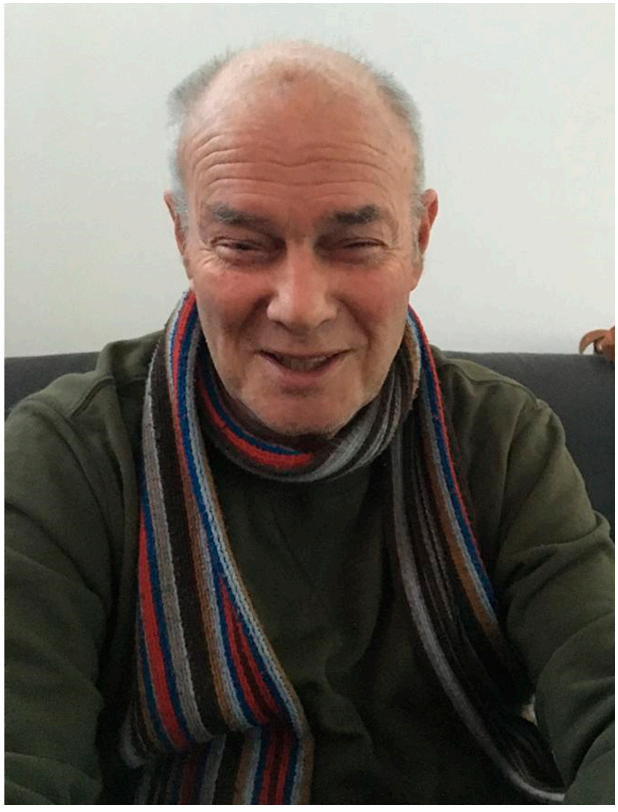
Int. J. Dev. Biol. 64: 393-395 (2020)
https://doi.org/10.1387/ijdb.200236vn

IN MEMORIAM



Antony J. Durston (1944-2020)

Antony Durston, Tony to friends and colleagues, died on February 21, 2020 following sepsis caused by an underlying medical condition. He made important and highly original contributions to our understanding of the principles that underlie multicellular organisation and development (see Supplementary Material). The attitude which he brought to bear while doing science is as noteworthy as his research. What follows is a brief sketch of his career and persona. After obtaining a Bachelor of Science degree with Botany as his major from the University of Nottingham in 1965, Tony joined Neville Symonds to do a PhD in bacteriophage genetics at the University of Sussex, where he was influenced as well by Brian Goodwin and John Maynard Smith. It was Symonds who inspired him to develop his natural tendency to think outside the box.

After completing his PhD in 1969, Tony taught Botany for a year at University College, Nairobi (Kenya), an experience which he used to recall with relish. Then, after a short stint as Tutorial Fellow in the School of Biological Sciences at Sussex, he moved to the University of Chicago to join Morrel Cohen and Anthony Robertson as Post-doctoral Fellow and later, Lecturer (1971-1974) at what used to be the Committee on Mathematical Biology (founded by Rashevsky). This later became the Department of Theoretical Biology and later, the Department of Biophysics and Theoretical Biology. In 1974 Tony was invited to join the Hubrecht Laboratory, Utrecht (Netherlands), as a principal investigator and remained there until 2005. He was also an Extraordinary Professor in Embryology at the University of Utrecht from 1991 to 2005, and, in 2005, moved to Leiden as Professor, where he established close interactions with Herman Spaink. At the time of his passing, he was Emeritus Professor of developmental biology at the University of Leiden. His interest in the regulation of form and pattern via spatio-temporal oscillations, extending to a view of biological tissues as excitable systems, was awakened in Chicago. It had a determining influence on the rest of his career; he told one of us that the experience of working there convinced him of the fundamental role of theory (even) in biology. One consequence was that the concepts of 'clock' and 'map' were woven into most of his later published work.

In common with everyone who hears of it, the unusual life cycle of the social amoeba *Dictyostelium discoideum* had aroused his wonder. At Chicago, he got the opportunity to probe the cell-cell communication mechanisms responsible for development and pattern formation in this organism. John Bonner had shown that the cells aggregated by chemotaxis; Bonner, together with Brian Shaffer, Theo Konijn and others, found that the cells used cyclic AMP for chemo-attraction and as a transmitter that stimulated other cells to make and release it. This made it possible to analyse the dynamics of the cAMP-mediated cell-cell communication system using a combination of quantitative experiments and modelling. Under the influence of Cohen and Robertson, Tony made use of time-lapse cinemicrography as a powerful analytical tool to follow the temporal profile of oscillatory cyclic AMP signalling by quantifying complex coordinated cell movements. In combination with theoretical work by others, his observations led to insights on how the aggregation centres acted as pacemakers to regulate cell-cell signalling dynamics and the resulting cell movements. That work led to the identification of 'clock' mutants; unfortunately the absence of an amenable methodology for genetics in *D. discoideum* prevented it from being exploited further (Durston, 1974). Fortuitously, working in the same department, Arthur Winfree was investigating the dynamics of excitable chemical waves in the Belousov- Zhabotinsky reaction, and each stimulated the other's thinking. It was an exciting multidisciplinary research environment that proved to be of seminal influence for the renaissance of interest in pattern formation in biology. It laid the foundations for Tony's appreciation of the importance of theorising led by observations, and not

Supplementary material (Durston's bibliography) for this paper is available at: https://doi.org/10.1387/ijdb.200236vn

ISSN: Online 1696-3547, Print 0214-6282

being afraid to challenge convention.

In 1974, Tony took up a Group Leader position in the Hubrecht Laboratory, a developmental biology research institute in Utrecht in the Netherlands led by Pieter Nieuwkoop. Initially he remained concerned with morphogenesis in *D. discoideum*, with the focus shifting to the later, multicellular, stages. By tracking the movements of vitally stained prestalk cells during late aggregation and slug formation, his first PhD student Kees Weijer and he worked out that during mound and early slug stages, cAMP-mediated signalling manifested as complex three-dimensional scroll waves, the first observation of scroll waves in biological matter (Durston, 2013a). He showed that the slug tip, which Kenneth Raper had shown to be analogous to the embryonic organiser, also acted as an inhibitor: it suppressed new tip formation with a strength that declined with distance, in line with the ideas of pattern formation formulated by Turing and developed further by Gierer and Meinhardt (Durston, 1976). With Soichi Matsukama, his first postdoc, he showed that the axial pattern of cell types was influenced by differential chemotactic cell sorting, mechanistically very different to the common notion of differential adhesion- based cell sorting championed by Malcolm Steinberg and co-workers (Matsukuma and Durston, 1979). All these findings have become standard features of our understanding of patterning in the multicellular stages of *Dictyostelium* development.

Some years after joining the Hubrecht Lab., interactions with Pieter Nieuwkoop, a giant of the late 'cut-and-paste' phase of developmental biology, caused Tony's interests to shift to early development in the amphibian embryo. He decided to tackle a phenomenon of historical importance that dated from the work of Spemann and Mangold, namely embryonic induction and anterior-posterior axis formation; the organism of choice was *Xenopus laevis*. After some years, he started to work on early *Xenopus* development. He began by investigating the molecular basis of neural induction and showed that all-trans retinoic acid caused anterior-to-posterior transformations in the nervous system (Durston *et al.*, 1989). The significant findings were that activation of Protein kinase C, resulting in adenylyl cyclase activation, is a key aspect of signal processing during acquisition of competence for neural differentiation (Otte *et al.*, 1988); and that all-trans retinoic acid, especially its breakdown product 4-oxo retinoic acid, is found in early embryos and modulates positional specification, raising the possibility that specific retinoid ligands regulate different physiological processes *in vivo* (Pijnappel *et al.*, 1993). The effect turned out to be due to inappropriate *Hox* gene expression, which suggested that anterior-posterior transformation originally described by Nieuwkoop could be explained by the graded activity of retinoic acid in signalling anteroposterior patterning. These findings were later substantiated by studies in the chick and mouse and kindled his interest in understanding the role of *Hox* genes in anterior-posterior patterning. Tony continued to engage himself with the *Hox* genes, especially the question of how the enigmatic 3'-5'collinearity of their organisation in the genome with their temporal expression is related to the spatial anterior-posterior pattern of their expression. He continued studying the spatio-temporal patterning of tissues during gastrulation in frogs and fish. That work, initiated in the Hubrecht Laboratory and continued in Leiden, culminated in the development of a hypothesis he named TST (Time Space Translation) (Wacker *et al.*, 2004). It proposes that the temporal organisation of the opening of the Hox clusters in the non-organiser mesoderm is translated into a spatial pattern of Hox expression via the sequential interaction of non-organiser mesoderm with signals emitted by the Spemann organiser brought about by the convergent extension movements during gastrulation. These organiser signals freeze the progression of the Hox activation timer in tissues close to the organiser, so that cells that interact with the organiser early during development have their timer stopped early and take on an anterior identity, while cells interacting late have the timer stopped late and take on a posterior identity (Durston and Zhu, 2015). Tony provided further compelling evidence that this interaction depended on modulation of BMP signalling via BMP inhibitors produced by the organiser. The Hox expression pattern in the non-organiser mesoderm is transferred to the overlaying neuro- ectoderm through vertical signalling, a process likely involving direct transfer of Hox proteins themselves (Bardine *et al.*, 2014). In an influential Perspective published in the *Int. J. Dev. Biol*, (downloaded from the journal web over 3,000 times and cited 26 times as of 9/2020), Tony challenged the mainstream idea that Hox temporal collinearity is due to progressive chromatin opening by proposing that collinear Hox interactions are the key to understanding it (Durston *et al.*, 2011, Zhu *et al.*, 2017). He further suggested that the temporal expression might be correlated with the somitogenesis clock. The original and fascinating TST hypothesis and underlying mechanisms are likely to be of fundamental importance; it typified the original way in which he thought about large questions. Much of the TST hypothesis and supporting evidence has been published, but inevitably some of his most recent work is still in preprint form.

Tony focused on the interplay between both the genetic/molecular mechanisms at the subcellular level and intercellular communication at the supracellular level. This interplay is thought to underlie the the temporal and spatial patterns which control development. The focus was primarily supracellular in his early slime mold work. By switching to *Xenopus*, he was able to attack that connection between subcellular activity and spatial and temporal patterning in the embryo. Yet slime molds were never forgotten, and in 2013 he introduced the concept of dislocation (Durston, 2013b) observed in slime molds, in which patterns dislocate, i. e. split, and proposed that it could generally initiate the development of distinct tissues. In 2018, with Joao Peres and Morrel Cohen, he reported the observation of spiral patterns developing in the presomitic mesoderm of *Xenopus* and argued that such spirals first seen in slime molds could play an essential role in the development of handedness in vertebrate embryos (Durston, Peres and Cohen, 2018). After his last PhD student Kongju Zhu left and he closed his lab in 2018, Tony remained engaged with

research and publishing until the very last.

Tony was a highly interactive scientist who collaborated successfully and participated in the organisation of Europe-wide research consortia ("Cells into Organs"). Furthermore, he organised and actively participated in scientific meetings and thrived on scientific discussions on large topics. He projected an easy-going style of doing science, but it masked an approach that was both rigorous and creative. He did not suffer fools gladly and was not afraid to speak his mind in public. He liked original thought, enjoyed working out his own ideas, and disliked it when scientists followed the ruling dogma in their field without question. He was prepared to stick his neck out to help someone who followed an unconventional line. He felt the current publication culture actually blocked progress in science, because the people who developed the ideas that are currently the norm, are in a position to stop new ideas that challenge them. He was fond of working with bright, young people and encouraged them to think out of the box. With students he was a hands-on supervisor who loved doing experiments himself and discussing the results and interpretations with the right combination of guidance and encouragement. He was a very supportive mentor and always encouraged and helped his trainees to pursue their interests and to find their own career paths. To associates he was a generous and fun-loving colleague.

Tony had a great passion for the outdoors, and liked going with students on birdwatching and camping trips in the Netherlands and the UK. He was immensely proud of his family, his wife Jenny and three daughters Sarah, Rebecca and Emily. Sarah followed his footsteps and holds a chair in Developmental Disorders of the Brain in the University of Utrecht. We remember him for the warm and inspiring person he was, and will miss him greatly.

Acknowledgements

We are grateful to Sarah Durston for several valuable inputs and for providing the bibliography which is included with the online version. Our thanks to Rebecca Durston for the photograph of Tony taken in Christmas 2019.

References and Selected Key Publications

BARDINE, N., LAMERS, G., WACKER, S., DONOW, C., KNOECHEL, W. and DURSTON, A. (2014). Vertical signalling involves transmission of Hox information from gastrula mesoderm to neurectoderm. *PLoS One* 9: e115208.

DURSTON, A.J. (1974). Pacemaker activity during aggregation in Dictyostelium discoideum. *Dev Biol* 37: 225-35.

DURSTON, A.J. (1976). Tip formation is regulated by an inhibitory gradient in the dicytostelium discoideum slug. *Nature* 263: 126-9.

DURSTON, A.J. (2013a). Dictyostelium: The Mathematician's Organism. *Curr Genomics* 14: 355-60.

DURSTON, A.J. (2013b). Dislocation is a developmental mechanism in Dictyostelium and vertebrates. *Proc Natl Acad Sci USA* 110: 19826-31.

DURSTON, A.J. and ZHU, K. (2015). A time space translation hypothesis for vertebrate axial patterning. *Semin Cell Dev Biol* 42: 86-93.

DURSTON, A.J., TIMMERMANS, J.P., HAGE, W.J., HENDRIKS, H.F., DE VRIES, N.J., HEIDEVELD, M. and NIEUWKOOP, P.D. (1989). Retinoic acid causes an anteroposterior transformation in the developing central nervous system. *Nature* 340: 140-4.

DURSTON, A.J., JANSEN, H.J., IN DER RIEDEN, P. and HOOIVELD, M.H. (2011). Hox collinearity - a new perspective. *Int J Dev Biol* 55: 899-908.

DURSTON, A.J., PERES, J. and COHEN, M.H. (2018). Spiral waves and vertebrate embryonic handedness. *J Biosci* 43: 375-390.

MATSUKUMA, S. and DURSTON, A.J. (1979). Chemotactic cell sorting in Dictyostelium discoideum. *J Embryol Exp Morphol* 50: 243-51.

OTTE, A.P., KOSTER, C.H., SNOEK, G.T. and DURSTON, A.J. (1988). Protein kinase C mediates neural induction in *Xenopus laevis. Nature* 334: 618-20.

PIJNAPPEL, W.W., HENDRIKS, H.F., FOLKERS, G.E., VAN DEN BRINK, C.E., DEKKER, E.J., EDELENBOSCH, C., VAN DER SAAG, P.T. and DURSTON, A.J. (1993). The retinoid ligand 4-oxo-retinoic acid is a highly active modulator of positional specification. *Nature* 366: 340-4.

WACKER, S.A., JANSEN, H.J., MCNULTY, C.L., HOUTZAGER, E. and DURSTON, A.J. (2004). Timed interactions between the Hox expressing non-organiser mesoderm and the Spemann organiser generate positional information during vertebrate gastrulation. *Dev Biol* 268: 207-19.

ZHU, K., SPAINK, H.P. and DURSTON, A.J. (2017). Collinear Hox-Hox interactions are involved in patterning the vertebrate anteroposterior (A-P) axis. *PLoS One* 12: e0175287.

***Address correspondence to the authors:** Morrel H. Cohen[1], Vidyanand Nanjundiah[2], Cornelis J. Weijer[3] and Kongju Zhu[4].
[1]Department of Chemistry and Chemical Biology, Princeton University, Princeton, New Jersey, USA, and Department of Physics and Astronomy, Rutgers University, New Brunswick, New Jersey, USA. e-mail: mhcohen@prodigy.net;
[2] Centre for Human Genetics, Bangalore 560100, India. e-mail: vidyan@alumni.iisc.ac.in;
[3] Division of Cell and Developmental Biology, School of Life Sciences, University of Dundee, Dundee DD1 5EH, UK. e-mail: c.j.weijer@dundee.ac.uk;
[4] Department of Pathology, Brigham and Women's Hospital, and Department of Genetics, Harvard Medical School, Boston, MA 02115, USA
e-mail: kzhu4@bwh.harvard.edu

Submitted: 18 June, 2020; *Accepted:* 2 September, 2020.

Further Related Reading, published previously in the *Int. J. Dev. Biol.*

Hox collinearity - a new perspective
Antony J. Durston, Hans J. Jansen, Paul In der Rieden and Michiel H.W. Hooiveld
Int. J. Dev. Biol. (2011) 55: 899-908

Molecular mechanisms controlling brain development: an overview of neuroepithelial secondary organizers
Claudia Vieira, Ana Pombero, Raquel García–Lopez, Lourdes Gimeno, Diego Echevarria and Salvador Martínez
Int. J. Dev. Biol. (2010) 54: 7-20

Retinoid signalling is required for information transfer from mesoderm to neuroectoderm during gastrulation
Ferran Lloret-Vilaspasa, Hans J. Jansen, Koen de Roos, Rosh A.S. Chandraratna, Maija H. Zile, Claudio D. Stern and Antony J. Durston
Int. J. Dev. Biol. (2010) 54: 599-608

Identification of hoxb1b downstream genes: hoxb1b as a regulatory factor controlling transcriptional networks and cell movement during zebrafish gastrulation
Willem M.R. van den Akker, Antony J. Durston and Herman P. Spaink
Int. J. Dev. Biol. (2010) 54: 55-62

Head-tail patterning of the vertebrate embryo: one, two or many unresolved problems?
Claudio D. Stern, Jeroen Charité, Jacqueline Deschamps, Denis Duboule, Anthony J. Durston, Marie Kmita, Jean-François Nicolas, Isabel Palmeirim, Jim C. Smith and Lewis Wolpert
Int. J. Dev. Biol. (2006) 50: 3-15

Novel interactions between vertebrate Hox genes.
M H Hooiveld, R Morgan, P in der Rieden, E Houtzager, M Pannese, K Damen, E Boncinelli and A J Durston
Int. J. Dev. Biol. (1999) 43: 665-674

Discovery of a morphogen.
T Durston
Int. J. Dev. Biol. (1999) 43: 625-627

Neural induction and patterning in embryos deficient in FGF signaling.
S F Godsave and A J Durston
Int. J. Dev. Biol. (1997) 41: 57-65