

Eukaryotic Cell Function and Growth

Regulation by Intracellular
Cyclic Nucleotides

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Eukaryotic Cell Function and Growth

Regulation by Intracellular
Cyclic Nucleotides

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Preface

The day it rained in Wépion

The NATO Course on Regulation of Function and Growth of Eukaryotic Cells by Intracellular Cyclic Nucleotides was organized in Wépion (Belgium) from September 23 to October 1, 1974, by L. Birnbaumer (Chicago), B.L. Brown (London), R.W. Butcher (Worcester), J.E. Dumont (Brussels), M. Paiva (Brussels) and G. Van den Berghe (Louvain), under the benevolent and most efficient aegis of Dr. T. Kester (NATO, Brussels).

The formula of the Course was inspired by the Gordon Conference with its combination of a pleasant, friendly and easygoing atmosphere together with a solid and critical scientific diet offered in the morning and evening, the afternoon being free. For these reasons, the meeting was located in a pleasant motel in beautiful surroundings by the side of the Meuse river, in the country, but close to the town of Namur. Everything, absolutely everything, from swimming to tennis, to horse riding, was available to make the afternoons agreeable and to facilitate social contacts. As we said in the announcement "The weather is often, but not always, very good at that time of the year". On the Sunday we arrived in Wépion the sun shone brightly ... at the end of the afternoon it began to rain ... and our arrival proved to be the signal to start rain for the next four months. Already, after one week in Wépion, the radio was proudly announcing that all records had been broken and that Belgium had replenished its badly depleted water reserves ...

Despite this drawback the general opinion was that the Course had been a success. The audience came from many countries : Belgium, Canada, France, Germany, Italy, Israel, Netherlands, Norway, Portugal, Switzerland, United Kingdom and United States. It was formed of a rather unusual mixture of chemists, biochemists, physicists, mathematicians, biologists and morphologists, and physicians, amongst others, working on a wide variety of pro-

blems ranging from purely clinical to totally fundamental ones. Some of the participants, as well as some lecturers like ourselves, felt they had a deep but far too narrow experience in one part of the field and wanted to broaden their outlook : others wanted to get at the very bottom of one specialized area. We hope we catered for all tastes, and all departed satisfied.

The Course was designed to be a Course, i.e. "to be" didactic and to cover for an unspecialized audience the subject in breadth and in depth. However, it was well understood that to give the talk the flavour of the most recent research, each speaker would make full use of his own results. In fact, while some talks were very instructional, others were more oriented as presentations of personal results. On the whole the balance is reflected in this book.

The formula of the Course was to have a long session with 4 talks in the morning and a short session with 2 talks at the beginning of the evening. Each talk was supposed to last 35 to 45 minutes with the rest of the hour left for questions and discussion. Most of the speakers respected this rule. The organizers stated in the programme : "We would greatly appreciate if this Course is not confused with a church service, where a few authorities deliver the gospel without discussion or questions. The talks should be a critical evaluation of present knowledge and we would expect that issues be discussed, changes of interpretation and discrepancies be brought forward and the unknown pointed out, at least in the discussion, in a friendly and relaxed atmosphere. The chairman's job will be to approach this ideal." Thanks to the chairmen (L. Birnbaumer, B.L. Brown, R.W. Butcher, J.D. Corbin, N. Crawford, J.E. Dumont, J.H. Exton, J.G. Hardman, K.D. Hepp, C. Jacquemin, R. Kram, J. Nunez, J. Otten, G.A. Robison, G. Schultz, G. Van den Berghe, M. Vaughan), this ideal was approached. After each talk there were first questions for information and then sometimes very acute discussion. Few issues, disagreements or discrepancies were shunned and in general the audience felt they had received a sound and critical evaluation of the field. After a slight lag period, questioning increased exponentially - a goal difficult to achieve in Europe and even elsewhere. A great part of the merit for this atmosphere should be attributed to R.W. Butcher (Worcester) who, from the very beginning, decided he would not let anything unclear, incomprehensive, debatable or incorrect pass. By doing this he greatly contributed to the success of the Course, and we express our gratitude.

As this field and the Course owed so much to the Nashville School, it was quite fitting that the Course began by a talk by R.W. Butcher on the life and philosophy of E.W. Sutherland and ended up with the announcement that the highest Belgian Scientific

Award, the Francqui Chair for 1974, had been attributed to J.G. Hardman.

We should like to thank NATO Advanced Study Institute which sponsored and supported the Course, the Caisse Générale d'Epargne et de Retraite and the Fonds National de la Recherche Scientifique which support most of the Belgian research presented at the meeting, and Boehringer Pharma, S.A., and Sandoz, S.A. which helped to defray some of the expenses. The programme of the Course was set up with Drs. L. Birnbaumer, B.L. Brown, R.W. Butcher and G. Van den Berghe, who also organized the sessions and the discussions with us. Our thanks to them for having made the Course so stimulating. This Course could not have been a success without the organizational prowess, and artful public relations of Mrs. Ch. Borrey who, with the help of Mrs. D. Legrand and Miss M. Opdenberg, carried most of the burden of administrative and secretarial work. We extend our thanks to these ladies. We would also like to thank all the researchers of the Institut de Recherche Interdisciplinaire en Biologie Humaine et Nucléaire who organized the sessions and helped with the organization. Of course, lastly and not least, our thanks to Mrs. F. Morent who typed this book.

J.E. DUMONT

M. PAIVA

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INTRODUCTION: A COMMEMORATION OF EARL W. SUTHERLAND, JR.

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It seems most appropriate that the introduction to the course and to the proceedings which derived from it should start with a few words about Earl W. Sutherland, Jr., who discovered cyclic AMP and thus in a real sense provided the initial impetus for our gathering. However, it is impossible to properly evaluate or even describe the contributions which he made to our understanding of control systems in living organisms. It will be more for future generations to judge his greatness than those of us who write or read these words.

Nonetheless, even a cursory listing of his accomplishments is most impressive. Standing first among them, of course, is research, signalled by the discovery of cyclic AMP. However, many other entries, although seemingly less dramatic are very important. An early example was the identification of phosphorylase as the rate-limiting step in glycogenolysis when the whole concept of regulatory enzymes was only dimly perceived. Another, and one of great significance, was the demonstration of the chemical nature of phosphorylase activation. Shortly thereafter with Henion he reported that liver and muscle phosphorylases differed with respect to immunological properties although they catalyzed the same reaction. This was, to my knowledge, the first demonstration of isozymes.

One of the most striking things about Sutherland's research was that he, at least to the best of my recollection, never made an error in the strategy of his research. This is, there were many crossroads along the trail from his initial interest in the hyperglycemic effect of the catecholamines to the identification of cyclic AMP as the heat stable factor responsible for phosphorylase activation in homogenates, yet he never took a wrong turn. This was partially because he had a very clear sense

of the question he was asking: "*How do hormones act?*" Thus, he resisted taking any sideroads which might lead him to other (albeit interesting) answers. As a matter of fact, he often said that one of the most difficult decisions in science was what not to do. However, this is only one of the several reasons for his successes.

Another very important ingredient was his scientific intuition. Along with an intense curiosity about all things biological, he had a knack of sensing how things might work in a living cell. Occasionally he might be startled by a new development in our understanding of biological functions, but he could always rationalize the value of the function in terms of survival value to the organism (if the observation was valid). As an example, he had a clear concept of allosteric enzymes and effector interactions long before the formal theories were enunciated. His conceptualisation was less elegant than allosterism because he referred to effectors as "quirking" enzymes. However, it was perfectly logical to him that effectors could interact at sites distinct from the active sites of key enzymes and alter their activities.

Another characteristic of Earl Sutherland, and one which was legendary to all of us who were privileged to work with him, was his memory. Long after I had forgotten even doing experiments (the results of which I had told him about) he could come up with the actual numbers. This could involve the span of five or ten years. I think he worked very hard on his memory and made a conscious effort to remember those things which he considered important. As a matter of fact, we all came to know a far-away look in his eyes which meant that he wasn't particularly interested in what we were talking about - probably because he considered it irrelevant - and would change the subject as quickly as possible. Fortunately, he never seemed to remember things he was told during such incidents.

Not unexpectedly, since Earl did seem to be able to direct himself down the proper scientific road at every crossing, he had a highly disciplined mind. Whenever confronted with a decision of any moment, he would write down a list of pros and cons on a piece of yellow legal-sized paper. His lists of pros and cons were extremely interesting, for they were free of bias. That is, he was sufficiently disciplined and sufficiently objective that his pros and cons were unweighted by any preconceived notion about what his decision should be. An enjoiner which he dispensed frequently and freely upon his younger associates was that, "*You should never fall in love with your hypothesis*", and this was a precept he lived by. Indeed, one is struck by the fact that science in general would be far better off if this attitude towards hypotheses could be maintained by all of us.

Earl tried to maintain as much independence as possible. This was not so much a state of being but a state of mind, for he wanted to avoid the plague of commitments and anxieties which seemed to debilitate so many scientists. I think this had much to do with his giving up a departmental chairmanship and his move to Vanderbilt in 1963. It also, at least in part, explains why he sometimes allowed mail to go unanswered for weeks or even months. It was not that he was unkind nor unfeeling, because he was a kind and considerate man, most especially to his junior colleagues. Rather, he wanted to keep his mind clear and his memory bank as free of extraneous material as possible so that he could concentrate upon his science. While this may be of little consolation to those who waited months for an answer to a letter, it is a fact. He simply wanted to retain his independence and his concentration on research, free of distractions, to the best of his ability.

Dr. Sutherland was a very pleasant and easy-going man to work for. He was amiable and informal, and always willing to spend time with other scientists, especially younger ones, when available. During all of the time I was in his group, I never heard him speak critically of or to any of his people. Indeed, he always went out of his way to praise those who were productive and he would omit mention of those who were not.

Earl also had a deep and abiding commitment to open scientific communication. This was consistent with his view of science; that is, that it should be an open society of talented individuals seeking new truths about nature. Therefore, there were no withheld items of data, either internally or externally, in his group. This was not because he was lacking in competitive spirit, because he was fiercely competitive. However, above all he was very curious and he wanted to understand how things worked. Since that could only occur with all available information, secrets were anathema to him.

Finally, Earl was a master at writing experimental protocols. He had a clear sense of the controls needed to prove or disprove a particular point, so much so that his experiments were almost always free-standing.

These then, were some of the attributes which went into the making of what I consider a quintessential man of science. As an individual he was considerably more complex than he was as a scientist, and as he saw more of the world, he became more pessimistic. As a rationalist, he felt that it should be possible to solve human problems by the application of human intelligence, just as he had brought his intelligence to bear upon the problem of catecholamine-induced hyperglycemia. As a matter of fact, for