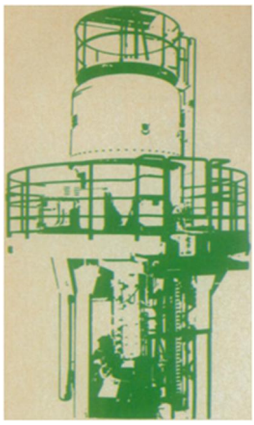


HVEM The Big Picture of Small Structures

By JULIE ANN MILLER

Through pairs of special glasses, biologists view two slides projected side by side on a screen. They perceive a three-dimensional subcellular panorama, extending out from and into the screen. Microscopist Keith Porter calls this vision "the depth dimension of biology." In one image, there is a dense network of fine threads and cables; in another, a stack of dark plates; in yet another, a set of intimately interlacing structures. These images were each created by high-voltage electron microscopes (HVEMs) — the largest and most expensive microscopes in use for biological research today.

The costly, cumbersome instruments are in something of a crisis. Their utility has been scrutinized in the past year by leading microscopists, who have asked whether the technique has lived up to its past promise and whether it is likely to have a significant place, worthy of its cost, in future biological research.

"The high-voltage electron microscope is an orphan, looking for parents in the form of new enthusiasm," said Porter at the recent Symposium on High-Voltage Electron Microscopy in Neurobiology, held in Boulder, Colo. These deliberations arose because of the impending retirement or relocation of its original enthusiasts, the aging of the equipment and the appearance on the horizon of a new generation of electron microscopes — intermediate in cost and power between current standard electron microscopes and the high-voltage instruments. In addition, there has been some disappointment with the overall accomplishments of the decade-old high-voltage technique.

But there are also indications of a resurgence of interest in high-voltage electron microscopy. Technical achievements in sample preparation and in computer analysis of images are promising to increase greatly the power of the method. And the National Institutes of Health (NIH) —which funds, at a cost of about $1 million a year, the operation of the three high-voltage electron microscopes devoted to biological research in the United States — has renewed its commitment to support the microscopes. "We [at NIH] are committed to supporting the microscopes as long as they are needed," says Suzanne Stimler, director of the Biomedical Research Technology Program of the NIH Division of Research Resources (DRR) in Bethesda, Md.

A committee appointed by NIH recently gave the instruments both a clean bill of health and a statement of support for the future. The committee concluded in a report to the DRR, "To those with an understanding of the physical basis of the power and advantages of HVEM as well as the character of unsolved problems in cellular and functional biology, it is clear that the research potential of the HVEM is even greater today than it had been first imagined to be when these instruments were installed."

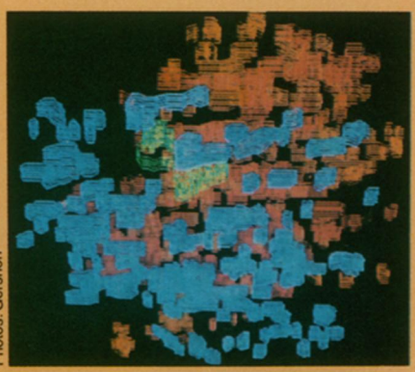
And by the end of the recent Boulder meeting, where a variety of research projects employing or planning to employ high-voltage microscopy were described, Porter observed that "guardians" seemed to be coming forth in the form of new challenges for the technique.

Amorphous material shapes up

Where does a cell store information regarding its three-dimensional shape? And how is this information passed on from one generation to the next? Observations of dividing cells indicate that cell structure is organized by an area called the cell center. The movement of this center seems to direct the formation of the mitotic spindle, the array of fibers that provides the three-dimensional framework for cell division.

With the light microscope, the cell center of an animal cell is seen to include a pair of organelles called centrioles and a cloud of densely staining matter, unimaginatively named pericentriolar or amorphous material. Because plant cells lack centrioles, and animal cells can still divide when their centrioles have been destroyed, the amorphous material is thought likely to be the organizational focus for the dividing cell.

Nahum Gershon of the National Institutes of Health in Bethesda, Md., and Keith Porter and Mark McNiven of the University of Maryland in Catonsville are using the high-voltage electron microscope to determine whether the amorphous material has any three-dimensional organization that can be related to cell shape or function. They have examined skin cells in the scales of squirrelfish.



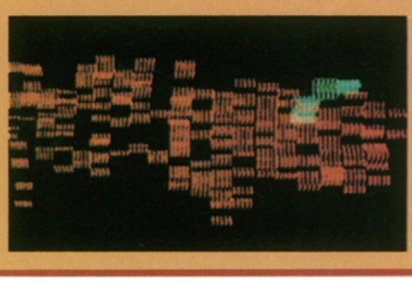
Photos: Gershon

Computer graphic of cell center, with three parallel plates of amorphous material, assigns one color (blue, red or orange) to each plate and green to the centrioles. Viewed in 3D, the representation above shows the three layers. The view at left shows edges of the plates and, at right, a single plate.

"We found that the amorphous material of the cell center is highly ordered in layers," Gershon says. It forms a set of parallel plates; different cells have different numbers of plates, ranging from three to seven.

A special property of these fish skin cells is that they contain red pigment granules, which, when dispersed throughout the cell, make the fish appear pink, and, when concentrated in a small spot within each cell, make the fish appear white (SN: 10/15/77, p. 250). Porter finds that in the cells the pigments migrate along fibers radiating from the various plates of the cell center. "When the pigment aggregates, the amorphous material is like a parking garage with granules going to the different floors," Gershon says.

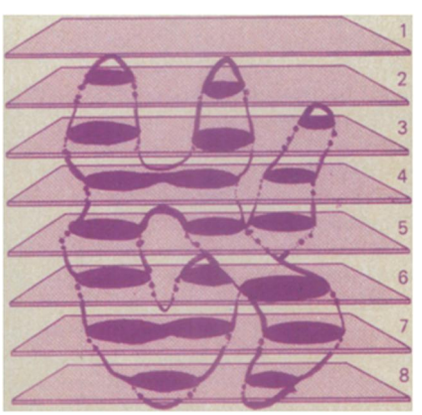
Now the scientists want to examine the amorphous material during cell division to see whether its structural organization is passed on from one cell generation to the next. This organization may carry information about the shape of the cell. —*J.A.M.*



"Neurobiology has perhaps some of the best problems for HVEM," Porter says. High-voltage electron microscopy is particularly adept at capturing the dramatic shapes of the many-branched nerve cells, with their bushlike processes and complex connections. Another current challenge is the three-dimensional organization of chromosomes in cells and the structural changes in chromosomes during cell division and gene activity.

What is the difference between high-voltage and conventional electron microscopy? "The [HVEM] machine is bigger, it is more cumbersome to use and very few are available," says Mark Ellisman of the University of California at San Diego. A high-voltage electron microscope stands about three stories high instead of the usual 6 feet, so it requires its own building to house it. The image is created with a million-volt beam of electrons instead of a 100-kilovolt beam. The cost of such a microscope today is about $3 million, compared with $200,000 for a conventional electron microscope.

Yet the technique has powerful advantages. Its major appeal is that its electron beam can penetrate a slice of tissue as thick as 1 micron (10,000 angstroms). Conventional electron microscopy, by comparison, is restricted to slices less than 200 angstroms thick. The cut edge of each of these thin sections distorts or destroys some material, and it may be impossible to determine how the cross sections of adjacent structures match up in a series of slices. Therefore, thick sections are essential for, among other things, examining cells that have many fine processes extending in all directions and for exploring the complex networks of structures within a cell.



Alberts et al, *Molecular Biology of The Cell*. ©1983, Garland

Diagram of mitochondrion shows how thin sections can present misleading images. In a single section, the organelle appears to be oval and might even be thought to be dividing in section 7.

Perhaps high-voltage electron microscopy's most important contribution has been to reveal the structural arrangement of a cell's cytoplasm. This material, once thought to be no more organized than a bowl of soup, is now recognized to

Tour through a taste bud

Taste buds are among the most dynamic systems in the body. Each of the 50 to 150 cells that make up a bud is thought to be replaced every 10 to 14 days. These cells, arranged like the staves of a barrel, sense sweetness, sourness, saltiness and bitterness. The site at which the taste cells interact with chemical stimuli is at the taste bud pore, where thin taste cell processes, called microvilli, meet the surface of the tongue. The taste cells transmit a signal, via chemical synapses, to nerve cells that penetrate the taste bud; and the nerve cells carry the signals to the brain.

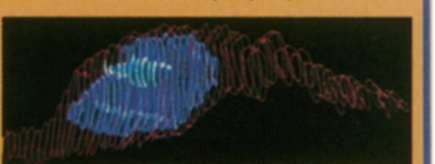
Scientists have characterized taste bud cells according to their appearance in the microscope as light or dark. There has been a long-standing controversy over which of these cell types sense the chemicals responsible for tastes and which merely play supporting roles. High-voltage electron microscopy is contributing to the resolution of this argument.

Preliminary evidence in high-voltage electron microscopic studies now indicates that the dark and light cells are not two distinct cell types, but rather that the dark cells mature into light cells. When mice were injected with a radioactive chemical that is taken up by newly born cells, in the first days only the dark cells were labeled, but after four days the label began to appear in light cells, report Rona Delay, John C. Kinnamon and Stephen Roper of the University of Colorado Medical School in Denver.

Kinnamon, X1,000

Taste bud: Taste cells (tc) send processes to the taste pore (tp).

Artist's view of a taste cell (outer membrane shown in orange and nucleus in violet) making two synapses onto one nerve fiber (blue) and one fingerlike synapse onto another (green). Below: Computer reconstruction of a taste cell (red = cell membrane, blue = nucleus, white = synapse).



Kinnamon

Because the presence of synapses is an indication that a taste cell has a gustatory function, Kinnamon and colleagues have examined synapse distribution in the taste bud. About 25 percent of taste cells have synapses. The synapses have an unusual location: Virtually all are positioned near the cell nucleus, and many are sunken deeply in invaginations of the taste cell membrane.

Kinnamon and Terri A. Sherman are using computer graphics to examine the structure of taste buds, taste cells and their synapses. They combine images from high-voltage electron microscopy thick sections and conventional electron microscopy thin sections. Then they put together a film of the structure as it rotates on different axes, as well as static three-dimensional reconstructions. "By using real-time rotations, we observed characteristics of the 3D structure which were not apparent in static 3D displays," Kinnamon and his colleagues say. The software for the computer graphics was developed by Timothy Edwards of Colorado State University in Fort Collins and Stephen Young of the University of California at San Diego.

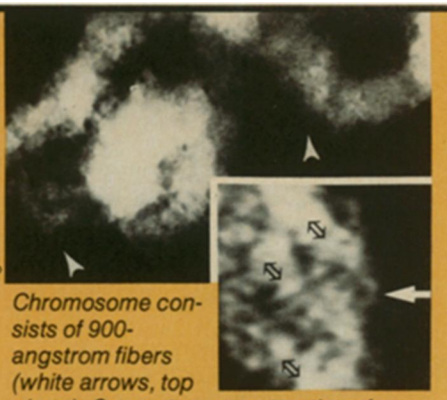
In preliminary work, the investigators find no difference between light and dark cells in the number or the characteristics of the synapses they make on the nerve cells that carry signals to the brain. Previously some scientists had assigned the gustatory function to the light cells, some had assigned it to the dark cells, and some to yet a third cell type. But Kinnamon, on the basis of his recent results, reasons that both light and dark cells participate in gustatory chemoreception. —*J.A.M.*

Microscopy untangles chromosome intricacies

When it comes to chromosome structure, biologists are just learning the ropes. "The best image for a chromosome is one of those hairy nautical ropes," says David Agard of the University of California Medical Center at San Francisco. High-voltage electron microscopy is helping to demonstrate that the chromosome, like a thick rope, is made up of coiled bundles of fibers, and that those bundles are themselves composed of smaller bundles, he explains.

The basic fiber of the chromosome — the DNA double helix and its associated proteins — is condensed several thousandfold when a chromosome is in its most compact state, during the metaphase period of cell division. The complicated structure of this condensed chromosome can be divided into several levels, or domains. The structure of the chromosome is thought to hold important clues to the control of gene expression. "To understand the structure of metaphase chromosomes we are attempting to trace the fibers that make up the various structural domains," Agard says.

Recent work using high-voltage electron microscopy (at a microscope devoted primarily to physical science research at the University of California at Berkeley) and computerized three-dimensional reconstructions reveals several levels of bundles intertwined in a complicated and somewhat irregular macrame. "This work is at an early stage," Agard says, "but for the first time we have a view into how a structure as complicated and as large as a chromosome is built."



Agard

Chromosome consists of 900-angstrom fibers (white arrows, top photo). Computer reconstruction of chromosome section (bottom inset) shows three 900-angstrom bands (open arrows) each made up of 400-angstrom bands, one of which is visible at edge (white arrow).

Agard, John Sedat and Andrew Belmont find that chromosomes in embryonic cells of the fruit fly *Drosophila melanogaster* are made up of coiled structures about 900 angstroms in diameter. These coils are actually incredibly complicated structures organized from finer substructures, Agard says. Three-dimensional reconstructions of high-voltage electron microscopic images show that several bands, 400 angstroms in diameter, are intertwined to make up each 900-angstrom fiber. In some areas at the outer edge of the image, the 400-angstrom fiber has been observed to make a helix. Agard speculates that there will be one more level of fiber between the 400-angstrom fiber and the basic, completely stretched out chromosomal fiber. In mammals, there also appears to be one more level at the top, a thicker coil, than in the fruit fly.

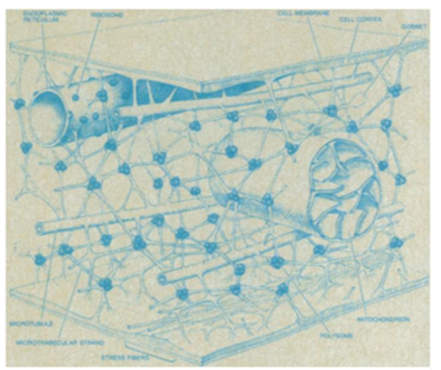
Examination of chromosomes from a variety of organisms — from fruit flies to humans — has revealed the motif of structures within structures, often coils within coils. "We think that this motif is part of the organization of all chromosomes," Agard says. "This work should help us to understand the complex topology of DNA and protein in chromosomes."

—*J.A.M.*

be made up of a solid gel, called the microtrabecular matrix (SN: 10/15/77, p. 250). The matrix is richly studded with intracellular structures, called organelles, held like chunks of fruit in a gelatin mold. Because most biologists now accept this once-controversial image of the cell interior, demand for high-voltage electron microscope use in this area has decreased. But current HVEM work on intracellular networks may again modify major tenets of biology.

For instance, Ellisman reports a network of fibers that run within and among nerve cells. He calls his finding a "major surprise with respect to the level of 'cytoskeletal' autonomy assumed by cells forming tissues." The network consists of filaments, 10 nanometers in diameter, which sometimes form cables of greater thickness. Within nerve cells, this network includes components within the nucleus that radiate in all directions. These filaments extend through the cytoplasm and cell membrane — sometimes crossing synaptic junctions, sometimes linking components of a cell with components of the extracellular matrix or with adjacent cells, Ellisman says.

This network, which Ellisman calls the transcellular organelle system, is difficult to observe even with high-voltage electron microscopy because it is characterized not by an electron-dense stain but by its lack of electron contrast. This light (rather than dark) structure cannot be recognized in electron micrographs except when viewed in 3D, Ellisman says. And even then, seeing it is so difficult that some microscopists who tried to do so at the Boulder meeting remained skeptical. The presence of a transcellular network would challenge one of the basic postulates of cell theory: Each cell has a discrete boundary. "This concept," Ellisman says, "is likely to undergo modification soon, as recent developments in electron microscopic imaging technology enable a more detailed and complete visualization of the structural organization of cells and tissues."



Porter, Tucker/Scientific American © 1981

Microtrabecular matrix is now recognized as the structure within cells.

One important advance in imaging technology is the application of computer analysis to electron micrographs. In the past, microscopists have generally dealt with the information contained in a thick section by simply perceiving two appropriately photographed images as a three-dimensional view. But these microscopists were limited in what they could see and measure. It was like analyzing a forest from the periphery, without being allowed to enter it.

Recently computers have been enlisted in dealing with the large amounts of information captured in a single high-voltage electron micrograph. In one technique a series of images is taken at different angles, the microscopic equivalent of a clinical computerized tomographic (CT) scan. The computer then generates a three-dimensional representation that can be viewed on the computer display screen and examined from any angle or even sliced on any plane. It is as if the observers now can enter the forest and photograph any view that interests them.

To make the computer representation even more useful, colors can be assigned to individual structures, and structures thus can be distinguished from the camouflaging environment and clearly displayed. In the forest analogy, only oaks and elms would be colored to show their distribution in a stand with many other types of trees. These data handling procedures make it easier for microscopists to display graphically their analyses of the complex structures of cells and their interactions.

Other new, but less widely used, methods of displaying three-dimensional images include making holograms and projecting images with a vibrating mirror.

Recent developments in sample preparation are also aiding analysis of thick sec-

tions. These include new staining techniques selective for structures of particular interest. These methods allow structures to be visualized without being obstructed by overlying cellular components. In the forest analogy, it is as if a special photograph could be taken in which only oaks are visible.

Staining techniques in the past have been predominantly trial and error. But recent work with antibodies offers the possibility of very deliberately targeting a specific structure with a marker that is readily detectable by the electron microscope.

The critical considerations of the future potential of high-voltage electron microscopy weighed these achievements and potential advances against some recent concerns. One worry was whether the two microscopes, now more than 10 years old, at the University of Wisconsin in Madison and at the University of Colorado in Boulder have become obsolete. (The third microscope, at the New York Department of Health in Albany, is only three years old.) In its report, the NIH advisory committee on high-voltage electron microscopy stated that, because the microscopes have been carefully maintained and new components added, "it is fair to say that ... the quality and reliability of both instruments is better today than it was when they were first purchased."

Another concern has been just who will be using the microscopes. Until recently, their use was directed by the original champions of the technique for biological investigation. But the University of Wisconsin is searching for a new leader for its high-voltage electron microscope facility because longtime director Hans Ris is planning to retire. Porter, who set up and directed the high-voltage electron microscope facility at the University of Colorado, recently left it to join the University of Maryland in Catonsville. After a period of uncertainty, Colorado's orphaned microscope has been put under the direction of Porter's former colleague at Colorado, Richard McIntosh.

Has high-voltage electron microscopy truly lived up to its promise of more than a decade ago? The NIH advisory committee notes that "...the impact of HVEM has not been widely apparent and that some may think the results have been rather modest."

Why isn't its reputation stronger? Ris attributes the technique's poor public image to its low profile."Its advantages have not really become well known, for reasons that I don't understand," he says. Whenever he gives a lecture on the technique, biologists tell him that they "hadn't been aware of its potential," Ris explains.

One problem, the committee suggests, is that many users make only a few visits to the microscopes and do not have the time, funds or interest to work out appropriate methods for specimen preparation and for analyzing the images obtained. Almost 60 percent of the more than 600 scientists who have used the three facilities have traveled from other institutions. The committee says, "A difficult climate for research funding and perceived dangers of engaging in high-risk projects probably has contributed measurably to the failure of large numbers of people to give up significant blocks of time to this new venture."

Continued on p. 399

A spiny story

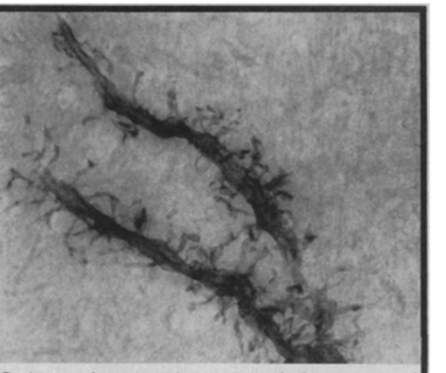
Nerve cells reach out to collect signals transmitted from other nerve cells. Often a complex branched pattern of thin cell extensions, called dendrites, acts as a receiving net. In many areas of the brain, the dendrites are further specialized for information collection. They bristle with numerous appendages called spines, which contain the sites that receive input from nerve cells extending from other parts of the brain. More than 30,000 spines have been counted on a single dendrite.

Originally these spines were envisioned as structures shaped like doorknobs — a spherical head on a cylindrical neck or stalk. Thin-section electron microscopy demonstrated that there are one or a few input sites, or synapses, located on each spine head. The spines are of special interest because they may reflect an animal's past interaction with its environment, and thus be a component of learning.

Scientists have speculated that the shape of the spine determines the strength of the electrical signals it sends to the cell body in response to synaptic input from other cells. But testing this hypothesis requires accurate measurement of the spine lengths and diameters, a task impossible with light microscopy. The neck diameter, for example, is generally less than 0.3 microns. And when a specimen is sliced thinly for standard electron microscopy, it is usually impossible to trace an individual spine neck. Charles Wilson of the University of Tennessee in Memphis has used the high-voltage electron microscope to examine dendritic spines from the area of the rat brain called the neostriatum.

The greatest surprise when Wilson first looked at the spines under the high-voltage electron microscope was the variety in their shapes. He did not find distinct spine types, which some investigators had proposed, but rather a continuous variation of spine head diameter, neck diameter and neck length. Furthermore, each dimension was independent of the others. A long spine could be either thin or fat, and a short one could have a large or a small head. Branched spines and curved spines also were commonly seen. Spine neck diameters ranged from less than 0.1 micron to 0.5 micron, neck lengths from 0.35 micron to 3.8 microns and head diameters from 0.11 to 0.95 micron.

One correlation revealed by the high-voltage electron microscopic study is that the larger the surface area of the spine head, the larger the area devoted to synaptic contacts. The study did not support another correlation that had been proposed—a spine's shape was not seen to vary systematically with the spine's position along the dendrite.



Wilson

Spines of many shapes and sizes extend in all directions from nerve cell dendrites. Spines are up to 4 microns long.

Wilson uses his measurements to predict the effect of spines on signal transmission. He calculates that, due to the electrical properties of the dendrite, an excitatory signal produced in a spine by a signal from another nerve cell is reduced dramatically when it travels to the main trunk of the dendrite. This attenuation is little affected by the size and shape of the spine head and by the diameter of the dendrite trunk.

However, the length and diameter of the spine neck does appear to affect substantially the signal size. When the neck diameter was relatively large, spines of all different lengths within the natural range gave the same maximum synaptic current. But the size of this signal fell off more rapidly with decreasing neck diameter for long-necked spines than for short-necked ones. Thus, Wilson concludes, a spine's size and shape can affect its output and how influential the spine is in the overall activity of a cell.

The next step for the investigator is to determine how the size and shape of a spine is controlled. "There is some evidence it is determined by the history of the synapse," Wilson says. Inside the spine is "wispy filamentous material" that seems to emanate from the synaptic site. This material may react to synaptic activity in a manner that influences the size and shape of the spine, Wilson suggests. "We are looking for a subcellular view of what this nerve cell does."

—*J.A.M.*

Science on the Air

Science News prints the latest written word of scientific development and noteworthy news. We've set this space aside to inform our readers of programs of scientific interest that are scheduled on television and radio. Check your local listings for exact times. (R) indicates a repeat broadcast.

Jan. 1 (PBS) Nova — "Salmon on the Run" An examination of how business and technology are changing the fishing industry, and the salmon itself.

Jan. 5 (PBS) Newton's Apple—A weekly family science show covers topics from the space shuttle to Beluga whales. Saturdays.

Jan. 6 (PBS) Nature — "Resurrection at Truk Lagoon" (R) Examines the life system in the Truk Lagoon. A former World War II Japanese supply depot was destroyed by the Allied forces, leaving an environment of sunken artifacts which now hosts a colorful variety of underwater plant and animal life.

Jan. 8 (PBS) Nova — "The Garden of Inheritance" Looks at the life, times and work of Gregor Mendel, whose revolutionary scientific experiments in selective breeding made him the Father of Genetics.

Jan. 9 (PBS) Smithsonian World — "A Desk in the Jungle" Marine biologists descend 2,000 feet to an ocean depth where no sunlight can penetrate and the sea is rich in discovery. Also featured is a trek to the Smithsonian's Tropical Research Institute in Panama to observe anthropologist Katie Milton's study of the Howler monkey.

Jan. 10 (PBS) Wild America — "All-American Animals" A look at some of North America's wild creatures found nowhere else on earth, including the pronghorn of the western plains and the scissor-tailed flycatcher of the midwest.

Jan. 13 (PBS) Nature — "Tumbler in the Sky" A look at the African Bateleur eagle's astonishing acrobatics performed during mating and hunting.

Jan. 15 (PBS) Nova—"Edgerton and His Incredible Seeing Machines" Explores the fascinating world of Harold E. Edgerton, inventor and electronics wizard, whose invention of the electronic strobe has enabled the human eye to see the unseen.

Jan. 17 (PBS) Wild America — "Feathered Jewels" The many species of exquisite, iridescent hummingbird are seen in an extreme slow-motion sequence that reveals all of their beauty.

Jan. 20 (PBS) Nature — "Kinabalu: Summit of Borneo" A visit to the lush mountain forests of Kinabalu, the highest point between the Himalayas and New Guinea. Many of the plants that adorn these forests are found nowhere else in the world; some are living fossils, older than the mountain itself.

Jan. 22 (PBS) Nova — "Global Village" An in-depth look at the consequences of India's attempt to use satellite technology to leapfrog into the era of space communications.

Jan. 24 (PBS) Money from Heaven: A Successful Space Salvage (R) An updated look at NASA's recovery of two wayward satellites by the space shuttle astronauts and the story behind the November 1984 mission.

Jan. 24 (PBS) Wild America — "Ringtailed Rascals" A look at the raccoon, ringtail and coatimundi which combine in a special way the features of several other animals.

Jan. 27 (PBS) Nature — "Plight of the Bumblebee" This film compares the life cycle of the bumblebee to that of a human being, showing the unique and very serious "energy crisis" confronting these insects.

Jan. 29 (PBS) Nova — "Conquest of the Parasites" Examines parasites, parasitic disease and the exciting work currently being done by a new breed of medical researchers working to conquer the world's number one medical problem.

Jan. 31 (PBS) Wild America — "Canyon Creatures" A visit to Monument Valley, the Grand Canyon and the sandstone arches of Utah to learn how these spectacular landscapes exert a powerful influence on the wild creatures that live within their realms.

CABLE NETWORKS

Satellite Program Network

"Medicine Man"—Mon 1 pm; Wed 7 pm; Thus noon; Sat 11 am, 4 pm.

"The Personal Computer Show" — Tues 6:30 pm; Wed 1:30 pm; Thurs 7:30 pm; Sat 2 pm.

Cable News Network

"Healthweek" — Sat 9:10 am, 2:10 pm; Sun 1:10 am, 4:10 pm.

Lifetime

"Medical Video Clinic"—Sat 9 am; Sun 11 pm.

Continued from p. 395

On the horizon is yet another form of electron microscope that may effectively bridge the risky chasm between conventional and high-voltage electron microscopy. The new technique may also, on its own, meet at least some of biologists' demands for three-dimensional, highly magnified images of relatively thick slices of the materials they study. The intermediate-voltage electron microscopes (IVEMs), expected to be more convenient and less expensive than high-voltage electron microscopes, soon may affect the popularity of the older technique. But no one is certain whether the IVEM will add to or subtract from the demand for HVEM facilities.

Two companies — one in the Netherlands, the other in Japan—have just begun to manufacture intermediate-voltage electron microscopes. These instruments employ electron beams of 300 to 400 kilovolts, rather than 1 million volts. They can handle specimens thicker than those for conventional electron microscopy, but not as thick as the thickest used in high-voltage electron microscopy.

"It is anticipated that many of the results obtainable at 1 millivolt could also be obtained at these intermediate voltages, with considerable saving in cost and effort," the NIH committee says. In addition to costing only about $1 million apiece, the intermediate-voltage microscopes will fit in normal laboratory rooms and will not need specially constructed buildings to house them.

The NIH committee recommends that as many as 10 IVEMs be in operation in biomedical research laboratories in the United States within the next three years. According to Stimler, NIH is already considering applications for the purchase of these instruments.

"Maybe they [IVEMs] will take people away from HVEM facilities in the beginning," Ris says, "but then they should bring people to them." The NIH committee agrees that although the intermediate-voltage instruments will be used for some work now done with high-voltage electron microscopy, they are also expected to generate increased interest in high-voltage microscopy.

"The IVEMs can be expected to act as feeders for the HVEMs in those projects where it becomes clear that the full capability or special features of the higher voltage instruments are needed," the committee says.

High-voltage electron microscopy thus is not expected to remain an orphan of biological research. It is finding foster parents in the form of new research directions — especially in neurobiology and in chromosome structure analysis — and in continued financial support. "It's true there is a change of direction," Stimler says. "But people have solved problems with it and are still solving them." □