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CHRONOLOGY OF CHOLELITHIASIS

Dating Gallstones from Atmospheric Radiocarbon Produced by Nuclear Bomb Explosions

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Abstract We investigated the natural history of cholelithiasis in 59 samples of stones from the gallbladder or common bile duct in 15 patients, using as a tracer for the timing of stone formation the ^{14}C released into the environment during nuclear weapons testing. The ages of the stones were correlated with the dates of onset of symptoms and with other clinical data.

None of 11 symptomatic patients had symptoms or complications until at least two years (mean \pm SD, 8.0 ± 5.1 years) after stone formation began. There was a lag time of 11.7 ± 4.6 years between initial stone formation and cholecystectomy. The growth rates of

stones from 11 symptomatic patients and 4 asymptomatic patients were similar (2.6 ± 1.4 and 2.6 ± 1.1 mm per year). Studies of two stones retrieved from the common bile duct showed that one had the same age as a cholecystic stone; the other, removed two years after cholecystectomy, apparently grew in the common bile duct.

The long latency period between the formation of gallstones and the onset of symptoms indicates that interruption of the natural progression of gallstone disease is potentially possible with medical therapy. (*N Engl J Med* 1986; 314:1075-7.)

SMALL¹ proposed that the formation and progression of cholesterol gallstone disease could be divided into five stages — metabolic, chemical, physical, growth, and symptomatic. To interrupt or reverse the natural progression of gallstone disease, the temporal relations between the stages of calculus formation should be defined, so that appropriate clinical strategies can be planned. We have developed a method to investigate the growth pattern of gallstones and to determine the “latency period” between stone formation and the onset of clinical symptoms. This method uses excess ^{14}C in the atmosphere, a result of atomic weapons testing, as a marker of the age of biologic material. Both symptomatic and asymptomatic patients were studied. Some patients had solitary stones, whereas others had multiple stones. In addition, two of the patients had stones in the common bile duct, which were compared with the cholecystic stones.

METHODS

Patients

Thirteen men and two women were studied. The diagnosis of cholelithiasis was confirmed at operation in 13 subjects and at autopsy in 2. None of the patients had been exposed to therapeutic or diagnostic radiochemicals. Patients were selected because they had no previous radioisotope exposure, they were willing to donate their gallstones for analysis, and information on previous cholecystography was available. The available stones were inspected carefully; those that contained substantial amounts of organic material were considered suitable for ^{14}C determination by the methods described below. Some of the patients were under the care of one of us (H.Y.I.M.), who interviewed and examined all the patients. On the basis of clinical findings, the patients were divided into two groups: those who were symptomatic (11 patients) and those who were asymptomatic (4 patients). The symptomatic subjects had unmistakable symptoms of gallbladder disease (including biliary colic) or complications due to gallstones, or both. The date of onset of symptoms was defined as the time when the symptoms were bothersome enough to cause the subject to seek medical attention. The asymptomatic subjects had no symptoms attributable to stones; their

stones were discovered incidentally during evaluation for other conditions, at operation, or at autopsy. All subjects were followed for at least six months postoperatively or until death, and their clinical courses were consistent with the classification of the disease.

Theory

Because of specific variations in ^{14}C over the past 30 years, it is possible to date a recent carbonaceous sample to within $1/2$ to 2 years.² The testing of thermonuclear devices in the stratosphere during the late 1950s and early 1960s resulted in the production of a large amount of ^{14}C . This ^{14}C was rapidly oxidized to $^{14}\text{CO}_2$ and was distributed in the troposphere, causing ^{14}C levels nearly to double over natural levels by 1963. Since the atmosphere provides CO_2 for plants, which in turn provide food for animals, the ratios of ^{14}C to ^{12}C in the biospheres are virtually identical to those in the atmosphere. During the initial input of excess $^{14}\text{CO}_2$ into the atmosphere in the 1960s, there was a delay of approximately two years between the deposition of ^{14}C in tree rings and the deposition in human organs (Fig. 1).³⁻⁸

Experimental Method

Large stones (>20 mm in diameter) were analyzed in concentric layers. Smaller stones, particularly those from a gallbladder that also contained one or more large stones, were also examined for comparison. Because of the limited material available from each small stone, multiple layers or whole stones were combined and analyzed as one sample. It was assumed that the growth characteristics within a family of small stones were similar, since each family had a uniform appearance, similar percentage compositions of cholesterol, and similar dissolution rates when placed in a bile acid solution.⁹

Carbon dioxide generated from each sample by combustion with oxygen was purified in a calcium oxide oven and by passage through activated charcoal, and was analyzed for ^{14}C with a gas proportional beta-counting system.¹⁰ Each sample was counted for a minimum of three days, and all measurements were corrected for isotope fractionation.¹¹ Dates were assigned to layers by matching the ^{14}C value of each sample to the corresponding date, with use of a composite curve for human blood, organs, and hair (Fig. 1). Two sets of dates were possible — one set from each side of the ^{14}C curve. Assignment of dates of the layers was based on the assumption that the nucleus of the stone had been present for the longest time. Therefore, the oldest date was assigned to the innermost layer; the outer layers were assigned more recent dates than the nucleus. Previous cholecystographic data provided additional aid in the assignment of dates. For example, Patient 5 had an oral cholecystogram in 1968 that demonstrated a single large stone. Excess ^{14}C values ($\Delta^{14}\text{C}$, Fig. 1) for the nucleus, the middle layer, and the outermost layer of his stone were 195, 350, and 680 parts per thousand, respectively. The dates assigned to these layers were 1960, 1963.8, and 1965.9 (as read from Figure 1), since cholecystographic data showed

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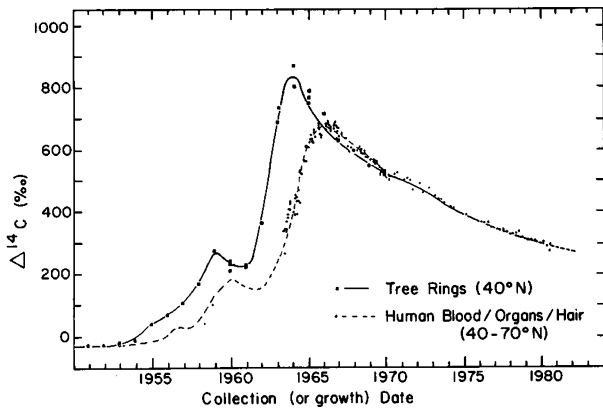


Figure 1. Levels of ¹⁴C in Two Carbon Reservoirs: Tree Rings (at Latitude 40° N) and Composite Human Blood, Organs, and Hair (at 40 to 70° N).

The curves are indistinguishable after 1970. The curve for human blood, organs, and hair was used to assign dates to gallstone layers in this study. By convention, the ¹⁴C concentration is expressed as Δ¹⁴C, which is the parts per thousand deviation from the ¹⁴C level in wood in the 19th century, before the Industrial Revolution; that level is defined as 0 parts per thousand.

that the stone had existed before 1968. Using each date as the time of formation of the midpoint of each layer, we calculated rates of growth between the innermost and outermost layers as Δ radius/Δ time (millimeters per year).

Results are expressed as means ± 1 SD. Statistical analysis was by unpaired t-test. A difference was considered significant when P was less than 0.05.

RESULTS

Chronology of Gallstones

Radiocarbon levels and their ages were determined in 59 samples of material from gallbladder and ductal stones. The results are summarized in Tables 1 and 2. Most stones grew over a number of years. The rate of growth of a stone may be determined by relating the

Table 1. Chronology of Gallstones from Symptomatic Patients.

PATIENT No.	STONES ANALYZED*	DATE OF FORMATION OF MID-PORTION OF LAYERS OF STONES†
1	Gallstone	1964.8; 1969.6
2	Gallstone	1963.7; 1964.0; 1964.4; 1964.8; 1967.3
3	Gallstone, 1 multiple	1964.6
	Gallstone, 2 multiple	1965.0; 1964.8; 1964.6; 1968.7
4	Gallstone, 1 multiple	1964.7; 1969.8; 1974.6
	Gallstone, 2 multiple	1965.3; 1972.6
	Gallstone, 3 multiple	1964.2
	Common-bile-duct stone	1964.0
5	Gallstone	1960.0; 1963.8; 1965.9
6	Gallstone	1973.9; 1973.7
	Common-bile-duct stone	1974.6; 1975.6
7	Gallstone, 1 multiple	1964.5; 1964.8; 1966.0
8	Gallstone	1967.1; 1969.9; 1969.4; 1971.1
9	Gallstone, 1 multiple	1968.8; 1972.5; 1973.7
10	Gallstone	1964.4; 1970.2; 1974.8
11	Gallstone, 1 multiple	1975.7; 1981.3

*Multiple small stones or corresponding layers of stones were combined and analyzed as one sample.

†The number of dates after each stone corresponds to the number of layers studied. The first date is that of the innermost layer.

period of growth to stone size. Mean periods of growth (7.8±4.9 years for symptomatic stones vs. 9.7±0.7 for asymptomatic stones) as well as growth rates (2.6±1.4 mm per year for symptomatic stones vs. 2.6±1.1 for asymptomatic stones) were similar in the two groups of patients.

Special Aspects of Chronology of Symptomatic Stones

The latency periods between stone formation and the "symptomatic" or "clinical" phase and between stone formation and the time of cholecystectomy were determined in symptomatic patients. None of the patients had unmistakable symptoms until at least two years after stone formation had begun; in many cases the period was considerably longer (mean, 8.0±5.1 years; range, 2.0 to 17.9). There was an additional delay of almost four years from the onset of symptoms to the time of cholecystectomy; the mean latency period between stone formation and cholecystectomy was 11.7±4.6 years (range, 3.5 to 20.4).

Table 2. Chronology of Gallstones from Asymptomatic Patients.*

PATIENT No.	STONES ANALYZED	DATE OF FORMATION OF MID-PORTION OF LAYERS OF STONES
A	Gallstone, 1 multiple	1962.3; 1968.2; 1970.4
	Gallstone, 2 multiple	1970.1
B	Gallstone, 1 multiple	1964.1
	Gallstone, 2 multiple	1959.4; 1964.0
C	Gallstone	1956.5; 1955.0; 1958.6; 1958.8; 1959.0; 1964.0
D	Gallstone	1964.4; 1965.0; 1965.3; 1968.4; 1971.6

*See footnotes to Table 1.

Chronologic Data on Large and Small Stones from the Same Gallbladders

In four patients, ¹⁴C determinations on gallstones of different sizes were obtained (Tables 1 and 2). In two symptomatic subjects (Patients 3 and 4), the stones appeared to have developed more or less simultaneously (in about 1964.4 in Patient 3 and 1965 in Patient 4), after which some stones continued to grow and attained a larger size than others. In two asymptomatic subjects (Patients A and B), the small stones were formed at a later time than the larger stones (eight years later in Patient A and five years later in Patient B). The development of these small stones corresponded to the time when the larger stones stopped growing (~1970 in Patient A and 1964 in Patient B).

Common-Bile-Duct Stones

Both common-bile-duct and gallbladder stones from two symptomatic subjects (Patients 4 and 6) were analyzed. In Patient 4, the stones were recovered during the same operation. The ductal stone and the gallbladder stones had formed at the same time (about 1964), suggesting that the ductal stone had originated in the gallbladder and had passed into the common duct. Patient 6 had a cholecystectomy in

August 1975; two small gallstones were found and analyzed. Two years later, a second operation was required because of cholangitis, and a common-bile-duct stone was recovered. The inner layer of this stone was formed in 1974.6, before the patient's first operation (August 1975). Its outer layer was dated at 1975.6. This suggests that the patient had a residual common-bile-duct stone that had grown since the first operation.

DISCUSSION

We have studied the chronology of gallstones, using profiles of ^{14}C incorporated into human organs from the $^{14}\text{CO}_2$ in the atmosphere resulting from nuclear bomb tests as a growth indicator. Stones from four asymptomatic subjects were present in the gallbladder for at least 10 years but still remained "silent." Stones from symptomatic patients were present for at least two years before the patient became aware of their presence. These data are consistent with those from previous epidemiologic studies of the natural history of gallstones. Many stones are discovered incidentally at postmortem examination, never having caused symptoms during life.¹² Gracie and Ransohoff¹³ reported the outcome of 123 subjects with gallstones (diagnosed by screening cholecystography) who were followed prospectively for up to 24 years; only 18 percent ever had severe biliary pain. Furthermore, our results are consistent with the findings on the temporal relation between the various stages of cholelithiasis reported in Pima Indians, a population known to have a high incidence of gallstones.¹⁴ Apparently, Pima Indians have a biliary lipid composition similar to that of whites until puberty, when the cholesterol saturation of their bile rises sharply. Several years later, gallstones are detectable; several more years later, some of the subjects become symptomatic.

It is not known whether any inherent characteristics of stones predispose them to cause symptoms. Bouchier and co-workers¹⁵ studied the number and size of gallstones and the gallbladder content of mucous substances and found no difference between symptomatic and asymptomatic subjects. We studied the period of growth and the rate of growth of gallstones and found no significant difference between our symptomatic and asymptomatic subjects. The variable growth rate of stones appears to range from 1 to over 4 mm per year (mean, 2.6 mm per year), which is not surprising in view of the multiple factors controlling stone size. Previous limited data obtained from measurements in serial cholecystograms indicated a growth rate of 0.6 mm per year for cholesterol gallstones.¹⁶ In the National Cooperative Gallstone Study, 38 percent of 305 placebo-treated patients had definitely increased stone size on repeat cholecystography performed after two years.¹⁷

Limited data are available on the chronologic re-

lations of multiple stones from four individual patients. In two symptomatic subjects, the stones were formed more or less simultaneously. Some stones then continued to grow and attained larger sizes. Presumably, the surface characteristics of these stones favored further precipitation. In two asymptomatic subjects, some stones appeared first and grew larger. Multiple small stones then developed; at the same time the larger stones stopped growing, presumably because all further precipitation occurred on the small stones. There are other reasons for a stone to stop growing, however, such as formation of a calcium rim that is resistant to the addition of further concretion or desaturation of bile as a result of metabolic changes (e.g., weight reduction). More patients will have to be studied before we can determine whether our preliminary finding of an apparent difference in the developmental pattern of multiple stones between symptomatic and asymptomatic subjects is of any clinical importance.

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REFERENCES

- Small DM. The formation and treatment of gallstones. In: Schiff L, Schiff ER, eds. *Disease of the liver*. 5th ed. Philadelphia: JB Lippincott, 1982:151-66.
- Cain WF, Suess HE. Carbon-14 in tree rings. *J Geophys Res* 1976; 81:3688-94.
- Nydal R, Loveseth K. Tracing ^{14}C in the atmosphere 1962-1980. *J Geophys Res* 1983; 88:3621-42.
- Harkness DD, Walton A. Further investigations of the transfer of bomb ^{14}C to man. *Nature* 1972; 240:302-3.
- Stenhouse MJ, Baxter MS. Bomb ^{14}C as a biological tracer. *Nature* 1977; 267:828-32.
- Broecker WS, Schulert A, Olson EA. Bomb carbon-14 in human beings. *Science* 1959; 130:331-2. abstract.
- Nydal R, Lövsøth K, Syrstad O. Bomb ^{14}C in the human population. *Nature* 1971; 232:418-21.
- Linick TW. La Jolla radiocarbon measurements X. *Radiocarbon* 1984; 26:75-110.
- Park Y-H, Igimi H, Carey MC. The "mirroring" of gallstones: description of a novel silvering method to determine the surface area of an irregular object: in vitro demonstration that multiple gallstones from the same gallbladder dissolve in unsaturated "bile" at the same rate. *Gastroenterology* 1983; 83:1071-8.
- Friedlander G, Kennedy JW, Miller JM. *Nuclear and radiochemistry*. 2nd ed. New York: John Wiley, 1964:144-6.
- Olsson IU, Osadebe FAN. Carbon isotope variations and fractionation corrections in ^{14}C dating. *Boreas* 1974; 3:139-46.
- Newman HF, Northrup JD. Autopsy incidence of gallstones. *Int Abst Surg* 1959; 109:1-13.
- Gracie WA, Ransohoff DF. The natural history of silent gallstones: the innocent gallstone is not a myth. *N Engl J Med* 1982; 307:798-800.
- Bennion LJ, Knowler WC, Mott DM, Spagnola AM, Bennett PH. Development of lithogenic bile during puberty in Pima Indians. *N Engl J Med* 1979; 300:873-6.
- Bouchier IAD, Rhodes K, Brien M. A study of symptomatic and "silent" gallstones. *Scand J Gastroenterol* 1968; 3:299-304.
- Wolpers C. Morphologie der Gallensteine. *Leber Magen Darm* 1974; 4:43-57.
- Thistle JL, Cleary PA, Lachin JM, et al. The natural history of cholelithiasis: the National Cooperative Gallstone Study. *Ann Intern Med* 1984; 101:171-5.