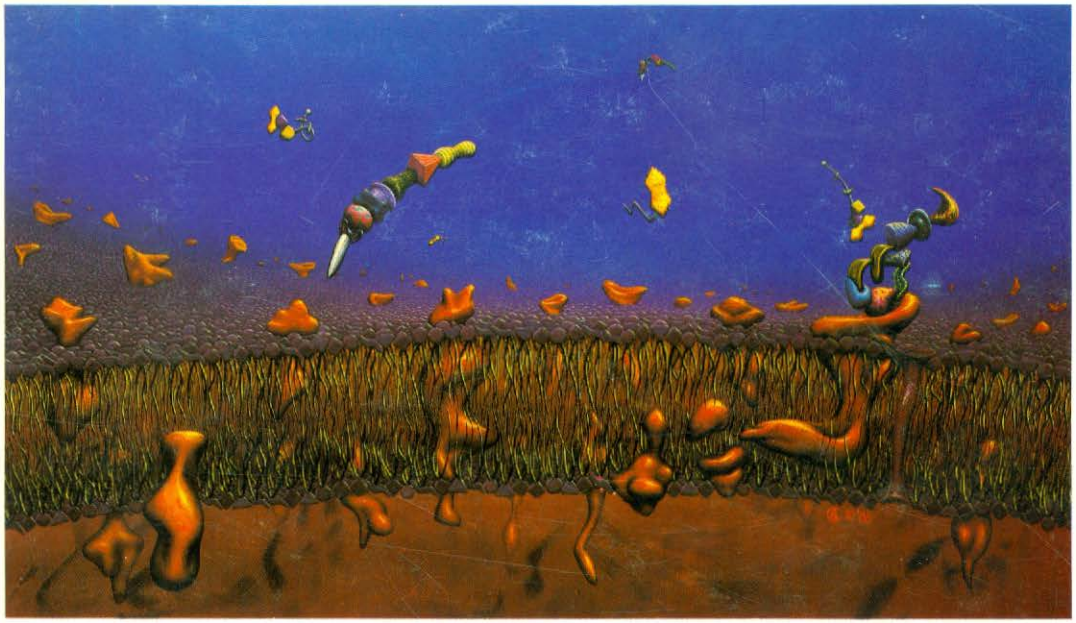
UNIVERSITAT AUTÒNOMA DE BARCELONA

DOCTOR
HONORIS CAUSA

JOHN H. EXTON



DISCURS LLEGIT A LA CERIMÒNIA
D'INVESTIDURA CELEBRADA
A LA SALA D'ACTES D'AQUEST RECTORAT
[illegible] DE JULIOL DE L'ANY 1988

BELLATERRA, 1988

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d'Alan Clark
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PRESENTACIÓ DE JOHN H. EXTON, L'HOME ALFA

PER

JOAN J. GUINOVART

Excel·lentíssim i Magnífic Senyor Rector,
Dignísimes Autoritats,
Benvolguts Col·legues,
Senyores i Senyors:

Som aquí per honorar el Dr. John Exton i la raó principal d'aquestes paraules és presentar la justificació de la nostra proposta de nomenar-lo Doctor Honoris Causa per la Universitat Autònoma de Barcelona. Aquesta justificació es basa en l'extraordinària obra científica que ell ha dut a terme en el camp de l'estudi de la regulació metabòlica i les bases moleculars de l'acció hormonal, especialment del mecanisme d'acció dels agents alfa-adrenèrgics.

El Dr. John Exton va néixer a les antípodes, a Nova Zelanda, un lloc lluny de tot arreu, i per poder seguir la seva vocació investigadora va haver de pagar el preu de la immigració. Així, la major part de la seva tasca científica ha estat realitzada als Estats Units.

El seu interès per la bioquímica va desvetllar-se mentre estudiava medicina a la Universitat de Dunedin. Això el va portar a obtenir un doctorat en aquesta matèria un cop completada la seva formació mèdica. En aquesta orientació va jugar-hi un paper decisiu el seu professor de bioquímica, el Dr. Norman Edson, un home que s'havia format a Cambridge i havia estat company de Hans Krebs.

El seu mentor als Estats Units va ésser el Dr. Charles Park, que havia estat deixeble del Dr. Carl Cori a St. Louis. D'aquesta manera el Dr. Exton va entrar a formar part d'una de les més grans famílies científiques, la familia Cori, a la qual pertanyen molts dels bioquímics presents en aquest acte. Alguns són descendents dels Cori en primer grau, com el Dr. Park o el Dr. Sols, que van treballar directament amb ells. Altres són néts, besnéts o fins i tot resbesnéts dels grans mestres.

El Departament de Fisiologia a la Universitat Vanderbilt a Nashville on es va integrar el Dr. Exton era, als anys seixanta, probablement el millor centre del món pel que fa als estudis sobre acció hormonal. Al mateix temps que el Dr. Exton, hi va arribar el Dr. Earl Sutherland, que poc temps abans havia descobert l'AMP cíclic i que posteriorment va rebre el premi Nobel per aquesta raó. En aquest ambient d'entusiasme i d'alt nivell científic el Dr. Exton va trobar el millor lloc per acabar de completar la seva formació. A aquesta època corresponen les seves publicacions sobre la regulació de la gluconeogènesi hepàtica que van definir els mecanismes de control hormonal d'aquesta via i van aclarir el paper fonamental que hi té l'AMP cíclic. Aquests treballs són considerats uns clàssics dins el camp del mecanisme d'acció de les hormones i per si sols ja constitueixen una obra suficient com per considerar el seu autor un científic de primeríssima categoria.

El Dr. Exton mai no va abandonar Nashville. Encara avui continua a la mateixa Universitat, on ha assolit els càrrecs de professor de fisiologia i d'investigador del Howard Hughes Medical Institute. El seu laboratori s'ha convertit en un centre al qual acudeixen científics d'arreu del món atrets per l'alt nivell de la investigació que s'hi du a terme. Allí va realitzar una estada post-doctoral na Fàtima Bosch, membre del Departament de Bioquímica i Biologia molecular de la nostra Universitat. La Dra. Bosch no solament

hi va rebre una magnífica formació científica, sinó que hi va ésser acollida amb gran hospitalitat per la família Exton.

No és possible en aquesta intervenció fer una descripció de totes les comunicacions científiques del Dr. Exton. Em limitaré a mencionar les seves publicacions cabdals que contribuïren de forma definitiva a establir el mecanisme d'acció dels agents alfa-adrenèrgics, l'elucidació del qual ha estat un dels fets més importants en l'estudi de les bases moleculars de l'acció hormonal durant els darrers anys.

Com a conseqüència dels treballs del Dr. Sutherland s'acceptava que l'acció de l'adrenalina al fetge era meditatitzada pels receptors beta-adrenèrgics i que l'AMP cíclic era l'únic missatger d'aquesta hormona. De fet, aquests eren els treballs pels quals li varen donar el premi Nobel. Els experiments duts a terme pel Dr. Exton indicaven, però, que els efectes fisiològics de l'hormona eren encara evidents en presència d'un blocador beta-adrenèrgic. En aquestes condicions no es produïa cap increment en els nivells d'AMP cíclic. Aquests resultats estaven en absoluta contradicció amb la teoria acceptada fins aleshores. El Dr. Exton, però, va persistir en les seves investigacions i així va demostrar que existeix un altre mecanisme per a l'acció de l'adrenalina al fetge, que s'exerceix a través del receptor alfa-adrenèrgic i en el qual no participa l'AMP cíclic.

Com es pot fàcilment imaginar, aquests resultats representaren una revolució en el camp de l'estudi dels mecanismes d'acció hormonal. Aquest és un magnífic exemple de fe en els propis resultats i de com de vegades cal no acceptar el dogma quan les dades experimentals hi estan en contra.

Posteriorment, el Dr. Exton va demostrar que el missatger intracel·lular que participava en aquest nou mecanisme d'acció de l'adrenalina al fetge era el calci. D'aquesta manera es feia palès que la

mateixa hormona podia actuar en diferents òrgans per mitjà de diferents mecanismes. Així, mentre que al múscul els efectes de l'adrenalina són realment mediatitzats per l'AMP cíclic, en el fetge aquesta hormona exerceix la seva acció principalment per mitjà d'un mecanisme independent de l'AMP cíclic i que involucra el calci.

Altres treballs del Dr. Exton van permetre descobrir que aquest mecanisme mobilitzador de calci en el fetge no era exclusiu de l'adrenalina o dels agents alfa-adrenèrgics, sinó que era compartit per altres hormones com la vasopressina, l'angiotensina i l'oxitocina. El mecanisme, doncs, no era una particularitat d'una sola hormona, sinó que tenia un abast més general. Avui en dia hom el considera de la mateixa importància que el de l'AMP cíclic pel que fa a la regulació hormonal del metabolisme hepàtic.

Estudis posteriors li van permetre demostrar que l'increment en els nivells intracel·lulars de calci no solament era el resultat de l'entrada de calci extracel·lular, sinó que també s'alliberava calci de reservoris intracel·lulars.

L'impacte de tots aquests treballs sobre la comunitat científica internacional fou molt fort, i va desencadenar un gran nombre d'estudis encaminats a aclarir els passos intermedis entre la unió de les hormones als seus receptors a la part externa de la membrana de la cèl·lula i la mobilització de calci intracel·lular. Els treballs del Dr. Exton van contribuir, sens dubte, a obrir el camí que conduiria finalment al descobriment de l'inositol trisfosfat, que enllaça la unió de l'hormona al receptor amb l'alliberament de l'ió.

Els treballs més recents del Dr. Exton sobre el mecanisme alfa-adrenèrgic han estat centrats a demostrar l'existència de proteïnes acobladores, del tipus de les proteïnes G, entre el receptor i el sis-

tema efector, i en l'aïllament i la identificació de nous possibles missatgers de l'acció hormonal.

El Dr. Exton va visitar per primera vegada la Universitat Autònoma de Barcelona l'any passat (1987) per participar en el Simposi «Metabolisme glucídic i acció hormonal», que es va celebrar al campus de Bellaterra. Durant aquesta visita va tenir nombrosos contactes amb estudiants de la nostra universitat que pròximament fructificaran en estades a Nashville, on treballaran al seu laboratori.

Per tot això, Excel·lentísim i Magnífic Senyor Rector, en reconeixement dels mèrits del Dr. John Exton, demano avui que l'investiu amb el grau de Doctor *Honoris Causa* per la Universitat Autònoma de Barcelona. Estic segur que el Dr. Exton rebrà amb gran orgull i honor aquest títol que tan justament decidireu atorgar-li a proposta de la Facultat de Veterinària i del Departament de Bioquímica i de Biologia molecular de la nostra universitat. Moltes gràcies.

IN SEARCH OF THE MESSAGE
AUTOBIOGRAPHICAL REFLECTIONS

BY

JOHN HOWARD EXTON

I received all my formal education in New Zealand, a beautiful country far from the economic and cultural centers of the world. My early years were spent by the seashore where I developed a fascination for the various life forms that inhabit this wonderful ecological zone. When my family moved to the city my interest changed to the exploding field of Atomic Physics. I was sent to a high school patterned after the public schools of Victorian England in which discipline was strict and punishment severe. Although the emphasis was on a classical education, I was also able to study Physics, Chemistry and Biology. As was, and still is, the custom in New Zealand, I proceeded directly from high school to university. This meant that I had to make a career choice at a comparatively early age, and I found it extremely difficult to decide between Science and Medicine. It is interesting to reflect that my mentors felt that the only way these careers could be combined was to first study Medicine. I entered New Zealand's only Medical School in Dunedin in 1953, after spending one year studying Natural and Physical Sciences. The head of the Biochemistry department was

Norman Edson who had studied under Gowland Hopkins at Cambridge and had been a colleague of Hans Krebs. He was possessed of an encyclopedic memory and a fervid commitment to research. He was also a confirmed socialist and, coming from a very conservative family, I was initially shocked by his radical views. I became intensely fascinated with Biochemistry because it felicitously combined my two major interests —Biology and Chemistry. After two years in Medical School, I spent one year studying the breakdown of pyrimidines and was able to disprove one of the existing hypotheses. I was still undecided about my career, but Norman Edson advised me to continue studying Medicine. It was the right decision since Medicine provides an unexcelled education in the normal and abnormal structure, function and behaviour of Nature's most complex species.

After a year as an intern, I returned to Medical School to study for a Ph. D. in Biochemistry under Norman Edson. I remember vividly his warning that if I entered upon this course, I had better realize that I would probably leave New Zealand forever. These were prophetic words, since at that time there was still only one Medical School, one Biochemistry Department and one Professor of Biochemistry. However, I wanted to continue research in Biochemistry so much that I did not consider the consequences. My thesis involved biochemical studies of an early preparation of isolated liver cells. It was later discovered that, despite their normal appearance under the microscope, their plasma membranes were damaged and this work is best left forgotten!

At that time, 1963, it was considered mandatory for New Zealand Ph. D. graduates in the Sciences to spend a postdoctoral period overseas. The preferred course was to do a second Ph. D. at Oxford, Cambridge or London, which fact provides an interesting commentary on the perceived value of the New Zealand Ph. D. I applied

for a scholarship to work under Hans Krebs at Oxford and was duly awarded the princely sum of 900 pounds per annum and advised to leave my wife and two children in New Zealand for the two years it would take me to get a D. Phil. Because of the uncertainty of receiving the Oxford scholarship, I had also applied to several laboratories in the United States. One of these was the Physiology Department at Vanderbilt University under the leadership of Charles (Rollo) Park who had studied under Carl Cori at St. Louis. In contrast to the parsimonious English, Rollo welcomed my family as well as myself and even contributed to our travel expenses.

Rollo and his associates had recently published a series of classic papers on the effects of insulin and diabetes on glucose transport and intracellullar metabolism using the perfused rat heart preparation. Just prior to my arrival in November of 1963, Earl Sutherland had joined the department. Earl had also studied under Cori and he brought a large group from Cleveland, Ohio. Everyone who was in the Physiology Department at Vanderbilt during the years of 1963 through 1966 remembers these halcyon times with great nostalgia. One felt that one was at the center of the universe as far as hormone action and metabolic regulation were concerned. Spurred on by Rollo's credo that «it is far better to collaborate than to compete», the groups of Sutherland and Park poured forth a series of papers on the role of cyclic AMP in hormone actions, to which I made a small contribution. At that time, we were all thoroughly convinced that Earl would receive the Nobel prize for Medicine or Physiology, but it was not until 1970 that the phone call came from Stockholm.

A research conference with Earl was an exercise in mental gymnastics since he frequently switched thoughts in mid-sentence and was apt to use unusual abbreviations. During one meeting, he kept referring to TG, which I assumed was triglyceride. However, he

meant transglucosylase (glycogen synthase). Earl was convinced that cyclic GMP was the second messenger for insulin, and Joel Hardman and I set out to test this. Alas, for once, Earl's brilliant intuition failed him.

I became very involved in studies with Rollo of hepatic gluconeogenesis which is the process by which the liver synthesizes glucose for the needs of the body. We utilized a rat liver perfusion system, but this required considerable improvement of the existing makeshift equipment, which was an invitation to electrocution, flooding or incineration of the rats. Greatly helped by the design genius of Howard Morgan and the skills of the Vanderbilt Apparatus Shop, a new perfusion apparatus was constructed. A series of papers emerged from this work which helped define the mechanisms by which the pathway of gluconeogenesis was controlled by glucagon, epinephrine, insulin and other hormones. An important finding was the central role played by cyclic AMP. There were many others involved in this work including Jim Jefferson, Tom Miller, Larry Mallette and Michio Ui, who have all gone on to make major contributions to Biochemistry and Endocrinology. We wre all continuously inspired in this work by Rollo Park whose unswerving pursuit of the highest standards of scientific experimentation and publication ensured that our work would receive proper attention even if we were not always the first in print. For example, the time between first draft and final submission for my first major paper on gluconeogenesis was seventeen months. I vividly remember spending a whole day on the interpretation of one sentence, which was later removed at the behest of an editor.

Under Rollo's benevolent tutelage, I was rapidly promoted and became full Professor in 1970. In 1968, I was also appointed an Investigator of the Howard Hughes Medical Institute. In retrospect, I am not sure how much of an honor that was, since at that time

the scientific side of the Institute was essentially run by an «Old Boys Club» and Rollo happened to be a member of the club. In its defense, it should be pointed out that the «Club» had an excellent track record of appointing first-rate investigators.

In 1970 I spent a six-month sabbatical period at the University of Geneva working with Albert Renold and Bernard Jeanrenaud. Growing up in New Zealand, I had been intensely fascinated by Europe with its long cultural heritage as the cradle of Western Civilization. My first exposure to European culture was greatly enhanced by having the gracious and cultivated Bernard and Albert as my guides. It is with great fondness that I remember this period in Geneva. Weekdays were spent experimenting in the cramped quarters of the converted villa that constituted the Institut de Biochimie Clinique or in the converted wards of the Pavillon H of the Hospital Cantonal, whereas weekends were spend on the skislopes or exploring the beautiful French and Swiss countryside with my family.

On return to the United States, I studied the metabolic changes in the livers of spontaneously diabetic mice and alloxan diabetic rats and received the Lilly Award and later an Established Investigatorship from the American Diabetes Association. I was assisted in these studies by two very talented experimenters, Tim Chan and Sandy Harper. I then turned to another project provoked by some experiments carried out by Alan Robison and myself. It was accepted at that time that the entire action of epinephrine on the liver was mediated by beta-adrenergic receptors and involved cyclic AMP —this was the work for which Earl Sutherland received the Nobel Prize. However, we found that the physiological effects of the hormone on rat liver were still evident when a beta-adrenergic blocker was present and there was no increase in cyclic AMP. Alan trained under Earl and was one of his leading disciples. It was therefore very difficult for him to believe these results, but I persisted

and it became clear that there was another mechanism for epinephrine action which did not involve cyclic AMP and was mediated by alpha-adrenergic receptors.

Further work revealed that the intracellular message involved in these alpha-adrenergic effects was ionized calcium, and it was shown that these ions mediated other hormone actions. Later it was found that the calcium ions increased in the cell not only because of the opening of a calcium channel in the cell membrane, but also due to the release of these ions from stores within the cell. Peter Blackmore played a crucial role in these discoveries and other contributors were Nancy Hutson, Francoise Assimacopuolos-Jeannet, Alan Cherrington and Jackie Corbin.

In later work, we found that the receptors for epinephrine were located exclusively on the outside of the cell. This meant that a message had to be generated at the cell membrane which then caused calcium to be released from its internal stores. The search for this message began in earnest. A popular candidate at that time (1980) was myoinositol cyclic phosphate a potential product of the breakdown of phosphatidylinositol, a phospholipid in the cell membrane. However, in work with Vera Prpic we soon found that this was not the message, and this negative finding discouraged our interest in this hypothesis. However, events moved very rapidly, with the recognition by the group of Bob Michell in England that a related compound, phosphatidylinositol bisphosphate, was the first phospholipid to break down, and the discovery by Michael Berridge that a product of the breakdown, inositol trisphosphate, was the true signal for internal calcium release.

In earlier studies with Mahmoud El-Refai, we had shown that alpha-adrenergic receptors had different affinity states for agonists and that these were influenced by guanine nucleotides, implying

that the receptors were coupled to G-proteins. However, these findings were treated with derision by one of the leading experts in the field who believed that only receptors that were linked to cyclic AMP had such properties. In 1985, we reexamined the coupling between the receptors which mobilized calcium and the phospholipase C enzyme which broke down phosphatidylinositol bisphosphate to inositol trisphosphate. We obtained, simultaneously with several other laboratories, further proof that a G-protein provided the coupling. We subsequently succeeded in purifying this protein and the phospholipase C and are currently working on the reconstitution of the system. Major contributors to our work in the area have been and are Ron Uhing, Chris Lynch, Thom Fitzgerald and Stephen Taylor.

In more recent work, we have discovered that another cell membrane phospholipid, phosphatidylcholine, is broken down in response to hormones. This involves a G-protein linked to two other phospholipases acting on phosphatidylcholine. The key researchers in this area were and are Helen Irving and Steve Bocckino. Because of the newness of the findings, we do not yet fully comprehend the physiological significance of these new signalling system, but it seems very likely that some of the breakdown products will turn out to be new messages for the control of cell function.

In closing, I would like to point out some general conclusions that may be drawn from my experiences as a biomedical researcher. The first, learned from Norman Edson, is to familiarize yourself thoroughly with the body of scientific knowledge in your discipline, but not to be wedded to any specific ideology. The second, learnt from Rollo Park, is to examine your experiments and conclusions rigorously and to be willing to put your hypotheses to the harshest tests. The third, learned from Earl Sutherland, is to persistently pursue a problem even though the solution may sometimes seem beyond your reach, and to be willing to trust your scientific

instincts when there is no clear direction. The fourth, learned from my experience with the alpha-adrenergic system is that if you know your experimental results are correct you should always trust them, even though they are opposed to a widely-held hypothesis. The fifth, learned again from Rollo and all my other scientific colleagues over the years, is that Science fluorishes in an atmosphere of trust, generosity and collaboration, and founders in an atmosphere of mistrust, parsimoniousness and fear. I have been privileged to work with an exceptional group of collaborators over my scientific career and I only regret that space does not permit me to document more than a few of those superb students, post-doctoral fellows, mentors and other colleagues. To all of them I owe a very deep sense of gratitude.

CURRICULUM VITAE

DE

JOHN H. EXTON

Date and Place of Birth

August 29, 1933, Auckland, New Zealand

Marital Status

Married, Janet Mary Buchanan, 1957
4 Children - Richard, Susan, Peter, Stephen

Education

University of New Zealand, Dunedin, New Zealand
B.Med.Sc. 1955
M.B.Ch.B. 1958
University of Otago, Dunedin, New Zealand
Ph.D. 1963
M.D. with Distinction 1984

Present Position

Professor of Molecular Physiology and Biophysics, Vanderbilt University School of Medicine, 1970-present.
Investigator, Howard Hughes Medical Institute, 1976-present.

Honors

University National Scholar, New Zealand, 1952-1957
Teaching Fellow, N. Zealand Medical Research Council, 1954-1955
Auckland Prize for Medicine (1st in class), 1958
Fellow, N. Zealand Medical Research Council, 1960
United Kingdom Commonwealth Scholar, 1963
Investigator, Howard Hughes Medical Institute, 1968-1974
Lilly Award, American Diabetes Association, 1972
Established Investigator, American Diabetes Association, 1976

Editorial, Review and Academic Activities

Editorial Board, *Journal of Biological Chemistry*, 1975-1980, 1985-present
Editorial Board, *American Journal of Physiology*, 1973-present
Associate Editor, *American Journal of Physiology: Endocrinology and Metabolism*, 1984
Member, Metabolism Study Section, NIH, 1975-1979
Member, Council of Endocrinology and Metabolism Section of American Physiological Society, 1982-1985
Member, Committee on Research, American Diabetes Association, 1983-1986
Director, Medical Scientist Training Program (M.D., Ph.D.), Vanderbilt University School of Medicine, 1982-1986

Memberships

Biochemical Society
American Physiological Society
American Society of Biological Chemists
American Diabetes Association

Publications

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