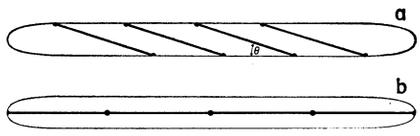

Fig. 3. (*a*) Model of a smooth muscle fiber in which the contractile units are in parallel with one another and insert obliquely into the sides of the fiber. If θ is 10 degrees, then the maximum tension of this fiber in the longitudinal direction is 4 cos 10 = 3.94 times that of the fiber in *b*. (*b*) Model of a striated muscle fiber in which the same number of contractile units are in series with one another and insert into the ends of the fiber.

A second consequence is that the extent to which the "smooth fiber" in Fig. 3*a* will shorten is approximately equal to the shortening of one contractile unit whereas the shortening of the "striated fiber" in Fig. 3*b* is equal to four times the shortening of each contractile unit. Furthermore, assuming that the velocity of shortening of each contractile unit is the same in both fibers in the unloaded state, it follows that the velocity of shortening of the "striated fiber" is approximately four times greater than that of the "smooth fiber."

Thus, the design of the "smooth fiber" model permits it to exert a relatively large force through a short distance at low velocity. In contrast, the "striated fiber" model exerts a relatively small force through a long distance at high velocity. Both fibers are capable of doing the same amount of work. However, approximately four times as many of the "striated fibers" in Fig. 3*b* would be needed to develop the maximum tension of the one "smooth fiber" in Fig. 3*a*. Consequently, during isometric contraction, a muscle composed of "striated fibers" would be expected to be less efficient and therefore to generate more heat than one composed of "smooth fibers", for production of the same tension.

In Fig. 3, pure series and pure parallel arrangements of contractile elements are illustrated. The same considerations apply equally well, however, to fibers in which there are combinations of series and parallel arrangements. If, for example, the contractile units in a smooth fiber were relatively short, and the oblique distance from one side of the fiber to the other were traversed by a row of such units, then the adjacent rows would be in parallel, but the units within each row in series. The importance of oblique orientation of the contractile elements is simply that it permits a greater proportion of them to be in parallel—that is, the rows are shorter, but more numerous than they would be with no obliquity, and as a result the fibers can develop a correspondingly greater tension. In a muscle fiber 50 times as long as it is wide, whose contractile elements, regardless of their size, are at an angle of 10 degrees to the long axis of the fiber, the maximum tension which the fiber can develop is almost ten times greater than it would be if the same number of contractile elements were parallel to the fiber axis (*8*). An obliquity of only 1 degree would still increase the contractile force of the fiber twofold.

These considerations apply to single fibers. On a grosser level, various combinations of series and parallel arrangements occur among the muscle fibers themselves (*9*). Thus the properties of a whole muscle are a function not only of the properties of the component fibers but also of the arrangement of the fibers within the muscle. Prediction of the characteristics of a muscle therefore requires information about both. The "smooth fiber" model presented here permits prediction of the characteristics of single fibers, and provides a simple structural basis which accounts, at least in part, for several well known physiological properties of smooth muscle.

JACK ROSENBLUTH

Department of Anatomy,
Albert Einstein College of Medicine,
New York 10461

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7. In order to simplify this discussion, the contractile elements of the two models are assumed to be equivalent except with regard to their orientation. This assumption is not intended to suggest that there are not also other differences between the contractile elements of smooth and striated muscle fibers which may underlie differences between the properties of the respective fibers.
8. If the fiber is assumed to have the shape of an elongated rectangular solid of length L and width W and to contain contractile units which are at angle θ to one longitudinal plane through the fiber and parallel to the perpendicular longitudinal plane, then the ratio R of maximum axial tension in this fiber to that in an equivalent fiber with no obliquity of the contractile units can be calculated from the expression
$$R = \frac{L}{W} \sin\theta \cdot \cos\theta + (\cos\theta)^2$$
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10. Supported by NIH grants 5T1-MH-6418 and NB-05219.

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Gallstones Produced Experimentally by Lithocholic Acid in Rats

Abstract. *Administration of lithocholic acid (1 percent in the diet) consistently produces choledocholithiasis in 8 weeks in rats on an 8-percent protein diet. The gallstones consist predominantly of the calcium salts of free and glycine-conjugated lithocholic and 3α,6β-dihydroxy-5β-cholanic acids. Conjugation of bile acid with taurine can be enhanced and stone formation can be inhibited by an increase in the dietary protein or by a diet supplemented with taurine.*

Lithocholic acid (*1*) is a highly irritating steroid acid that produces inflammation of the liver and other tissues and hyperplasia of the bile ducts in several species. Rats are relatively resistant to this effect, possibly owing to the peculiar ability of rat liver to hydroxylate (and thus presumably inactivate) lithocholic acid. In experiments designed to overcome this resistance by feeding large amounts of lithocholic acid, common duct gallstones were observed in 100 percent of treated rats after 8 to 16 weeks. I now report on the production of gallstones induced by lithocholic acid and on their chemical composition, their pathogenesis, and their prevention by an increase in the sulfur-containing amino acids in the diet.

A control group of 20 young (150- to 200-g) Sprague-Dawley rats of both sexes was fed an "8 percent Low Protein" (*2*) diet for 4 months, and a similar group was fed the same diet containing lithocholic acid (1 percent). The 16 surviving rats treated with bile acid had markedly distended common bile ducts filled with single or multiple, round or faceted, gallstones (Fig. 1). None of the corresponding con-

Table 1. Effect of dietary protein and taurine supplementation on gallstone formation and bile acid conjugation with taurine.

Diet composition			Animals (No.)	Gallstones (%)	Urinary taurine (μmole/24 hr)	C^{14}-bile acids conjugated with taurine (%)
Protein (%)	Lithocholic acid (%)	Taurine (%)				
8	0	0	9	0	15.9	12.7
8	1	0	9	100 (large)	17.6	11.1
27	1	0	10	20 (small)	31.0	50.4
8	1	1	10	0	69.7	62.7

trol rats showed such changes. Most of the calculi observed in the treated rats were yellow, but some varied in color from green to black. Analysis of stones from individual animals gave an average composition of 70 percent bile acids, 12 percent ash, 0.7 percent total lipid (including cholesterol), and 0.14 percent bilirubin. The major anionic and cationic components were (meq/g): bile acids, 1.6 ± 0.2; Ca, 1.6 ± 0.2; Na, 0.32 ± 0.18; and K, 0.02 ± 0.01 (means ± standard deviations). The bile acids were analyzed by thin-layer chromatography and assayed enzymatically with 3α-hydroxysteroid dehydrogenase (*3*). The extent of conjugation varied from predominantly glycine-conjugated to predominantly free bile acids; practically no taurine conjugates were observed. The bile acids, after alkaline hydrolysis, consisted of roughly equal quantities of lithocholic acid and its derivative, 3α, 6β-dihydroxy-5β-cholanic acid. In addition, small amounts of hyodeoxycholic, chenodeoxycholic, and cholic acids were present. The important role of the 6β-hydroxylating system under these circumstances was an unusual and highly interesting finding.

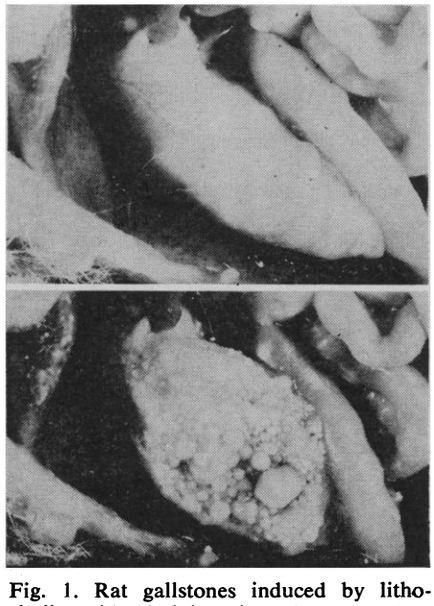

Fig. 1. Rat gallstones induced by lithocholic acid administration. Common duct before and after opening to reveal stones.

Since bile acids normally are conjugated to a large extent with taurine in the rat liver, the unusual absence of taurine conjugates in the stones raised the question of whether glycine conjugates were being selectively incorporated into the stones, or whether, under these experimental conditions, taurine conjugation was impaired. To answer this question, the effect on stone formation of supplementing the diets with protein and taurine was studied in four groups of rats (male and female) over an 8-week period (Table 1). The rats were then killed and autopsied. In each group two males and two females, prior to their being killed, were given an injection of sodium lithocholate-24-C^{14} intraperitoneally. Their urine was collected and examined for taurine. They were killed 3 days later, and the intestinal contents were analyzed for taurine- and glycine-conjugated bile acids which bore the C^{14} label (Table 1). Animals on a low protein diet, either with or without lithocholic acid, had a markedly reduced capacity to conjugate labeled bile acids with taurine. However, the animals which formed stones had retained some capacity to conjugate with taurine, so that the absence of taurine conjugates in the stones indicated preferential incorporation of free and glycine-conjugated compounds.

Apparently, enhanced taurine conjugation, presumably secondary to the increased supply of taurine formed from the larger cystine and methionine content of the 27-percent protein diet or present in the taurine supplemented diet, was associated with protection against choledocholithiasis induced by lithocholic acid. Histological sections of livers in animals in which stones were formed showed precipitates, presumably the calcium salts of free or glycine-conjugated lithocholic and 3α, 6β-dihydroxy-5β-cholanic acids (which lack the strongly polar taurine sulfate group and therefore are less soluble than taurine-conjugated bile acids), in the small hepatic ducts. These precipitates apparently grew in size and accumulated in the common bile duct. The situation is somewhat analogous to the production of gallstones in rabbits after the administration of cholestanol (*4*), where a major factor appears to be precipitation of the calcium salt of glycoallodeoxycholic acid in the gallbladder (*5*). In addition, the inflammatory characteristics of lithocholic acid and its derivatives may have contributed to stone formation by the production of cellular debris, adjacent—as seen by histological techniques—to the precipitated steroid in small bile ducts.

Lithocholic acid administration constitutes a unique method of consistently producing experimental choledocholithiasis. Gallstones with a composition closely simulating that of naturally occurring pig gallstones have been induced by oral administration of an endogenous bile acid which participated directly in the stone formation. The pathogenesis of these lithocholic acid–induced gallstones may have relevance to the etiology of certain types of cholelithiasis in humans.

ROBERT H. PALMER
Department of Medicine and
Argonne Cancer Research Hospital, University of Chicago, Chicago, Illinois 60637*

References and Notes

1. Trivial names of bile acids used in the text are as follows: *lithocholic acid*, 3α-hydroxy-5β-cholanic acid; *hyodeoxycholic acid*, 3α,6α-dihydroxy-5β-cholanic acid; *chenodeoxycholic acid*, 3α,7α-dihydroxy-5β-cholanic acid; *cholic acid*, 3α,7α,12α-trihydroxy-5β-cholanic acid.
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