Address to the Assembled Faculties of Charles University, Prague.

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Introduction

“Rector Magnificus, Dean Spectabilis, Academicians and Scholars, vázeni hosté, dámy a pánové: Je pro mne velkou cti, ze mohu oslovit toto slovutné shromázdeni.”

I hope, Rector, that you will permit me to revert to my native tongue, as I am not anxious to risk any misunderstanding that might lead to defenestration – a subtle expression of disapproval established in these Hallowed Halls.

Charles University

As a graduate of University College London – an institution founded as recently as 1826 – you will understand my admiration and esteem for your University, founded here some 500 years earlier (in 1348) by the King of Bohemia, the Holy Roman Emperor Charles IV.

Charles University has a long and distinguished history of scholarship and its alumni and teachers include luminaries such as Jan Hus, Bernard Bolzano, Jan Purkyne, Tomas Masaryk, Albert Szent-Györgyi, Carl Ferdinand and Gerty Cori, Albert Einstein and Jaroslav Heyrovsky.

Szent-Györgyi, the Coris, Einstein and Heyrovsky were recipients of Nobel Prizes for their work. Einstein formulated his General Theory of Relativity whilst teaching here in Prague, and Heyrovsky (the inventor of polarography) forms a link between our institutions, as his postgraduate studies were at Univesity College with Sir William Ramsey and Frederick Donnan. I had the privilege of knowing Albert Szent-Györgyi personally, and benefitted from his wisdom in the field of free radical reactions.

The strong tradition of research and teaching has made Charles University an internationally admired institution of Higher Education and, in addition to its distinguished scholastic history, it is rightfully acknowledged as a contemporary centre of excellence.

In conferring on me an honorary doctorate I am indeed deeply honoured and I am greatly privileged to be numbered among such notable and distinguished previous recipients such as James Watson, Paul Nurse, Thomas Cech, Günter Blöbel, Richard Ernst and my UCL colleague, Salvador Moncada.

Of course, science is not a solitary undertaking and I consider the recognition awarded to me, marks not solely my modest contribution to the advancement of knowledge, but celebrates a wider ambit that includes the work of many colleagues with whom I have had the privilege to collaborate in the field of pigment cell biology. I gladly acknowledge the debt that I owe to them – notably my friends and supporters present here today.

Pigment Cell Research

As well as its major contributions in other disciplines, Charles University is one of the most important centres in the world of work on pigmentation and pigment cells. It was the famous Czech physiologist, Jan Evangelista Purkyne, who began pigment cell research here in Prague. In 1833 he was the first to describe neuromelanin granules in the substancia nigra of the human brain. Twentyfive years later (in 1858), a lecturer in the Faculty of Medicine, Bohumil Eiselt, described the occurrence, in patients with melanoma, of melanogenuria (that is the presence in the urine of colourless precursors of the dark pigment, melanin). And in 1932 Heinrich Waelsch analysed the pigment in the retinas of horses and concluded that natural melanins were complexed with protein – so-called melanoprotein – a view that we now know to be correct. In 1954 Antonin Felix Richter and Jiri Duchon were able to show that natural melanins were composed of several fractions (which were subsequently classified as sulphur-containing pheomelanins and eumelanins).

In the 1960s Jiri Duchon went on to found here at Charles University a centre for research on the biosynthesis of melanins. With the collaboration of several young colleagues, including Stanislav Pavel, Bohuslav Matous and Jiri Vachtenheim, the first reports were published on the identity of excretory metabolites of melanogenic intermediates, which were to become important metabolic markers of melanoma. Duchon was also closely involved in the identification of the intracellular organelles in which melanin synthesis occurs (now called melanosomes) and, with Jan Borovansky and Petr Hach demonstrated the basic internal structure of these particles. Also, Milan Elleder characterised the phenomenon of photodegradation of melanin.

Not only has Charles University spawned this rich seam of fundamental work in pigment cell research, which continues to this day, but several important clinical aspects have emerged from here including the studies of Jiri Trapl on the histological classification of melanoma and the well-known description of the syndrome of albinism associated with haemorrhagic diathesis by Hermansky and Pudlak in 1959.

The pre-eminence of Charles University in this field has been recognised by the pigment cell community and Prague has hosted many International meetings devoted to melanin and melanogenesis including the important 3rd European Workshop on Melanin Pigmentation in 1981, the symposium on Cancer at the 14th Conference of the International Union of Biochemistry in 1988, the 8th meeting of the European Society for Pigment Cell Research in 1998 (commemorating the 650th anniversary of Charles University), and the symposium on Melanins and Melanosomes at the recent successful 34th FEBS Congress (2009), presided over by your distinguished Dean, Tomas Zima.

Acknowledgements

All of us who have laboured in the field of pigment cell research owe a debt of gratitude to the work emergent from Charles University and I would like especially to acknowledge the important influence of Jiri Duchon (now sadly no longer with us), Jan Borovansky, and Stanislav Pavel.

I should also like to take this opportunity to acknowledge my indebtedness to the colleagues who have shaped my career as a pathologist including Claude Rimington, Peter Sutton, and the late Trevor Slater, who was so influential in guiding my work on free radicals. And no listing of acknowledgements would be complete without mention of my wife, Christine, whose constant and uncomplaining support has sustained me in my professional career.

Research

My interest in pigment cells arose from some early studies in the laboratory of Arthur Jarrett on vitiligo, which is a condition in which there is loss of cutaneous pigmentation in a segmental distribution. I identified an industrial depigmentation in tannery workers due to rubber gloves as a possible clue to the pathogenesis. The component of the rubber gloves which was responsible for the loss of pigment was an antioxidant – the monbenzyl ether of hydroquinone. The formation of melanin involves oxidation of the aminoacid tyrosine and it had been thought that the anti-oxidant might inhibit this process, but it turned out that the monobenzyl ether of hydroquinone was converted by the melanin-forming enzyme to a toxic quinone product which eliminated the pigment cells in the affected areas. It seemed that we had in our hands a potential means of specifically targeting pigment cells, and thus a possible way of directing chemotherapy to malignant cells of the pigment cell lineage, and much effort has been directed to exploring this approach. I have to tell you that, regrettably, we have not yet succeeded in subduing melanoma metastasis, but novel initiatives are still being developed.

Another area that we have explored which has turned out to be very exciting is the strong metal binding exhibited by melanins. This is one of the properties of melanins discovered here at Charles University and described in a series of major publications by Jan Borovansky. Jan and I were able to carry out some significant collaborative studies with the aid of grants from the British Council and we have continued to work together under the auspices of the Quintox Group (with some financial support from the European Union) on biochemical aspects of melanogenesis. Recently we co-edited the first monograph on melanosomes which will shortly be published.

Ontology and Epistemology

As I have intimated, the general advancement of knowledge is not a singular achievement and we are all engaged in a search for a true understanding of the world. I was fortunate to graduate from UCL at a time when it was full of brilliant men. One of my mentors, Sir Peter Medawar, made an interesting distinction between ‘truth’ by definition (what he called apodictic truth) and truth by comparison with ‘reality’. Ontologically we may argue that there **is** a external reality, but its nature is epistomologically unprovable because (as another of my teachers, J.B.S.Haldane, pointed out) we are part of it, and self-reference excludes axiomatic provability (as demonstrated by Kurt Gödel).

However, we can construct analogue arguments which are comprehensible to us, and test the similarity of behaviour between the analogy and the real world. This idea of the basis of knowledge seems to have had a continuous development through Kant, Hegel, Descartes, Hume to Popper. I was introduced by my colleague Richard Spearman to the philosophy of science promulgated by Karl Popper**,** and I believe that his notion of the ‘vulnerability of theory to disproof’ is the most useful approach to understanding. There are two corollaries to this. One is that it is the hypothesis and not the proposer that is vulnerable – so it is quite in order to be wrong! Secondly, to be capable of refutation a hypothesis must represent a process that can be tested and thus must posit a mechanism. This requirement overcomes the elementary fallacy of non-mechanistic statements such as ‘All swans are white’ since ‘whiteness’ is not a property mechanistically linked to ‘swan-ness’. To us, the possibility of the existence of black swans is evident from an understanding of the mechanism of pigmentation.

Conclusion

The generation of knowledge involves the arrangement and organization of categories of data, but it consists of more than this. It requires an imaginative ability to devise a system of the world that might be represented by the observed reality (insofar as we are able to perceive it) Within this framework, a greater order may be conceived and tested against the ultimate reality of our amazing Universe.

In this noble tradition I have tried to make a genuine contribution to knowledge in my small sphere. But I am conscious of the short way we have progressed and, as expressed so eloquently by Isaac Newton, we face a long path ahead:

Magnus Oceanus Veritatis totus ignotus adhuc ante nos iacet.