meq/kg. Analogous to the lean body mass relations found by Forbes and Anderson, is the resulting equation

$$CM = \frac{K}{92.5} = 0.0108 \times K \qquad (3)$$

In its basic form of

$$CM = \frac{K}{K_{CM}} \qquad (3a)$$

this equation is also applicable for certain animals, since a relation comparable to Eq. 2 is found also for rats, rabbits, and pigs (*7*). Furthermore, it can be inferred from Eqs. 1 and 2 that the intracellular potassium concentration will be 138 meq/lit. of fluid, the extracellular proportion of potassium being neglected. Since the organs and muscular tissue grow at a different rate (as can be deduced from the different allometric functions), the variation of tissue proportions in *CM* does not influence the total intracellular potassium concentration. Thus, it must be concluded that potassium concentration will not only remain constant during growth, but also that it is equal in all cells.

To establish the relation between *CM* and lean body mass, it must be considered that lean body mass consists of *CM*, extracellular fluid, and extracellular solids (S_e). The extracellular fluid (*ECF*) can be calculated from the body surface area (*SA*):

$$ECF = 6.04 \times SA \qquad (4)$$

(*SA* being calculated according to the equation of Dubois and Dubois (*8*) in square meters). This function was developed with the determination of the thiosulfate space (*3*). It is as valid with adipose as with dystrophic persons.

The relation of extracellular solids and *CM* should be a linear one, as the composition of *W* minus *ECF* is a rather constant one during growth (*3*). The corresponding relation

$$S_e = 0.1 \times CM \qquad (5)$$

is only assessed. A deviation up to 0.04 *CM* is possible. The resulting function for lean body mass (*LBM*) is

$$LBM = 1.1\ CM + ECF = 0.0119\ K + 6.04\ SA \qquad (6)$$

The lean body mass of a male adult (weight, 68.9 kg; height, 172.7 cm; *K*, 3870 meq) will thus be 57.0 kg and the lean body mass of a newborn infant (weight, 3.0 kg; length, 49 cm; *K* calculated from Eq. 2, 130 meq) is 2.7 kg. These *K*/*LBM* quotients correspond very well to those of Forbes *et al.* (*1*). I found 67.9 meq/kg compared with 68.1 meq/kg (*1*); for newborn infants my value is 48.1 meq/kg, while that of Forbes *et al.* (*1*) is 48.0 meq/kg.

The total body water (*TBW*) is calculated according to the function:

$$TBW = 0.67\ CM + ECF = 0.0072\ K + 6.04\ SA \qquad (7)$$

The total body water for the examples given would thus be 38.8 and 2.09 liters, respectively, and consequently the water content of lean body mass would be 68.1 and 77.4 percent.

Finally, *CM* must be examined as a basis for allometric functions. Although Eq. 1 is an allometric function biologically, it does not appear to be very reasonable, because, during growth, weight (*W*) develops as a function of *CM* and not vice versa. Thus the equation should read:

$$W = 2.16 \times CM^{0.00} \qquad (1b)$$

If, however, weight is a function of *CM*, all allometric functions should be based on *CM*. The original form of the allometric function is transformed from

$$Y = a \times W^b \qquad (8)$$

to read

$$Y = a_1 \times CM^{b_1} \qquad (8a)$$

where *Y* is the relative growth of the body size; *a* and *b* can be transformed into a_1 and b_1 by a simple calculation process, as was demonstrated by Adolph (*9*). Differentiated by time and divided by itself, Eq. 8a will read

$$\frac{dy}{dt} \times \frac{1}{y} = b_1 \times \frac{dCM}{dt} \times \frac{1}{CM} \qquad (8b)$$

That is, an allometric function is given, if the relative growth of the body size examined has a linear relation to the relative growth of *CM*.

Allometric organ functions do not offer a basis which would be very advantageous for the assessment of the capacity of these organs (for example, renal function is related to body surface area since the weight of the kidneys is proportional to $W^{0.7}$). During growth the amount of cellular mass in the organs may change considerably. It is much more advantageous to calculate the *CM* proportion CM_{org} present in an organ from its potassium content, K_{org}, according to

$$\frac{K_{org}}{K_{CM}} = CM_{org} \qquad (9)$$

since the cells contained in an organ are doing the work of the organ. The corresponding allometric function would thus read

$$CM_{org} = a \times CM^b \qquad (10)$$

Finally, it should be noted that cell mass provides a good reference standard for the total energy conversion, for renal functions, and elimination of creatinine.

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12 April 1965

Smooth Muscle: An Ultrastructural Basis for the Dynamics of Its Contraction

Abstract. *Electron micrographs of vertebrate and invertebrate smooth muscle indicate that the myofilaments are oriented obliquely to the long axis of the muscle fibers containing them and insert along the sides of the fibers. As a result, a greater proportion of the contractile elements are in parallel with one another and a smaller proportion are in series than would be possible if the myofilaments were strictly parallel to the fiber axis. From this ultrastructural organization it is possible to predict several well-known, but previously unexplained, physiological properties of smooth muscle.*

Smooth muscle is distinguished from striated muscle not only by its histological appearance but also by its physiological properties, notably its ability to sustain forceful contractions for prolonged periods with a minimum expenditure of energy and its relatively low velocity of shortening (*1*). Ultra-

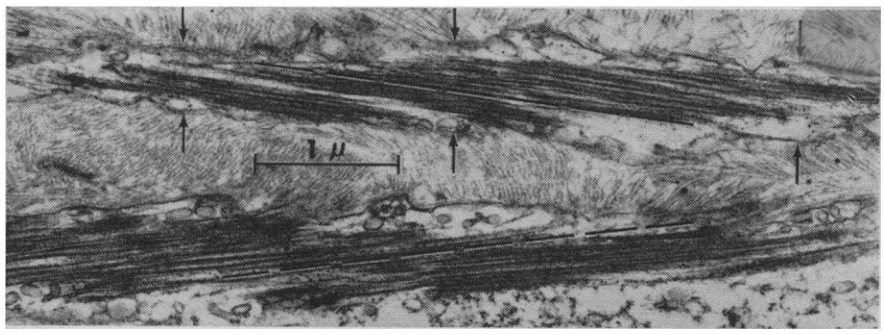

Fig. 1. Two *Aplysia* muscle fibers. Each contains a sheaf of coarse paramyosin filaments which are oriented obliquely (dashed lines) with respect to the fiber axis. Arrows dicate the plasma membrane of the upper fiber.

structural studies of smooth muscle have not heretofore helped to account for these properties, but have demonstrated only that the specific arrangement of myofilaments that characterizes striated muscle (*2*) is absent from smooth muscle (*3*). In this report observations are presented on the orientation of the myofilaments in two smooth muscles, and a corresponding structural model is described that accounts in a simple manner for several of the properties of smooth muscle.

Circular muscle from the jejunum of the toad *Bufo marinus* was fixed with buffered glutaraldehyde followed by osmium tetroxide. Epineurial muscle from the gastropod *Aplysia californica* was fixed with buffered osmium tetroxide alone. In the case of the toad jejunal muscle, a segment of the intestine was "inflated" with fixative before being immersed in it and as a result the muscle cells were under stretch when fixed.

The *Aplysia* muscle fibers contain thick paramyosin filaments, which are oriented obliquely to the long axis of the fiber—that is, they extend from one side of the fiber toward the other side rather than from end to end (Fig. 1). Other evidence indicates that the contractile elements within the fiber exert their force on the plasma membrane at the sides of the fiber (*4*). Presumably, this force is transmitted to the surrounding connective tissue. The angle of the filaments with respect to the long axis of the cell is approximately 10 degrees. Obliquity of myofilaments probably also occurs in other invertebrate "helical smooth muscles" (*5*).

The toad muscle fibers contain only thin filaments, which, in one plane at least, are also oriented at a small angle to the long axis of the cell containing them (Fig. 2). Although it has not been possible to trace the individual filaments for any considerable distance, their general direction is again from one side of the cell to the other rather than from end to end. Presumably, they insert into the dense patches (*6*) that occur along the plasma membrane at the sides of the fiber (Fig. 2).

These observations serve as a basis for a model of smooth muscle fibers (Fig. 3*a*). Contractile units are indicated by obliquely oriented heavy lines extending between the two sides of the cell. Figure 3*b* shows a corresponding model of a striated muscle cell in which the contractile units are parallel to the fiber axis (*7*).

The essential difference between the two models illustrated is that in the "smooth fiber" the contractile units are in parallel with one another and in the "striated fiber" they are in series. This difference in arrangement has a number of important consequences. For one, the "smooth fiber" in Fig. 3*a* is capable of developing almost four times as much tension in the longitudinal direction as the "striated fiber" in Fig. 3*b* with no increase in the number of contractile units. This consequence follows directly from the fact that forces acting in parallel are additive whereas forces in series are not.

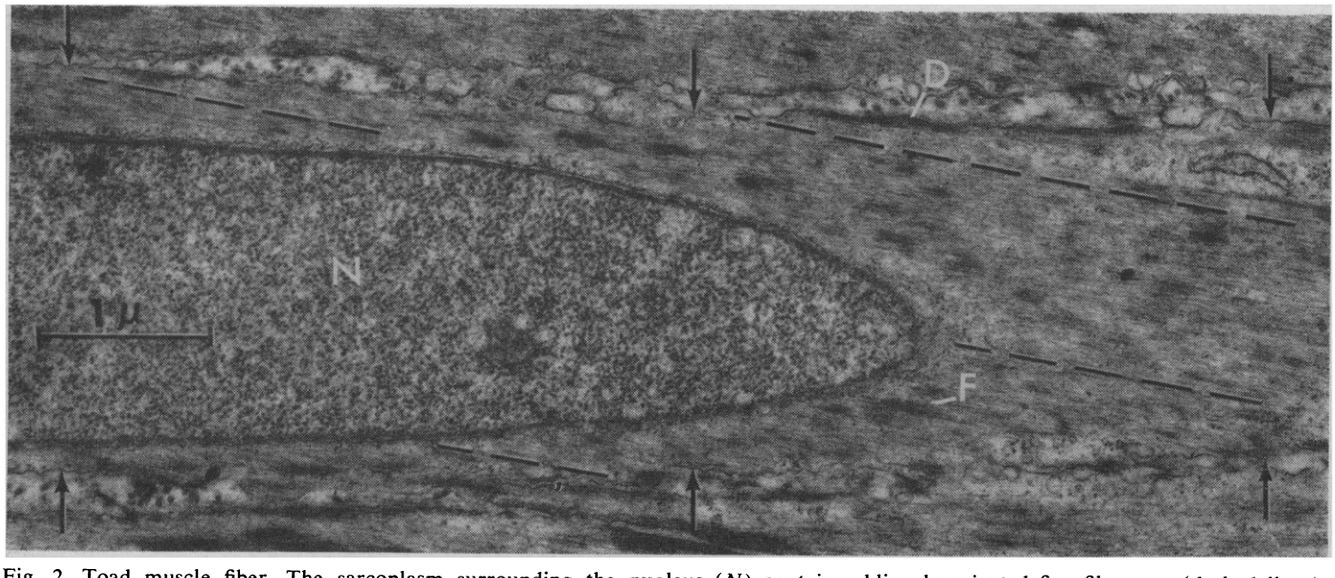

Fig. 2. Toad muscle fiber. The sarcoplasm surrounding the nucleus (*N*) contains obliquely oriented fine filaments (dashed lines). The obliquity is in the same direction both above and below the nucleus. The "fusiform densities" (*F*) also have an oblique orientation. Arrows indicate the plasma membrane; *D*, dense patches along the plasma membrane.

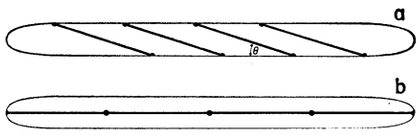

Fig. 3. (*a*) Model of a smooth muscle fiber in which the contractile units are in parallel with one another and insert obliquely into the sides of the fiber. If θ is 10 degrees, then the maximum tension of this fiber in the longitudinal direction is 4 cos 10 = 3.94 times that of the fiber in *b*. (*b*)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

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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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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-