Hypothesis

The possible roles of the myosin heads

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It is suggested that, in the conditions which exist *in vivo*, one head of a myosin molecule interacts with another head of the opposite molecule, inside the backbone of the thick filament. The other head lies outside and can interact with actin. This model is based on the fact that a dimer of the myosin heads exists and that there is a close correlation between the properties of the dimer and those of the thick filament diameter. In natural filaments, there are myosin molecules in excess and it is suggested that these molecules have their two heads outside the backbone.

Myosin filament *Head-to-head interaction*

1. INTRODUCTION

'What is the significance of the fact that each myosin molecule has two heads?' [1]. The problem is of major importance, but has not been given sufficient attention. Offer and Elliott [2] were the first to propose a working hypothesis: in the case of insect flight-muscles, the heads of a myosin molecule can attach to two different actin filaments. This model is applicable to well-organized myofilament lattices, but maybe not to all types of muscles. However, the model seems to be correct for insect flight-muscles, but incomplete. From new experimental findings (discoveries of skeletal myosin S1 dimers [3], of cardiac myosin S1 polymers [4] and of a regulation of the synthetic myosin filament diameter by Mg-(phosphate compounds) [5]), we suggest that one head/crossbridge is stuck to one head of the opposite myosin molecule inside the backbone, in the conditions which exist in vivo. The other head lies outside and can interact with actin. This model is applicable to most types of muscles, since it is independent of the arrangement of the actin filaments. In most types of muscles, there are more than 2 myosin molecules/143 Å repeat (crown) and we suggest that only 2 opposite myosin molecules are arranged according to our model. The myosin molecules in excess might be arranged according to the model in [2]. Thus, both models would be complementary, especially in the case of insect flight-muscles. For this reason, we shall develop only our model here. Many arguments we present below are valid for synthetic filaments, but we believe they could be extrapolated to natural filaments with minor modifications.

Abbreviations: ADP, adenosine diphosphate; ATP, adenosine triphosphate; P_i, inorganic phosphate. S1, myosin subfragment 1 (head); S1 (A1), S1 containing only the A1 (or LC1) light chain; S1 (A2), S1 containing only the A2 (or LC3) light chain; DTT, dithiothreitol; $\bar{v}$, apparent specific volume.

2. ROLE OF THE Mg-(PHOSPHATE COMPOUNDS) IN THE FORMATION OF SYNTHETIC FILAMENTS

Studies on actomyosin mixtures appeared in [6–9]. We shall briefly recall the results obtained at

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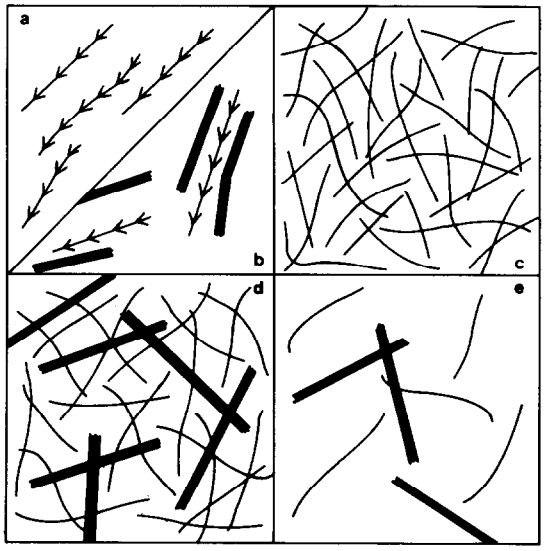

Fig. 1. Schematic representation of actin–myosin mixtures at variable MgATP concentrations, in absence of Ca^{2+}. (original micrographs in [6–9]: (a,b) MgATP < 2×10^{-7} M. When the actin and myosin concentrations are comparable, an arrowhead complex is usually observed. When myosin is in excess (b), the arrowhead complex is still observed, but the myosin molecules in excess form thick filaments; (c) MgATP $3 - 8 \times 10^{-7}$ M. The arrowhead complex disappears and the myosin filaments are no longer observed. However, the actin filaments form a superprecipitate; (d) MgATP $1 - 2 \times 10^{-6}$ M. Myosin filaments reappear and a second superprecipitation is observed, with both types of filaments; (e) MgATP > 3×10^{-6} M. A usual clear phase is observed. The disappearance of the myosin filaments seems to be in contradiction with the structuring power of MgATP (see text). The head-to-head affinity is an increasing function of the concentration of Mg-(phosphate compounds) [3]. If the tail-to-tail affinity is a decreasing function of this concentration, the overall myosin–myosin affinity may present a minimum. At this minimum, the myosin filaments may be disrupted in presence of F-actin, which exerts a strong attraction on the myosin molecules at low MgATP concentrations. It is the reappearance of myosin filaments which shows that MgATP has a structuring power.

physiological pH and KCl. Two series of experiments have been done: one with a fixed excess of ATP and variable [Mg^{2+}]; another with a fixed excess of Mg^{2+} and variable [ATP]. It appears that the role of ATP, at fixed [Mg^{2+}], and Mg^{2+}, at fixed [ATP], are rigorously parallel. This means that MgATP induces the 'phase transitions' recalled in fig. 1. When its concentration increases, MgATP progressively inhibits the myosin–actin interactions and simultaneously decreases, then increases, the myosin–myosin interactions. The most striking finding is that the myosin filaments disappear, before reappearing. This observation suggests that MgATP plays a role in the myosin–myosin interactions.

Pinset-Härström and Truffy [5] have studied the effects of Mg^{2+} and ATP (or P_i) on the formation of synthetic filaments (P_i has qualitatively the same effects as ATP). They have found 4 important results:

(i) In absence of Mg^{2+} and ATP, the filaments are 30–50 nm wide; i.e., 2–3-times the physiological diameter (16 nm);
(ii) In absence of Mg^{2+}, ATP disrupts the filaments;
(iii) In absence of ATP, Mg^{2+} has no effect on filament diameter (30–50 nm);
(iv) In presence of Mg^{2+} and ATP, the filaments display physiological diameters (16 nm).

The obvious explanation of these findings is that MgATP (or MgP_i) is responsible for the formation of physiological filaments. The apparent role of Mg^{2+} suggested in [5] is purely coincidental. In fact, it is hard to understand how Mg^{2+} might play a role, since, in absence of ATP, it has no effect on filament diameter, in the physiological range of concentration [5]. The apparent lack of relation between the formation of physiological filaments and the concentration of MgATP would be merely due to the fact that the concentration of free ATP was not controlled. Under such conditions, the disruptive power of free ATP and the expected structuring power of MgATP are in competition: MgATP can play its role only when it is in sufficient concentration as compared with free ATP.

The first conclusion we draw from these observations is that MgATP (or MgP_i) plays a role in the myosin–myosin interactions. Since MgATP sites of fixation are localized on the heads, we reach the second conclusion that the heads might play a role in filament formation. Indirect observations support this point of view: the myosin rods alone form ribbon-like filaments, very different from the thick filaments (unpublished observations [10]).

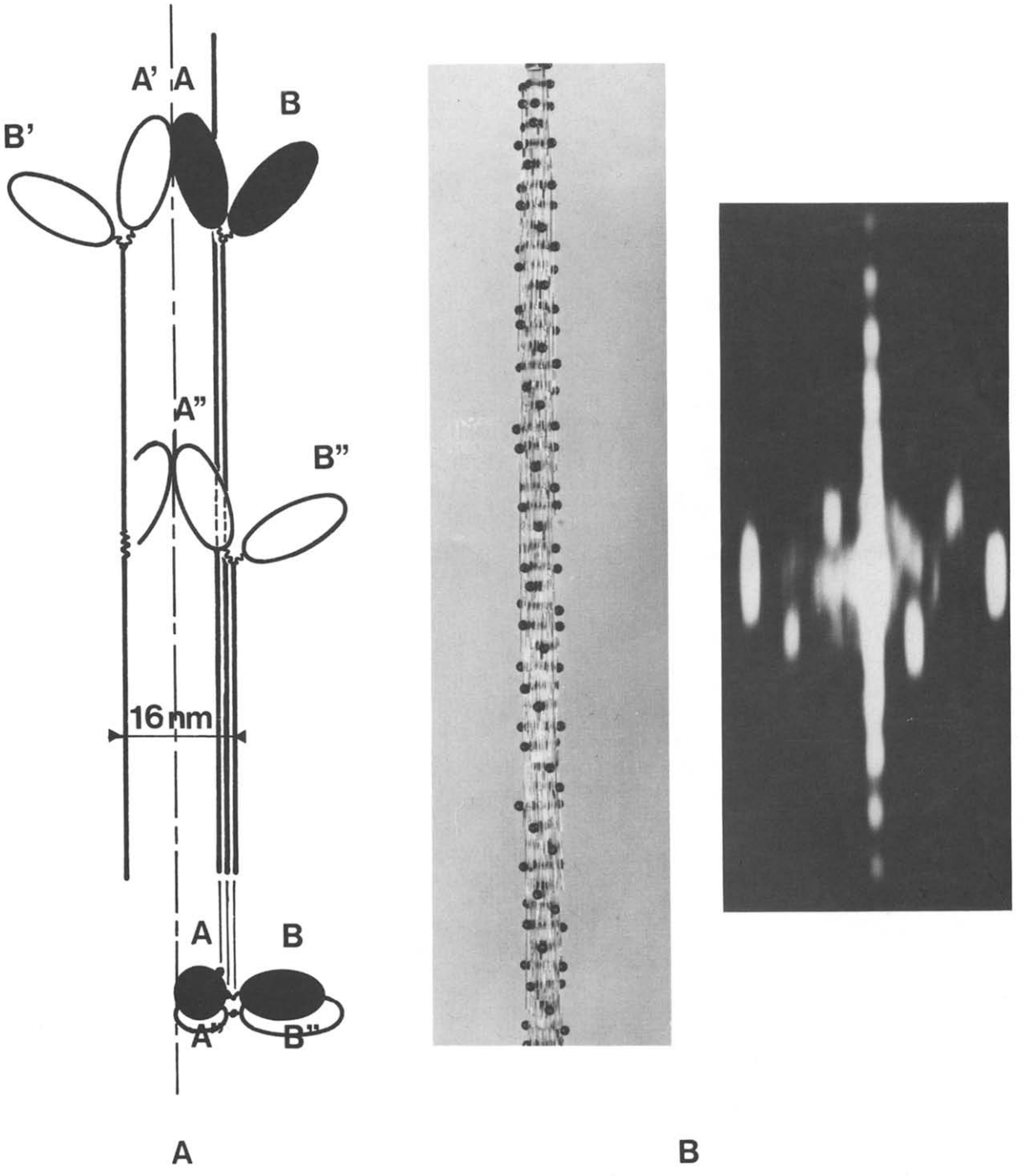

Fig. 2. (A) Proposed model for the structure of the myosin filaments in presence of a Mg-(phosphate compound), with the arrangement of the heads on the tails. (B) A complete model, with half of the heads inserted in the backbone. Note the slight distortions in the arrangement of the tails and the extruding heads. However, the helical-type arrangement is maintained, as shown by optical diffraction on a photograph of the model: this diffraction pattern is highly characteristic of a helical structure.

3. A NEW MODEL FOR THE MYOSIN FILAMENTS

We have shown that skeletal myosin S1 forms dimers in solution [3]. Our most important finding is that the S1's making up the dimer are much more tightly-bound in presence of a Mg-(phosphate compound) (MgADP) than in its absence. This result, together with the results recalled above, leads us to suggest that the heads A and A′ are bound inside the backbone, in presence of a Mg-(phosphate compound) (fig. 2A). A steric hindrance might arise from such an arrangement: how can the myosin tails be close-packed with this structure? If we take the value of the diameter of the heads given by Lowey et al. [11] (7 nm), they can be easily inserted in the backbone (diam. 16 nm). If we consider the heads as prolate ellipsoids or pear-shaped [2], they can be inserted as shown on fig. 2A. A difficulty might arise from the arrangement of the myosin molecules lying along the same generatrix and separated from a given molecule by distances of 42.9–85.8–128.7 nm, the length of the tails being greater than these values (130–160 nm). However, the tails can pass through the spacing between the heads (fig. 2A). This model leads to limited distortions in the close-packing of the tails and the helical arrangement of the extruding heads (fig. 2A,B). The synthetic filaments are not stiff geometrical crystals, but polymers presenting disordered regions [12]. Notwithstanding, these filaments present all the characteristics of natural filaments [12]. These findings confirm that distortions are possible, but that the overall characteristics are not necessarily modified. This conclusion is clearly borne out on a complete model (fig. 2B).

The problem now arises of the role of the Mg-(phosphate compounds). We have shown that, in the absence of these compounds, the S1's making up the dimer are extremely weakly-bound [3]. Now, all the myosin molecules are negatively charged. Hence, in the filaments, these molecules are submitted to electrostatic repulsive forces and to van der Waals–London attractive forces. The balance between these forces corresponds to a filament diameter of 30–50 nm. In this case, most myosin heads are not in direct interactions inside the backbone, since their mutual affinity is weak. However, this fact does not at all rule out the possibility that many heads are inserted in the backbone (fig. 3). In presence of Mg-(phosphate compounds), the attractive forces between the myosin heads are strong [3] and these latter are stuck together inside the backbone (fig. 2). Thus, the diameter of the myosin filament is minimum and is mostly determined by the geometry of the

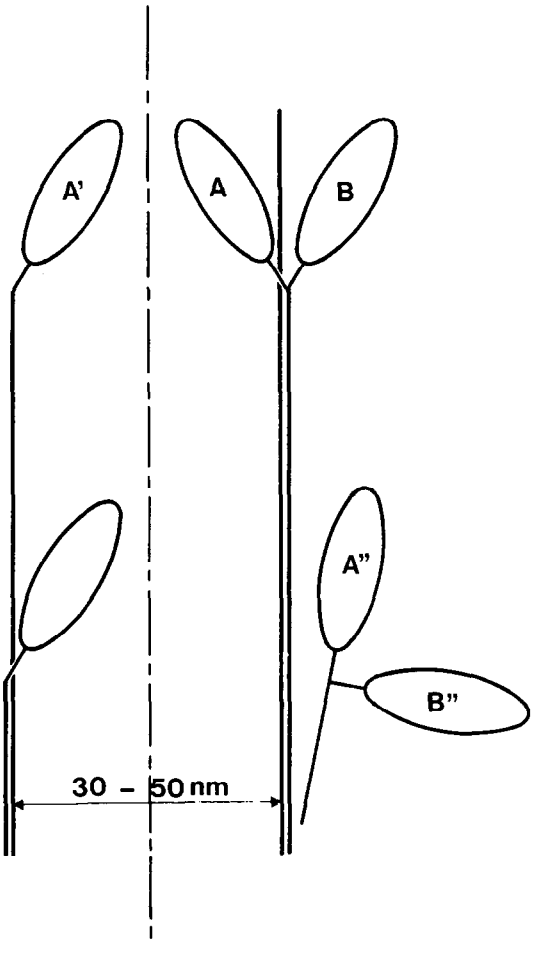

Fig. 3. Proposed model for the structure of the myosin filaments in absence of Mg-(phosphate compounds). Many heads are inserted in the backbone, but most of them do not interact with the opposite head (A,A′). The head-to-head affinity is weak, but not zero (3) and it is possible that some heads are stuck together inside the backbone, as proposed in fig. 2. However, since the filament diameter is higher than the physiological one [5], such a possibility necessarily induces large distortions in the myosin molecules, at the level of the heads. Finally, some heads lie entirely outside the backbone (A″,B″).

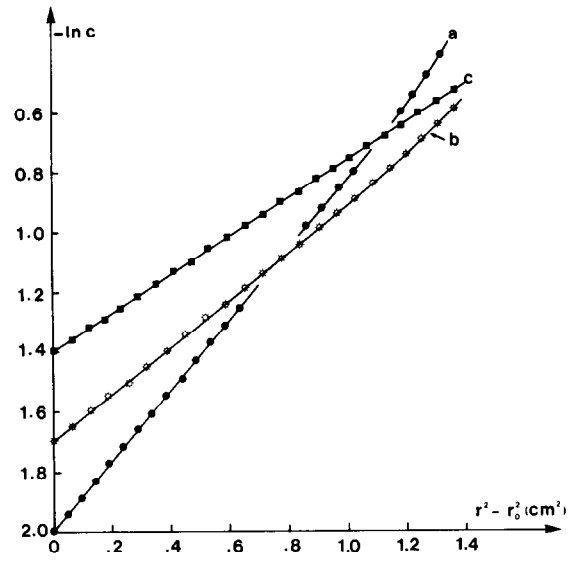

Fig. 4. Variations of ln c vs $(r^2 - r_o^2)$ (r_o = radial position of the meniscus) in three double-checked sedimentation–diffusion equilibrium experiments. We used the Yphantis 6-channel cell and the Rayleigh interference optical system: S1 loading concentration for all the experiments, 0.38 mg/ml; column length, 1 mm; rotor speed, 10000 rev./min; Temp. 4°C; duration of the experiments, 24 h. Composition of the buffers: (a,●) KCl 0 mM, $MgCl_2$ 0.1 mM, ADP 0.1 mM, DTT 2 mM, Imidazole 50 mM (pH 7.5); (b,☼) same composition, except ADP 5 mM (ionic strength ~25 mM); (c,■) same composition, except ADP 10 mM (ionic strength ~50 mM). Curve (a) corresponds to an almost pure dimer (K = 38 ml/mg), as expected from [3]. Curve (b) corresponds to a monomer–dimer mixture, with a value of K considerably lowered (K = 0.9 ml/mg). Curve (c) corresponds to a pure monomer. In light of fig. 2 in [3], this drastic effect of increasing the concentration of ADP cannot be mistaken for an effect of the ionic strength. We have checked this fact by performing two complementary experiments in the Yphantis cell and by replacing ADP by KCl, to have the same ionic strength; i.e., 25 mM KCl in one experiment and 50 mM in the other. In the limit of the experimental error, the equilibrium constants were close to 35–40 ml/mg in both experiments; i.e., the same as in the case where KCl was absent. Thus, these experiments clearly show the disruptive power of free ADP on the S1 dimer.

myosin molecule (especially the angle between the heads and the tails).

In presence of ATP or P_i, but in absence of Mg, the filaments are disrupted [5, 13]. In presence of

Table 1

Comparative properties of the S1–S1 interactions and the synthetic myosin filament properties

Conditions	S1–S1 interactions	Myosin filament diameter[c]
No Mg^{2+}-PC	Extremely weak[a]	30–50 nm
Mg^{2+} alone	Weak[a]	30–50 nm
	(0.8 or 5 mM)	(0.1–5 mM)
Free PC	Dimer disrupted[b]	Filaments disrupted
	(ADP 5 or 10 mM)	ATP 2–5 mM
		P_i 10–20 mM
Mg^{2+}-PC	Strong[a]	16 nm
	(MgADP 2 mM)	MgATP 0.1–4 mM
		MgP_i 0.3–5 mM

Data from: [a][3]; [b]fig. 4; [c][5]

PC = a phosphate compound (ATP, ADP, P_i)

This table is valid at physiological pH and ionic strength, except in the case of S1–S1 interactions in presence of free PC (fig. 4). Note that free PC also disrupts the tail assemblages [13]; thus, free PC acts on both the tails and the heads, in a disruptive manner.

Mg-(phosphate compounds), no dissociation occurs [5, 13]. Therefore, the disruptive power of these compounds is close to zero. In sharp contrast, they have a structuring power. These results prove that free ATP, ADP, P_i, on the one hand, and MgATP, MgADP, MgP_i, on the other hand, do not at all play the same roles. This fact is also clearly confirmed in fig. 4 and table 1.

Yagi et al. [14] have found, in whole frog muscles, that ~80% of the heads attached during contraction return rapidly to the thick filaments (< 500 ms) after cessation of a tetanus. The rest return slowly (> 5 s).

The rapid return coincides with the fall in tension and, during the slow return, no tension is recorded. This means that the heads which remain in the vicinity of the thin filaments, during the slow return, are most likely not attached to actin, except the small proportion of them which remain attached at rest [15]. The results in [14] have been confirmed by Matsubara and Yagi [16]. The rapid return would be related with A-heads which rapidly recover their position inside the backbone after detachment of the B-heads from actin. Contrarily, the slow return would be related with A-heads which cannot rapidly recover their positions. Therefore, the corresponding B-heads would re-

main in the vicinity of the thin filaments for several seconds. This second class of A- and B-heads would correspond to A-heads which have accidentally left the core of the thick filament during contraction, under the action of the tractions exerted by the B-heads to reach actin. The slow return of these A-heads would be due to a steric hindrance arising from the myosin tails which have recovered their close-packing arrangement after the A-heads have left the core of the myosin filaments. Thus, our model gives a straight-forward explanation for the biphasic return, which is not at all the case for the usual models, in which all the heads lie outside the shaft and play the same role.

When the B-heads attach to actin, the A-heads have the tendency to be drawn out from the core of the filaments (see above). Thus, the A-heads can produce large distortions in the close-packing of the tails and, in a more general way, in the overall arrangement of the thick filaments. During contraction, most of the B-heads are attached to actin or in the vicinity of the thin filaments [14, 17] and the distortions in the myosin filaments are certainly considerable. This conclusion agrees with the findings of Huxley et al. [18,19], who have observed the disappearance of some layer-lines arising from the thick filaments and a more blurred structure of these latter, during contraction.

At physiological pH, the monomer–dimer equilibrium constant for S1 decreases when the [KCl] increases [3]. Therefore, it is probable that the A- and A′-heads dissociate at high ionic strength and that the stability of the myosin filaments is altered in these conditions. This fact gives a simple explanation for the solubilization of the filaments at high ionic strength. Moreover, fig. 4 shows that ADP disrupts the S1 dimer, just as free ATP or P_i disrupt the synthetic filaments. Thus, there is a close correlation between the properties of the S1 dimer and those of the synthetic filaments (table 1). These are further arguments in favour of our model.

4. HOW TO DIRECTLY TEST THE MODEL?

Although the indirect evidence presented above is considerable, it is important to test the hypothesis directly. There are two electron microscopic observations of myosin filaments: (i) with native filaments [20]; (ii) with synthetic filaments [5]. Let us analyse these two studies, in the light of our present hypothesis.

4.1. *Native filaments*

The study is concerned with native filaments from rabbit psoas muscle [20]. In these filaments, ~300 heads/native filament are seen [20]. Now, according to Squire [21], there are ~100 levels of crossbridges (crowns; 143 Å repeats). Since each crown contains at least 2 crossbridges [21], this value corresponds to ~200 crossbridges/native filament. In table 7.2, Squire [21] gives the number N_M of myosin molecules/native filament and the number n of myosin molecules/crown. The average of the 8 values given in table 7.2 [21] is N_M ~330 ($n \sim 3.30$). As pointed out by Trinick and Elliott [20], all the myosin heads are not seen with their technique. If the whole length of a filament and a large number of filaments are considered, which is the case for the calculation of Trinick and Elliott [20], all the orientations of the myosin heads, with respect to the plane of the carbon film, are possible. For a given crown, one may reasonably assume that the proportion of external heads not seen lies approximately between 0 (all heads seen) and 50% (50% heads seen). These minimum and maximum values occur with the same probability, since all the orientations of the external heads are possible (see above). Therefore, the mean proportion of external heads not seen would be ~75% heads seen for a whole filament. Let us assume that, according to the usual concepts all the heads lie outside the backbone. In this case, the average number of heads seen/native filament would be $\sim 100 \times 2n \times 0.75 = 495$, which is considerably higher than 300 and which is not at all in favour of the fact that all the heads lie outside the backbone. Let us now assume that, according to our model, 2 heads/crown, (i.e., 1 head/crossbridge) are buried in the backbone. In this case, the number of external heads seen/native filament would be $\sim 100 \times (2n - 2) \times 0.75 = 345$. This value is in excellent agreement with the observations, and this is a considerable argument in favour of our hypothesis.

4.2. *Synthetic filaments*

The study is concerned with synthetic filament, also from rabbit or rat psoas muscle [5], showing that the myosin heads are unexpectedly replaced by

long 'whiskers'. We may propose 5 possible explanations for this behaviour:

(i) The whiskers observed, instead of globular heads, might result from an artifact of dilution. In fact, Siemankowski and Dreizen [22] have reported, and we have confirmed in our laboratory by means of laserlight-scattering (unpublished), that myosin loses its light-chains at the low concentrations used by the authors.
(ii) Uranyl acetate used for the negative staining has a low pH (3–4).
(iii) The precipitation of myosin might be a too drastic procedure.
(iv) The Lang-Kleinschmidt spreading method might be denaturating.
(v) The carbon membranes are hydrophobic, in contrast with the heads, which are highly hydrophilic.

All these possibilities (or only some of them) may result in a denaturation of the heads, with a subsequent unfolding and loss of the light-chains. We see below that this suggestion might be well founded. Note that the unfolding of the heads would be observed only on the external heads, not on the internal heads, for also 5 reasons:

(i) The head concentration is necessarily very high inside the backbone.
(ii) Uranyl acetate remains outside the shaft.
(iii) The heads buried in the shaft would be preserved from denaturation during the course of the polymerization process.
(iv) The internal heads would be insensitive to the spreading procedure.
(v) The internal heads are not in contact with the hydrophobic carbon film.

In spite of these possible difficulties, the study is interesting and supports our model. As far as the whiskers may be considered as unfolded heads, from which the light-chain have been removed, it is important to notice that these whiskers are never double-stranded (fig. 9 of [5]). Moreover, the mean width of the whiskers we have measured in fig. 9 of [5] is ~2.3 nm. Now, Morel et al. [12] have found that the most probable width of the myosin tail is ~2.0 nm and that the apparent width, after staining, is ~2.8 nm. The difference of ~0.8 nm is very likely attributable to the staining width, which leads to a true width for the whiskers of ~1.5 nm. By taking a maximum length of the whiskers of ~60 nm [5], we get $M_r \sim 88000$ (by taking $\bar{V} \supset 0.730$ ml/g). This value is extremely close to 90000 for a single S1 heavy chain [23]. Both the single-stranded character and the M_r of a whisker are strong presumptions that only one unfolded and light-chain-free head lies outside the backbone. Obviously, it should be of major importance to confirm this conclusion on globular heads, by taking into account the 5 possible sources of artifacts mentioned above or by applying to synthetic filaments the elegant technique in [20]. Such a study would be highly informative, since, in view of fig. 9 in [5], it seems that $n \sim 2$ in synthetic filaments, with the immediate consequence that only 50% of the heads lie outside the filament core.

5. DISCUSSION AND CONCLUSION

Convergent evidence shows that in vivo, one head of a myosin molecule may be inserted in the backbone of the thick filament, to interact with another head of the opposite molecule. In this model, there is no need that the two heads of one and the same myosin molecule are different, provided they each bear a dimerisation site. The existence of such a dimerisation site on each head is clearly shown in [3]. We have shown, on a mixture of S1(A1) + S1(A2), that a pure dimer can be obtained and suggested (section 1) that our model might be complementary to that proposed in [2], at least in the case of insect flight-muscles. The complementarity of both models, together with the fact that, in our model, the myosin molecules in excess have their two heads outside the shaft, shows that the usual concepts are not at all challenged here. In fact, in rabbit psoas muscle, for instance, there are ~3.30 myosin molecules/crown (see above); i.e., ~6.60 heads/crown. In our model, there are 2 heads/crown inside the backbone and, therefore, ~4.60 heads/crown outside. Hence, ~70% of the heads lie outside the shaft. In insect flight-muscle, there are ~12 heads/crown [21] and, in view of our model, ~83% of the heads outside. Therefore, in the limit of the experimental errors, the behaviour of the heads in vivo or in native filaments are mostly determined by the heads lying outside the backbone. For example, the fact that in rigor the myosin heads appear to form approximately a unique angle to filament axis, the fact that in relaxa-

tion almost all the myosin heads are mobile, the fact that it is possible to digest almost all the heads in native filaments (unpublished), do not contradict our model, since the proportion of heads immobilized inside the backbone lies between only ~30% (rabbit psoas) and ~17% (insect flight-muscle) in natural filaments. As concerns the synthetic filaments, in which we probably have $n \sim 2$ (section 4.2), it has been shown [24] that 'under conditions conductive to filament formation, the rotational mobility of the S1 moieties is sharply restricted compared to the high swivel mobility of S1 moieties that are membranes of individual myosin molecules'. Such a behaviour is easily explainable on the basis of our model, in which 50% of the heads are immobilized in the core of the synthetic filaments. Therefore, this is another important argument in favour of our concepts, which must be added to the arguments developed above.

Obviously, some problems will appear with our working hypothesis and it would be important to work on it in the future, particularly at the structural point of view. Is should be important to compare it with the existing models for the filament structure (review [21]). In particular, it should be confirmed that, in natural filaments, 1 head/cross-bridge can be inserted in the backbone and can interact with the opposite head. This seems to be structurally possible since, according to [21], the most probable case is that corresponding to a hollow center of the core ~50–100 Å in diameter: this is sufficient to insert two adjacent heads, with their long axis approximately parallel (fig. 2A). It is important to confirm our opinion on natural filaments, since our model might be connected with the mechanism of contraction. In fact, Morel and Gingold [25] have proposed a model of contraction based on head-to-head interactions inside the backbone, modulated by the MgATP concentration. In this context, we may suggest that the myosin molecules arranged according to our concepts may be the only 'functional' molecules. The myosin molecules in excess, whose heads lie outside the backbone, may play a role in the biogenesis of the thick filaments: they may be awaiting replacing the 'dead functional' molecules. This proposal would be supported by the fact that extremely active muscles (e.g., insect flight-muscles), have a considerable number of myosin molecules in excess. Moreover, the reported values of N_M are variable ($254 \leq N_M \leq 432$; table 7.2 in [21]). Such a variability may be related to the age of the animal, owing to the age-dependent metabolism: the young animals would have more myosin molecules/filament than the old animals. This proposed absence of 'functional' role for the myosin molecules in excess leads us to suggest that these molecules are not necessarily regularly arranged at the periphery of the filaments. Only the 'functional' modecules, with one head inside the shaft, would be arranged on a two-strand 6/1 helix. As clearly shown by table 7.4 in [21], such a model is sufficient to give a good explanation of the X-ray diffraction pattern, since $2/3.30 = 61\%$ of the myosin molecules are arranged on a two-strand 6/1 helix. In these conditions, the arrangement of the molecules in excess have no influence on the overall diffraction pattern. Whether these suggestions are grounded or not, it appears that the myosin molecules, with one head inside the backbone, play a role, at least, in filament diameter regulation. In any case, it would be necessary to account for the two roles of MgATP (enzymatic and structural) and, in a more general way, of all the Mg-(phosphate compounds). For instance, the dependence of the maximum speed of shortening and the tetanic tension on the MgATP concentration [26,27] might be interpreted in terms of actin–myosin and also myosin–myosin interactions and, maybe, in terms of the mechanism of contraction itself.

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