent of the Rowan County residents (350 persons), to obtain information about gallbladder disease in this area. The average household in the county contains 3.85 persons; therefore, roughly 100 households were needed to obtain the necessary 350 persons. An additional 10 households were selected to insure an adequate number.

We stratified the survey sample according to population, with approximately two-thirds of the households interviewed from rural areas and approximately one-third from urban. The residents of 70 rural households and 40 urban households were to be interviewed.

Household maps of the city and county were divided into 1-inch grids, and the grids were numbered consecutively. The desired number of grids were then chosen by the use of a table of random numbers. The households within each grid were numbered, and two households were selected in each grid by the same random method. Thus, 35 grid areas were selected for the county, and 20 were chosen for the city. If the occupants were not present when the initial visit was made, subsequent visits were made until an interview was completed. In all interviews an adult member of the household was the respondent.

Basic demographic data such as age, sex, race, occupation, and parity of persons living in the household were obtained. A detailed series of questions were then asked in the vernacular to determine if any members of the family had ever had a cholecystectomy, oral cholecystography, or symptoms of cholecystitis. We also obtained information on the cholecystectomies of family members living outside the household. The name of the hospital or clinic where diagnosis and treatment occurred and the name of the physician were also obtained. To assure that all medical information concerning gallbladder disease was accurate, hospital records, including reports on operative procedures, pathology, and radiology were used to confirm the history obtained in the interview.

We classified gallbladder disease as definite or probable. Definite gallbladder disease included either, or both, a hospital record with a pathological evaluation or a documented record of a positive oral cholecystogram (defined as the presence

Table 1. Incidence and prevalence of gallbladder disease in Rowan County

Disease status	Rural			Urban			Total		
	Number at risk	Cases	Rate [1]	Number at risk	Cases	Rate [1]	Number at risk	Cases	Rate [1]
Prevalence of definite disease	230	22	96	119	8	67	349	30	86
Cholecystectomy		13			6			19	
Positive oral cholecystogram		9			2			11	
10-year incidence of definite disease	226	18	80	117	6	51	343	24	70
Cholecystectomy		9			4			13	
Positive oral cholecystogram		9			2			11	
Probable disease	208	8	88	111	5	45	319	13	40

[1] Per 1,000 population.

Table 2. Comparison of age-specific incidence rates of gallbladder disease history in three populations

Sex and age group	Framingham			Pima Indians			Rowan county		
	Number at risk	Number with disease	Percent	Number at risk	Number With disease	Percent	Number at risk	Number with disease	Percent
Men									
30–39	832	1	0.1	51	1	2.0	23	0	0
40–49	779	7	.9	45	1	2.2	19	0	0
50–74	725	23	3.2	57	7	[1] 12.3	45	2	4.4
Total	2,336	31	1.3	153	9	[1] 5.9	87	2	2.3
Women									
30–39	1,037	23	3.3	45	16	[1] 35.6	18	5	[1] 27.8
40–49	963	38	6.0	51	20	[1] 39.2	19	5	[1] 26.3
50–74	873	88	10.1	62	21	[1] 33.8	56	18	[1] 32.1
Total	2,873	149	5.9	158	57	[1] 36.0	93	28	[1] 30.1
Grand total	5,209	180	3.8	311	66	[1] 21.2	180	30	[1] 16.7

[1] $P<0.01$.

of stones or nonvisualization twice). These criteria closely corresponded with those used in two other epidemiologic studies of the disease—one of residents of Framingham, Mass. (*3*), and the other of the Pima Indians of southern Arizona (*4*). Regular occurrence of three of the four following symptoms indicated probable gallbladder disease: (*a*) belching or passing gas after eating fatty foods, (*b*) nausea and vomiting, (*c*) fever and chills with stomach pain or pain under the right ribs, and (*d*) pain under the right ribs.

Results

Of the 110 households originally selected, we completed interviews in 107 (97.2 percent). There were 349 persons in these 107 households, and they represented 2.5 percent of the county's population. Persons in one household refused to be interviewed, and two houses in the city had recently been destroyed.

Definite gallbladder disease. The total general prevalence rate of gallbladder disease was 86 cases per 1,000 based on 30 "definite" cases in 349 persons at risk (table 1). The 10-year incidence of gallbladder disease diagnosed between 1960 and 1969 was 70 cases per 1,000 (table 1). This rate is signficantly higher than the 2.05 yearly cases per 1,000 persons cited by the National Health Survey (*5*). Twenty persons interviewed had had cholecystectomies; however, we were unable to verify the type of operation performed on one patient in another State.

Of the 349 persons at risk, 19 had had cholecystectomies or cholecystitis that had been confirmed by a pathological examination. Pathological reports of these 19 patients revealed chronic cholecystitis in one, chronic cholecystitis with stones in four, and acute cholecystitis with stones in 14. The prevalence of cholecystectomies in all age groups was 54 per 1,000.

Fifteen persons had had an oral cholecystogram. One person had been informed that his X-ray did not show gallbladder disease, and the remaining 14 thought their X-rays showed an abnormal condition. A review of hospital records revealed that X-rays showed abnormalities for 11 of these 14 people and that the X-ray of one person was normal; we were unable to obtain two reports. Thus, the 30 definite cases included 19 persons who had had cholecystectomies and 11 persons whose oral cholecystograms showed disease.

Thirteen persons had probable gallbladder disease by our criteria, and, indeed, seven of these 13 had been told by a physician that they had gallbladder disease. Only three of those 13, however, had had oral cholecystograms. One cholecystogram was normal, and two reports were unavailable. These probable cases were included in the negative group for data analysis.

Population distribution of gallbladder disease in Rowan County. The general prevalence of definite gallbladder disease in the rural areas of Rowan County was 96 per 1,000 as opposed to a prevalence of 67 per 1,000 in the urban areas (table 1). This urban-rural inequality is statistically significant ($P < .05$). Our age-adjusted prevalence rate for the 180 persons over 30 was 167 per 1,000. The prevalence of gallbladder disease in this county remains relatively stable in the 30–50 age groups but rises after age 50 (table 2). This increase was marked in the women, and the 6 percent rise after age 50 is statistically significant ($P < .05$). This age-adjusted 10-year incidence rate was 138 per 1,000 (table 3).

Table 4 indicates the prevalence of definite gallbladder disease in various socioeconomic groups, using occupation of the head of the household as an indicator of socioeconomic status (*6*). The professional-managerial rate was extremely low (seven cases per 100 households), although the rate for the skilled workers' families was 28 cases per 100 households and for unskilled workers' families, 33

Table 3. Comparisons of prevalence and incidence of gallbladder disease in three areas, by age, sex, and mean pregnancies

Area	Age-adjusted rate		Sex rate	Mean pregnancies	
	Prevalence	10-year incidence	Female to male	Definite disease	No disease
Rowan County	[1] 167	[1] 138	14 to 1	6.50	3.27
Framingham study	[1] 39	[1] 45	5.4 to 1	2.87	2.24
Pima Indians	[1] 213	(2)	6.3 to 1	5.83	4.40

[1] Rate per 1,000 population.
[2] Data not available.

Table 4. Socioeconomic status of persons with history of definite gallbladder disease

Occupational group	Rural			Urban			Total		
	Number of households	Cases	Cases per 100 households	Number of households	Cases	Cases per 100 households	Number of households	Cases	Cases per 100 households
Professional-managerial	4	0	0	11	1	9	15	1	7
Skilled workers	16	5	28	7	2	28	25	7	28
Unskilled-unemployed	47	14	30	20	8	40	67	22	33
Total	67	19	58	38	11	77	107	30	68

NOTE: Socioeconomic status is based on occupation of head of household.

cases per 100 households. There was no statistically significant difference in the rates between the last two groups, but the difference between these two groups and the higher socioeconomic group is significant at the .01 level.

Table 3 shows that two men had definite disease as opposed to 28 women—a female to male ratio of 14 to 1. The parity of the women in the diseased and the nondiseased groups was examined closely to attempt to explain this unexpected distribution by sex. The women with definite gallbladder disease had a mean total of 6.50 pregnancies, and the nondiseased women had a mean of 3.27 (table 5). This divergence in mean parity is statistically highly significant ($P < .005$).

Eighty-five percent of the group with definite gallbladder disease had at least one immediate relative who had had a cholecystectomy, in contrast with 25 percent in the nondiseased group.

Table 2 compares age-specific prevalence rates in our study and previous epidemiologic studies in Framingham and among the Pima Indians. Both of the previous studies focused on persons over age 30 who were most at risk for gallbladder disease. Our age-adjusted prevalence rates (above age 30) were four times that of the Framingham residents but were less than those observed among the Pima Indians. The age-adjusted 10-year incidence rate of 138 per 1,000 in Rowan County is three times that reported in the Framingham residents. The ratios in the three studies by sex show a marked divergence in the Rowan County population. Although the mean pregnancies in both the Pima and Framingham groups show a statistically significant difference between those with and without disease, in neither study is this as marked as in Rowan County (table 3). The mean number of pregnancies in our group with definite disease is 1½ times that of the Pimas and three times that of the Framingham group.

Table 5. Parity and gallbladder disease

Population and diagnosis	Number	Mean pregnancies
Rural:		
Definite disease	22	6.74
No disease	46	3.70
Urban:		
Definite disease	8	5.86
No disease	31	2.77
Total:		
Definite disease	30	6.50
No disease	77	[1] 3.27

[1] Significant at $P < .005$.

Discussion

The magnitude of the incidence of gallbladder disease is not fully known. In many areas, including southern Appalachia, the incidence is believed to be higher than in the country as a whole, but few epidemiologic studies have been made to determine its severity. A non-Indian population with a high incidence of gallbladder disease would provide a suitable group for biochemical and physiochemical studies similar to those recently made of Indian populations (7).

Our study reveals the existence of "pockets" of gallbladder disease in groups other than the American Indians. Our age-adjusted prevalence rate of 167 per 1,000 (table 3) is four times that reported in the Framingham study (39 per 1,000) but is slightly lower than that experienced by the Pima Indians (213 per 1,000). Our adjusted 10-year incidence rate is also three times higher than that observed in the residents of Framingham. In the population we studied, gallbladder disease is predominantly a disease of parous rural women of low socioeconomic status.

The relationship of gallbladder disease to parity has been disputed despite the common clinical impression that women with cholecystitis are "fer-

tile." The predominance of gallbladder disease in women has been well established (*8*), but the role of pregnancy in gallstone formation is controversial (*9, 10*). Alterations of cholesterol metabolism and decreased gallbladder motility are observed during pregnancy, both possibly being significant factors in the etiology of gallbladder disease (*11, 12*). McSherry and co-workers (*13*) recently demonstrated that pregnant baboons have an increased cholesterol content of hepatic bile and a reduced amount of bile salt in gallbladder bile which would favor the development of gallstones.

In the Framingham and Pima Indian studies, parity was the only common factor studied that appeared to be a determinant of gallbladder disease. In our study, there was a strikingly significant association between the number of pregnancies and the presence of disease. This finding lends support to the theory that pregnancy is an important predisposing factor to gallbladder disease. In the Pima Indian study, the incidence of gallbladder disease was high even in young women and increased with age in both women and men (*4*). Pregnancy may lead to earlier formation of gallstones, thus causing an increased incidence of gallbladder disease in young women.

The incidence and prevalence of gallbladder disease in the rural population of Rowan County is 1½ times that in urban residents. This high rate might be related to a low socioeconomic status or high parity for rural residents, but table 4 shows that socioeconomic status operates independently of place of residence. One possible explanation for the increased incidence of gallbladder disease in the low socioeconomic group and rural residents is the diet of these persons. In other studies (*14,15*) of this area, it has been noted that most families in eastern Kentucky and rural Appalachia have excessive intakes of fats, meats, and cholesterol. The intake of cholesterol and fats alters the volume and content of bile in experimental animals (*16*), but various clinical studies of the effect of diet on gallstone formation have produced conflicting results. In the Framingham study, no difference was seen in the dietary habits of those with and without gallbladder disease. Friedman and co-workers, however, emphasized that the dietary histories had been generally taken after the diagnosis was made; therefore, many persons had deliberately altered their diet (*3*).

Using occupation of the household head as a measure of socioeconomic status (*6*), the low and middle class skilled and unskilled workers have a higher prevalence of gallbladder disease than do persons of the professional-managerial group (table 4). This finding differs from the Framingham data, which show no distinction in prevalence by socioeconomic class, and it may reflect the increased parity rate or the excessive intake of dietary fat in the low socioeconomic group, as well as some other factors not studied.

The finding of a history of cholecystectomies in the families of persons with gallbladder disease may indicate a biochemical defect in these families that is genetically determined. However, it may simply indicate that persons in the same family are subject to similar environmental conditions that cause gallbladder disease. Ultimately, the reason for the increased incidence of gallstone formation in certain populations will be determined by biochemical and physiochemical studies of these populations. Tompkins and co-workers (*17*) studied the ratio of phospholipids to cholesterol in patients with and without gallstones. Although bile cholesterol was similar in both groups, the phospholipids to cholesterol ratio was 6 to 1 in normal controls but only 2 to 1 in patients with gallstones.

Small and Rapo (*7*) studied a group of American Indians in the southwest who were known to have a high incidence of gallstones. They found a phospholipid to cholesterol ratio of 1.6 to 1 as compared with a normal of 3.4 to 1. Hepatic bile in this population was supersaturated with cholesterol, leading to speculation that the metabolic derangement was at the canalicular level. This concept is supported by Kurral and co-workers (*18*), who demonstrated an increased conversion of C_{14}-labeled acetate to cholesterol in the livers of patients with biliary tract disease.

We have examined epidemiologic factors that may contribute to the high incidence of gallbladder disease in Rowan County. We are now conducting further studies to elucidate biochemical abnormalities in this population which might be responsible for the high rate of gallbladder disease.

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RICHARDSON, J. DAVID (University of Texas Medical School), SCUTCHFIELD, F. DOUGLAS, PROUDFOOT, WARREN H., and BENENSON, ABRAM S.: *Epidemiology of gallbladder disease in an Appalachian community. Comparisons with the Framingham and Pima Indian studies. Health Services Reports, Vol. 88, March 1973, pp. 241–246.*

In 1969 gallbladder disease was four times more prevalent in an Appalachian community than in Framingham, Mass., 167 cases per 1,000 to 39 cases per 1,000. Among the Pima Indians, the rate was 213 cases per 1,000. The 10-year prevalence rate (1960–69) for persons over age 30 was 138 cases per 1,000. Gallbladder disease in this community is primarily a disease of parous women of low socioeconomic status. In the female to male ratio, more women than men were diseased. The diseased women had a mean of 6.50 pregnancies as compared with 3.27 pregnancies for the nondiseased.

Only seven cases per 100 households occurred in persons of professional-managerial families, whereas 28 cases per 100 households occurred in households of skilled workers, and 33 cases per 100 households occurred in households of unskilled workers. Areas exist with high concentrations of gallbladder disease. Further studies of such populations may elucidate the factors responsible for gallbladder disease.