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THEODORE ALVIN HALL: A BIOGRAPHICAL SKETCH AND PERSONAL APPRECIATION

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Abstract

As the first in a series of two papers contributed on the occasion of a special program held at the Scanning Microscopy/1989 meeting in Salt Lake City in honour of Dr. T.A. Hall, and in recognition of his achievements for biological electron probe X-ray microanalysis, this paper provides a biographical sketch of Dr. Hall, as well as a bibliography.

Key Words: Dr T.A. Hall, biological microprobe analysis, Cambridge

Ted Hall, as he is generally known, was born on the 20th of October 1925 in Far Rockaway, Queens, New York, USA. He obtained his B.S. in physics *cum laude* from Harvard University in 1944, and his Ph.D. from the University of Chicago in 1950. For his Ph.D. he worked on the state of charged particles beam passing through thin metallic films. This topic seems to have foreshadowed Ted's subsequent dedication to the use of an electron beam impinging on thin films or sections of biological specimens. From 1950 to 1952 Ted Hall was a postdoctoral Fellow in Biophysics at the Institute of Radiobiology and Biophysics in the University of Chicago. Distressed by the application of particle physics for developing the atomic bomb, Ted Hall switched his interests to the application of physical techniques in biomedical research. From 1952 to 1962 he worked in the Biophysics Department of Sloan-Kettering Institute at the Memorial Centre for Cancer, and also Cornell University Medical School in New York City, on developing the application of X-ray fluorescence analysis to tissue-sections from clinical and experimental specimens, particularly from the urogenital tract of mammals. This was the period when the importance of zinc in the male reproductive maturation in mammals was being discovered. Ted Hall used X-ray fluorescence for measuring zinc contents in prostate gland and seminal spermatozoa of rat, dog and man.

However, the limited degree of localization afforded by X-ray fluorescence analysis was frustrating and the then emerging technique of electron probe X-ray analysis seemed to hold more promise for *in situ* characterization of chemical elements in biological tissues. He wrote to Dr. V.E. Cosslett at the University of Cambridge, in whose laboratory in the late 1950's, Peter Duncumb had developed the first scanning microanalyser from an RCA electron microscope. Following a meeting with Cosslett at a New York Academy of Sciences conference in 1961, Ted Hall, his spouse Joan, and three daughters, Ruth, Deborah and Sara, arrived in Cambridge on July 17, 1962, little suspecting that they were to remain enmeshed in the legendary web of Cambridge and never

return to the USA.

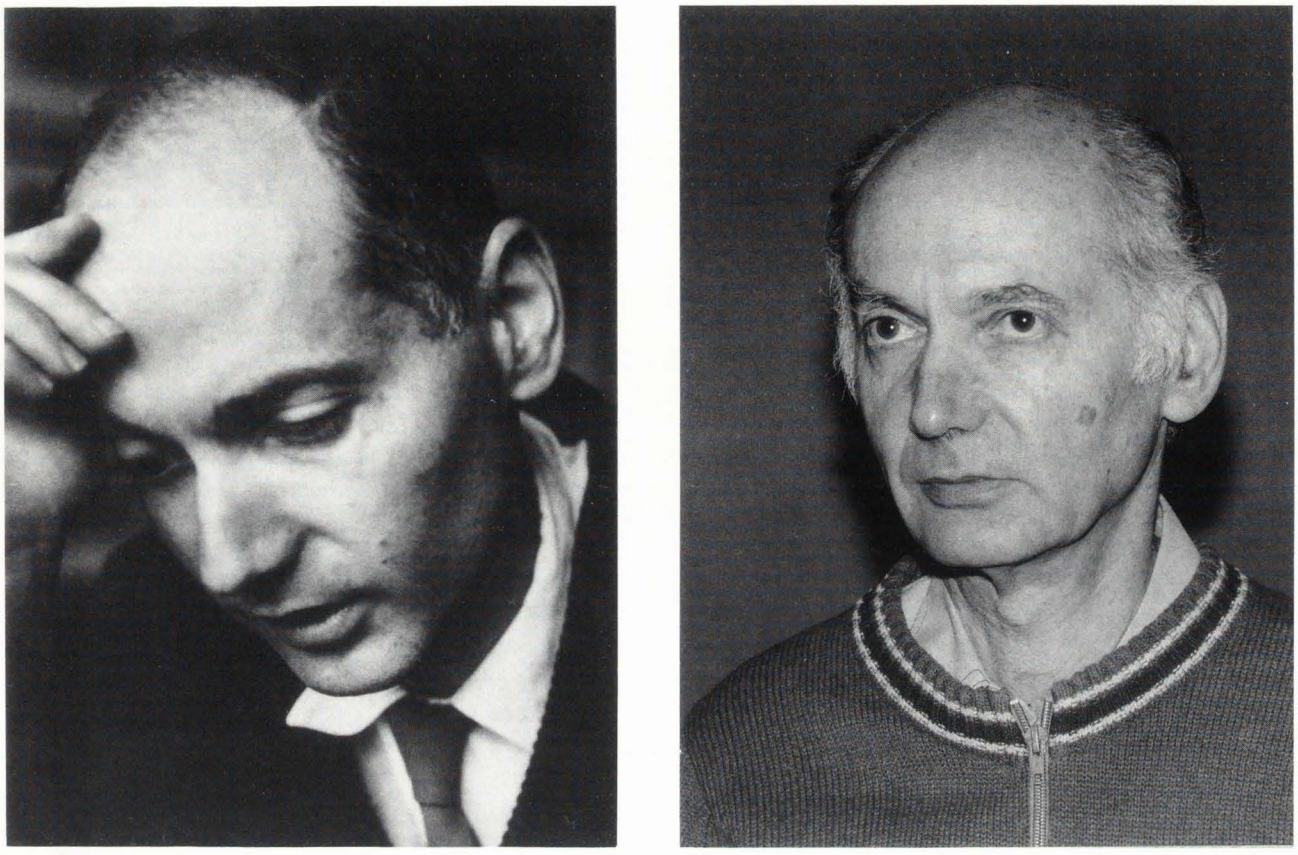
Whether it was by coincidence or as a consequence of Karma from ones previous incarnations - as we Hindus would have you believe, Ted Hall followed Peter Duncumb into a room in the Cavendish laboratory where J.J. Thomson had discovered the electron. Ted occupied that room from 1962 to 1976, first with a home-made "microscan" and later with the Associated Electrical Industries (AEI) EMMA-4 (electron microscope microanalyser). It was in this room where Ted developed his well-known method of *continuum normalization* (commonly known in the trade as the 'Hall method') for the absolute quantification of chemical elements in 'thin' biological specimens.

My acquaintance with Ted started in 1970. I was a research associate with the late Professor Torkel Weis-Fogh in the Zoology Department. There was, at that time, a great interest in the mechanisms of ion and water transport in cells and epithelial tissues in the departments of Botany, Physiology and Zoology in Cambridge. The first analytical electron microscope microanalyser (EMMA-4) based on Peter Duncumb's prototype had just been made commercially available by AEI in the UK. Torkel Weis-Fogh and I thought that perhaps the time had come to study the distribution of ions and other chemical elements in cell and tissues *in situ* in order to address many basic biological questions. We went to see Ted Hall and after many discussions decided that the biological questions involving diffusible elements of most interest to physiology can be tackled properly only by using cryo-methods of specimen preparation and analysing 2 μm thick frozen-hydrated sections in a 'microscan'-type instrument based on a scanning microscope. This led to the establishment of the Biological Microprobe Laboratory (BML) in the Zoology Department with Ted Hall as one of the five Principal Participants (the others being Torkel Weis-Fogh - the grant holder, Patrick Echlin from Botany, Roger Moreton and myself). Much of the *technical development programme*, comprehensively outlined in our extensive grant application to the Science Research Council (SRC) of the UK was based on Ted Hall's previous experience and on the manuscript for a chapter in the *Physical Techniques in Biological Research*, 1971.

The very idea of analysing frozen-hydrated specimens in an electron microscope under relatively high beam currents required for using fully-focussing wave length dispersive X-ray spectrometers, was a leap into complete darkness to some, and evidence of madness to all others. Nevertheless, the funding council and its peer-committee then worked on the principle that progress in any creative activity can be achieved only by supporting novel approaches and by allowing the right of failure to the adventurer. Unfortunately this positive approach to funding was to gradually disappear under the pressure of continued financial cuts imposed by the successive governments in the UK. Even more unfortunate for us, Professor Weis-Fogh died prematurely in 1975. This led to a dispersal of the group and by 1979 it was essentially reduced to Ted Hall, myself and 2 junior technicians. It now seems miraculous that virtually all of the technical and biological (zoological) programmes proposed in 1971 in our original application to the SRC have actually been accomplished! This success in a technical approach which most other laboratories still find impossible, is a tribute to Ted Hall's fortitude, his deep understanding of the physical problems, his foresight in selecting the use of 1-2 μm thick sections for the analysis in frozen-hydrated form, and his commitment to addressing the biological projects proposed. We did not allow ourselves to be totally embroiled in developing **the perfect method** first, before doing any biology - a common failing in many laboratories.

In parallel with the Biological Microprobe Laboratory (BML) in the Zoology Department, Ted Hall was awarded funds to set up an EMMA-4 facility for microanalysis in ultrathin sections at a resolution higher than afforded in 1 μm thick frozen-hydrated sections. Patricia Peters was Ted's research associate for all the work on EMMA-4. Thus for the period from 1971 to 1976 Ted was deeply involved in research work in both laboratories and was essentially responsible for the regular modifications and proper usage of the analytical instruments. However, in 1974 the Cavendish laboratory was moved to new premises outside the centre of Cambridge and only Cosslett's electron microscope unit remained at the old site. The physics department lost interest in the biological application of microanalytical techniques. In 1976 Ted Hall finally moved to the Zoology Department with his EMMA-4 and remained in-charge of the Biological Microprobe Laboratory until 1984. In that year a complete curtailment of funds forced him into an early retirement and lead to the complete closure of the laboratory. It also proved to be the demise of all biological microprobe work, based on direct analysis of cryo-prepared material, in Cambridge. The closure of BML also removed the only proven facility anywhere, however limited, which permitted direct measurements of ions and water in 1 μm thick frozen-hydrated sections with a demonstrated analytical spatial resolution of about 0.2 μm.

During 40 years of active science Ted Hall authored, singly or jointly, some 160 publications (see list appended). He co-authored a book and co-edited several major Symposia Proceedings in the formative period of the technique. For the biological work, he collaborated with a large number of workers from the UK and abroad, who came to him either to make a quick spot-



Photographs of Ted Hall: Left - in 1962, starting in Cambridge; right - in 1988, retired in Cambridge.

check for the presence of an element in their specimens, or for an initiation into the art of electron probe X-ray microanalysis (EPXMA).

Ted Hall's definitive influence on biological microanalysis cannot be gauged solely by his scientific output in print. His expert advice has been constantly sought (and readily proffered) by workers from New Zealand to South America, either during personal meetings, by telephone, or by intensive correspondence often extending over months. The problems ranged from anomalies in results, quantification procedures, sources of and corrections for extraneous X-rays, conversion of X-ray data to physiological quantities, instrumental configurations, and the choice of suitable equipment for new laboratories embarking on EPXMA work. The benefit of his expertise to others also permeated through his constructive and elaborate reviews of manuscripts submitted for publication to a variety of journals, the evaluation of grant applications for the funding bodies in many countries, his specialist membership of the Referee's Panels for the Science Research Councils in West Germany, and not least, his tutorial lecture-courses in the UK, Sweden, Denmark and Germany (European Molecular Biology Organisation, EMBO, laboratory). Ted has championed the use of EPXMA in biology and medicine with a missionary zeal, always regarding his knowledge as 'public property'. He freely discussed the unpublished results from his labs even when on occasions, and to our chagrin, the beneficiaries, wittingly or unwittingly, 'scooped' us in publication.

In spite of Ted Hall's unshaken faith in EPXMA as the only proven method available at present for a fully quantitative measurement of total concentrations of all the chemical elements *simultaneously* in biological specimens *in situ*, he overtly counselled the freshly inspired enthusiasts to contain their expectations within the realistic limits of practical analytical resolution (about 0.1 μm) and the lowest measurable concentrations (about 1 mM). His extreme caution and low-key approach can sometimes be mistranslated into an apparent pessimism. An anecdotical example is from 1977, when Ted said in his lecture in Stockholm, that given the problem of poor image detail and mass loss in frozen-hydrated sections, it may never be possible to measure ionic concentrations

in narrow intercellular spaces in epithelia. Ironically, and unknown to him, at that very time in Cambridge, I was actually making such measurements in rabbit ileum! As fate would have it, the publication of these results in *Nature* (1978) generated a discomforting threat to the established dogmas, and antagonised many domineering physiologists, especially in Cambridge. Their reaction finally resulted in the withdrawal of funds for our biological microprobe laboratory. To defend against private accusations of fraud and grossly exaggerated claims, Ted and I even published our X-ray data in an article in *Federation Proceedings* (1978), but could not stop the bulldozers from rolling. These 'offending' results have since been confirmed in many other laboratories! It may be that in the modern age of commercial advertising and aggressive marketing, the genuine and almost self-effacing modesty of Ted Hall, hitherto considered a virtue in science, is now punished as inadequacy!

Impressed by the biological output from Ted Hall's laboratories in Cambridge, admiring visitors often expected to find space-age technology on display. To their amazement, they only saw rather aged preparative and analytical facilities, still equipped with a range of home-made Heath-Robinson prototype accessories. Our frozen tissues were still sectioned on a custom built 1972 version of SLEE-cryostat; our Kevex-Link energy dispersive spectrometer did not have the ultrathin window of the modern versions, and we did not have an on-line computer facility for data-processing on our Link system until 1981. Until then we collected our X-ray data *manually* and processed it with a pocket calculator. It could be that in this way, we learnt what we were doing! Ted was brought up in the old Cavendish tradition of the 'string and sealing wax' approach to experimental science which I too had learnt in the Zoology Department. It is a tribute to Ted Hall's deep understanding of EPXMA and his patient approach to data scrutiny, that our 'primitive' but reliable facilities could be used for the creation of Link-Systems QUANTEM-FLS software, in collaboration with Peter Statham - another Cavendish product. Many 'bugs' in the prototype versions of this software packet were identified during the actual biological work on our JEOL JXA-50A microanalyser, some only in the final year of the laboratory's operation.

It is gratifying that the scientific community concerned with the microbeam analysis has publicly acknowledged its gratitude to Ted Hall. In 1985, the *Microbeam Analysis Society* (USA) elected Ted Hall to the rare distinction of its *Honorary Membership*. The proceedings volume of a recent International Conference On the *Progress in Electron Probe Microanalysis in Biology and Medicine*, held at Ringberg castle in Bavaria (November 1988) is dedicated to Ted Hall. Since inception in 1968, the annual conferences of *Scanning Microscopy*, (formerly *Scanning Electron Microscopy*, originally sponsored by the IIT (Illinois Institute of Technology) Research Institute (IITRI) of Chicago, have served as a major platform for reporting and discussing the methodology of microbeam analysis, and its application in biology and related sciences. In 1970, when Ted Hall, Torkel Weis-Fogh and I first demonstrated that an approximately 4-μm thick 'iced' section of a blow-fly muscle, maintained at -145°C to -120°C on a prototype LN_2 - cooled stage in a Cambridge 'Stereoscan' scanning electron microscope, was stable under a static probe with a beam-current of 2.10^{-8} A, the results were reported by Patrick Echlin at the 4th Annual SEM Conference in Chicago (1971). Prevented by Ted Hall's conventional modesty and the pressures of setting up new laboratories, we never published these results as a separate paper, even though this simple experiment heralded the use of cryo-prepared and frozen-hydrated specimens in biological microanalysis. It is only befitting that Scanning Microscopy International sponsored the present Symposium to honour Ted Hall in his retirement and plan to publish the proceedings as a *Festschrift* in his 65th year. One might bask in Ted's deserved glory and consider these tributes as a vindication of the work in Cambridge BML - previously dismissed by many as 'highly controversial' or (privately) even fraudulent.

Ted Hall's efforts to promote EPXMA have now resulted in highly sophisticated and operatively efficient cryo-preparative and analytical instruments manufactured commercially. It may be salutary to ponder over the reasons why Ted Hall and his collaborators succeeded in achieving what many others still regard as impossible, even with all the 'mod cons'. In my considered opinion, the shortcomings in many a laboratory are that the 'physicists' in-charge of the analytical facilities do not attempt to understand the biological questions and the analytical demands imposed by these systems. The 'biologists' not blessed with the collaboration of an understanding physicist tend to too readily accept the data generated by their 'black-box' analytical packets. Ted Hall learnt to appreciate biological systems from the start and always listened to his collaborating biologist. During the inception of BML in Cambridge, Torkel Weis-Fogh and Ted Hall got on famously, each understanding the other's 'language' with respect and deep insight. Ted Hall has become so apt at communicating biology that his audience often regard him as the *biologist* member of our laboratory. It may be that those frustrated by their biological EPXMA at present should *think* more of how their analytical systems see their biological specimens and rely less on the readily generated data, whatever the claims of the manufacturers of their instruments. If all else fails *talk to Ted Hall.*

As a person, Ted Hall never took to the formal pomposities of Cambridge College life. Whenever an opportunity arises, he loves to caricature the traditional use of the academic gown by acting as a 'batman'. He makes a sincere friend but keeps a limited social circle. Although he religiously participated in all the national and international meetings on microbeam analysis, he does not actually enjoy travelling except when holidaying with his dear wife. Amongst his many endearing idiosyncrasies is his nervous habit of getting to the station or the airport *long* before the schedule requires, lest the transport should leave before the appointed time! Another is his absolute need for a *gooey* sweet after a meal. Until I discovered Ted's addiction, I could never understand why after a working lunch of a sandwich during our marathon microanalytical sessions, he would go into a totally non-communicative 'withdrawal' coma. His non-scientific passions include economic sociology of politics, classical western music, and playing tennis (especially with the late Ellis Cosslett, after his official retirement from Cavendish). *All in all, Ted Hall is a Jolly Good Fellow, and we all wish him a happy retirement.*

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