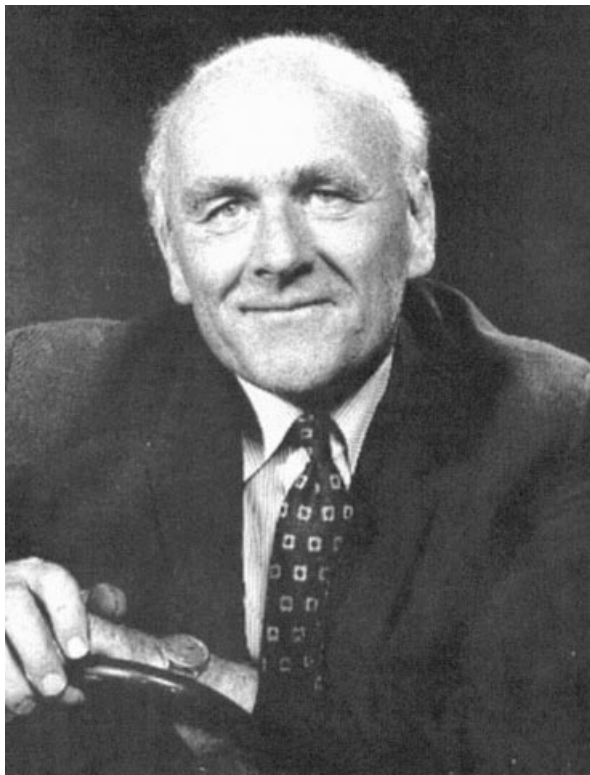


Obituary



**Aodán Seosamh Breathnach BAO, BSc, MSc, MD
(1922–2000)**

Aodán Breathnach, Emeritus Professor of Anatomy at the University of London at St Mary's Hospital Medical School, and Honorary Senior Research Fellow Division of Physiology and Institute of Dermatology, UMDS, St Thomas' Hospital, died in London after a prolonged illness on 17 April 2000, at the age of 77. He had been a member of the Anatomical Society of Great Britain and Ireland since 1949, of the Societas Dermatologica Italica from 1978, of La Société Française de Dermatologie Syphiligraphie since 1979, and of the Society for Investigative Dermatology since 1984. He is survived by his wife Babs, his two sons Stephen and Richard, and their families, to whom our deepest sympathy is extended.

Born in Roscrea, Co. Tipperary, on 20 August 1922—the youngest son of an extensive family—he studied for an intermediate certificate at the local Cistercian college, Mount St Joseph's. After matriculating at the early age of 17 he decided to study medicine, and was registered as a student at University College Dublin (UCD). Being too young to enter the medical faculty, he completed an identical course at

the Faculty of Science, and resumed the medical course in the second year: but again, because of his youth, was obliged to do it again (once without the stress of the forthcoming examinations). In this way he acquired a deep interest in anatomy by perfecting his dissection skills and extending his knowledge over the 2-year period. At the end of these studies, his interest in the anatomical studies resulted in a BSc and MSc in Anatomy. There followed a conventional career as house physician in Dublin Hospital; however, lack of prospects for promotion and the rather old-fashioned stifling environment turned his thoughts to anatomical research. The resulting appointment as an assistant lecturer in Anatomy at UCD was also a disappointment. The medical field in England offered more prospects, and a vacancy for a house surgeon at St Luke's Hospital in Guildford was his choice. Shortly after his appointment in 1947, his future wife, Babs, a Norwegian physiotherapist, arrived at St Luke's. After 5 months they married, and needed to set up a home, which was rather difficult on a house surgeon's salary. At that time, an advertisement in the *British Medical Journal* from St Mary's Medical School for a lectureship in the Department of Anatomy provided a way out. A substantially higher salary and a career in Anatomy seemed irresistible. This post, to which he succeeded in 1949, started a very distinguished teaching and research career.

At that period, the research interests of the head of department, Professor Frank Goldby, were in the field of comparative neuroanatomy. Very shortly after his appointment he was involved in a research project concerned with the involution of the olfactory system in the brains of Cetaceans, a system that was supposedly essential for the development of many important brain centres. A comparison with the relevant brain olfactory centres of Cetaceans and other mammals possessing a highly developed sense of smell was the general direction of the project. After 10 years of actively pursuing dolphin and whale neuroanatomy, the overall conclusion was that the absence of olfactory impulses and connections was not essential to the development of the so-called tertiary olfactory centres, which are currently grouped with the limbic system.

In the 1960s his attention turned to skin biology and especially its pigmentation. In the mid 1950s the general knowledge of skin pigmentation was very basic. The discrete pigmentation of a freckle was a

considerable mystery, which up to that time was completely ignored by dermatologists and skin biologists. Concurrently, the research carried out by Peter Medawar's group, which involved skin immunological responses, provided some very useful techniques, which were developed by George Szabo. This included the splitting of a skin layer which contained melanocytes, followed by handling, staining and analysis of the resulting sheets, which proved to be a very fruitful exercise. Surprisingly, melanocyte counts revealed that the number per unit area did not change within the area of a freckle when compared to that of normal skin. Breathnach's interest in melanocytes expanded to a sufficient degree to interest dermatologists in the USA. Among others, active cooperation developed with Bill Montagna (Head of the Primate Research Centre in Oregon), Walter Quevedo (Brown University), Stephen Katz (NIH Bethesda), Richard Winkelmann (Mayo Clinic) and Tom Fitzpatrick (Chair of Dermatology at Harvard Medical School) for whom George Szabo was then working. The logical next step in this pursuit concerned the identity of the Langerhans cells, regarded by some researchers as 'effete' melanocytes. The nature of these cells (which were originally described 130 years ago by Paul Langerhans) remained a mystery for a long time, and has only recently been glimpsed. In the early 1960s other workers using electron microscopy had demonstrated the ultrastructure of melanocytes, and an obvious step forward was to apply this method to Langerhans cells. Skin from patients suffering from patchy depigmentation affected by vitiligo was chosen, and with Michael Birbeck (an electron microscopist at the Chester Beatty Research Institute) and John Everall (a dermatologist at St Mary's) a definitive paper on skin ultrastructure was produced. The presence of the characteristic organelles within the dendritic cells provided a starting point for future studies on the lineage and nature of these cells.

In the mid 1960s, the award of a substantial grant by the Wellcome Trust towards an electron microscope proved to be a great boost to current research projects. Aodán Breathnach, by then Reader in the Department of Anatomy, took to the new instrument with great enthusiasm. Despite his lack of technological training, he very soon mastered the instrument. A large number of high-quality micrographs of human skin were his pride and joy, a joy that was shared by his coworkers. Eventually in 1971 this large portfolio of electron micrographs was brought together in his *Atlas of the Ultrastructure of Human Skin; Development, Differentiation and Post-Natal Features*, which remains, after

30 years, the definitive publication in this field. Novel methods for the observation of cell ultrastructure were also actively encouraged and supported by Aodán. One of these was the freeze-fracture replication technique, which was applied to the study of skin, its constituent cells and their intercellular junctions. The same technology was also used to unravel the structural aspects of normal and diseased peripheral nerve. This last study was performed in cooperation with Professor P. K. Thomas of the Department of Neurological Sciences at the Royal Free Hospital School of Medicine. Additionally, the early junctional complexes of the developing chick embryo were investigated with Professor Ruth Bellairs of the Department of Anatomy and Embryology at University College.

A study of a range of human fetal skin specimens was also undertaken at that time, in order to clarify the assumed relationship between melanocytes and Langerhans cells; it provided vital new evidence for the separate nature of the two types of cells. Combined evidence from ultrastructural and histochemical studies identified this family of cells as a living functional entity, negating previous ideas about their 'effete' nature. These investigations, in conjunction with the studies of Dr Françoise Basset at the Hôpital Bichat in Paris on Histiocytosis X (a granulomatous condition of the connective tissues of skin and other organs), in which cells with numerous organelles identical to those in Langerhans cells were found, pointed towards the final understanding of the monocyte-macrophage lineage of Langerhans cells.

In 1968 Aodán Breathnach was appointed to the chair of the Department of Anatomy at St Mary's, and in later years he also served as a Deputy Dean of the Medical School: although his new administrative duties did not diminish his contribution to research, to which he continued to devote his talents and energies.

In the 1970s, St Mary's received a request from an Italian histopathology laboratory at the San Gallicano Institute of Dermatology in Rome, to examine a sample of skin from patients suffering from hypopigmentation caused by Pityriasis Versicolor (a yeast infection of the epidermis). This started a completely new and exciting avenue of research. It very soon became apparent on ultrastructural investigation that there was widespread destruction of melanocytes in the affected regions. The swollen cell bodies and burst mitochondria of the melanocytes pointed to an unknown agent, emanating from the *Pityrosporum* yeast. Biochemical investigations at the San Gallicano Institute revealed that this causative agent was a rather simple chemical, in the form of azelaic acid, a



Relief sculpture by T. Zieliński, based on a freeze-fractured *Pityrosporum* yeast image and presented in 1987 to Professor A. S. Breathnach at the occasion of his retirement from St Mary's.

straight chain 9-carbon atom dicarboxylic acid. This was subsequently found to be a non-toxic and non-teratogenic substance, which potentially could be effective in treating a range of hyperpigmentary disorders of the skin. A series of collaborative trials run by Dr Marcella Nazzaro-Porro, Aodán Breathnach and Siro Passi revealed the beneficial effects in Lentigo Maligna (melanoma in situ). The most surprising observation was that azelaic acid was more active against abnormally hyperactive and proliferative melanocytes than in normal cells of this lineage. Subsequently, in collaboration with Professor Giuseppe Zina, Director of the Department of Dermatology at the University Clinic of Turin, clinical trials of patients with invasive melanoma were undertaken. The first encouraging results were published in the *Lancet*, and further research covering biochemistry, pharmacology, ultrastructure and tissue culture was carried out in Rome, Turin and London. Significant information was obtained on the mechanism of action of the azelaic acid, which selectively destroyed the malignant cells. These results indicated that the mitochondrion is prime target of the azelaic acid, affecting enzymes involved in the synthesis of deoxyribonucleotides, DNA polymerase and general DNA synthesis. These biochemical activities most likely explain the effect of azelaic acid on abnormally active cells, while not affecting normal cells.

There also was a surprising effect of the topical application of the cream containing this substance in

the case of some patients treated for Lentigo Maligna. During treatment, acne spots were reported to improve. A subsequent study of a large group of patients, in addition to an international multicentre trial organised by Schering AG, Berlin, confirmed the beneficial effects of this treatment.

In 1987, retirement from the Chair of Anatomy and Cell Biology approached. As a memento of their long and fruitful collaboration, the departmental staff presented Aodán with a relief sculpture of the *Pityrosporum* yeast. From that day onwards, it graced the wall of his study as a reminder of one of the most rewarding and potentially important projects that he directed.

During Aodán Breathnach's years as Head of Department, the staff received an enormous amount of help in furthering their own careers, and were actively encouraged to pursue their individual line of research in an effective way.

For the next 11 years Aodán settled down as Honorary Senior Research Fellow at the UMDS Division of Physiology, St Thomas' Hospital Campus. Several publications resulting from cooperative studies with Italian and German laboratories further confirmed and publicised the usefulness of azelaic acid as a new palliative at the disposal of the medical profession.

Over the years, running the Department of Anatomy and Cell Biology required not only administrative skills but also a skilled diplomatic approach during

some minor and major crises. Robert Smith, Head of the Pharmacology Department, remembers Aodán from that period in an especially fond way:

I was fortunate to have known Aodán in several capacities during our careers at St Mary's Hospital Medical School. Firstly, we were colleagues in the sense that we both ran preclinical departments and this brought us into frequent contact regarding issues of school administration. Secondly, I seemed destined to succeed Aodán in his terms of office as Deputy Dean and Chairman of various committees, including the vexatious 'Accommodation Committee'. During that time we forged a considerable friendship based not on scientific interests but on our mutual love of Italy, its language and culture. Aodán knew that I had family ties with the West of Ireland, hence the language and culture of Celts and all things Celtic formed an additional point of interest. Aodán was a fluent speaker of Irish Gaelic and indeed his father and grandfather I believe had been involved in the revival of the Gaelic language in the West of Ireland.

Two aspects of Aodán spring to mind. The first was his fierce and loyal defence of his beloved Department of Anatomy against all would be assailants. In this sense he carried on a tradition first established by his predecessor Frank Goldby. Secondly, there was his love and commitment to the Italian language, which he studied with vigour and mastered quite late in his life. I can readily recall one occasion when Aodán turned to me and announced: 'My invited lecture in Italy will be given in Italian!' He was immensely proud of this. Aodán was in many ways a larger-than-life character. He had presence and Gaelic charm, and like his countrymen he had a gift for conversational skill so that minor events and peccadilloes in Medical School life would be defused by Aodán style and wit.

Aodán Breathnach was an experimental biologist who adopted John Hunter's celebrated motto 'But why think? Why not try the experiment?' His careful and meticulous approach to projects earned him the admiration of the scientific community, especially in the United States. To quote from Walter Quevedo: 'Almost as significant as Aodán's own research was his ability to attract the attention of more molecularly oriented individuals who eventually closed the door

on a melanocyte and Langerhans cell relationship by definitively determining that the specific role played by Langerhans cells in mammalian epidermis was immunological'. Walter Quevedo also wrote:

Charles Darwin maintained that good scientists are ones that know how to speculate 'with a curb on'. I take that to mean that the concrete inductive evidence that motivates a scientist to seek a new explanation for a natural phenomenon, by generating a testable hypothesis, also sets limits on the extent of the speculation that is an essential ingredient in the formulation of a hypothesis. I believe that Darwin would have approved of Aodán's style of pursuing research. Aodán never abandoned a possibility until it was shown to be untenable, and when conceiving possible explanations his speculations never went beyond those justified by the evidence in hand. Graduate students embarking on research in pigment cell biology should be encouraged to read Aodán's papers on melanocytes and Langerhans cells.

In a similar vein, the words of Dr Des Tobin, one of his students, describe a poignant event:

I once had a problem getting some normal control skin, and in my naïveté I did not think of myself as a potential donor. In great theatrical style, Professor Breathnach rolled up not just one sleeve but both, to reveal numerous small white biopsy areas, the description of which (in print and image) must surely have educated many eager dermatological researchers all over the world. He could have coded these sites and related them directly to stages in his own development via articles and presentations.

It sums up Aodán's determination that, despite severe illness, he continued to work to the end on his final publication *The Story of the Langerhans Cell*, which recalls his own and his colleagues' investigative efforts concerned with the function and nature of the dendritic cells of the skin, while interweaving it with autobiographical events. Unfortunately, in the end he was not well enough to correct and review the text entirely to his satisfaction. The book nonetheless has now appeared in print.

CHRIS STOLIŃSKI