Defining shock at the cellular level

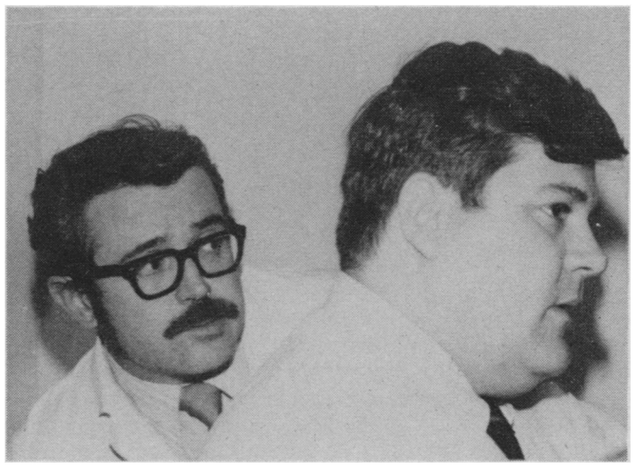
Innovations have brought about a revolution in the study of shock

by Joan Lynn Arehart

Curiously, the darkened room resembles the cockpit of a spaceship. The chrome cylinder of an electron microscope looms overhead. Panel lights flanking the microscope flash intermittently. A pathologist peers through the microscope's porthole. He is viewing one of the 180 billion cells of the human body, blown up 30,000 to a million times larger than life. Cautiously his eyes scan the ridges, craters and other cell topography for any changes that might reflect the effects of shock at the cellular level . . .

Such intense scrutiny under the massive electron microscope occurs regularly at the University of Maryland School of Medicine's Center for the Study of Shock and Trauma. The center is one of the most progressive shock research complexes in the United States. It is a collaborative effort between the medical school's departments of surgery and pathology. Benjamin Trump, chairman of the department of pathology, is also director of research at the shock-trauma center. R A. Cowley of the department of surgery is program director of the shock-trauma center.

Shock research at the center is unique for several reasons. The work the pathology team—Trump, Jane Dees, Wolfgang Mergner and Jon Valigorsky—has been doing on human autopsy tissue over the past year was preceded by a decade of animal experimentation on shock. Second, Trump and Cowley have devised an "immediate autopsy," a virtual revolution in pathology. Under state law and where the necessary family permission has been obtained, an immediate autopsy may be performed. Organs and tissues can then be rushed to the pathology laboratories for study within two to five minutes after a shock patient dies in the center's shock ward. "From a pathologist's view, the innovation is fantastic," Trump declares. "In the past ultrastructural and biochemical specimens obtained by routine autopsy have often been useless for studying shock."



Trump (left) and Valigorsky view shocked cells.

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Thus the pathology team is then able, with the help of sophisticated equipment like the electron microscope, the centrifuge, freeze-etching (cells are cleaved like ice so that different cell membrane surfaces can be viewed under the microscope), to explore the intricate effects of trauma at the organ, tissue and cell levels. Such efforts, the team anticipates, will give clinicians a better understanding of the phenomenon of shock, and will bring better care and treatment to shock victims—both at the Maryland medical school and elsewhere.

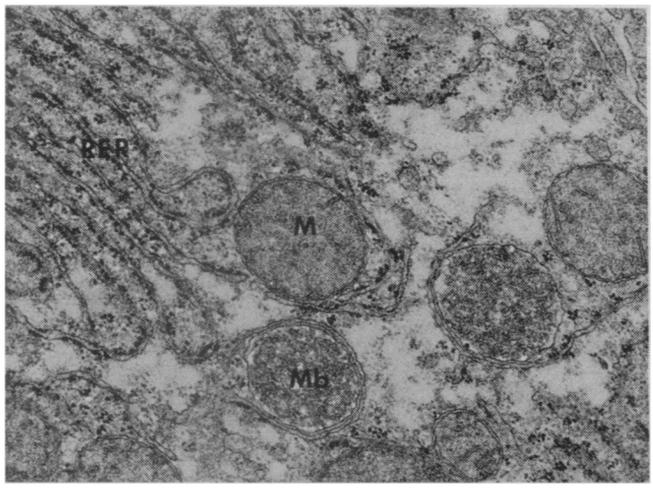
As Trump and his colleagues explained in an interview, shock has been traditionally difficult to diagnose even at the general clinical level. Shock may follow conditions as diverse as automobile accidents, major surgery, massive hemorrhage, dehydration, heart attack, infection, poisoning or drug reactions. There may often be little correlation between the cause of shock and its effects in the human body. Shock, in brief, is difficult to describe beyond the fact that its victims nearly always suffer a collapse of blood circulation and some secondary changes in their systems and organs.

Now, after a first year of performing some 20 immediate autopsies on shock victims, the Baltimore pathologists believe they are in a position to better define the effects of shock. Shock, they have found, can harm various organs selectively. The effects can be extremely fast and severe. If injury at the cellular level is critical enough, the cell may die. If enough cells, tissues, organs and systems are impaired, a shock victim may have to fight for his life.

Over a century ago, Rudolph Virchow, the father of modern pathology, boldly avowed that disease is the reaction of cells to injury. "He was right," Trump confirms, "which is not surprising. What is surprising is the extent of injury that can take place not just at the cellular, but at the subcellular levels."

Trump and his colleagues describe several of the autopsy histories upon which they base their conclusions . . .

In one case a youngster fell off the back of a farm truck, hit his head on the pavement and was rushed by helicopter to the trauma center ward. The patient was treated immediately, but he did not improve and remained in a deep stupor. After death his organs were examined for injury. All of them appeared normal under the electron microscope except for the brain. Mitochondria, or energy plants, isolated from liver, heart and kidney cells were able to make ATP, or energy molecules, in the test tube. The brain cells were not able to do so. The pathologists thus



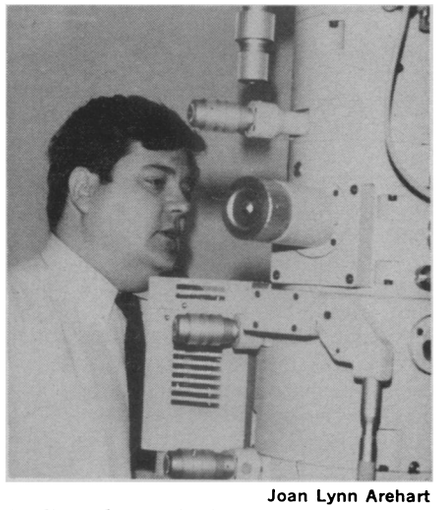
Liver cell from youngster who died of brain damage appears normal, including the mitochondria (M).

Pathology Dept., U. of Md.

concluded that the victim had died from brain injury, and not from injury to other organs.

In another case a 29-year-old mother was driving her children to school when the automobile overturned. She was pinned under the vehicle with her head in a ditch of water. The patient was rushed by helicopter to the shock ward, but she did not respond to therapy and succumbed. The pathologists placed her organ cells under the electron microscope.

Her kidney and liver cell mitochondria were swollen and contained dark blobs. In contrast her lung, pancreas and heart cell mitochondria revealed less swelling and fewer blobs. In the test tube the kidney and liver cells were not able to make ATP, but the pancreas and heart cells were able to do so. The structural characteristics of the mitochondria that did not work were identical to mitochondria the team had previously found in dead cells from experimental animal material. Here again shock seemed to have impaired organs selectively, and such impairment at the cellular level seemed to have curtailed energy production. The pathologists had also found that an arrest of energy production, by shock, kills cells from animal tissue rapidly.



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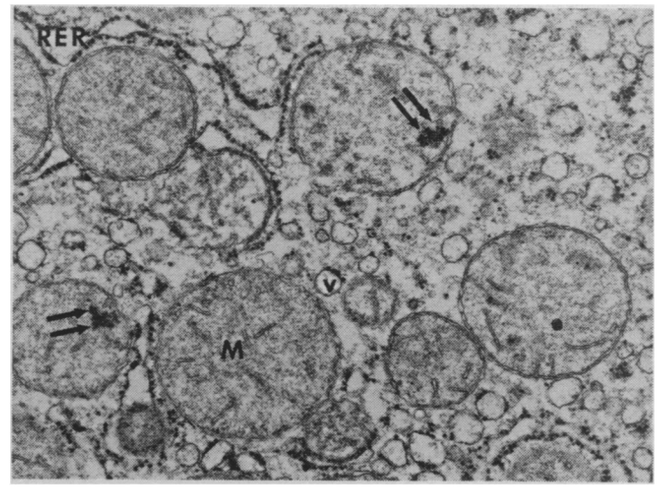
Valigorsky and electron microscope.



Liver cell from drowned woman does not appear normal. The cell's mitochondria (M) contains dark blobs.

Not cell mitochondria, but cell lysosomes appeared to be the target for shock in a third case. The lysosomes, like the mitochondria, are membrane-bound "craters," or vacuoles, situated in various parts of the cell cytoplasm. They contain enzymes that are believed to perform different functions within the cell. This time a 35-year-old man was crushed in a local factory. Although he was operated on at the trauma center, and lived several months there, he ultimately died. Electron microscope studies revealed damage to his liver and kidney cells—not by shutting down the mitochondria, but by touching off an abundant production of lysosomes.

Why more lysosomes might be formed in a cell in response to shock is unknown, but lysosomes have been known on occasion to "eat" other parts of the cell. Thus shock's triggering a step-up in lysosome production could conceivably mean that traumatized liver and kidney cells had received a message to "self destruct." The Baltimore group is working closely with a Finnish physician, Antti Arstila, who is particularly anxious to unravel lysosomes' response to shock.

The shock researchers are now testing their hypotheses further on animals and animal tissues. Wolfgang Mergner, for example, has explored the ability of shock to arrest energy production in the mitochondria of rat cells. From what he has gleaned so far, the damage seems to center within the mitochondrial membrane. The team has found that some of the damage to cells from shock seems to involve swelling and movements of water ions. The investigators are looking for agents that might prevent the swelling. One compound that appears particularly promising is a sugar called mannitol. It can help shocked cells keep on producing ATP. Ability to turn swelling in shocked cells on and off might eventually result in some kind of shock therapy, Trump speculates. Current treatment for shock is nonspecific in most cases—having the patient lie in a certain position, controlling external hemorrhage, keeping a patient breathing and his blood circulating, giving appropriate sedatives, and so forth.

The Maryland physicians have also found that when acid is added to normal cells they act like shocked cells. So do isolated mitochondria when acid is added. "So we are trying to neutralize the shocked cells to see if this might modify the response," Trump says. Here too some shock therapy might be in the offing. The team is also looking at antihistamines, which are believed to stabilize cell membranes. It is also examining adrenal steroid hormones and other drugs—some already used in shock treatment—to see whether they are truly capable of reversing shock damage at the cellular level.

These and similar research efforts, the group hopes, will not just shed light on the effects of shock at the organ, tissue, cellular and subcellular levels, but will also help elucidate normal functions of these anatomical parts. For, even in this remarkable era of molecular biology, scientists are only awakening to the dozens upon dozens of biochemical operations that take place within seconds in each human cell. □