**From soldier to subject.** Researchers are collecting data from casualties like this one in Afghanistan.

CREDIT: AP

# War as a Laboratory For Trauma Research

**The military is sending scientists onto the battlefield to find ways to improve emergency medicine, but the research faces a practical and ethical minefield**

**KANDAHAR AIRFIELD, AFGHANISTAN—** Easing back into a borrowed chair in a tiny trailer office here on the base, Cmdr. Lisa Osborne should be enjoying a moment of calm. But all she can talk about is work. "I saw a guy show up here in trauma. You wouldn't believe the condition he was in," she says, recalling the victim of an improvised explosive device (IED). The extent of the injuries was shocking, even to the hardened medics working here in Afghanistan. "He was missing both legs and his whole backside. But he was alive, breathing on his own."

For most people, a scene like that would fill them with nothing but horror. But for Osborne, a U.S. Navy anesthesiologist and medical researcher, it was a reminder of hard-earned progress. "Years ago, that kind of patient would be dead," she says. "No question." What saved him was a series of extremely rapid interventions, including new techniques for applying tourniquets, drugs, and blood products. Those insights came from medical research conducted in Iraq and Afghanistan, orchestrated through a U.S. military program called the Joint Combat Casualty Research Team (JC2RT). As its deputy director, Osborne runs the show.

In many ways, war is the perfect laboratory for trauma medicine research. On any given day, dozens or even hundreds of casualties arrive by helicopter to military hospitals across Afghanistan. IEDs are the number one risk, often combining burns, deep lacerations from shrapnel, and brain trauma from blast waves. Injuries like these are too rare to study in peacetime. And because all the patients in these studies are military personnel, they come with exhaustive data relating to preinjury health and postinjury outcome. Many of the insights gained from battlefield studies have found their way into civilian emergency medicine. But war is also the most chaotic and stressful environment imaginable for doing science. "Someone has to take down all this data," Osborne says. "I saw this poor girl trying to turn this blood-smeared page, trying to get data off of it. … That's the reality. Until you've lived that, you don't realize how difficult it is."

Adding to the difficulty, controversy has dogged JC2RT projects, including charges by journalists that researchers rushed experimental treatments onto the battlefield without proper ethical review or sufficient safety testing, needlessly risking the lives of soldiers. *Science* investigated these issues with the help of two bioethicists and several sources from both civilian and military trauma medicine.

### Exploring the golden hour

From the moment a bullet or piece of shrapnel hits the body, the clock is ticking. Trauma medics call it the "golden hour," the small window of time in which the patient's life can be saved. Death can come in a mat-





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ter of minutes, hours, or days, but the most crucial interventions must be made immediately. War has been "an amazing learning environment," says Osborne, with each conflict pushing trauma medicine forward. New motorized ambulances in World War I saved wounded soldiers by getting them from the front lines to the hospitals quickly. World War II saw the first large-scale use of antibiotics. Medics in the Korean War pioneered repair and grafting techniques for vascular surgery. In the Vietnam War, portable radiology equipment and ventilators were tested in the field.

With the wars in Afghanistan and Iraq, combat medicine has faced a new problem. "The difficulty for the current generation is getting approval for research," says Col. Martin Bricknell, a senior doctor in the U.K. Royal Army Medical Corps who hosted this reporter's visit to military facilities in Kandahar (see p. 1256). "It is considerably more rigorous than it used to be, and therefore the lag between good idea to outcomes is much greater." JC2RT was created in 2006 to streamline that process.

"We're a team of eight," says Osborne, a petite, blonde 42-year-old in the middle of her 6-month tour of duty in Afghanistan. When she is not at war, Osborne is the director of anesthesiology research at the Uniformed Services University of the Health Sciences in Bethesda, Maryland. "Most of us have Ph.D.s," she says, "but we're not data collectors." Instead, JC2RT is a gatekeeper and overseer. Ideas for projects are put forward by researchers from all branches of the U.S. military, often with university-based scientific partners. As the proposals roll in, Osborne says, "I'm the one who has to give people the bad news that their research project isn't going to work."

A typical problem is feasibility. "The people who are writing these [proposals] are just coming into theater," Osborne says. "They don't realize that there's no way they're going to be able to do it." As an example, she describes a project that would have required infrared photography of injured soldiers' limbs. "You often have a whole sea of people working on the patient. You can't tell them, 'Okay, everybody step back. I'm going to snap some photos.' "

Another fatal flaw is the use of experimental medical devices. "It's a deal-breaker," Osborne says, because of U.S. federal regulations. "If you use them, you must have informed consent from the patient. Period." Most wounded soldiers plucked from the battlefield are in no state to grant consent for a new device, even if they are conscious.

**Whole blood.** These empty transfusion bags from a single patient in Afghanistan show the 1-to-1 ratio of blood products now used.

Once a research project passes this prescreening, it must be approved by an independent U.S. Army institutional review board (IRB) based at Fort Detrick, Maryland. That review process is identical to those at any research institution, Osborne says, sourcing outside experts as needed. Osborne and her colleagues identify issues likely to cause problems with reviewers, giving researchers a chance to address them early "so that when [the proposal] goes to IRB it has a chance," Osborne says. At least one of the investigators must be present to undertake the study in the field. "Most of these folks, they're only here for a short amount of time. If their stuff gets held up in IRB for 6 months, they miss the boat. We try to prevent that from happening. But it does happen."

To date, about 100 projects have made it through this gauntlet and into the field, so far producing dozens of peer-reviewed research papers (see table on p. 1263). All of them take advantage of data from the U.S. military's Joint Theater Trauma Registry (JTTR), a continuously updated record of trauma cases in Iraq and Afghanistan. JTTR currently contains the case histories of 40,000 patients, including medical observations, treatments, and outcomes in minute detail. Most of the research has yielded incremental improvements to existing treatments. But some have overturned paradigms of trauma care, says Osborne. One example is blood transfusion.

Some battlefield injuries are so severe that patients require massive transfusions, sometimes as much as five times the volume of blood in the body. The standard transfusion practice begins with concentrated red blood cells in a saline solution, with the other blood components—plasma containing platelets and clotting factors—added sparingly later. "What we realized," says Osborne, "is that if you wait on those clotting factors, then you're always behind. You can keep putting in red blood cells and they just keep pouring right out [of the wounds]." The transfusion protocol for severe injuries has now been revamped based on JC2RT research. For injuries that require massive transfusions, the equivalent of whole blood is now given immediately, including a full complement of clotting factors. The researchers found that it reduced mortality rates in these patients from 65% to 17%.

Another dramatic change from JC2RT research is how "damage control" surgery is performed. "We found that it's critical that we not close some injuries when they come in here," Osborne says, "because the outcomes are massive infections and sepsis." Instead, blood vessels are tied off and the wound is left open, sometimes for several days, vigorously cleaning it with saline. "We used to close that wound 7 years ago," she says.

Other problems have yet to be solved. One of the most urgent is compartment syndrome, the accumulation of fluid between tissue layers that can result in amputation or even death if the pressure cuts off blood to organs. One JC2RT project is testing whether the pressure in an injured limb can be diagnosed earlier by detecting a drop in oxygen in the tissue. Another unsolved problem explored by JC2RT projects is how to diagnose brain trauma, for example, using ultrasound to measure the blood pressure of vessels within the eye.

Because of the streamlined process, insights from those projects will move quickly onto the battlefield. In medical research, says Osborne, "you normally have a 10-year pipeline" between the first experiment and a new treatment for patients. "For us, it can be half a year," she says.

The speedy turnaround has doubtless saved lives. But at the same time, it has invited intense scrutiny.

### Serious charges

Wartime medical research has a troubled history. The most notorious examples are the experiments performed on prisoners by German and Japanese doctors during World War II. As a 2002 directive by the U.S. Department of Defense states, "The involvement of prisoners of war as human subjects of research is prohibited." So even harmless experiments on detainees are forbidden by JC2RT, says Osborne. Nonetheless, its research projects have attracted their share of controversy.

CREDITS: ISAF

## Trauma Research on the Battlefield

| Research topic | Summary | Example of output or project status |
|---|---|---|
| **Damage control resuscitation** | Methods for resuscitating patients with massive blood loss | M. A. Borgman *et al.*, The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. *J Trauma* **63**, 805 (2007). |
| **Compartment syndrome** | Using oxygen concentration and other markers to detect dangerous fluid buildup in injured limbs | Ongoing |
| **Prehospital lifesaving interventions** | Assessing the performance of immediate interventions in trauma care | Ongoing |
| **Vascular surgery** | Comparing the effectiveness of vascular injury treatment for wounded soldiers | S. M. Gifford *et al.*, Effect of temporary shunting on extremity vascular injury: an outcome analysis from the Global War on Terror vascular injury initiative. *J Vasc Surg* **50**, 549 (2009). |
| **Traumatic brain injury** | Biomarkers and quantitative EEG for detecting brain injury and characterizing immunodeficiency | Ongoing |
| **Critical Care Air Transport Team (CCATT)** | Analysis of resuscitation and early clinical outcomes as a function of aeromedical platform | M. D. Goodman *et al.*, Traumatic brain injury and aeromedical evacuation: when is the brain fit to fly? *J Surg Res* **164**, 286 (2010). |
| **Combat medicine training** | Assessing the effectiveness of medical training in the context of Iraq and Afghanistan | J. A. Tyler *et al.*, Current US military operations and implications for military surgical training. *J Am Coll Surg* **211**, 658 (2010). |
| **Tourniquets** | Optimizing the use of tourniquets for improving survival and reducing amputations | J. F. Kragh Jr. *et al.*, Survival with emergency tourniquet use to stop bleeding in major limb trauma. *Annals of Surgery* **249**, 1 (2009). |
| **Soft tissue injury** | Assessing the effectiveness of the vacuum assisted device and other innovative treatments for soft tissue damage | R. Fang *et al.*, Feasibility of negative pressure wound therapy during intercontinental aeromedical evacuation of combat casualties. *J Trauma* **69**, S140 (2010). |
| **Explosive mass casualty** | Developing guidelines for intensive care for multiple casualties caused by explosions | B. W. Propper *et al.*, Surgical response to multiple casualty incidents following single explosive events. *Annals of Surgery* **250**, 311 (2009). |

SOURCE: JC2RT

A 2009 investigative report by *The Baltimore Sun*, which has been widely circulated among civilian and military doctors, alleged that researchers sidestepped standard ethical practices in Iraq and Afghanistan. "The military exposed hundreds of soldiers and Marines to the risks of unproven treatments that were unlikely to do much good," the report claims. U.S. Air Force Lt. Col. Todd Rasmussen, deputy commander of the U.S. Army Institute of Surgical Research in San Antonio, Texas, who oversees JC2RT, declined to comment, saying only that the article reflected "vigorous but appropriate academic deliberations" within the medical research community.

*Science* asked two bioethicists, Daniel Wikler of Harvard Medical School in Boston and Norman Fost of the University of Wisconsin, Madison, to assess the issues raised by the article and, more generally, JC2RT's procedures for ensuring that battlefield research is carried out ethically. Fost, who is the architect of the current standard ethical procedures for trauma medicine research, pulled in several other experts. "I talked at length with four experienced surgeons, three of whom specialize in trauma and have military experience, two of whom have served multiple tours in Iraq and/or Afghanistan," he says. He also reviewed numerous articles in peer-reviewed journals and U.S. Food and Drug Administration documents. Both bioethicists posed questions about JC2RT research directly to Osborne through a series of e-mail exchanges.

Fost's conclusion: None of the examples of unethical research held up under scrutiny. But the criticism is not surprising. "There is scarcely a disease or treatment in the world without strong disagreement among knowledgeable people about the best approach," Fost says. As for the charge of lax ethical review, Fost found the opposite to be true. "There was a continuous dedication to evaluating practices in a way that many civilian medical centers would envy," he says. Beyond the standard IRB approval process, new treatments are evaluated in real time with weekly "morbidity and mortality conferences" that include military physicians from around the world. They are part of a "serious quality-improvement program," Fost says, which is "beyond anything I'm familiar with in civilian medicine."

Wikler agrees that there is no clear evidence of wrongdoing but adds that the extra scrutiny is justified. "There is a long tradition of using soldiers as guinea pigs for research," he says. "And trauma medicine research in general has the problem of a lack of consent from unconscious patients," which raises the bar on what types of experiments are permissible. JC2RT research "falls into this double shadow," Wikler says. "But that doesn't mean it was wrong."

"The moral of this story is that continuous research is not only desirable but ought to be seen as obligatory, barring insuperable ethical barriers," Wikler says. "All of us hope that if we are injured in a traffic accident and are brought to a hospital, the ER docs won't be using primitive medical techniques because research on banged-up patients was forbidden."

This is also the view of Peggy Knudson, a trauma surgeon and researcher at the University of California, San Francisco, who has trained U.S. military doctors in Iraq and has advised the military on JC2RT research. Knudson says some of the treatments tested in Iraq and Afghanistan are already being applied in civilian hospitals in the United States. "I copied the military burn protocol and brought it back to my [hospital]," she says. She was also impressed by the new methods for applying tourniquets and temporarily shunting blood vessels. "I use them both." She says that the military's massive blood-transfusion protocol is being tested at 11 civilian trauma centers across the United States.

Here in Afghanistan, Osborne has to get back to work supervising the research projects. "I can't wait for tomorrow," she says. Once per week, she stops being a scientist and becomes a doctor, waiting for the injured to arrive from all directions.

**–JOHN BOHANNON**

# War as a Laboratory For Trauma Research

John Bohannon

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