Meetings

High-Voltage Electron Microscopy

Early studies in electron optics in the 1940's indicated that increases in accelerating voltages offered promise of improved specimen penetration and resolution. With the hope of increasing the amount of information derived from electron microscopy, microscopes capable of accelerating and focusing electrons with energies up to 3 million volts have been constructed. The design and operating characteristics of microscopes of 5 million and more volts have been delineated and their operating characteristics projected. The initial problems that plagued high-voltage instruments have been overcome: circuitry is now stable and reliable, alignment is no more difficult than on ordinary instruments, and operation by the average electron microscopist is now practical.

The current state of high-voltage electron microscopy was reviewed at a conference held at Monroeville, Pennsylvania, from 17 to 19 June 1969, under the sponsorship of the National Science Foundation, the National Institute of General Medical Sciences, and the United States Steel Corporation. About 190 participants from more than 10 countries met in the research laboratories of the U.S. Steel Corporation, where one of the three high-voltage instruments in operation in the United States at the time of the conference is located. This instrument is supplied by a million-volt open-air Haefely generator and was designed and built by the Radio Corporation of America (RCA). The University of Virginia at Charlottesville is operating a 500-kv RCA instrument and the University of California at Berkeley a 650-kv Hitachi microscope.

Gaston Dupouy reported that in 1969 at his laboratory in Toulouse, where in 1962 the first operating million-volt microscope was installed, the first picture was taken with an instrument designed for 3 million volts. The column of the new instrument is nearly 0.75 m in diameter and more than 3 m high. Dupouy indicated that the instrument had not yet operated at voltages of more than 2.2 million but that the pictures taken at that potential give promise of good performance.

In outlining some of the applications of the 750-kv microscope at Cavendish Laboratory, Cambridge, V. E. Cosslett said that there have been extensive studies of electron radiation damage, of magnetic domain structures in thick foils, and of crystallization of cement. The Cavendish microscope served as the prototype for a million-volt model designed and built by Associated Electrical Industries (AEI). Six such instruments, in which the column is mated to a Haefely pressurized twin-tank generator and electron accelerator, will be installed by AEI in British laboratories. Cosslett emphasized the advantages of readily variable accelerating voltage and the necessity for adequate radiation shielding.

Developments in Japan, summarized by Hatsujiro Hashimoto (Kyoto University), began with the building of a 300-kv instrument in 1950. Three manufacturers are now marketing well-tested and well-designed instruments of 650 to 1000 kv. The quality of Japanese work is high, and Japanese contributions to theory have also been notable. Worthy of special mention are Hashimoto's own contributions to contrast theory as related to interaction of high-voltage electrons with crystalline materials.

One especially striking presentation was given by Toru Imura (Nagoya University), who showed motion pictures in which dislocations could be seen moving in silicon steel under applied stresses determined with a microload cell; the speed of edge and screw dislocations was thus measured. H. Fujita (Osaka University) and K. R. Lawless (University of Virginia) demonstrated, in independent studies, spectacular effects of specimen thickness in dynamic studies of recovery and recrystallization in aluminum and in the oxidation of tantalum, respectively. In other reports, P. R. Swann and R. H. Duff (U.S. Steel Corporation) elucidated a recognized mechanism of corrosion in nickel-gold alloys, and M. J. Makin (Harwell) described his studies of atom displacement damage produced in copper by electron bombardment at energies greater than 400 kv.

Convincing support was given to the view that high-voltage electron microscopy offers opportunities to acquire structural information of importance in biology well beyond what can be expected at 100 kv and below. Here of special interest were pictures presented by Kiyoshi Hama (Osaka University Medical School). The photographs showed fixed, embedded, and sectional samples of trachea, muscle, and other tissue taken at 650 to 1000 kv. Stereo pairs of sections 1 μm or more thick showed satisfactory beam penetration and enough resolution to present the trilaminate structures of cell membranes in vivid three-dimensional clarity. In work performed at 800 kv, Hama and Fumio Nagata (Hitachi Company) succeeded in displaying spacings of about 0.45 nm in crystals mounted on Epon sections of tissues that were 1 μm thick; the resolution capabilities of high-energy electrons traversing plastic sheets of substantial thickness were thus demonstrated. Hama and Nagata also made densitometric tracings of cell membranes in micrographs of "thin" (20 to 49 nm) sections of Epon-embedded tissues taken at 75 and 800 kv. At the higher voltage the tracings of micrographs showed sharper profiles and higher resolutions. The merits of high voltages were further demonstrated in micrographs of rabbit muscle taken by R. V. Rice (Carnegie-Mellon University), of chromosomes presented by Hans Ris (University of Wisconsin), and of insect flight muscle taken by Keith Porter (Harvard and University of Colorado) and K. Hama.

Much attention was given to design of high-voltage accelerators. Gunter Reinhold of Switzerland reviewed the progress to date in development of highly stable Cockcroft-Walton generators of 1 to 3 million volts. The E. Haefely Company of Basel has made generators for million-volt microscopes in Great Britain and the United States and has provided the power supplies for high tension for both the 1- and the 3-million-volt instruments in Toulouse. The Swiss have, until recently, preferred huge open-air million-volt generators, but they are now providing more compact twin pressure-enclosed supplies, one member of which contains a generator connected through a pressurized tube to a second container, which houses the accelerating tube. The Japanese manufacturers, Hitachi, Shimazu, and Japan Electron Optics Laboratories, have each designed their own Cockcroft-Walton machines and have chosen from the start to place each generator in its own single pressurized housing, which also encloses the accelerator tube. The High Voltage Engineering Corporation of Burlington, Massachusetts, has made a very satisfactory and stable three-phase insulating core transformer power supply operating at 500 kv for the lens column built by RCA for the University of Virginia in Charlottesville; this power source was described as inherently suitable for electron microscope applications up to 3000 kv. The possibilities of using Van de Graaff generators or superconducting linear accelerators for electron microscopes also received attention.

Various methods of optimizing the design of conventional magnetic lenses for high-voltage microscopy were proposed by Z. S. Basinski of Ottawa, J. L. Farrant of the Commonwealth Scientific and Industrial Research Organisation, Australia, and A. Strojnik of Cornell University. Progress in developing superconducting lenses for electron microscopes was reported by M. I. Dietrich (Siemens A.G., Germany), by H. Fernández-Morán (University of Chicago), and by a group at the Oak Ridge National Laboratories in Tennessee. Several persons expressed the view that superconducting lenses offered much promise for instruments operating at 5 megavolts. Status reports were presented from several of the more than ten new high-voltage facilities which have gone into operation or will do so during the coming year in Britain, Sweden, Japan, Australia, and the United States.

A new method for measuring energy losses of electrons traversing samples was presented by J. S. Lally (U.S. Steel Laboratories) in a session on diffraction contrast. In collaboration with C. J. Humphreys (Oxford University), who has been a visitor at the U.S. Steel Laboratories, Lally showed by experiment, supported by theory, that the crystal orientation which maximizes penetration of high-voltage electrons through heavy materials is not the same as the orientation offering the best penetration at 100 kv. Beam effects in diffraction contrast from crystals were discussed by W. K. Bell (University of California, Berkeley), and by A. Metherell (Cambridge University). The fundamental mechanisms of inelastic scattering at high voltages were reviewed by P. B. Hirsch (Oxford University).

The final session of the meeting was devoted to the least mature aspect of high-voltage microscopy—image contrast of molecular structures. The fundamental scattering mechanisms and phase relationships determining contrast at this level were discussed. Increased penetration with higher accelerating voltage was anticipated, but the lack of a corresponding large loss in contrast was a surprise. The feasibility of achieving "atomic" resolution at high voltage was the subject of lively debate and much skepticism. The direct readout of molecular structure from visualization and recognition of single atoms in single molecules has been the dream of some electron microscopists, but the conference ended with this prospect unresolved.

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Chronic Non-Psychiatric Hazards of Drugs of Abuse

A conference on Chronic Non-Psychiatric Hazards of Drugs of Abuse was held in San Francisco, 29–30 October 1969. The conference was cosponsored by the Center for Studies of Narcotic and Drug Abuse of the National Institute of Mental Health and by the recently formed Environmental Mutagen Society.

The conference focused on biological hazards of drugs of abuse and excluded their psychiatric and psychopharmacological effects. The major categories of hazards considered were toxicity, carcinogenicity, teratogenicity, and mutagenicity. The object was to review existing toxicological information on these drugs and to identify productive strategies for future research. A particular effort was made to interpret current data on biological hazards due to LSD.

Hazards posed by drugs of abuse were viewed against the perspective of therapeutic and prophylactic drugs, as well as from the wider perspective of environmental chemical pollutants. Drugs of abuse, however, present unusual toxicological problems. Their use, which has increased dramatically over the last decade, is generally restricted to young adults. Such drugs are self-administered in a variety of ways, including ingestion, injection, and inhalation; they are generally administered in unquantitated doses. They are often administered in highly impure or contaminated states in combination with a variety of other drugs and chemicals, and for prolonged periods of time. Finally, intercurrent infection and malnutrition are sometimes prevalent in user populations. In part, as a result of the restricted availability of these drugs, their chronic biological effects have been less well studied than other categories of drugs or environmental pollutants. The concept of matching benefits against hazards, generally considered appropriate in toxicological evaluation of therapeutic drugs, pesticides, or food additives, is complicated by other concerns implicit in the concept of "drug abuse."

Chemical structures of major categories of drugs of abuse were reviewed. The chemical crudity of most synthetic and semisynthetic formulations, and also the possibility of important biological activity of misidentified or unidentified chemical contaminants were emphasized. For example, the anesthetic Sernyl is commonly sold on the streets as synthetic marihuana. Background information on psychiatric, sociological, and pharmacological aspects of drug addiction and dependence were considered. Barbiturate dependence merited particular concern in view of the high mortality associated with abrupt withdrawal of this drug.

Biological interactions between different drugs of abuse and between them and other environmental pollutants were considered in relation to hepatic