# 44
# Motility of Cilia and the Mechanism of Mitosis*

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THE movement of cilia and chromosomes are interpreted in terms of the microscopic and fine structures in cells. Section 1 discusses structure and motility of cilia; Sec. 2, microscopic structure of the mitotic spindle; Sec. 3, centers of organization in spindle and cilia; and Sec. 4, on the physicochemical nature of the spindle; and Sec. 5, relation of cilia and chromosome movement to muscle contraction.

## 1. STRUCTURE AND MOTILITY OF CILIA

Many small organisms—bacteria and protozoa, sperm and embryos of larger organisms—are propelled by beating their thin whip-like cilia or flagella (used interchangeably here). Also, ctenophores even a foot long and several inches wide can swim about or adjust their gravitational orientation by coordinated beating of their ciliary bundles. When the cell or organism is fixed, as in the gills of mussels and clams and in the human trachea, cilia create a current capable of pumping a considerable quantity of liquid or mucous material.[1–3]

The length of cilia may range from a few microns to several millimeters, and there may be one to several thousand cilia per cell but their diameter is quite constant, usually between a tenth and a half micron. Where a number of cilia occur in a row, adjacent cilia beat slightly out of phase with each other and a regular propagating wave is observed.

At the base of each cilium is found a characteristic bulbous enlargement, the basal granule. Further, proximal to the basal granule, rootlets sometimes are found which may function as anchorage or serve to conduct impulses. The membrane of the cilium appears continuous with that of the cell body.

Examined with an electron microscope (Fawcett and Porter,[4] and also dicussed in the following), cilia reveal a characteristic inner fibrillar pattern of amazing uniformity. Near the periphery of the cilium, there are usually nine (or occasionally a multiple thereof) fibrils, each composed of two filaments (or tubules?) some 100 to 200 A in diameter. Surrounded by the outer nine are two additional central fibrils of somewhat smaller diameters (Figs. 1 and 2). The nine outer fibrils reach the base of the cilium and appear to merge laterally into a hollow tube to make up the basal granule. The two central filaments also extend the whole free length of the cilium but apparently do not reach the basal granule. At the tip of the cilium, the outer nine and inner two fibrils are said to merge. In cilia with distinct directional beating, the line intersecting the two central filaments lies at right angles to the direction of beat.

The pattern of nine plus two has been found in cilia from a wide variety of cells, in fact, in practically all cilia observed with adequate resolution. The eleven fibrils are unlikely to be artifacts formed during preparation for electron microscopy, as sperm-tail flagella macerated in distilled water also show the frayed eleven fibrils in dark field illumination.

Given this structure, how does one explain the mechanism of ciliary beat? The pattern of beat may be relatively simple, as shown in Fig. 3(a). There is a recovery stroke in which the limp cilium stiffens from the base up, and an effective stroke where bending is mostly at the base and the rest of the cilium acts as if it were stiff. The same flagellate organism which swims forward by this

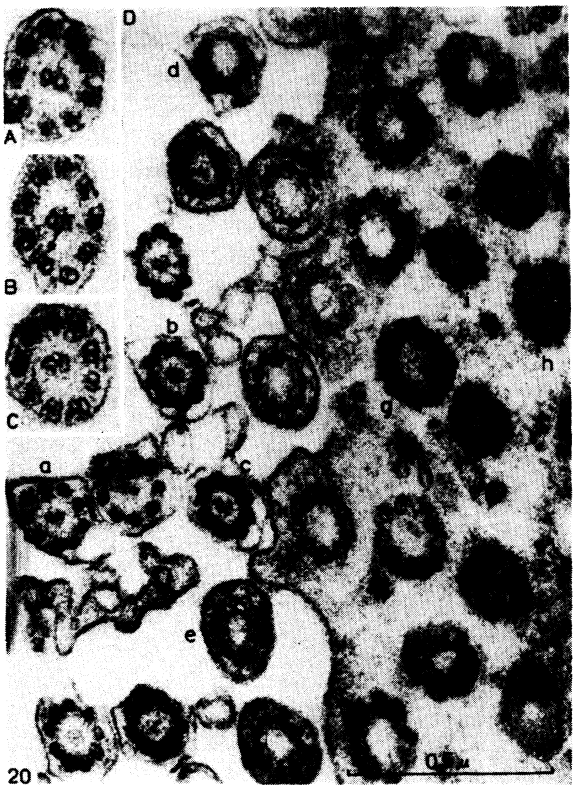



FIG. 1. Electron micrograph of cross sections of rat-trachea cilia. Compare with interpretive diagram, Fig. 2 [from J. Rhodin and T. Dalhamn, Z. Zellforsch. u. mikroskop. Anat. 44, 345 (1956)].

* Original work appearing in this paper was supported in part by the Public Health Service, U. S. Department of Health, Education, and Welfare (G-3002-C), and by the American Cancer Society.

beat may swim backward, also sidewise or circularly, as shown in Fig. 3(b).[2,5] Bradfield[6] postulates that waves of contraction proceed along the length of the outer nine fibrils with a message perhaps traveling in advance along the two inner ones. The waves of contraction may be started at the base by a commutator-like device which would result not in a synchronous contraction but in waves with various phase lags. It is more likely, however, that the outer fibrils may be the conductive elements, the inner two at least partaking a more active function in beating. For, in certain sensory cells (see following) and at the embedded base of each cilium[4,7] where one would expect conduction but not contraction, one in fact finds the outer nine fibrils and not the inner two.

It was tacitly assumed in the foregoing that contraction of the fibrils was the basis for cilia beat. Actually, the only evidence for contraction of cilia components (at the molecular level) appears to lie in the x-ray diffraction studies of Astbury *et al.*[8] There they find in flagella collected from bacteria, in addition to an $\alpha$-protein pattern (which is characteristic of many fibrous proteins, such as keratin, myosin, elastin, etc., and is believed to reflect the fundamental spacing of the polypeptide backbone), a folded $\beta$ pattern. This supercontracted pattern they believe reflects the folding of a fraction of the polypeptide chains responsible for contraction. The protein isolated from this bacterial flagella preparation lacks sulfur-containing amino acids and appears dissimilar to any of the muscle components so far known.

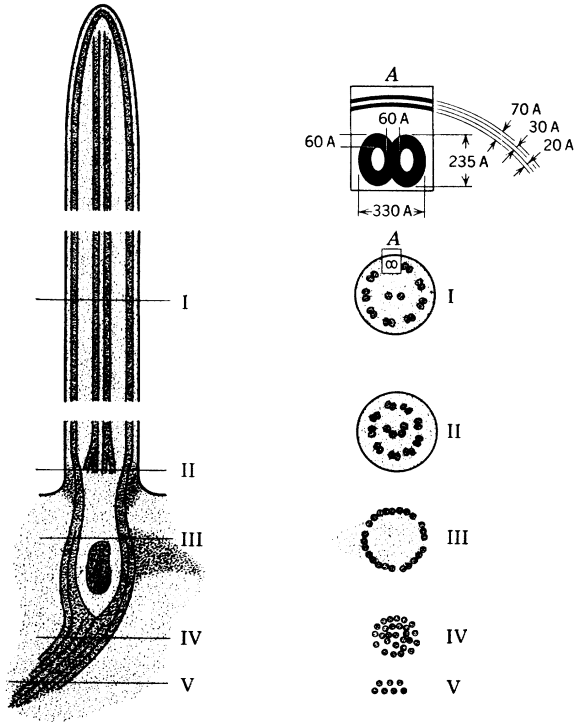



FIG. 2. Interpretation of electron micrograph (Fig. 1) showing fine structure of cilia [from J. Rhodin and T. Dalhamn, Z. Zellforsch. u. mikroskop. Anat. 44, 345 (1956)].

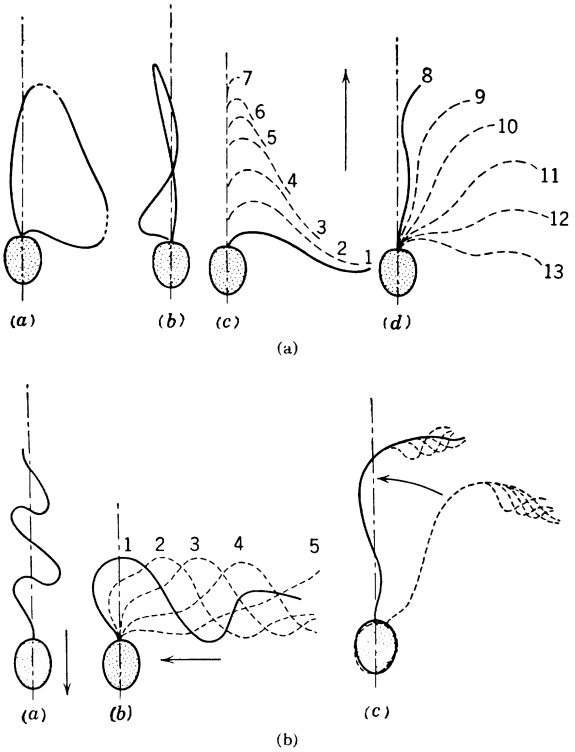



FIG. 3. Various patterns of beat of a *Monas* flagellum. Arrows indicate directions of swimming [from M. Hartmann, *Allgemeine Biologie* (Gustav Fischer Verlag, Stuttgart, 1953), fourth edition; after Krijgsman[6]].

Aside from localized contraction, the mechanism of ciliary beat has been interpreted by other schemes also, such as local swelling, reciprocal pumping of a liquid in and out of the cilium, or discontinuous flow of material through the cilium.[1,3,9] The exact site of the motor function in the cilium is also disputed, but nevertheless there exist certain observations (Secs. 3 and 5) which link the structure and function of these minute structures to other specialized motile structures of the cell.

DeRobertis, Sjöstrand, and others[10,11] made an interesting discovery related to the structure of cilia in the filaments of the retinal-rod cells and of the sensory-hair cells of the inner ear. These fibrous elements, believed for some time to be derived from embryonic cilia, also show a fine structure similar to that of cilia described in the foregoing. In these apparently nonmotile fibers, the same outer nine fibrils are found, but the inner two are missing.

## 2. MICROSCOPIC STRUCTURE OF THE MITOTIC SPINDLE

Cilia may beat as frequently as a hundred cycles per second. Chromosomes, on the other hand, move extremely slowly, the maximum velocity being a few

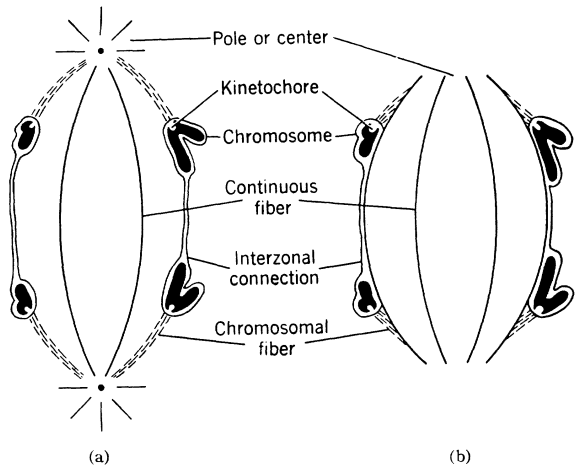



FIG. 4. Schematic diagram of mitotic spindle. (a) with centrioles and (b) without (modified from Schrader[19]).

microns per minute at anaphase (for reviews of mitosis see references 12 to 21). However, certain elements of the mitotic apparatus responsible for chromosome movement may be identical to, or at least have properties common to, portions of cilia. Before discussing this problem in Sec. 3, the structure of representative mitotic apparatuses are described.

Using Schrader's description,[19] the following terms are used. A dot or rod-like structure, the "centriole," is found at the poles of the mitotic spindle of many animal cells and occasionally in plant cells. The centrioles are morphologically the focal points for the spindle fibers and the astral rays [Fig. 4(a)]. In an average plant cell [Fig. 4(b)], both the centrioles and the astral rays are missing and the spindle fibers show less tendency to converge at the poles. Between the two spindle poles lie "continuous fibers." From the "kinetochores," a specific region of the chromosomes "chromosomal fibers" extend to or toward the spindle poles.

For half a century, the reality of these fibers in *living* cells has been disputed, for, with very few exceptions, they could be seen only in cells after fixation and staining. Recently, however, with improvements of the polarizing microscope, the author has been able to show these fibers clearly in living cells of many animals and plants by virtue of their positive birefringence (strength of birefringence $10^{-3}-10^{-4}$).[22,23] In animal cells, the fibers converge and their birefringence is stronger adjacent to the chromosome kinetochores and near the centrioles [Fig. 5(a)]. In plant cells, the situation is similar at the kinetochore region, but toward the "poles" the birefringence is weaker and the fibers are more diffuse [Fig. 5(b)]. During anaphase movement, the birefringence of the chromosome fibers persists and always is strongest adjacent to the kinetochores and the centrioles. The birefringence of the continuous fibers falls once and then rises again after complete separation of the chromosomes. The midregion containing fibers with strong secondary birefringence becomes the phragmoplast of plant cells [Fig. 5(c)]. Within the phragmoplast, small granules align, fuse, and become the cell plate, which divides the original cell into two. In animal cells, the cytoplasm generally cleaves inward at right angles to the spindle remnant forming two new cells with one nucleus each. Time-lapse motion pictures of these processes have been made by the author using a special polarizing microscope and were shown at the meeting.

The material of the mitotic apparatus has been isolated from sea urchin and other eggs by Mazia, Dan, and their collaborators in quantities sufficient for chemical analyses.[24–26] Amino-acid composition of their protein fraction (molecular weight *ca* 45 000) shows, unlike the bacterial flagella protein, a fair content of sulfhydryl-containing amino acids.

Although the spindle isolated after alcohol treatment by Mazia and Dan is stable, the fibers of the mitotic spindle in living cells are apparently extremely labile. The spindle fibers may disappear by slight mechanical agitation or by low-temperature treatment of the cell, only to reform in the course of a few minutes (see Sec. 5, also Carlson[13,27], Chambers,[28] Inoué,[29] and Östergren[30]).

### 3. CENTERS OF ORGANIZATION IN SPINDLE AND CILIA

Although the apparent velocity and very probably the stability of the spindle fibers differ by orders of magnitude from the cilia, the fibrous elements of the two structures may be formed or organized in a very similar fashion. The argument follows.

(A) The birefringence of the spindle fibers and astral rays is strongest adjacent to the kinetochores and centrioles throughout metaphase and anaphase (Inoué[23] and Schmidt[31]). The fibers are arranged radially (within restricted cones, in the case of the kinetochores) from these centers, and the growth of the spindle (at least in animal cells) takes place by lengthening of the fibers joining the centers. This strongly suggests that both the centrioles and the kinetochores are centers of fiber orientation.

(B) Growth of the axial filament of the sperm-tail flagellum starts from the basal granule, which same structure during the last mitosis acted as a centriole of the spindle.[21,32] In certain protozoa, flagella and the mitotic spindle both grow simultaneously from common giant centrioles.[14,32]

(C) In abnormal divisions of snail spermatocytes, some chromosomes lose their kinetochores and cannot partake in mitosis. The Pollisters[33] have shown that a clear correlation exists between the number of such chromosomes and the number of supernumerary basal granules, which migrate to the cell periphery and form the same number of extra sperm tails. Also, those kinetochores earlier dissociated from chromosomes form small extra astral rays while the spindle for the next division is formed.

(D) With the electron microscope, centrioles of the mitotic apparatus have been shown to exhibit the same general structure and dimensions as that earlier described for the cilia basal granules, namely, a cylindrical structure containing nine groups of rods or tube-like elements.[34–37] This same structure is observed for the basal granule of sperm-tail flagellum.[38,39]

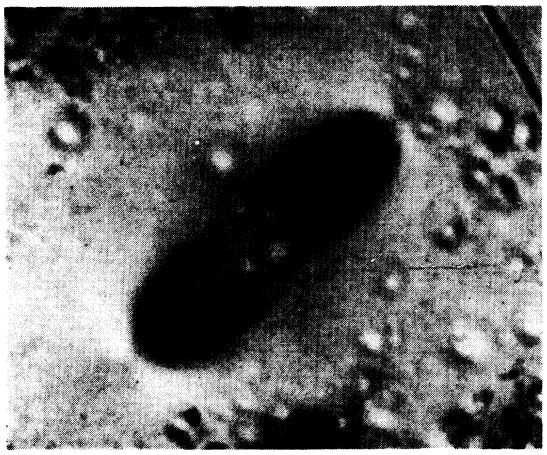
Thus, it appears that basal granules of cilia, kinetochores, chromosomes, and centrioles of the mitotic apparatus all act as centers of fibrous organization in cells. The basal granules, centrioles, and kinetochores, may be in fact identical structures, taking on different functions at different loci within the cell (see also Meves[40]).

### 4. ON THE PHYSICOCHEMICAL NATURE OF THE MITOTIC SPINDLE

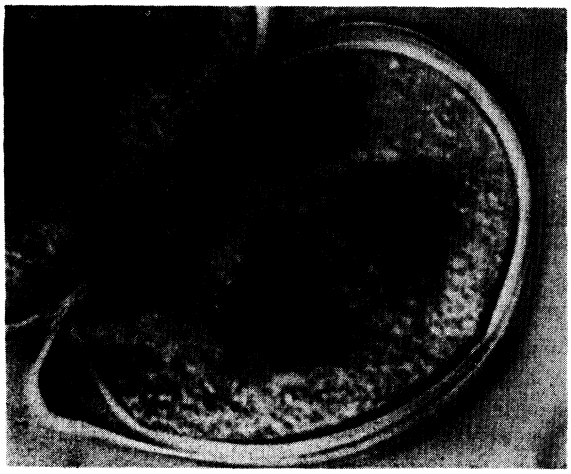
Electron-microscope studies have revealed a characteristic fine structure in cilia (Sec. 1). The possible identity of their basal granules to centrioles of the spindle also was strengthened (Sec. 3). However, this technique as yet has revealed rather little of the structure and behavior of spindle fibers and kinetochores.[25,41,42] The lack of success, I believe, is attributed to the difficulty or impossibility of preserving the spindle material in a reasonably native form after fixation and electron bombardment. In contrast, the polarizing microscope enables one to observe birefringence of spindle fibers in actively dividing cells (Secs. 2 and 3). Although the fine structure cannot be resolved directly, measurement of birefringence allows one to interpret the changes taking place in the microscopically unresolvable domain. This section describes further polarization-optical observations which may shed some light on the physical chemistry of the mitotic spindle.

The spindle of the egg cell (of a marine worm *Chaetopterus*) can be stretched if the cell is flattened very gently. The length of the spindle is then found to be strictly proportional to the diameter of the compressed egg.[22] This relation is explained by the attachment of the spindle poles through astral rays[43,44] to the cortical-gel layer. Immediately upon stretching, the spindle is thinner and more pointed at the poles, while in a minute or two it grows fatter and the birefringence increases. When the egg is compressed suddenly, the link between spindle poles and the cortical gel is apparently broken and the spindle shortens as it loses its birefringence (Fig. 6).

At a given length, the birefringence of the spindle fibers is a function of temperature.[29] With abnormally low temperature (4° to 6°C), the spindle birefringence is abolished completely. When the temperature is raised, the birefringence returns. The loss of birefringence with low temperature is rapid (less than half a minute), but when the temperature is raised the birefringence and structure of the spindle fluctuate until, after several minutes, they reach an equilibrium specific for the new



(a)



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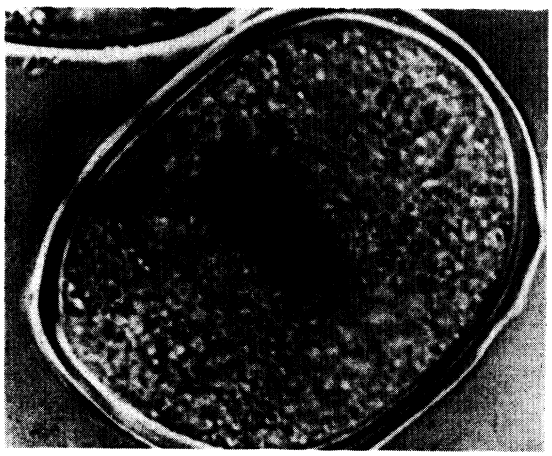

(c)

FIG. 5. Birefringent spindle fibers in living cells. Photographs are printed as negatives and show spindle fibers parallel to spindle axis black. (a) *Chaetopterus pergamentaceous* metaphase; (b) *Lilium longiflorum* early anaphase; (c) the same, phragmoplast with early cell-plate formation (modified from Inoué[23]).

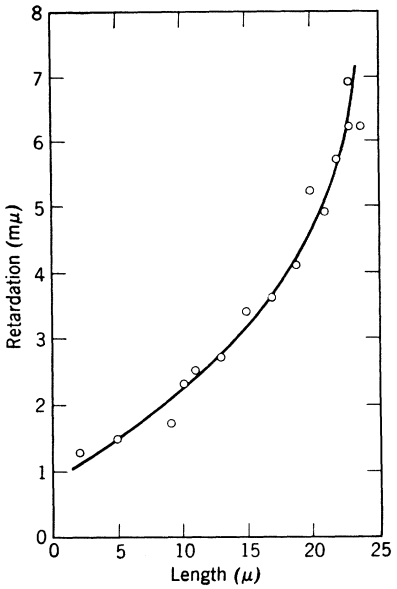


FIG. 6. Retardation of *Chaetopterus* spindle plotted against length [from S. Inoué, J. Exptl. Cell Research Suppl. 2, 305 (1952)].

temperature. The native spindle is, therefore, in a temperature-sensitive equilibrium.

The equilibrium birefringence at various temperatures is plotted in Fig. 7. If it is assumed that the birefringence of spindle fibers is directly proportional to the amount ($B$) of material oriented in that region, that only the equilibrium constant [$k(T)$] between oriented and nonoriented material is influenced by temperature, and that the total amount ($A_0$) of the orientable material in the same region remains constant, then the equilibrium is expressed by

$$A_0 - B \overset{k(T)}{\rightleftarrows} B.$$

$A_0$ was assumed constant since the spindle in the *Chaetopterus* egg is in metaphase equilibrium and also

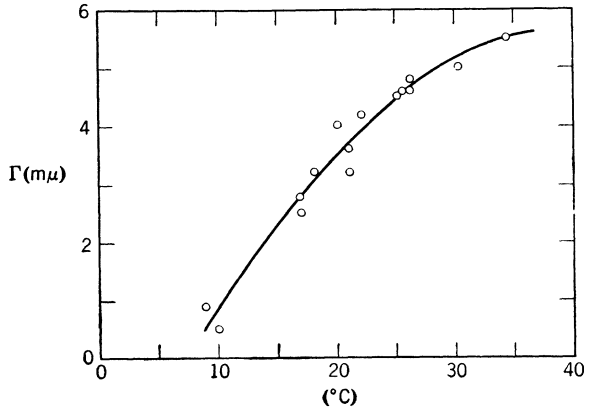


FIG. 7. Equilibrium retardation (Γ) of *Chaetopterus* spindle at various temperatures.

because cells which already have entered metaphase can go through division even in the presence of metabolic inhibitors such as cyanide and carbon monoxide.[45]

$A_0$ then is determined as the asymptote of the curve in Fig. 7. Were these assumptions warranted, one should expect a linear relationship between log $B/(A_0-B)$ and $1/T°K$. Figure 8 shows this plot. From the slope and intercept we (Morales[46] and Inoué) calculate the evolution of 28 kcal of heat per mole reacted, while at 25°C a free-energy change of $-1.8$ kcal/mole and an entropy increase of 100 eu/mole is observed.

The very low free-energy change agrees with the proposed lability of the spindle structure (weak gel with small number of active hydrogen bonds?), while

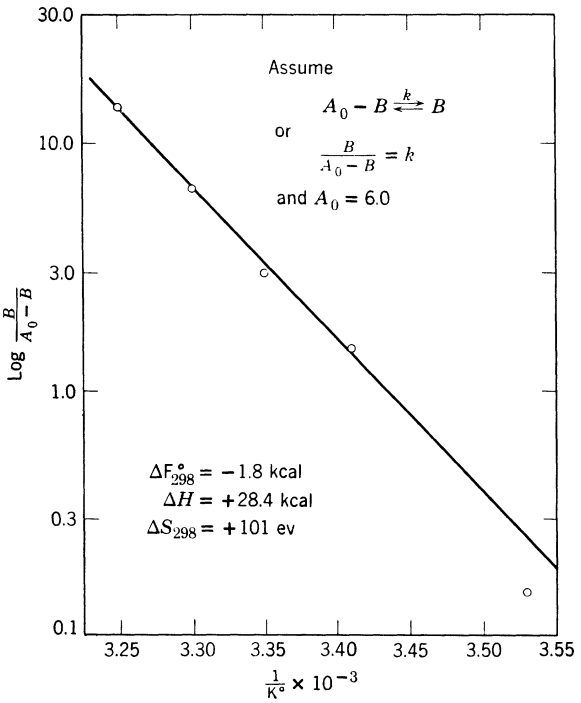


FIG. 8. Log plot of spindle reaction equilibrium *vs* inverse absolute temperature.

the high heat of reaction and the high positive entropy which nearly cancel each other explain the apparent decrease of entropy (increase of spindle birefringence) at higher temperatures. At high temperature, the still-unoriented protein molecules presumably absorb a considerable amount of heat, thus, for example, releasing bound water which could have prevented their orientation. The melting and randomizing of the bound water then could account for the large increase in entropy (also see Anderson[12]).

It appears that the spindle fibers are regions with high degrees of orientation, although very labile, expressing the orienting influence of the kinetochores and centrioles. As Östergren's earlier observation on the chromosome behavior of a plant *Luzula* also suggests,[30]

spindle fibers are undoubtedly almost fluid in nature and are not stably crosslinked gels as the term "fibers" may imply. With dehydrating agents (e.g., alcohol) and in an acidic environment the crosslinking is probably enhanced until the spindle is finally "fixed."

On this basis and from observations described in Sec. 2, anaphase movement of chromosomes may be explained by local reduction in the quantity of oriented material and the consequent shortening of chromosomal fibers. The orienting forces of kinetochore and centriole must be just as actively at work throughout this process. The continuous fibers, either actively elongating or at constant length, could function as supports to counteract the pulling action of the chromosomal fibers. This mechanism of contraction of the chromosomal fibers is similar to that postulated by the author for the action of low concentrations ($<10^{-3}M$) of colchicine.[22] It is, however, in distinct contrast to the mechanism suggested by Swann[47,48] whose microscope lacked the power of resolution for detecting individual spindle fibers.[49]

### 5. RELATION OF CILIA BEAT AND MITOSIS TO MUSCLE CONTRACTION

The sole evidence for molecular contraction in cilia appears to lie in the x-ray diffraction data on isolated bacterial flagella (Sec. 1). Hypotheses involving mechanisms other than contraction (e.g., differential swelling) also have been postulated, but discriminating experiments are lacking.

Anaphase movement of chromosomes was explained by an orientation equilibrium of spindle fibers (Sec. 4). The action of centrioles and kinetochores—the center of foci of orientation in the spindle—appears similar to that of basal granules of cilia during fibrogenesis (Sec. 3).

Occasionally, cilia are resorbed or re-formed, but the process is much slower than the formation and disappearance of the mitotic spindle at each cell division. It appears that the cilia fibrils are quite stable while the molecules in spindle fibers probably are barely crosslinked (Sec. 4). In comparison, the contractile material in muscle may have a stability lying in between that of cilia and spindle fibers. The primary function of muscle and cilia is repeated rapid contraction, while with the spindle it is a single successful partition of the chromosomes into two new cells.

Mechanisms of muscle contraction are discussed in other papers of this symposium. It is interesting that one of the most widely discussed (and rather widely accepted) current hypotheses is that involving the creeping of two sets of filaments past each other.[50,51]

Regardless of the exact mechanism of choice, one may not overlook the muscle model systems which can contract and produce the same force per cross section as live muscles. This is true in muscle fibers extracted with 50% chilled glycerol, and in an oriented gel fiber formed by mixing two purified muscle proteins, actin and myosin. In either case, contraction is induced specifically by the addition of ATP (adenosine triphosphate) in the presence of magnesium and potassium ions.[52–54]

Hoffmann-Berling has shown further that motility can be induced in glycerol-extracted cells other than muscle, again by the addition of ATP. Thus, he was able to induce glycerinated sperm-tail flagella to undergo prolonged beating, chromosomes to separate, and extracted dividing cells to complete formation of their cleavage furrow (motion picture commercially available[54,55]). These models respond to approximately the same concentration of ATP as muscle models.

To what extent the movements induced by ATP in various cells reflect the same molecular mechanisms still is not clear. For example, the elongation of the central spindle, apparently responsible for the separation of chromosomes in the cell model, is not prevented by the same poisons to which the muscle and cilia model are very sensitive. Furthermore, although the organic triphosphate ATP (and ITP) specifically induces movements in extracted cells, the responding proteins show significant difference in their amino-acid compositions (see Secs. 1 and 2). It is nevertheless encouraging that movements closely resembling those found in living cells can be induced by the same reagent in cells from which much of the complex structures and materials have been removed.

In conclusion, evidence for the long-sought molecular folding is still weak, and no unifying molecular mechanism has been found for cilia beat, anaphase chromosome movement, and muscle contraction. Developments in recent structural and physicochemical analyses are, however, encouraging, and with a concerted intelligent approach, one may acquire before too long a much clearer understanding of the mechanisms underlying these cellular movements.

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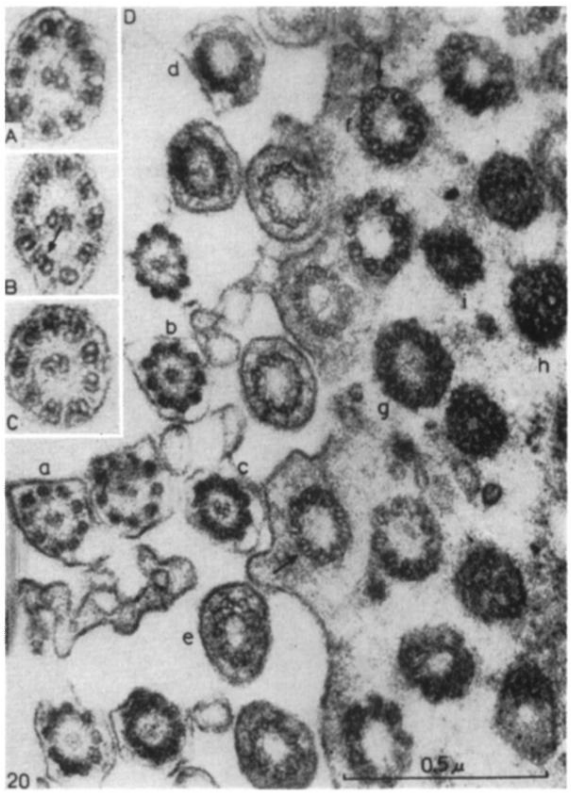



FIG. 1. Electron micrograph of cross sections of rat-trachea cilia. Compare with interpretive diagram, Fig. 2 [from J. Rhodin and T. Dalhamn, Z. Zellforsch. u. mikroskop. Anat. **44**, 345 (1956)].

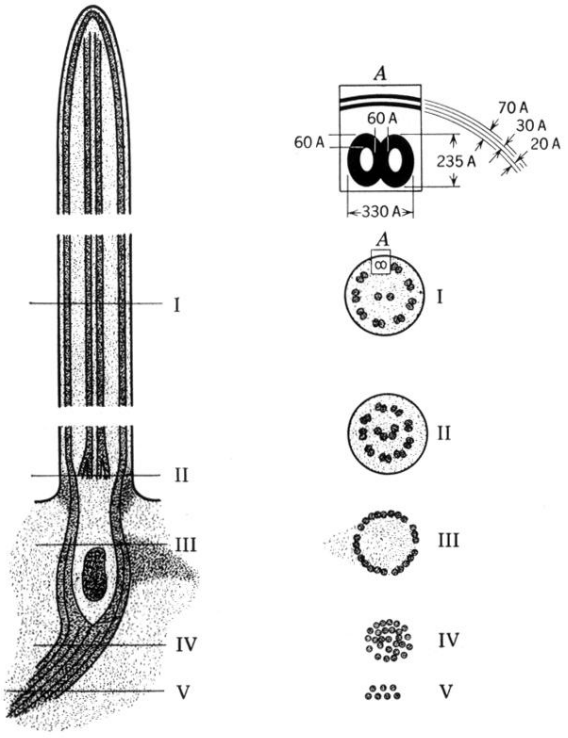



FIG. 2. Interpretation of electron micrograph (Fig. 1) showing fine structure of cilia [from J. Rhodin and T. Dalhamn, Z. Zellforsch. u. mikroskop. Anat. 44, 345 (1956)].

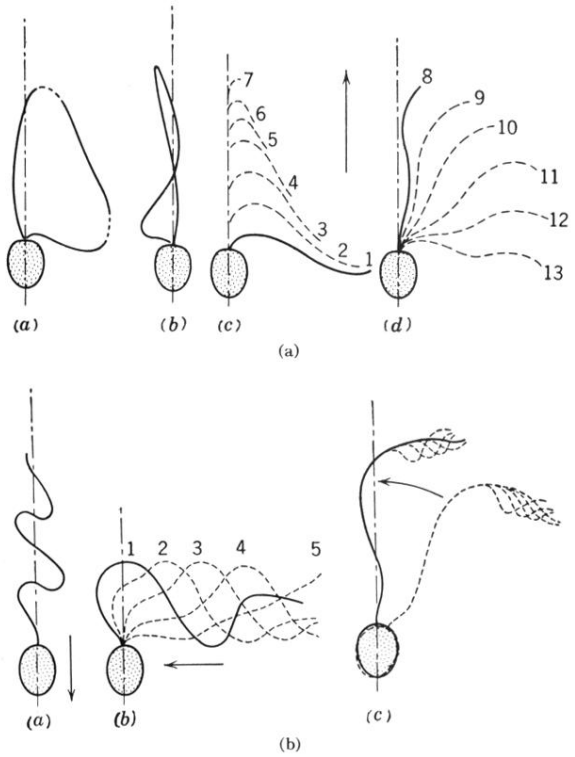
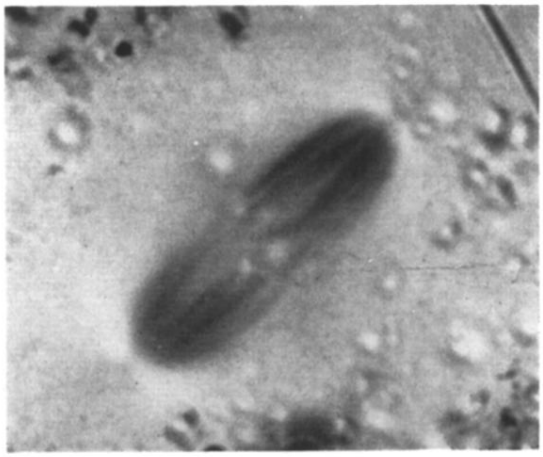
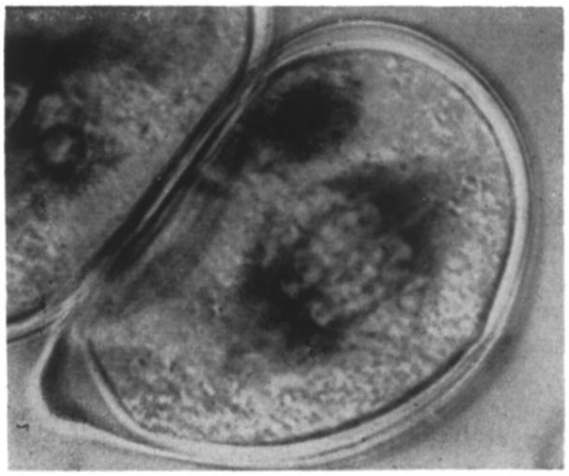



FIG. 3. Various patterns of beat of a *Monas* flagellum. Arrows indicate directions of swimming [from M. Hartmann, *Allgemeine Biologie* (Gustav Fischer Verlag, Stuttgart, 1953), fourth edition; after Krijgsman[5]].



(a)



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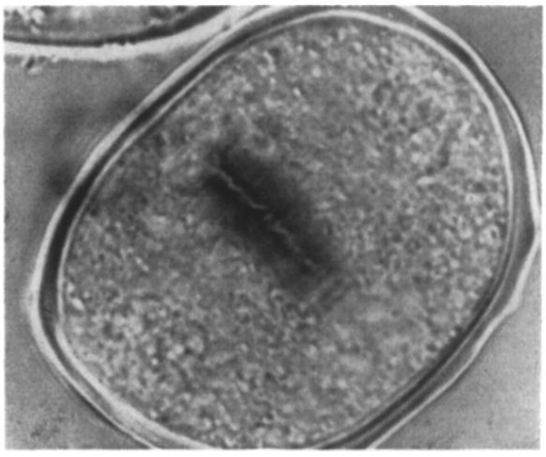

(c)

FIG. 5. Birefringent spindle fibers in living cells. Photographs are printed as negatives and show spindle fibers parallel to spindle axis black. (a) *Chaetopterus pergamentaceous* metaphase; (b) *Lilium longiflorum* early anaphase; (c) the same, phragmoplast with early cell-plate formation (modified from Inoué[23]).