

**Bioenergetics
Molecular Biology,
Biochemistry,
& Pathology**

BIOENERGETICS

**Molecular Biology,
Biochemistry, and Pathology**

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FOREWORD

The emergence of the Biochemical Sciences is underlined by the FAOB symposium in Seoul and highlighted by this Satellite meeting on the "New Bioenergetics." Classical mitochondrial electron transfer and energy coupling is now complemented by the emerging molecular biology of the respiratory chain which is studied hand in hand with the recognition of mitochondrial disease as a major and emerging study in the basic and clinical medical sciences. Thus, this symposium has achieved an important balance of the fundamental and applied aspects of bioenergetics in the modern setting of molecular biology and mitochondrial disease. At the same time, the symposium takes note not only of the emerging excellence of Biochemical Studies in the Orient and indeed in Korea itself, but also retrospectively enjoys the history of electron transport and energy conservation as represented by the triumvirate of Yagi, King and Slater. Many thanks are due Drs. Kim and Ozawa for their elegant organization of this meeting and its juxtaposition to the FAOB Congress.

Britton Chance
April 2, 1990

PREFACE

This book contains the contributed papers presented at the "International Symposium on Bioenergetics: Molecular Biology, Biochemistry and Pathology", held in Seoul, Korea, August 18-21, 1989, sponsored by International Union of Biochemistry (as IUB Symposium No.191) and Ewha Womans University, Seoul, Korea.

The symposium was held in honor of Professor Kunio Yagi to commemorate his 70th birthday. Professor Yagi has not only made many scientific accomplishments in biochemistry, but also enormous contributions to the international biochemical communities such as International Union of Biochemistry and the Federation of Asian and Oceanian Biochemists. His unusual pleasant personality and ability to get many scientists together, have helped many biochemical societies of different countries to grow.

In the last several years, advances in bioenergetics, in particular molecular genetics, have facilitated detailed study of the structure-functional mechanism of mitochondrial electron transfer and energy transducing system, at the molecular level, and has been directed into the study of the molecular basis of mitochondrial disease, which is no longer a new field now. This is the very reason why the broad subtopics are chosen to be discussed in this symposium.

The purpose of this symposium was to bring together the scientists from those various disciplines of bioenergetics field to discuss recent developments in their fields so that they can exchange new ideas and interact each other to promote collaborations. It was our intention to provide an opportunity to discuss a wide range of bioenergetics topics that has previously been all too rare in Asian biochemical communities. Hopefully, a meeting like this can be continued regularly, in Seoul, Korea or in Nagoya, Japan.

The symposium was structured in a similar way to the previous "Symposium on Membrane Biochemistry and Bioenergetics", held in Rensselaerville, NY, August, 1986 (Kim et al., Plenum Press, 1987). Four lecture/discussion sessions and one poster/discussion session covered a variety of subjects from the molecular evolution of mitochondrial DNA to bioenergetic consequences of genetic disease. Drs. Y. Anraku, A. Azzi, M. H. Han, C. H. Kim, Q.-S. Lin, A. W. Linnane, T. Ozawa, S. Papa, P.S. Song, and C.-L. Tsou served as the session chairmen. All the participants were energetically involved in discussions of the subjects presented, giving us a lesson to plan a day more for the next meeting. All invited participants contributed a chapter to this volume except for a few, who could not make it with regret, due to various reasons.

This symposium was made possible with financial support from sponsors. We are grateful to sponsors, the Symposium Committee of the International Union of Biochemistry, Ewha Womans University, Korea Science Foundation, MIWON Co. Ltd, Seoul, Korea and Institute

of Applied Biochemistry, Gifu, Japan. We express our special thanks to Mr. Chae Bang Kim, President of MIWON Co. Ltd. for his generous support to this meeting without hesitation. We also thank to Dr. Young Bog Chae, Director of Korea Research Institute of Chemical Technology for his support.

We wish to express our warm thanks to Professor Hea Chung Yun, Ewha Womans University, for her constant help throughout the organization of the symposium. We give thanks to Ms. Kum Hee Cho, Jung-Sun Kim, Hae-Jin Kim, Hye-Gyu Lee, Yong-Nam Roh, Sang-Hee Shin and Sung-Hee Shin, from Ewha Womans University for their efficient assistance during the meeting. We also thank Ms. Akiko Hashimoto in Nagoya, Ms. Donna Hilbert and Stacey Hood in RPI for their assistance throughout the organization of the symposium. Our special thanks extended to Mr. Michael Seaman for his assistance in editing and Ms. Laura Waelder for her word processing service for this volume.

Finally, we are thankful for all the enthusiastic participants who made this symposium successful and hope that we can get together in the next meeting with further interesting results and ideas in the field of bioenergetics.

Chong H. Kim
Takayuki Ozawa
March 1990

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Opening Session

INTRODUCTORY REMARKS

Chong H. Kim

It is my pleasure to open the "International Symposium on Bioenergetics: Molecular Biology, Biochemistry and Pathology" in honor of Professor Kunio Yagi.

I welcome all of you to Seoul, Korea! I think that most of you - probably all of you who is not resident here - come to Seoul for the first time. Before I introduce Professor E.C. Slater, President of International Union of Biochemistry, for opening lecture, I would like to say a few words for having this symposium in Seoul.

It is a very exciting moment for me to have all of you here at the Symposium on Bioenergetics. Because there is a reason. It has been fifteen years since I left my homeland, Seoul, Korea, to pursue advanced studies in Biochemistry in the United States. At that time, it was very difficult to do any advanced biochemical experiments in Korea. I had already done a few rather simple biochemical experiments by that time. However, I had to run from one institute to another in order to accomplish even those simple experiments. Unfortunately, I could not find a good teacher to lead my enthusiasm towards biochemical research. Therefore, I decided to study biochemistry in the States, where I had already visited for a month in 1973, on the way of my return from Copenhagen, Denmark, where I spent a few months for the advanced courses in Clinical biochemistry.

Fifteen years later now, Korean Biochemical Society has impressively grown to the level, at which they can freely exchange and discuss their scientific progress with leading scientists from all over the world. Some of you must have seen such an example at the 5th FAOB (Federation of Asian and Oceanian Biochemists) Congress, which was held last week just before this symposium. I am very proud to see that such an excellent international scientific gathering has been held in Seoul.

Our decision to hold a Symposium on Bioenergetics in Seoul, Korea, came about a year ago in Prague, at the 14th International Congress of Biochemistry. It is my honor to have a "Symposium on Bioenergetics" participated by all you, leading scientists from 13 different countries, in the country I was born and educated, with the support of the institution at which I was educated. I am grateful to those of you, my teachers, friends and colleagues, who have nourished my knowledge in bioenergetics, and helped me to open this successful, I believe, symposium in Seoul. Above all, I thank my co-organizer, Professor Ozawa, who is an excellent partner. I must also mention about the person behind me to make the smooth running of this symposium, Professor Hae-Jung Yun, Dean of College of Pharmacy, Ewha Womans University. Her unaccountable help made my task for this meeting easier.

I hope all of you can have a joyful time during this meeting even though our schedule is too tight and this can be a momentum to bring another Bioenergetics meeting in Seoul near future. I especially invite you to experience the beauty of the city of Seoul at the end of this meeting, and now I would like to introduce Professor Slater for the opening lecture.

INTRODUCTION BY REMARKS

It is my pleasure to have the honor of introducing Professor Slater to you. He is a very distinguished and accomplished scientist and a very kind and friendly person. I hope you will all enjoy his lecture and his company during the meeting.

Professor Slater is a very well-known and respected scientist in the field of bioenergetics. He has made many important contributions to the field and is a very active and enthusiastic researcher. I am sure you will all find his lecture very interesting and informative.

It is a great pleasure to have Professor Slater here with us today. He is a very distinguished and accomplished scientist and a very kind and friendly person. I hope you will all enjoy his lecture and his company during the meeting. Professor Slater is a very well-known and respected scientist in the field of bioenergetics. He has made many important contributions to the field and is a very active and enthusiastic researcher. I am sure you will all find his lecture very interesting and informative.

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OPENING LECTURE

E. C. Slater

Thank you very much, Dr. Kim and Professor Yagi and Dr. Ozawa and to other colleagues. There are, of course, many reasons why I am happy to say a few words at the opening of this symposium. First, and foremost, it is my pleasure to be able to attend this meeting to honor Professor Yagi on the occasion of his 70th birthday. I shall have more to say about you and to you, Kunio, tomorrow evening, and it suffices now to congratulate you and welcome you to the select band of septuagenarians present at this meeting. Now another reason why it is a great pleasure for me to say a few words here is that this is a IUB symposium, it is #192 as a matter of fact and I have attended all of the IUB congresses since the first one in 1949. I, of course, cannot say the same thing about IUB symposia, even during the period in which I am president of IUB. This year alone IUB is sponsoring no less than 28 symposia through its two committees-Symposium Committee which is chaired by Arnost Kotyk who is here at this meeting and our so-called Interest Groups Committee. But, although we have allocated more than one-third of our total budget - our total budget is only about \$300,000 to support our symposia, a quick calculation will show you that our support is spread out pretty thinly. Actually, Dr. Kim has been most skillful in utilizing our resources efficiently. Since quite apart from direct subvention from our Symposium committee - three of the speakers are members of the executive committee of IUB who are meeting here in Seoul, earlier in the week, and have had their travel expenses paid by IUB under a different budget heading, namely of the executive committee. Moreover, others have attended the FAOB Congress which ended yesterday, which also received some support from IUB under yet another budget heading, and I am sure that our Treasurer, who is Tony Linnane, will be very pleased at your efficient use whereby money is spent twice.

This is actually the second IUB sponsored symposium on bioenergetics held in the FAOB area. I suppose those who were not at this very wonderful FAOB meeting earlier this week - really extremely well organized meeting with a good program indeed, and some of you who have just flown in may not know what FAOB is - well let me tell you - it is the Federation of Asian and Oceanian Biochemists. Now the first IUB symposium in Asia was held in Beijing, China in 1984, in Bioenergetics. I just want to sketch because Dr. Kim asked me to fill up the program up to 9:00 o'clock.

The Progress that I see or the sort of changes that I see have come into the field in the last five years - during much of the time which I have no longer been active in bioenergetics research. I think, of course, a lot of progress was made particularly by the application of techniques introduced from molecular genetics. Of course, cloning and DNA sequencing

had already, five years ago, given us the amino acid sequences of many subunits of the electron transferring and ATP-synthesizing proteins. This has been largely completed now in the intervening period. And the powerful tool of site-directed mutagenesis has been directed to the study of the function, mechanism of action and particularly in the biosynthesis also of the subunits. I think that we can say that the mechanism of electron transfer or the pathway, in any case, of electron transfer within the large electron transferring proteins of the mitochondrion has been largely worked out. Also, we now know rather more than we did five years ago about which electron transferring reactions are energy conserving, that is, they contribute to the charge separation across the membrane. Although I am not sure this will be discussed in this symposium – I hope it will be –. We now have a deeper insight into the forces which drive electron transfer between different well separated centers in the protein. I do not think we have progressed very far in our understanding of how an electric field across a membrane or protonmotive force, if you will, catalyses the synthesis of ATP or the dissociation of already formed ATP but I may be wrong – maybe you will prove me wrong at this meeting.

Perhaps the most striking and unexpected development – unexpected for me in any case – in recent years has been in the molecular basis of mitochondrial pathology, which is the last topic that will be dealt with in this meeting. For me, my first surprise came from Dr. Kadenbach's demonstration of the tissue-specific expression of cytochrome oxidase genes. In any case, this made it more understandable why certain inborn errors may lead to lesions in specific tissues. I have also been surprised by the change of attitudes to mitochondrial disease, since I left the laboratory. Where it was once thought to be very rare, it now appears that the cases examined are the tip of an iceberg or perhaps we should say for the investigators, the exposed reef of a gold mine. It is not only the genetically inherited disorders of the respiratory chain that are attracting attention, but also those that arise owing to mutations of the mitochondrial DNA after birth. Indeed, Tony Linnane and Takayuki Ozawa have suggested that the failures in function associated with aging – which is something, that is of interest to you and I, Kunio – are due to a progressive loss of respiratory capacity of tissues as a result of random mutation of the mitochondrial DNA. I must say that it is of some comfort to know that the field, in which I have worked during most of my scientific life, might now be providing me with an explanation of why I find it more difficult to follow the work of my younger colleagues nowadays – who, of course, still have beautifully operating mitochondria producing kilograms of ATP per hour, and even the increasing number of mistakes I make in proofreading papers and letters.

In the late 1940s and in the 1950s, bioenergetics belonged to the cutting edge of biochemistry, if you can excuse the jargon. New fields opened up by the discovery of the structure of nucleic acid superseded bioenergetics in the center of interest. In the middle of the 1960s, a new era opened up with the discovery that mitochondria have their own genetic apparatus distinct from that present in the nucleus. However, this did not have much impact outside of mitochondria – others considered it of secondary importance – a sort of evolutionary fossil, retained after bacteria established themselves as symbionts in the animal cells and evolved into mitochondria. For a short period in the 1970s bioenergetics became popular again with the granting agencies when it was suggested that the combination of photochemical reaction centers and hydrogenase could be utilized on a commercial scale to provide hydrogen gas to provide fossil fuel. This is not yet possible, but the relative priority given to this study, did I believe, lead to the discovery of the role of nickel in hydrogenase and related enzymes, and that of manganese in the oxygen evolving reaction

of photosynthesis a little more rapidly than otherwise might have been the case, because up till then support in the very rapidly productive field of photosynthesis was declining.

The concept that mitochondrial diseases are not only more important than we thought, but perhaps universal since all of us age – even you younger bioenergeticists age –, opens new possibilities and perhaps it will become a major field of medicine.

To those in the field – even if not always to those outside the field-bioenergetics, has always been exciting. To paraphrase Arthur Kornberg in another context, “I have never met a dull electron transferring protein.”

The fundamental importance of the electron transport chain and oxidative phosphorylation is, of course, obvious to everyone. But some might have felt that the main features have long been established and have been incorporated into textbooks – just like the Krebs cycle has – and it only remains to dot the “i”s and cross the “t”s. However, the recent developments in the importance of mitochondrial disease, for example, would never have taken place if the filling in of details – the dotting the “i”s and the crossing the “t”s, particularly in the connection of the mechanisms of biogenesis of mitochondria had not been pursued.

I would like to conclude this opening remark by thanking Dr. Kim and Dr. Ozawa for putting together this interesting symposium and inviting many of us. Practically everybody here visits Seoul for the first time. I can assure you that we are extremely impressed by what we have seen here in Seoul and how you organized the extremely successful meeting. I also would like to thank Ewha Womans University for sponsoring this meeting together with IUB and also those co-sponsors.

Thank you!