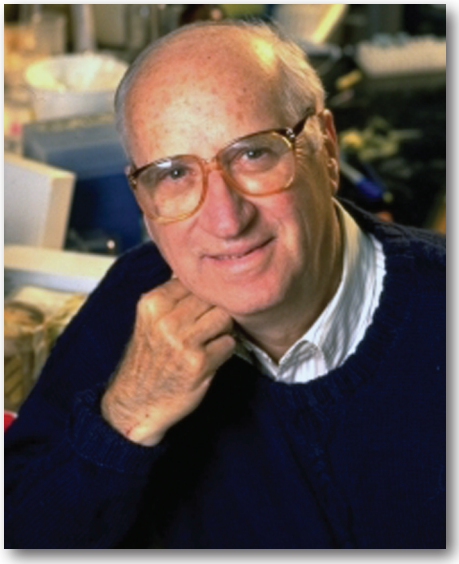
Daniel E. Koshland, Jr (1920–2007)



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Dan Koshland was one of the best-known biochemists of our time, and, as his interests were broad and his energy unlimited, it is certain that we do not all remember him for the same reasons. After war-time service in the development of ways to purify plutonium, he was one of the first graduate students of Frank Westheimer, and he has died just 3 months after his mentor. His last publication currently listed in PubMed is the obituary of Westheimer that he wrote for *ACS Chemical Biology*, published electronically just 3 days before he died in July himself.

He first came to fame as a young researcher in the 1950s, after he proposed his theory of induced fit. This has come to underlie so much of our understanding of protein chemistry that it is easy to forget that biochemists once thought that protein molecules were rigid. He was not the first to realize that they were not, but he was probably the first to realize (and certainly the first to emphasize) that conformational flexibility might have a function, so that it was an evolved property, not just an inevitable consequence of the polypeptide structure of proteins. He started with a simple observation: why is water not a good substrate for yeast hexokinase, despite being a more reactive molecule than glucose and easily small enough to fit into the active site? His answer was that it was too small to move the catalytic groups into positions where they could do their work.

This idea was strongly resisted by the experts of the day, but it is commonplace today, and provided an essential part of the theory of allosteric interactions that became prominent a few years afterwards. Without the possibility of functional conformational changes, there would have been no way of explaining interactions between distant sites in proteins, which were incompatible with the classic lock-and-key model of enzyme specificity.

Also in the 1950s, Dan proposed that the stereochemistry and isotope-exchange properties of enzyme-catalysed reactions with two substrates could be understood by classifying them into single- and double-displacement reactions. This idea, now usually based on kinetic arguments, has likewise been incorporated into the general view of two-substrate reactions, although Dan's terms are now little used.

Functional conformational flexibility was a central feature of the models of cooperativity that dominated much of biochemical discussion in the 1960s, not only Dan's sequential model, but also Monod, Wyman and Changeux's symmetry model, which preceded it by a year. The sequential model never achieved the same degree of popularity as the symmetry model, but this probably had more to do with the great difficulty of applying it to proteins with multiple ligands than with any more fundamental shortcomings. Dan continued to believe, as did I, that it was more firmly rooted in physical chemistry because it did not rely on any abstract notion of symmetry. (However, I must admit that a distinguished Nobel prizewinner was so angry when I expressed this view at a meeting of the Biochemical Society in 1988 that he asked for extra time to make a response.)

In the 1970s, Dan's attention turned to biochemical models of cognition. After preliminary work on mammalian tongue and *Hydra* had shown that these systems were too complicated to yield the sort of information that he wanted, he started to study chemotaxis in *Salmonella* typhimurium, and rapidly became one of the leaders in this field. An ingenious "tracker" designed in his laboratory allowed the movement of individual bacterial cells to be followed in three dimensions and related to the bulk movement of cell populations. In this way, he was able to explain how the apparently smooth movement of populations up or down a gradient could be explained as the averaged-out resultant of the much more chaotic movement of individuals, which followed a "biassed random walk". This presented the problem, however, that individual cells are much too small to detect the minute concentration gradient across their length, which would be swamped by random fluctuations. He explained it in terms of bacterial memory, whereby each cell compares the concentration now with the concentration of a short time ago and thus decides whether its current direction of movement is making things better or worse.

In the same period, he made fundamental contributions to a quite different area of biochemistry: the role of interconvertible enzymes (typically, although not necessarily, consisting of phosphorylated and dephosphorylated forms of the same proteins) in metabolic regulation. He always liked new terminology, and the term "zero-order ultrasensitivity" derives from this work.

Dan remained an active researcher until the end of his life at the age of 87. He never abandoned his old interests, and papers in the 21st century continued to feature propagation of conformational information, stereospecificity, substrate specificity and the mechanism of action of serine proteinases. At the same time, he added new ones, and a visit to his website at the University of California at Berkeley reveals, for example, that he was working on protein engineering as a tool in the search for therapies for Alzheimer's disease.

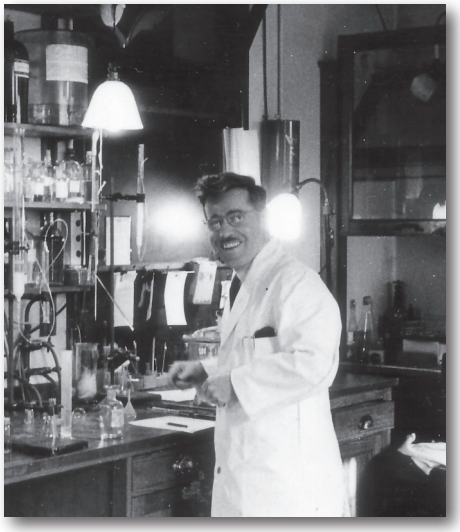
In addition to his highly active career

as a researcher and teacher, Dan somehow found time for major contributions to philanthropic, administrative and editorial work. Before he became Editor-in-Chief of *Science* in 1985, this task was regarded as a full-time job, but he was able to apply his formidable energy to it in Washington while continuing as professor and group leader in Berkeley. In his 10 years at *Science*, he transformed what had been regarded as a rather sleepy rival to *Nature* into the major journal it should always have been.

It is only too easy to dismiss obviously nonsensical contributions to science as just that, but Dan, to my knowledge, never did. As a referee and editor, he was willing to give serious consideration to the most crazy ideas, not dismissing them until careful thought had convinced him that they were untenable. Publication of the Comorosan effect in a leading journal of biochemistry came about because he refused to reject a paper just because neither he nor anyone in his laboratory found it plausible that irradiating the substrate of an enzyme could produce cyclical variations in enzyme activity. For him, the lack of a believable mechanism was not a reason for refusing to believe in an observation.

Despite his enormous fortune (which I would not mention at all if it were not that everyone who has read his obituaries in the daily press will know about it by now), Dan worked, and worked hard, during his entire adult life, and brought up his five children to live in a world based on work, not on inherited wealth. His first wife Marian, herself a distinguished immunologist at Berkeley, died in 1999, and is commemorated by the Marian Koshland Science Museum of the National Academy of Sciences, which was made possible by a gift from Dan. He is survived by his second wife, Yvonne, and by his two sons and three daughters. ■

Grant Henry Lathe (1913–2007)



G.H. Lathe in London, ca. 1955

Richard Lathe
(Pieta Research, Edinburgh)

Grant Lathe, Biochemist and social activist, eschewed honours but his contributions have endured.

Grant was born at Green House, Grand Forks, British Columbia, Canada, on 27 July 1913. While father Frank was in Chile mining nitrates for World War I, mother Annie travelled to Montréal with the young family (a 5-day rail journey), getting off the train to buy victuals that were cooked on a stove in the train car. On his father's return, the family settled in Aylmer, Québec, near Ottawa. Young Grant was considered 'backward'; his parents bought him a birdlife guide to stimulate his intellect. He recalled "as a result... I never looked back, which shows that it is good to be backward, as a child at least".

Lathe senior was later to be known as one of Canada's most outstanding scientists, with special expertise in mining, metallurgy and geology. As a result, around the house were all the materials young Grant needed to construct a cannon, which he used to great effect, breaking the house windows; the device exploded, Grant later confessed. The young Grant was a frequent visitor to the electrolytic refinery where Frank then worked, and he remembered his first geology lessons from his father. In the run-up to the 1930s economic recession, Grant's father was without a job, but later found employment at the National Research Council, eventually becoming Director of a section in his own right.

Winters were cold, about every 4 years the temperature fell to −40°C. There was an area of the garden they could flood with water and, if the snow was not too deep, they were able to skate upon. The family's first radio set was acquired in 1921, and, at times, they could get signals from as far away as Ottawa, 10 miles distant. In his teenage years, Grant developed an interest in palaeontology, and, with close friend G. Winston (Winnie) Sinclair (later of the Geological Survey of Canada), spent many hours roaming the countryside on bicycles searching for fossils; these were taken for identification to Dr Alice E. Wilson at the Ottawa museum who, he recalled, was never too busy to answer their questions. Grant joined the Royal Signal Corps, a cadet squadron, where he learned communication skills, including the use of the heliograph. He did well at school, excelling in biology, chemistry, physics and maths. To his mother's chagrin, he failed Latin.

In 1931, aged 18, Grant went to McGill University to study Biology and Chemistry. In the summer of 1932, he worked in the Biochemistry Department with Dr Hans Selye, then a young Austro-Hungarian researcher, later an internationally recognized authority on stress. Grant remembered assisting Selye in the large-scale preparation of rat pituitaries, noting this "left me reeking of ether as I was in charge of anaesthetic administration". On graduating in 1934, he registered for a medical degree and an MSc in Biochemistry.

He spent a summer vacation at a research laboratory, where his titrations produced extraordinary results, discovering that he was partly colour-blind. This was in the middle of the Depression, where he commented that conditions were "worse than anything we have seen since". His interest in social affairs was stimulated, and, in 1936, he became Chairman of the McGill Student Christian Movement, a radical student organization, and joined the Young Communist League. In his last year at medical school, he travelled

to China under the auspices of the World Student Movement where he met Mao Tse-Tung, and on the way back encountered Mrs Eleanor Roosevelt in New York.

On graduating in medicine in 1938, he held a Wyeth scholarship at McGill's Physiology Department, registered for a PhD, and became Editor of the New Advance, a communist magazine. World War II was beginning to make its impact felt in Canada, and, in 1941, he volunteered for the Royal Canadian Army Medical Corps. But his communist leanings had been noted and he was interred at the Isle aux Noix on the Richelieu River. He was only freed when he reported the Commanding Officer for failing to take typhoid injections, and was promptly transferred to Europe.

Through 1943, aged 30, Grant was attached to the British Army as a biochemist, until 1944 when the Unit moved to near Naples, Italy, where he took part in the forward Casualty-Clearing Station that accompanied the advance towards Rome. In, 1945 he returned to Britain and a further posting to Germany where his medical unit was among the first to enter a Nazi concentration camp. Although his medical training had led him towards surgery, as a result of his traumatic experiences at the frontline, notably in dealing with burns injuries, he formed the view that the chemical processes underlying human disease demanded his attentions more than the scalpel.

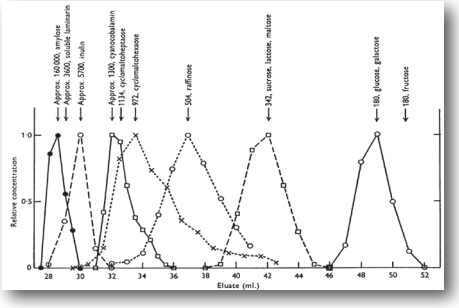
On 4 January 1946, Grant was demobbed from the Canadian Army as Major, and on his return to the UK (with the help of an ICI Fellowship) completed his PhD at the Department of Biochemistry in Oxford under Professor R.A. Peters. After a spell at the Royal Postgraduate Medical School under Professor E.J. King, he was appointed lecturer in Chemical Pathology at Guy's Hospital Medical School, and then, in 1949, became Consultant Chemical Pathologist at Queen Charlotte's Maternity Hospital, London. Here he performed his now classical studies on metabolism of bile pigments and their importance in neonatal jaundice. With Barbara Billing, he showed that bilirubin generates a glucuronide conjugate required for excretion[1,2].

While still at Queen Charlotte's, he made his most enduring invention, the technique of gel filtration, also known as size-exclusion chromatography. According to his own personal account, when his wife Joan suffered a cut while peeling potatoes, on attending to the wound, he was immediately struck how blood pigments diffused at markedly different rates through the potato starch matrix. He was able to recreate this effect in the laboratory, and, with Colin Ruthven, went on to describe a separation technique based on an entirely new principle[3,4]. In the conclusion to their paper they wrote, "it is suggested that columns of starch in water form a new type of partition system in which the volume of the stationary phase is determined for each substance by the depth to which it can penetrate the starch granules."

Whereas Lathe and Ruthven used starch gels, the Uppsala group later introduced dextran; other matrices now commonly employed include agarose and polyacrylamide. In 1971, Lathe and Ruthven received the John Scott Award (one of the oldest science prizes in the USA) for their invention, other recipients have included Thomas Edison, Marie Curie and Alexander Fleming. The discovery of gel filtration, which later gave rise to the company behind Sephadex, was never patented, as their wish was that the invention should be made available to all. The process is now used to purify the majority of FDA (US Food and Drug Administration)-approved biopharmaceuticals.

In 1957, Grant was appointed Professor of Chemical Pathology at the University of Leeds. His inaugural lecture entitled "Defective Molecules as a Cause of Disease" foreshadowed the later emergence of molecular medicine and attracted much attention. In Leeds, he was a founding member of the Association of Clinical Biochemists, and, over the next 20 years at the University, he built up a large department that encompassed many novel ideas in clinical biochemistry, research and teaching. Although he retired in 1977, he continued his research; his last formal paper in 1985 addressed the binding of steroids to graphites under conditions of steroid receptor assays.

Strikingly energetic in his later years, he still attended scientific meetings in his 90s and flew to Canada each summer to visit his wider family. His many interests included geology, ornithology and prehistory; he



Gel filtration: elution of neutral molecules in order of descending molecular masses, from columns of untreated potato starch in water. From Lathe and Ruthven[4], Figure 1 © 1956 The Biochemical Society

enjoyed tramping in the Yorkshire Dales and ice skating, a sport he had kept up since a boy. Active on the environmental front since much earlier in his career, when he, J.D. Bernal and others contributed to a volume addressing the impact of nuclear arms testing, he maintained these interests after retirement, for a time he was Vice-Chairman of the Leeds CND (Campaign for Nuclear Disarmament), and marched at least once on Aldermaston.

A fuller account would air his warm sense of humour, the convivial annual laboratory bonfires held on rough ground behind the house, the wide circle of friends and his whole-hearted support for a multitude of causes, from peace groups to the plight of minorities, and always at a deeply personal level. Even in his last days, he wrote every week, and talked on the phone, to his sister May in Canada who, he acknowledged with a smile, excelled at Latin.

His 90th birthday was celebrated with his children and grandchildren in Reykjavik, Iceland. He died at home in Leeds on 2 July 2007, aged 93. Sorely missed on both sides of the water, he is survived by four children, ten grandchildren and one great grandchild. ■

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