AARON KLUG – A LONG WAY FROM DURBAN
A BIOGRAPHY

The atomic structures of macromolecules provide the key to understanding how life works. Aaron Klug led the way to the development of methods for solving such structures and is one of the pioneers of structural molecular biology. He was awarded a Nobel Prize in 1982 for his work.

Illuminating both his personal life and scientific achievements, this unique biography begins with Klug's youth in Durban and his studies at Johannesburg, Cape Town and then Trinity College, Cambridge. Holmes proceeds to explore Klug's career from his work on the structure of viruses with Rosalind Franklin at Birkbeck College, London, to his time as Director of the MRC Laboratory of Molecular Biology (LMB) in Cambridge and as President of the Royal Society.

Drawing on their long-term collaboration, interviews and unique access to Klug's archives, Holmes provides a fascinating account of an innovative man and his place in the history of structural molecular biology.

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Foreword

It is unusual for a brilliant scientist to write a biography about another great scientist and even more unusual for the foreword to this wonderful biography to be written by yet another scientist who has known them both for almost fifty years. A fan of scientific biographies, I had read those of all my towering heroes of science including Max Perutz, Francis Crick, Fred Sanger and Sydney Brenner. These great scientists were all from the same Laboratory of Molecular Biology in Cambridge as Aaron Klug and indeed Ken Holmes. While these other biographies are beautifully written, they were not researched with the remarkable level of rigour demonstrated here by Ken Holmes. This biography of Sir Aaron Klug is so jam-packed with detailed observations that it serves to document not only the life and work of one great scientist, but indeed a period and place of unparalleled scientific discovery.

On a personal level, it revealed my many connections with Aaron Klug. Aaron and my father were both born in Lithuania. Aaron and my mother both grew up in Durban, South Africa. More generally, this book is not just a biography, it is encyclopaedic in its scope, serving to shed light on the history of some of the greatest discoveries including the structure of DNA, macromolecular crystallography, electron microscopy image reconstruction and more. And if this was not enough, the Appendix presents a crystal-clear easily approached introduction to diffraction, which continues to play a central and crucial role in the determination of the detailed structure of the tiny macromolecules that are at the heart of the secret of life.

Even better than the description of the science behind Klug's work provided by Ken Holmes is what he reveals about such icons of British science as Rosalind Franklin, who was very close to both Aaron and Ken; Francis Crick, who closely followed Klug's work on tRNA and chromatin; as well as Max Perutz, John Kendrew and Sydney Brenner, another South African, who also studied at Witwatersrand University in the 1940s and then subsequently came to England. Klug, Crick and Brenner really are for me the giants of twentieth-century science and they all played a huge role in my career.

FOREWORD

Although Sydney Brenner holds the unique distinction of having been scientific father to more Nobel Laureates than any other Nobelist, with five other winners who worked with him, I worked most closely with Aaron Klug and Francis Crick. Their styles were very different. I remember joking that if you had a new idea and went to tell Francis about it, you left his office quite sure that the idea had indeed been his. On the other hand, if you had no new ideas and went to talk to Aaron, he helped a new idea germinate and you left his office quite sure that his new idea was yours. In either case, science as a whole benefited, but Aaron's approach made people want to work for him. In this way, Aaron Klug brought out the best in others. His self-effacing manner, coupled to his reluctance to step in, made one feel empowered by what Holmes, in one humorous story, terms 'one of Aaron's endearing qualities: the ability to get someone else to take over onerous practical work by indicating a hesitancy that may be construed as a lack of competence'. In the context of scientific collaboration, it served to empower all those fortunate enough to work for him. The endorsers of this book also describe the influence of Aaron on collaborators and younger scientists. Klug was unique with his constructive ego-free approach to science.

Professor Michael Levitt
November 2016

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Introduction

The first half of the twentieth century saw the discovery of the chemical processes of life, including a sense of wonderment that yeast and humans used the same metabolic processes to burn sugar; the second half saw the unravelling of the processes whereby chromosomal deoxyribonucleic acid (DNA) is duplicated, the DNA sequence determines protein sequence and structure, and protein structure explains the magic of enzyme action. Together, these discoveries constitute the secret of life: the processes of life were revealed in their underlying physicochemical simplicity but cloaked in a bewildering complexity.

In the 1930s, John Desmond Bernal thought that the secret of life would be revealed by using X-ray crystallography to solve the structures of crystalline proteins. Max Perutz was Bernal's student in Cambridge, England. Twenty-five years later, Perutz and his co-worker John Kendrew realised Bernal's dream by determining the atomic structures of the oxygen-carrying proteins haemoglobin and myoglobin. In the end, the secret of life entailed more than protein structures, but structures are indeed an essential part of learning that secret. Proteins fulfil many functions: hair, skin, enzymes, pumps, or the multitude of nanomachines and motors that make muscles move and cells divide. Structure, together with the genetic approach founded by Salvador Luria and Max Delbrück, became the twin pillars of a new science, Molecular Biology.

Aaron Klug developed methods for structure determination of macromolecular assemblies at the atomic level – a prerequisite for understanding how life's clockwork actually operates. Aaron entered the field of structural molecular biology just as it was beginning. Thus our account perforce embraces many historical aspects of the development of Molecular Biology.

Aaron Klug was born in Zelva (other spellings include Zhelva or Želva), Lithuania, in 1926. His family emigrated to Durban, South Africa, when he was two. He attended the Durban High School and won a scholarship to Witwatersrand University in Johannesburg at 15. He attained his degree from Wits when he was 19 and moved to Cape Town University, where he took a master's degree. There, he worked

with the crystallographer R. W. James, who had an important formative effect. During this time, Aaron's first scientific publication appeared in the scientific periodical *Nature*. Two more papers published in *Acta Crystallographica* earned him an 1851 British Empire Fellowship and a Trinity College (Cambridge) Rouse Ball scholarship. He married Liebe Bobrow, a dancer and musician, in 1948, and in 1949 the young couple repaired to Cambridge, England, where Aaron did a PhD with Douglas R. Hartree on the kinetics of the formation of steel. For an ensuing year in Cambridge he did theoretical studies for Jack Roughton on the kinetics of oxygen uptake by the blood pigment haemoglobin. This experience reawakened his interest in biological phenomena.

Armed with a Nuffield Fellowship, Aaron joined John Desmond Bernal's Biomolecular Research Laboratory at Birkbeck College, London. Here he met Rosalind Franklin: after working on the structure of DNA at King's College London, Franklin had moved to Bernal's laboratory to lead a small group working on virus structure by X-ray diffraction. Meeting Franklin at Birkbeck College was Aaron's epiphany. This encounter determined his scientific future: solving the structures of macromolecular assemblies such as viruses. After Franklin's untimely death, he took over direction of the virus group. Together with John Finch, his collaborator for 40 years, he showed that poliovirus and small spherical plant viruses have closely related structures. A fruitful collaboration with Donald Caspar established the geometric rules for assembling 'spherical' viruses. In 1960 the virus group was invited to join the newly founded Medical Research Council's Laboratory of Molecular Biology (LMB) in Cambridge.

At the LMB, while working out the structures of spherical viruses by electron microscopy, Aaron developed the first applicable method for computing three-dimensional images from a set of two-dimensional projections of a structure (tomography). He and his collaborators solved the structure of tobacco mosaic virus. His group worked out the first atomic structure of an RNA-containing macromolecule, tRNA – a molecule containing thousands of atoms. Aaron also carried out structural analysis of the large macromolecular complexes involved in packaging DNA in chromatin (nucleohistones) and mapped out the organisation of the nucleohistone core. He discovered zinc fingers, protein domains that bind to specific DNA sequences, and he pioneered their application in gene therapy.

INTRODUCTION

In 1982, Aaron Klug was awarded the Nobel Prize for Chemistry. Between 1985 and 1995, he was Director of the Laboratory of Molecular Biology. As Director he was also instrumental in getting the British part of the Human Genome project started. From 1995 to 2000, he was President of the Royal Society of London. He was knighted in 1988 and awarded the Order of Merit in 1995.

Science is much held back because scientists concern themselves with that which is not worth knowing, and that which cannot be known[1]. Aaron was careful never to fall into either of these traps – he chose subjects that were at once topically important and likely to yield answers. Moreover, he never let himself be beholden to a technique. Aaron moved fluently between structure determination by X-ray diffraction or electron microscopy, and biochemistry. His endeavours were guided by an ability to choose topics that would yield to a sustained investigation. His consummate skill as a teacher and leader enabled him to draw forth exceptional performance from his co-workers and collaborators.

[1] *Die Wissenschaft wird dadurch sehr zurückgehalten, daß man sich abgibt mit dem, was nicht wissenwert, und mit dem, was nicht wißbar ist.* Goethe, J. W. in *Maximen und Reflexionen* (ed. H. Koopmann) p. 83 Deutsche Taschenbuch Verlag München (2006)