PROCEEDINGS OF THE
THIRD MEDICAL CONFERENCE
OF

Muscular Dystrophy

Associations of America, Inc.

NEW YORK, N. Y.
OCTOBER 8 and 9, 1954

MUSCULAR DYSTROPHY ASSOCIATIONS OF AMERICA, INC.
790 Broadway New York 19, N. Y.

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AMERICAN JOURNAL OF PHYSICAL MEDICINE
MUSCULAR DYSTROPHY ISSUE

Preface

Herewith the AMERICAN JOURNAL OF PHYSICAL MEDICINE presents to its readers another issue devoted entirely to one subject. All papers were presented at the Third Medical Conference, sponsored by the Muscular Dystrophy Associations of America, Inc. (MDAA), and held in New York on October 8 and 9, 1954. There were six symposia, four dealing with basic biochemistry and physiology of muscle, and two dealing with the clinical aspects of the dystrophy problem.

To all who participated, as authors, discussants, or simply as listeners, this conference brought a wealth of information. It was wide in scope, not limited to specific dystrophy problems only. By bringing research workers and research-minded clinicians together, an opportunity for exchange of ideas was created, which in this age of specialization occurs all too infrequently.

Planning a conference such as this requires much hard work, to be sure, but above that it requires vision and an understanding of the magnitude of the problem and its many ramifications. Most important is the realization that only by thorough research into the basic mechanism of muscle function, coupled with clinical research, can we hope for maximum results from our efforts. Dr. Ade T. Milhorat, Chairman of the Medical Advisory Board of MDAA, planned this conference with just such vision and understanding. The editor is sure that he speaks on behalf of all those who attended, in expressing to Dr. Milhorat both gratitude and admiration for the planning of this conference, not only for the large amount of work which he has done, but above all for realizing that by bringing together scientific men with widely different backgrounds, to focus their attention on a common problem, much can be accomplished which, in the future, may prove to be of more value than the work of one individual in isolation.

The Muscular Dystrophy Associations are to be congratulated for making this large-scale conference possible. In his opening address Dr. Hinsey points out that the Muscular Dystrophy Associations are only 4 years old. Besides vision, it took very real courage for a relatively young organization to plan such a large-scale undertaking. From the remarks heard in the corridors, the officers of MDAA may rest assured that this conference has served to bring the dystrophy problem to the attention of those engaged in research on muscle, in whose hands and minds the solution of this baffling problem may well rest. This journal considers it a privilege to cooperate with MDAA in making the material available in printed form as quickly as possible.

To Dr. Morton D. Schweitzer, scientific director of MDAA, and his staff, belongs the credit for getting the manuscripts in on time. The very effective way in which the conference was run, the discussions recorded, and those little things done that make the participants go home happy and satisfied, demonstrated not only his ability to cope with a complex situation but also his genuine love for the work he is doing.

Rapid publication of a symposium as large as this requires the cooperation of many beyond those responsible for the organization of the program. The editor wants to express his sincere gratitude to the authors of papers for having their manuscripts ready on time and for their immediate replies to our inquiries regarding points which needed clarification. A special word of thanks is due the discussants who, without fail, corrected their discussion remarks as taken from the stenographic transcripts, sometimes returning them within hours after receiving them. Without the whole-hearted cooperation of authors and discussants this publication obviously would have been impossible.

And finally, behind all this stands the group of lay workers who make up the MDAA chapters. It is tremendously impressive to see such cooperation between research workers, clinicians and the public, which gives rise to foundations such as the Muscular Dystrophy

Associations. Truly the public thus becomes a partner in medical research. Under the scientific leadership of men such as Drs. Milhorat and Schweitzer, and the organizational leadership of the officers of the Dystrophy Associations, both nationally and locally, truly important things have been and will continue to be accomplished. Ultimately the sufferer from the disease will benefit. To the quiet and unknown workers in the chapters of MDAA, we who had the privilege of attending this conference, which you made possible, say a sincere: thank you.

H. D. Bouman, M.D.
Editor

THE THIRD MEDICAL CONFERENCE SPONSORED BY THE MUSCULAR DYSTROPHY ASSOCIATIONS OF AMERICA, INC.

Opening Addresses[1]

ADE T. MILHORAT, M.D.[2], AND JOSEPH C. HINSEY, PH.D.[3]

Dr. Milhorat: Ladies and Gentlemen: On behalf of the Medical Advisory Board, the Board of Directors and the Executive Committee of MDAA, I bid you welcome to the Third Medical Conference.

The four years that have passed since the founding of the association, have seen many changes. Of these we may be justly proud. The cause of the patient with muscular dystrophy has entered the hearts of people everywhere. Great organizations such as the Letter Carriers, the Firefighters of America and the Tall Cedars of Lebanon, composed of persons mindful of their brothers' plights, have joined with MDAA and have lent their shoulders to bear the heavy burden of patients with this disease.

The accomplishments and aspirations of MDAA, Inc., are depicted in part in the program of this conference. There are reports from investigators from all sections of this country, and even from Europe, on research supported by MDAA. There are formulations of plans to bring various types of service to the patient in the clinic and in his home. There is no aspect of a patient's problem that is not being submitted for discussion and deliberation. There is evidence of growing cooperation between laboratories investigating muscular dystrophy and those organized primarily for the study of other major diseases of man.

Unfortunately, there is no report on effective treatment. It is for this reason that some of the symposia have been arranged, not only to give us fundamental knowledge and to relate this knowledge to the problem of muscular dystrophy, but to furnish us and those who will read the proceedings later with new ideas for research. Let us hope this conference will serve as a basis on which we may dedicate ourselves anew in our efforts to conquer a dread disease.

Perhaps the greatest hope is the growing interest of investigators such as you, who are present here today, and the great laboratories, clinics and medical centers that you represent.

It is appropriate that the speaker of today is a good friend of MDAA, and a representative of a medical center long devoted to the cause of the patient.

It is, therefore, with great pleasure I introduce to you the Director of the New York Hospital-Cornell Medical Center, Dr. Joseph C. Hinsey.

[1] Presented at a luncheon meeting for professional registrants during the Third Medical Conference, sponsored by the Muscular Dystrophy Associations of America, Inc., New York, October 8 and 9, 1954.

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[2] Chairman, Medical Advisory Board, MDAA, Inc.; Associate Professor of Medicine in Psychiatry, Cornell University Medical College, New York, N. Y.

[3] Director, New York Hospital-Cornell Medical Center, New York, N. Y.

Dr. Hinsey: Dr. Milhorat, Dr. Schweitzer, and those of you from all over this country who are devoted to solving the mysteries of the cause of this dread disease:

I couldn't help but think back—it was in 1924 that skeletal muscle first became of great interest to me, and in investigation I spent many hours and many days over a microscope trying to delve into some of its mysteries, particularly the innervation of muscle. Not very long after that it was my good fortune to be a student and work with this afternoon's chairman of your symposium on contractures, Dr. Herbert Gasser. I have a rather peculiar feeling coming to a meeting like this where there has been such a magnificent program as you have had this morning, and to know of the program that is ahead. I realize that the parade has gone ahead as far as I am concerned as an investigator. However, I shall always retain my interest in muscle and its many problems, including the problems of muscular dystrophy. I turned to our files and I thought it would be of interest to those of you here to know something about the early development of this association.

I am not prepared to give you an historical background, but I have two or three documents I believe will be of interest to you. Then I would like to make some comments relating to the general problem of foundations and funds of this type.

The first by-laws were formed, Dr. Milhorat tells me, in March of 1950. I couldn't help but be impressed with the wisdom of the things that this association was going to undertake:

a) To foster and promote the cure and alleviation of the condition of persons suffering from the disease known as muscular dystrophy or from any other similar or allied dis eases.

b) To promote research into the causes and cure of such diseases and the remedies therefor.

c) To promote the training of competent personnel to aid in the cure, care, education, adjustment and rehabilitation of sufferers from such disease.

d) To promote the training, vocational guidance and occupational placement of sufferers from such disease.

e) To promote adjustment to normal living of sufferers from such disease.

f) To disseminate information with respect to such diseases, the programs for the benefit of sufferers from such diseases.

g) To do all appropriate acts to carry out the foregoing purposes.

h) To receive by gift, device, bequest or otherwise, money or other property, or any estate therein, and hold the same and distribute the income therefrom for the promotion of the foregoing purposes.

One of the things that is significant to me, as I have talked to those who have worked with this organization, is the emphasis placed upon research; and, furthermore, the fact that the work is not confined to a narrow portion of muscle and its problems. There has been a broad view in regard to things that can be investigated, fundamental research on the biological problems related to muscle, as well as to the more specific and applied research.

Now, I have here the first certificate of incorporation, and I show it because it is a copy dated the sixth day of June, 1950. I want to emphasize the time. Then I have also a copy of the letter of the first grant that was made. This is a letter addressed to Dr. Stanhope Bayne-Jones, who was then president of the Joint Administrative Board of our institution; it was signed by Mr. Paul Cohen, who was President pro tem of the Muscular Dystrophy Association.

This letter reads: "Dear Sir: The Executive Board of the Muscular Dystrophy Association has voted to grant to the Society of the New York Hospital a sum of $1500 to be used by Dr. Ade T. Milhorat for research in muscle disease. Check to cover this grant is attached to this letter."

"The membership of this organization already comprises over three hundred individuals." I understand that you have 125 chapters in this association, and there will be 150,000 volunteers that will work in the campaign that begins this fall. That certainly is some growth in the period of four years!

Mr. Cohen continues by saying that he believes "this association will be successful in raising much larger sums of money which will be made available to the New York Hospital, to further Dr. Milhorat's work.

"The membership is unanimous in its viewpoint that the patients with this dreadful disease are indebted to Dr. Milhorat for any practical research in the treatment of this disease, and we all feel the hopes for the treatment and cure lie in his competent and devoted hands.

"At our first meeting five weeks ago, it was unanimously resolved that the very first objective of our association would be to make available to the New York Hospital the funds necessary to enable Dr. Milhorat to carry on and even expand his research in muscular diseases."

It is significant to me that work is now going on in institutions in eighteen states, at least, and two foreign countries, and that something in the neighborhood of seventy projects are now being supported by this organization.

"While we are still very much in our infancy," (this was May 17th, 1950), "it is clear that the organization will grow into a vigorous and healthy group and achieve its goal. We, therefore, tender this check to you with pride in the fact that, even though small, the funds have been made available for this purpose in such an extremely short time. We offer it with the promise that much more will be made available.

"We offer it also in the spirit of heartfelt admiration and deep gratitude to Dr. Milhorat and the New York Hospital for all it has done for us in these past years."

I read that because I want to emphasize when the first grant was made, and it was made a little over four years ago. Later that same year, in November of that year of 1950, the same men came to our institution and wanted us to be prepared to make use of a fairly large sum of money, in support of Dr. Milhorat's work.

I recall so distinctly how this matter was discussed and it was the judgment of our board that for us to undertake work of this size, it would be necessary for us to seek the support over a five year period. So the decision was made that

if at some future date the Muscular Dystrophy Association should have in its treasury the amount it had promised, and also could give evidence that it would be available over a period of five years, we would be sincerely interested in forwarding this work.

Then a little later, on June 18th of 1951, the Board of Governors of the New York Hospital made the commitment to change the facilities in the Payne-Whitney Clinic to take over the program that had been envisioned some months previously. I tell this because it illustrates what can be done by people who have faith and are willing to work.

I have been very much impressed in the dealings I have had with the lay people that are in back of this organization, Mr. Paul Cohen, Mr. Langer, Mr. Lehman, Mr. Mazer, and there have been others. These are men who are devoted to a cause. Sometimes in our scientific and medical work we are impatient with the lay people, and possibly we think they don't understand; if we realize how much they contribute to the work that we are doing in our medical and scientific institutions over the country, we would be a little more appreciative. I know how much this organization appreciates the work of these men, as well as the many thousands of people that work in the chapters over the country.

This program in its makeup and the people who are here, testify to the progress that has been made in the scientific work carried on by the Muscular Dystrophy Association.

In the last fifteen years we have had a great increase in the support of research in this country. Much of it has come from the government, but a significant portion of it has come from private sources. This increase in research money has been a great blessing to us; but at the same time, it has brought certain problems, particularly to those who are in administration in medical institutions.

All of these research funds are used by investigators in solving problems. These investigators have to be paid salaries, and they also need the facilities with which to work.

They come largely from our scientific laboratories, and to a great extent, from the nation's medical schools, as well as from those in Canada and foreign countries. In this country we have eighty medical schools and, as one who is very much interested in the whole problem of medical education, I have been impressed with the impact of these research funds upon the forward progress of medical education. There is no question that the development of research in our institutions has been very important in bringing American medicine to the point where it is today, and with that we have had larger numbers of people brought into research.

If we look at the budgets of the nation's medical schools for this year, we find we have about forty-four million dollars that is devoted to research from outside sources. The basic budgets of our medical schools total about ninety-four million dollars. We get research grants from outside sources somewhere in the neighborhood of forty-four million dollars.

There are other sources of funds that enter the picture, but when you bring

that amount of money into the operation of our medical schools, the problems that arise are those that come in maintaining balance between teaching and research and care. There is another place where balance must be maintained, and that is to see that fluid funds of each institution are so protected that they are not unduly diverted by the needs of the research programs. Many investigators are impatient with the covering of indirect costs and can't see what is known as overhead; they look at that money as taken away from them. The only trouble in most instances is that it isn't really enough to pay the cost. There is no question in the years ahead that the indirect costs for research in our institutions are going to have to be carried to a larger extent than they have been, or we will divert more money than we can afford from the basic programs of our medical schools.

It has always seemed to me that an organization that is devoted to the raising of funds for special research has an obligation to keep afloat the institutions that are supplying the personnel. I believe organizations like the American Red Cross and many of our other foundations could properly give consideration to the basic support of some of our institutions, laboratories, and medical schools. In the years ahead I believe that will happen, and the National Fund for Medical Education is just an attempt in that direction. There we have had a banding together of our medical schools and their supporters in industry and medicine to try to raise money to support all of the medical schools of this country.

When I see what an organization like yours does in terms of getting funds, it makes me wonder what we need to do to get more for our National Fund. However, you have a special appeal, and I think you have people that are interested in working that do not necessarily know about the needs of the medical schools as a whole.

In closing, again I would like to pay tribute to what has happened in this organization during these last four years. As I look ahead I see even a much greater development, because it seems to me that there has been an acceleration in the forward progress of this association. That acceleration has been mainly in the field of research interest and in the number of people who are participating. So, today, certainly it is to be hoped there will be a solution to the cause of muscular dystrophy, and when that solution is reached, undoubtedly other things of importance will be solved.

Again I want to tell you how much I appreciate the opportunity of being here with you, and also to have met as many of you as I have. Thank you very much.

A SYMPOSIUM[1]

RECENT ADVANCES IN BASIC MUSCLE CHEMISTRY, PHYSIOLOGY, AND PHARMACOLOGY

WALLACE O. FENN, PH.D., CHAIRMAN[2]

Chairman's Introductory Remarks

I have the honor to call to order the Third Medical Conference of the Muscular Dystrophy Associations of America. Looking at the impressive list of distinguished speakers on the program I confess that I feel very inadequate as a presiding officer. Because of my long interest in problems of muscle physiology, however, I am quite delighted at the opportunity to be present, even without a quiet seat in the audience.

The problem of muscular dystrophy is one which taxes the scientific imagination and knowledge to the limit. If it were an easy problem we should have had an answer long ago for there are few processes in the body which have been studied so intensively as muscular contraction and there are few cells about which so much is known as the muscle cell. And still the problem eludes us. Some tiny link in the long chain of events which constitute a muscle contraction appears to be missing but just what this link is, why it is so dramatically and tragically essential, and how it can be remedied are still unknowns. Indeed, we understand these links so inadequately that a deficiency in any one of them might conceivably be the cause of muscular dystrophy. The neuromuscular transmission and conduction of the wave of excitation over the muscle are not usually considered faulty but recently Hove and Copeland (1) have suggested that the formation of acetylcholine might be impaired by lack of vitamin E or an excess of some reducing system which would leave coenzyme A in the disulphide form which, in turn, does not participate effectively in acetylcholine synthesis. This is indeed an interesting suggestion but one of such very broad applicability in physiology that it is perhaps difficult to believe that all the defects would be confined to the muscles as they are in muscular dystrophy.

A consideration of the mechanism by which the wave of excitation stimulates the contractile machinery is perhaps too treacherous for a place in this introduction and we may therefore consider the contractile machinery itself as a possible cause of the deficiency in muscular dystrophy. Here we have the still unproved suggestion of Zierler (2) that because of some metabolic defect it may be impossible to synthesize proper quantities or qualities of actomyosin; and the

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[2] Professor and Chairman, Department of Physiology, the University of Rochester, School of Medicine and Dentistry, Rochester, N. Y.

MacKenzies (3) have given us reason to hope that such a defect might be supplied by tocopherylhydroquinone. Certainly, as my friend and colleague, Dr. Mason, could tell me, there is evidence in the histological picture that the contractile machinery is to some extent at fault, because the muscle does not *look* right under the microscope. Perhaps we could properly liken it to a bicycle without teeth on the back sprocket. There is plenty of power on the chain but no transmission.

There may be, however, some less obvious chemical defects in the contractile machinery. Both contraction and excitation are intimately related to the concentrations of electrolytes K and Na inside and outside the muscles. In dystrophic muscles it was shown long ago that the concentrations of K and Mg are low, while those of Ca and Na are high (4). This result is most simply interpreted as due to conversion from muscle fibers into extracellular space, for which there is good histological evidence; but it might also be true that each individual fiber contained abnormally high concentrations of Na and abnormally low concentrations of K, as in a fatigued muscle, and lacked the necessary metabolic pump mechanisms for removing Na and concentrating K. Such a muscle might well behave like a permanently fatigued muscle. In other words, I am suggesting as a possibility that this abnormal distribution of electrolytes may be to some extent the cause of the dystrophy rather than the result. Perhaps the muscle is unable to synthesize a suitable carrier for use in the Na pump mechanism. In this connection I might remind you that rats raised on a low K diet according to Cannon (5) develop heart lesions not unlike those seen in muscular dystrophy but only when there is a high concentration of Na in the diet. Professor McDowall (6), now visiting in this country from London, has suggested that a high Na concentration in muscle is an adequate reason for poor responses. This aspect of the problem might well bear further investigation as another way in which the contractile machinery itself might be out of order.

Finally, it might be suggested that the contractile machinery is in good order but the power supply is absent. The immediate source of energy for muscular contraction is believed to lie in the high energy phosphate bonds of ATP, and I suspect that some of the discussion during this meeting may center around this very basic problem of the time, place and mechanism whereby the ATP is broken down to ADP. If contraction is the active phase, then ATP should yield its energy during contraction but many workers seem to believe that ATP breakdown must occur in relaxation when potential energy is being stored for the next contraction. How this could occur without any outward sign of heat production or absorption, as A. V. Hill reports, is hard to understand but perhaps not impossible.

I cannot discuss these problems now, however. Unlike the distinguished speakers on the program, I am neither a student of the muscular dystrophy problem nor, in recent years, am I even a specialist in muscle physiology. My task is only to introduce the speakers and in so doing I would point out that this morning we hope to hear about some of the most recent contributions to our understanding of the normal process of muscular contraction so that we may be in

a better position to discover the cause of muscular dystrophy and to suggest a cure. I am sure that each speaker will need all the time allotted to him.

As a general text for the meeting may I suggest the Biblical quotation from the Psalms which reads—

"Day unto day uttereth speech and night unto night showeth knowledge." (7)

And now for the speeches, which are sure to bring before us an impressive array of new knowledge for us to ponder during the night.

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THE PROTEINS OF MUSCLE AND THEIR PARTICIPATION IN THE PROCESS OF CONTRACTION[1]

W. F. H. M. MOMMAERTS, PH.D.[2]

A discussion of the intimate nature of contractility at the opening of a conference on muscular dystrophy may require more justification than is immediately apparent. For, although the group of diseases of interest to this audience have their manifestation in a disturbed structure, metabolism, and function of the musculature, it is entirely uncertain that the deeper cause of this deviation is within the muscle itself. This paper is presented, therefore, with the understanding that it is not meant to make a contribution to the appreciation of the intimate cause of the disease, but to describe the main properties of the tissue that is ultimately affected.

That, of the many constituents of muscle, the proteins are singled out finds its explanation in the fact that these substances are quantitatively predominant, and that the contractile fibrils themselves constitute an ordered array of specific structural proteins. It would be unphysiological, however, to restrict this discussion to the proteins only. On the contrary, much significance will be attached to interpreting the interactions between structural proteins and those low-molecular constituents which are—rightly or wrongly—being regarded as the causative agents in contractile activity. Again, it must be recognized that it is not at all certain that even these problems are closely related to the direct manifestations encountered in degenerative muscle diseases. Rather, one would intuitively expect that studies on the metabolism (turnover) of the structure proteins might have a more direct bearing on a disease which essentially constitutes a failure of maintenance; but not enough is known to consider this possibility seriously in any detail. On the other hand, an effort has recently been made (2, 15) to consider muscle degeneration as a *molecular disease* in terms of an altered architecture of one of the structure proteins, and this viewpoint, even if not yet convincingly supported, will certainly deserve consideration.

In the intracellular organization of muscle, we can distinguish three major systems, both from a morphological and a functional point of view. These are

[1] The original researches discussed in this paper have been performed in collaboration with K. Seraydarian, P. A. Khairallah, M. D., R. G. Parrish, Ph.D., I. Green, Ph.D., J. R. C. Brown, Ph.D., J. C. Rupp, Ph.D., and J. Hanson, Ph.D. This work has at various times been supported by the National Heart Institute of the National Institutes of Health, the American Heart Association, the Rockefeller Foundation, the Muscular Dystrophy Associations of America Inc., the U. S. Army Medical Services, the Life Insurance Medical Research Fund, and the Cleveland Area Heart Society.

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[2] Established Investigator of the American Heart Association, and Associate Professor of Biochemistry, Western Reserve University School of Medicine, Cleveland, Ohio.

the fibrils, the sarcosomes or cytochondria, and the sarcoplasm. The former are the organels of the contractile function itself. In terms of metabolism, these are the structures which, with the purpose of generating mechanical work, utilize the metabolic agent which supplies chemical energy to be transformed into work. For about 20 years, it has been widely accepted that this metabolic agent is adenosinetriphosphate (ATP), and we shall take this standpoint during the larger part of this discussion. In this light, energy for work is derived from the splitting of ATP. Simple calculations show that in moderate activity the human body would utilize per day about 250 moles or over 100 kg. ATP. Since the body contains only about one thousandth of that amount of it is obvious that ATP must be regenerated to the extent that it is used. This regeneration is the task of metabolism. Ultimately this is respiratory metabolism, but many types of muscle can function anaerobically for a certain period, during which they glycolyze instead, whereby also limited amounts of ATP are formed. Glycolysis is carried out in the sarcoplasm, whereas respiration is the function of the sarcosomes. Correspondingly, the sarcosomes are abundant in those muscles which maintain a fairly intense activity over protracted periods, and which tend to keep a balance between the utilization and the aerobic generation of ATP. On the other hand, muscles which function intensively only for short bursts of time rely upon the complex temporary adjustments known as oxygen debt, and are not well supplied with sarcosomes. The sarcosomes have mostly been studied from an enzymological point of view, but recent progress in electronmicroscopy has revealed a richness of structural detail.

The soluble proteins of the sarcoplasm can be obtained by extracting minced muscle with water or dilute salt. Such extracts contain a multitude of individual proteins. A number of these have been identified with glycolytic enzymes and it may be a valid generalization to say that the entire sarcoplasmic protein (often called myogen) is nothing but a collection of catalytically active proteins. The multiple composition of this myogen is also revealed by means of electrophoresis, extensively applied by Dubuisson, which method separates a number of physicochemically distinct protein fractions. Some recent investigations have shown that the amount of certain individual enzymes or electrophoretic components is altered in different forms of muscular atrophy.

Due to their immediate relation to contractile function, the protein constituents of the fibril require a more detailed treatment. The fibril, as indicated by its optical anisotropy, must possess a highly ordered submicroscopic structure, and one would expect therefore that its protein constituents must be endowed with special physical properties suitable to make them participate in such a special organization. This was borne out by a study of these proteins in the isolated state. The first protein entity recognized was named "myosin," and was obtained by extracting freshly minced muscle with strong salt solution (e.g., buffered 0.5 M KCl). It forms viscous solutions which were discovered to be birefringent when flowing (Von Muralt and Edsall, 1930). Both these physical properties suggest that myosin in solution consists of highly elongated particles, a feature which would be of significance in the formation of fibrous structures. This possibility received even sharper formulation when Weber in 1934, on the