BIOCHEMISTRY OF MUSCLE CONTRACTION

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BIOCHEMISTRY OF MUSCLE CONTRACTION

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PREFACE

THIS volume contains the proceedings of a conference which originated in the desire of a number of people active in the field of muscle research to have an opportunity for a thorough discussion of problems of mutual interest.

In an early phase of planning for the conference it was decided that the practice customary in the discussions of the Faraday Society would be best. Papers to be presented were precirculated among the participants in order to make ample time available for discussion. The number of participants was limited, both by the physical capacity of Endicott House and by the decision made to keep the conference small enough for a lively and direct exchange of ideas.

Although new results—some of which have since appeared in print elsewhere—were presented at the conference, it was felt by all who attended that its greatest value was the opportunity it afforded to clarify ideas and bring controversial points to light. Hopefully, this volume will make it possible for others interested in muscle to share in this experience.

The topics covered include the chief myofibrillar proteins—myosin, actin and tropomyosin—and their interactions; the problem of the control of contraction and relaxation, both in terms of chemistry and structure; and the energetics and theory of muscle contraction. Developments which have taken place since the Conference are covered in notes added in proof whenever necessary and possible; efforts have also been made to annotate the discussions by supplying additional relevant bibliographical references.

The conference, held at Endicott House, Dedham, Massachusetts, in May, 1962, would not have been possible without a generous grant from the National Science Foundation. I am particularly grateful to Mr. W. V. Consolazio of the National Science Foundation, who greatly helped in formulating the plans for the conference. I am also indebted

to those who served as chairmen of the various sessions and helped in developing the program: J. T. Edsall, H. H. Weber, A. G. Szent-Györgyi, H. E. Huxley, R. J. Podolsky and D. R. Wilkie.

Special thanks are due to Albert Szent-Györgyi, who, with his characteristically witty introductory remarks, gave the conference an auspicious start.

Finally, I should like to express my thanks to Miss Mary Caulfield, my secretary, who greatly contributed to the success of the conference and who also, with the aid of Miss Joanne McGarvey, was of great help in the preparation of the manuscript.

J. G.

Boston

INTRODUCTORY REMARKS

Albert Szent-Györgyi

IT IS SAID that man is either a monogamist or polygamist; I should call a married man a polygamist when he betrays his mistress.

For twenty years I have been married to muscle, and my mistress was energetics. Now I am leaving energetics and so I am separated from muscle by two generations of thoughts. When Dr. Gergely telephoned me and said he wanted me to come, I said:

"What on earth do you want of me? I know nothing about muscle. Do you want to exhibit me as a museum piece, as one of the early workers in the field?"

He said: "Yes." And then added, in his hesitating manner: "But you will have to say a few words."

So here I am, and hope that you will excuse me if I display the most profound ignorance of muscle literature. In order to say a few words, I have to dig into my memories of twenty years ago to find points which I wasn't quite satisfied about.

Muscle contraction, whatever it may be, entails a profound change in physical state. The resting muscle is a loose gel, contractile muscle is what a poet calls "steel." Kuhn and Katchalsky (1949) have shown that colloidal systems can show such changes in state, can shorten and perform work with a high efficiency.

The only trouble to my mind was in the application of this experience to muscle. Kuhn and Katchalsky used strong acid or alkali to produce the effect. One has to have some very active agents to induce such a physical change. Muscle does not allow this. The problem arises, how can one produce a profound physical change in hydrophilic colloids without being rougher than such a subtle system as muscle can stand. I see only one possible way in which one can introduce a profound change in the physical state in a hydrophilic colloid, without being too crude, and this is by bringing two proteins to-

gether. You all know the interaction of antigen and precipitin. Both are hydrophilic colloids. When brought together they form a hydrophobic precipitate.

In muscle, you also have two hydrophilic proteins, actin and myosin, and I always thought that excitation means bringing these two together. In resting muscle they are separated and, in an equilibrium state, balanced on a razor's edge. As we know from superprecipitation, actin and myosin, in the presence of adenosine triphosphate, form a hydrophobic precipitate.

Hugh Huxley and Jean Hanson and A. F. Huxley then came along with a theory of interdigital creep, or whatever you want to call it. That theory does not allow, or gives no room for, physical change—just a creep of two colloids along one another. Their results were so beautiful and compelling that I had to accept them. I really had become a convert to this theory, but I never liked it, because it has done away with my old work, that is, superprecipitation.

I always thought there was an analogy to muscle contraction in superprecipitation. One can even produce contraction, contraction by the same reaction, in actomyosin threads that look like muscle, and there is no room for a "creep." Why and where should it creep? It makes no sense. Creep in this system will never make a contraction.

So this is a grudge that I kept, not against the Huxleys or Hanson, or against their theory, but just against fate, which seemed to disregard my old work. I am not going further into this question, but Andrew Szent-Györgyi will present to you some nice results, obtained lately, that seemed to bring together the old idea of actomyosin, superprecipitation, and some features of the Huxley-Hanson theory, so that, in the end, we might all be happy.

There is another point that I should like to bring up very briefly: the G-F transformation of actin. This is a very striking phenomenon. It is my experience, as a research worker, that if you see something very striking in a material which comes from the living system, that a very striking thing probably has something to do with life, directly or indirectly, and one should not lightheartedly dismiss it as an artifact. In this case, why should nature make threads out of globules, held together by relatively weak forces? The G-F transformation is exceedingly striking, and it is made much more striking by the fact that in the presence of myosin, it is instantaneous. In my crude experiments I couldn't even measure its rate. By the way, if one demonstrates it in a lecture, it usually occurs after the lecture is over, but in the laboratory it just occurs in a flash. This phenomenon must have something to do with muscle.

There is one point in muscle contraction which I think has never

been answered properly: how contracting muscle returns to its resting state. We have looked ourselves blind on contraction. It has been shown that G-actomyosin (the complex of G-actin with myosin) dissociates easier than F-actomyosin. So I could dream up the following cycle: in resting muscle F-actin and myosin are side by side, at a very close range, without interacting. Excitation brings them together, and the F-actomyosin thus formed folds up, ATP being present. In this folding the actin thread is broken up into globules. The G-actomyosin then dissociates into myosin and G-actin. Owing to the catalytic influence of the myosin, the G-actin then associates to F-actin and so F-actin and myosin are side by side again—that is, returned to the resting state—and the contraction cycle is complete.

Just one more thing. As you know, some work has been done in my laboratory on the catch mechanism. I asked myself, is there no catch mechanism in human beings? In the hypnotic state, one can make people stiffen up and then put them with their head on one chair and their heels on another, and they are stiff, like a piece of wood. One can go out for lunch and come back and still find them lying there, happily. I picked out the strongest fellow in my research group, and I put him on two chairs, in the same way, without hypnotizing him, and he couldn't hold such a position for one minute; in about twenty seconds he collapsed. This suggests that there may be a catch mechanism which can be demonstrated in the whole individual only in the hypnotic state.

These are my remarks. An additional one contains my best wishes for the success of your discussions.

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