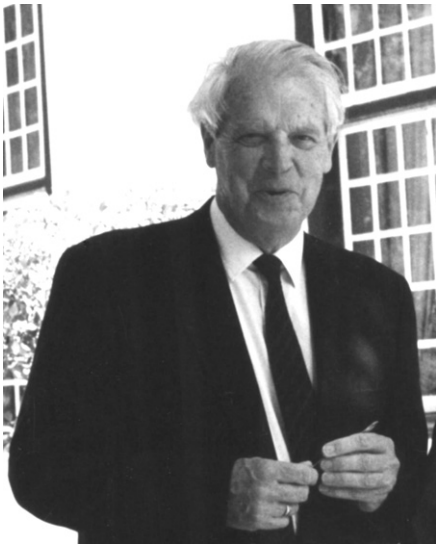
Claus von Holt (1925–2009)

Claus von Holt, professor and head of the Biochemistry department at the University of Cape Town (UCT) from 1967 to 1991, will be remembered for his pioneering work on histone structures. He retired to Valdivia, Chile where he died on 30 March 2009 at the age of 83.

After serving in the Germany navy during the war, von Holt qualified in medicine at the University of Hamburg. He then started his research career, studying diabetes and the function of the pancreas under the well-known physiologist Joachim Kuhnau. At this time biochemical thinking was still dominated by the work of Otto Warburg on cellular respiration and related phenomena, arising from the availability of labelled organic compounds. Early milestones of von Holt's career were classical metabolic studies on the amino acid hypoglycine, found in West Indian achee fruits. This toxin was known to cause vomiting, and had attracted considerable attention because of its strong hypoglycaemic properties. Von Holt isolated the metabolite methylenecyclopropaneacetic acid, demonstrating profound adverse effects on mitochondrial function and fatty acid metabolism—thereby putting an end to speculation that hypoglycine might be of therapeutic benefit for the treatment of diabetes. Among his other early studies of note were those on metabolite exchange between coelenterates and their algal (zooxanthellae) symbionts.

In 1967 von Holt was appointed to the chair of biochemistry at Cape Town, where he started work on histone structures. An interest in these basic nuclear proteins had developed in many laboratories, when the few available sequences from calf thymus and pea seedlings had hinted at strong conservation and a universal role. Convinced that information on molecular function must be forthcoming from primary structures, von Holt set out to tackle problems of histone isolation and purification from a wide range of organisms. Wolf Brandt and other members of his unit pioneered the use of chemical cleavages in obtaining large peptides suitable for sequencing.

Armed with an accelerating output of papers, von Holt succeeded in mobilising research support on an unprecedented scale at UCT. A new dedicated high tech building was opened in 1974, and new permanent positions and postdoctoral fellowships were made available. A remarkable outcome of such good stewardship was large-scale funding without the need for grant motivations: in 1984 von Holt and the Dean of Science Jack de Wet convinced Reinhardt Arndt of the Council for Scientific and Industrial Research to establish the rating system



and associated long-term support for established researchers. Some would argue that this innovation has stood the test of time; others that it has outlived its usefulness.

In his teaching von Holt emphasised the understanding of principles at the expense of dictionary detail. Both the strict requirements that practicals should be repeated when results fell outside a certain margin of error, and the introduction of oral examinations caused considerable distress amongst students. Unsurprisingly, the department quickly acquired the reputation of being under what one student publication of the time described as 'unsympathetic Teutonic management'. But growing numbers of publications and higher degrees awarded were sure signs of a successful strategy.

Milestones in von Holt's research included confirmation of the conservation of H3 and H4 histones. Using yeast, wheat germ, cycad pollen, marine invertebrates, and both avian and amphibian erythrocytes as evolutionary markers, the H2A and H2B groups of histones were identified as more variable, while a new group of isohistones was added, showing profound changes in residue number and composition, e.g. in sea urchin sperm and embryo's, particularly for H2B and H1. This gave rise to much speculation about an ontogenetic programme, and questions about the relationship between isohistones and protamines. Another significant development emanated from Brandt's sequences, showing the existence of acetylated and methylated lysine residues in the N-domains. The work of Deneys van der Westhuyzen demonstrated that a large H3H4 population and a smaller H2AH2B population exists at pH 5. This observation earned many flattering references when Kornberg and Thomas in Cambridge realised that histone fractionation under quasi native conditions resembles the natural oligomeric assembly in the nucleus, where dimers and tetramers exist as components of an octamer in the sub-particle.

The tendency of histones to aggregate; and the difficulty of isolating pure histone species landed on my desk. By applying charge-shielding effects pioneered by the Bradbury group in Portsmouth, we succeeded in modulating histone–histone interaction, and in changing their hydrodynamic behaviour for optimum separation by size exclusion. This technique was soon exploited commercially by Boehringer, but regrettably to no benefit of any of us. Strangely, the oligomeric contacts in H3 and H4 were not mainstream topics in Cape Town, and were taken up only later by myself during a visiting fellowship at Portsmouth. Using large H3 and H4 peptides and a peptide reconstitution scheme conceived by Crane-Robinson, we showed that the central hydrophobic domains in H3 and H4 were required for oligomeric contacts, leaving the basic N-terminal tails for a separate function. A concealed location of the hydrophobic domains in H3 and H4 was also apparent from immunological work conducted by Absolom and van Regenmortel, who demonstrated that H3 and H4 antibodies generated from RNA complexes do not detect the hydrophobic epitopes in chromatin preparations.

In subsequent work between Crane-Robinson (Portsmouth), Sautière (Lille) and my group at Stellenbosch, the boundaries between the central hydrophobic domains and the unfolded N-terminal regions were clearly identified from the cutting points in the trypsin resistant limit peptides. The N-terminal domains not restricted by histone–histone interactions were found to contain all the known modification sites, strongly suggesting that they must be exposed and perform a separate function. Their role in chromatin compaction and epigenetic regulation of the genome is now firmly established.

Von Holt was committed to high academic standards, and his influence is still felt today. Postgraduate students of his who are now in leading positions in South Africa include Wolf Brandt, Paul van Helden, Iqbal Parker, Janet Hapgood, Sylva Schwager, Peter Smith, Hugh Patterton and Robert Warren. Charles Boyd, Derek Woods, Dave Landsman and Deneys van der Westhuyzen have research positions in the U.S.A., while Martin Friede and Johan Greyling are in Europe. Von Holt's work generated much international respect, placing South African biochemistry firmly on the map. He is survived by his wife Margot, who has our condolences and sympathy.

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