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OBITUARY

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In memoriam – Alan P. Wolffe (21.6.1959–26.5.2001)

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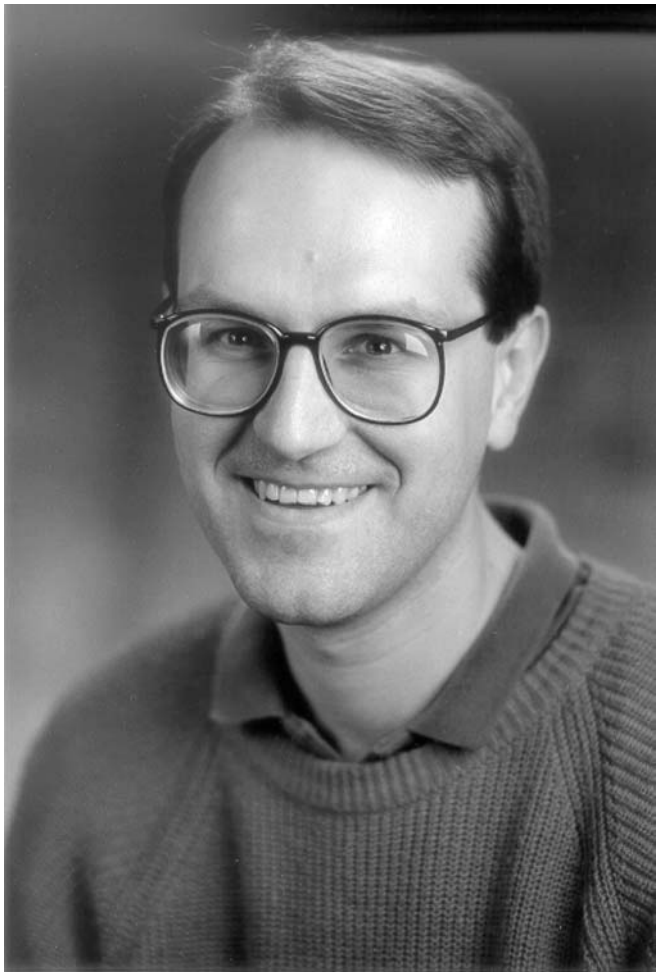
This issue of *Chromosoma* is dedicated to the memory of Alan Wolffe, a scholar of eukaryotic genome biology and an editor of this journal. In May of 2001, Alan was killed in a traffic accident.

Most readers of this journal will be familiar with Alan from his book, *Chromatin structure and function*. The standard reference work on this subject, it synthesizes data from ~1,700 primary research papers into a conjunct narrative. To Alan, such synthesis came with almost supernatural ease – as a colleague of Alan's said at his memorial service, "Watching Alan discuss existing scientific evidence was like listening to Arthur Rubinstein play Chopin!"

Indeed, on separate occasions I heard two very distinguished scholars of chromatin and transcription marvel at Alan's scientific erudition. "I thought I knew the literature pretty well until I met Alan Wolffe" – said one. "Alan was probably the only person on Earth who knew my own data better than I myself did" – said the other. Alan's passion for data, encyclopedic memory, and powers of instant recall were all quite extraordinary. For example, sometime in 2001 I told him about a "new" method to look at chromatin remodeling I naively thought I had "invented." "Yes," Alan said immediately, "there was a paper in 1992 in *Biochim Biophys Acta* by Bryant Villeponteau that described this method." Such incidents were legion, as anyone who worked with him can attest.

Even though he already knew the entire body of existing literature on genome function, Alan's interest in new data can only be described by the word "hunger." For example, in January 2000 *Mol Cell Biol* published a paper by Barra et al. (vol. 20, pp. 61–69) describing the consequences of linker histone knockout in *Ascobolus*. Among several interesting observations in that study, I was particularly struck by a dataset on a marked increase



of linker DNA accessibility to micrococcal nuclease in the absence of histone H1 (Fig. 5 in the paper). The following conversation I had wth Alan illustrates well, I think, the manner in which this man *devoured*, for lack of a more elegant word, the scientific literature. "Alan," I said, "did you see this recent *MCB* paper from a group in France...?" Alan interrupted: "Yes, Fougeron's paper on

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H1 in *Ascobolus*." "That's the one," I replied, surprised as always at his speed. "In particular, there was a gel showing...." Alan smiled broadly and interrupted again: "Yes, yes, the increased accessibility to micrococcal. Remarkable. Absolutely the single best result I've seen all winter!"

Several times since Alan's death I witnessed discussions about genome biology between his friends and colleagues that ended with "None of us here know what the published evidence on this particular matter shows, but we are sure Alan would have known."

The story of Alan's life in science can be stated quite succinctly. He was born in Burton-upon-Trent in England, went to Oxford to study nucleosomes with Ian Walker, did a Ph.D. with Jamshed Tata in London, then a postdoc with Don Brown at the Carnegie, was laboratory chief at the NIH from 1989 to 2000, and, for the last 1.5 years of his life, was chief scientific officer of Sangamo BioSciences, a biotechnology company in California. He was 3 weeks away from his 42nd birthday when he died.

Hidden in this dry narrative is a genuine mystery (sadly, we will not know the answer). For someone who knew so much about the history of scholarship in science, how did Alan manage to look into the future with such astonishing accuracy? How is it that knowing so much about where genome biology stands at the present time did not stifle his creative thinking about where it *needs to be*?

Indeed, Alan's initial work in the 1980s focused on transcriptional regulation in the well-established epistemological context of that time. In 1989, however, when Alan became the youngest Laboratory Chief in the history of the NIH, he switched to working on chromatin. Why? At the time, the problem of transcriptional regulation – in the famous words of Sydney Brenner, "along with other trivial problems of biology, such as membranes and structure of ribosomes" – was considered basically solved through studies in bacteria. Various transcription factors were thought to bind in various combinations to regulatory elements of genes (exactly as on the *lac* operon, or at the phage λ operator). In this "bag of transcription factors" model of the nucleus, differences in transcriptional behavior between cells were entirely explained by the composition and biochemical state of the transcriptional regulators they contained. Chromatin – the major difference in genome biology between prokarya and eukarya – was considered "transparent to the transcriptional machinery," i.e., was thought to be obstructive packaging that was removed to generate naked DNA – the stage on which the play of genome regulation unfolded.

Alan somehow – correctly – saw that this model was too simplistic. Inspired by a classic study showing that the glucocorticoid receptor *requires* chromatin to effect proper gene regulation (T. Archer and G. Hager, *Science* 255: 5051), Alan took on the nucleus in all its complexity. Over the next few years, data from his own laboratory and a very large number of other research groups unequivocally showed that chromatin is not "eliminated" nor is it "transparent," and, instead, lies at the core of all genome regulatory pathways in every eukaryote studied. This is particularly conspicuous in epigenetic phenomena – once again, with stunning prescience that will remain unexplained, Alan saw very early on that chromatin is the perfect vehicle to enabling epigenetic gene regulation, and his research group made several major contributions to our current understanding of this complex and rapidly evolving subject.

Alan's death is a tragedy for science. No words can adequately describe the enormity of the personal loss to Alan's family – his wife Liz, his daughter Kate, and his son Max. One can, perhaps, derive the tiniest sliver of consolation from knowing that Alan Wolffe lived to see chromatin, the scientific passion of his entire career, achieve the prominence it so rightly deserves, and that, however focused on the future, he must have taken some comfort in knowing that his own dedicated and courageous effort has made a major contribution to this dramatic paradigm shift in genome biology.

Donations in Alan's memory can be made to the Rett Syndrome research foundation (http://www.rsrf.org), the American Cancer Society (http://www.cancer.org), and an educational fund for Alan's children (http://www.sangamo.com).