Clinical Promise with New Hormones

Hematologic growth factors boost blood cell production in cancer patients, AIDS patients, and patients with kidney failure; they are now undergoing further clinical tests

A newly available group of hormones is likely to have a major role in medicine. The hormones, called hematologic growth factors, can stimulate the bone marrow to make red or white blood cells in essentially any desired quantity. Three of the four hormones are now being tested at medical centers throughout the country in patients with AIDS, various forms of anemia, cancer, and bone marrow transplants.

The first clinical result in humans, published in January in the *New England Journal of Medicine*, indicated that the red cell–stimulating hormone works beautifully and has essentially no side effects. Joseph Eschbach and his colleagues at the University of Washington in Seattle gave varying doses of erythropoietin to 25 anemic patients and reported that every patient who received an effective dose responded. Twelve patients who before treatment had required transfusions no longer needed them after they received the hormone.

On 21 April, at a closed session of the American Society for Hematology meeting in Durham, North Carolina, Janice Gabrilove of Memorial Sloan-Kettering Cancer Center reported results from a newly completed study showing that one of the white cell–stimulating hormones is also effective in humans. Gabrilove and her colleagues gave G-CSF, for granulocyte–colony-stimulating factor, to 16 cancer patients receiving chemotherapeutic drugs that are toxic to the bone marrow. G-CSF, she reports, significantly decreases the time it takes for the depleted bone marrow to reconstitute itself.

A third study, whose results will be announced by Jerome Groopman of New England Deaconess Hospital on 2 May in San Diego at the meeting of the American Society for Clinical Investigation, shows that another of the white cell–stimulating hormones is effective in humans. Groopman reports that the recombinant human hormone, GM-CSF, for granulocyte macrophage–colony-stimulating factor, can boost the white cell counts of AIDS patients to as much as 50,000 cells per microliter of blood. A normal white cell count is 4000 to 6000 cells per microliter and these patients, whose bone marrows were suppressed as a consequence of their AIDS infection, initially had white cell counts as low as 1600 cells per microliter.

The results of all three of the recent studies are consistent with those of previous studies in animals, including primates. But Groopman notes, "You never know until you test a substance clinically whether it's a blind alley or a home run. I'm not a hyper, but this is a home run." If the results of studies now under way continue to be positive, there are a number of immediate clinical applications for the hematologic growth factors.

"In my judgment, it's a revolution in medicine equal to antibiotics," Golde says.

For example, the hormones could transform blood banking. Patients anticipating elective surgery might take erythropoietin, which stimulates red blood cell production, and could then donate up to twice as much blood in advance of the operation as they can give now. After surgery, patients might receive erythropoietin to speed their recovery from any blood loss during surgery.

The hormones that stimulate white blood cell production, called colony-stimulating factors, are expected to boost flagging immune systems. If they work as anticipated, they will be the first treatment since the discovery of immunizations more than 100 years ago that actually increases a person's ability to fight infections.

Colony-stimulating factors also are expected to enable cancer patients to take higher, and possibly more effective, doses of chemotherapeutic drugs that destroy the bone marrow. While the bone marrow is growing back, patients are highly vulnerable to infections. Bone marrow toxicity is a limiting factor in the use of chemotherapeutic drugs.

In addition, the colony-stimulating factors are expected to help a diverse group of hospitalized patients fight infections. "Most patients who die in tertiary care die of infections," says David Golde of the University of California at Los Angeles School of Medicine. Burn patients, trauma patients, patients with organ transplants, including bone marrow, and diabetics all could potentially benefit.

"In my judgment, it is a revolution in medicine equal to antibiotics," Golde says. David Nathan of Harvard Medical School agrees. "It's very exciting. It is spectacular," he says.

Wall Street is far from oblivious to the medical potential of hematologic growth factors. "I think they're very attractive compounds," says Michael Sorell, a pediatric oncologist who is now an equity analyst for Morgan Stanley in New York. His estimates of the U.S. market include as many as 5,000 bone marrow transplant patients a year, at least 200,000 cancer chemotherapy patients, 10,000 to 20,000 burn patients, and the 20,000 known AIDS patients in this country.

The hematopoietic growth factors are expected to be expensive. Robert Kamen of Genetics Institute in Cambridge, Massachusetts, explains that "the development costs are very, very high. A lot of money has been sunk into these substances." Kamen estimates that a bone marrow transplant patient might pay as much as $1000 to $3000 for GM-CSF. But if the hormone cuts the patient's time in intensive care in half, as is anticipated, this could still represent a saving. Intensive care costs about $3000 a day, and the normal stay for a bone marrow transplant patient is 18 to 21 days.

Of course, this is not the first time in medicine that new substances have met with great enthusiasm. But, say the hematologic growth factor researchers, they are well aware of the hazards of exaggerating the effectiveness of new drugs and they do not believe they are inflating the potential of hematologic growth factors. "I think the people in this field are being cautious," says Lawrence Souza of AMGEN in Thousand Oaks, California. "We saw what happened with interferon and interleukin-2 and we just don't need that." Nonetheless, say these researchers, the hematologic growth factors seem to be fulfilling their promise.

"With this class of hormones, it's sort of a yes-no situation," says Groopman. Investigators know just what the substances are supposed to do and the only question is will they do it. With other initially promising substances, including gamma interferon and tumor necrosis factor, for example, "it was very hard to know in a physical way how they work. What does gamma interferon do in the body? Who knows?" Groopman said. "The exciting thing about the hematologic hormones is that they really are linked in a very direct way to the target tissue. It's the same as with other hormones, such as insulin and FSH [follicle-stimulating hormone]."

But, of course, as promising as the hematologic growth factors might appear in vitro, it still could have happened that they failed to perform in vivo. For that reason, the newly completed studies of the effects of G-CSF in cancer patients, GM-CSF in AIDS patients, and erythropoietin in anemic patients are significant.

The G-CSF study follows recent studies in monkeys that indicated the hormone might be effective in humans. In one experiment, Karl Welte and his colleagues at Sloan-Kettering showed that G-CSF works dramatically in monkeys. When he gave monkeys the hormone, the white blood cell count increased from the normal range of about 10,000 cells to as much as 100,000 cells per microliter of blood. The white cell count started to rise within 24 hours of treatment and the effects of G-CSF disappeared within 3 days after treatment ceased. Moreover, the G-CSF effects were dose-dependent.

Next, Welte and his associates gave monkeys cyclophosphamide, a chemotherapeutic drug, at a dose that nearly destroyed the bone marrow. They then gave the monkeys G-CSF and found that the marrow regenerated in 1 week rather than the usual 3 to 4 weeks.

In another experiment, Welte gave monkeys such high doses of chemotherapeutic drugs that the bone marrow was destroyed. Beforehand, he had extracted and saved some marrow from each monkey and he subsequently infused that marrow back again. Then he gave G-CSF. It took 10 days with G-CSF for the transplanted marrow to grow back to such an extent that the monkeys had functioning immune systems. Without G-CSF, it took 3 weeks.

Then Gabrilove and her colleagues, including Souza of AMGEN, who supplied the hormone, gave G-CSF to patients with cancers of the genital-urinary tract, mainly bladder cancers. They chose patients with these cancers because, Gabrilove says, the cancer virtually never affects the bone marrow and so the patients "have essentially normal bone marrows."

Jerome Groopman

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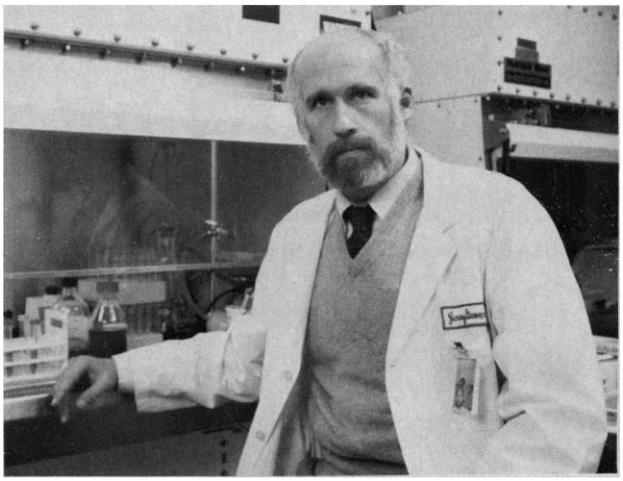

Because chemotherapy kills the cells that make G-CSF, including monocytes and endothelial cells, the researchers reasoned that it could simply be a lack of G-CSF that slows bone marrow regeneration. "The progenitors [of white blood cells] are there, waiting to be stimulated," Gabrilove explains. And when the cancer patients received G-CSF, they had essentially no side effects and their marrows responded in a way that was exactly comparable to the way the monkeys responded in Welte's experiments.

The rationale behind the AIDS study was the proposal that bone marrow suppression in AIDS might be caused by a GM-CSF deficiency. One possibility is that GM-CSF might be produced by T cells that are killed by the AIDS virus. In a collaborative study involving Golde, Dagmar Oette of Sandoz, and Steven Clark and his colleagues at Genetics Institute who supplied the GM-CSF, Groopman gave the hormone to 16 AIDS patients, all of whom had low white cell counts as a consequence of their AIDS infection.

The study was designed to determine whether GM-CSF increases white cell counts in a dose-dependent manner and whether there is a maximum tolerated dose. The hormone does have dose-dependent effects, Groopman reports, and the maximum tolerated dose is so high that patients who receive this much hormone produce 50,000 white cells per microliter of blood, which results in "low grade flu-like symptoms," Groopman says.

Patients receiving lower doses of GM-CSF had white cells counts that increased to the normal range or above within 10 days of treatment. Most of these patients, according to Groopman, "had no significant side effects." The exception was two patients who had active infections with mycobacteria at the time. Their temperatures increased when they received the drug, possibly, Groopman said, "because their white cells were stimulated" to fight the infection. White cells, he noted, "release proteins that cause fevers."

The erythropoietin study also was designed to look for dose-dependent effects and to establish a maximum tolerated dose. The investigators gave erythropoietin to patients with kidney failure because the hormone is produced by the kidney. Patients with kidney failure typically lack this red blood cell–stimulating hormone and, as a consequence, are anemic.

Eschbach and his associates at the University of Washington reported dose dependency and found that there is a minimal dose above which all patients respond. Moreover, says John Adamson, one of the investigators, "we have not seen significant side effects of the hormone." It can be difficult to determine whether the patients are actually healthier, but the investigators presume that since the patients are making more red blood cells, they most likely benefited from erythropoietin. Adamson remarks, "we certainly think their health has improved. If you took testimonials from the patients themselves, I think you'd be impressed."

As a result of the University of Washington group's success, an expanded multicenter clinical trial of the hormone in dialysis patients is now under way and a similar study is going on in Europe. In addition, a study of erythropoietin in kidney patients who are not yet on dialysis will soon be starting.

Although the hematologic growth factors are only now generating excitement, they have been studied for years. The first clinical evidence of a substance like erythropoietin was reported more than 100 years ago when the French physician Denis Jourdanet noticed that patients who lived in the highlands of Mexico had thick blood, with an increased number of red blood cells. Around the turn of the century, researchers began

looking in earnest for some factor that stimulates the bone marrow to make red blood cells, but the data were inconsistent and confusing. In the 1950s investigators showed that a substance present in the plasma of animals can stimulate red blood cell production and in 1957 Leon Jacobson of the University of Chicago showed that the substance—erythropoietin—is produced by the kidney. Finally, in 1985, the erythropoietin gene was cloned by Fu-Kuen Lin of AMGEN and human recombinant erythropoietin is now produced by AMGEN and by Genetics Institute.

The history of the hormones that stimulate white blood cell production begins in the mid-1960s when Donald Metcalfe and his colleagues at the Walter and Eliza Hall Institute of Medical Research at the Royal Melbourne Hospital in Victoria, Australia, and Dov Pluznik and Leo Sachs of the Weitzmann Institute in Israel discovered that they could grow mouse bone marrow cells in a semi-solid agar gel.

Blood cells, it was recognized, grow from primitive precursors in the marrow called stem cells. As a stem cell divides and starts to differentiate, it can take any of several paths. One path will lead to its becoming a red blood cell, for example, whereas another path will lead to a granulocyte, a white blood cell that prevents bacterial infections from taking hold.

But the marrow cells only grew and differentiated in culture if "factors" from body fluids were added. These mysterious substances, known as colony-stimulating factors, were apparently present in such small quantities that hematologists had great difficulty purifying them, and some investigators questioned whether they existed at all.

"I remember the kinds of abuse those guys took," said Groopman. "It was a messy system and some people suggested the whole thing was one massive tissue culture artifact."

Eventually, a number of researchers, including Metcalfe and Golde succeeded in isolating the colony-stimulating factors and recently all four have been cloned by either AMGEN or Genetics Institute, or both. In addition to GM-CSF and G-CSF, interleukin-3 is also available. Each acts to stimulate a different step in the maturation of bone marrow cells. The earlier the stage at which a colony-stimulating factor acts, the greater the variety of cells it will induce.

GM-CSF stimulates the production of a number of white blood cells, including neutrophils and monocytes, which are white blood cells that kill microbes, including bacteria, mycobacteria, and viruses.

G-CSF stimulates a smaller collection of white cells, but it appears to specifically stimulate the growth of granulocytes. It also may induce the immature white cells that are characteristic of leukemia to differentiate and mature. Thus it may possibly be useful in treating patients with leukemia.

Interleukin-3 acts at the earliest stage of stem cell differentiation and is thought to stimulate the growth of all the cells that GM-CSF and G-CSF stimulate and to stimulate the production of T cells as well.

Although the studies of G-CSF in cancer patients, GM-CSF in AIDS patients, and erythropoietin in patients with kidney failure are preliminary and small in scale, other studies are under way and results should be in within 6 months. But the findings so far are certainly promising and indicate that the preclinical data from animal experiments may hold true in humans as well.

Now, at long last, says Golde, it looks very likely that hematologists will be able to truly control blood production—"the hematologists' holy grail," he calls it. And researchers, including Nathan, who have been working with hematologic growth factors for more than a decade are seeing hints that the hormones could have a potential beyond the investigators' wildest dreams. "It's a wonderful feeling," Nathan says. ■

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ADDITIONAL READING

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On the Benefits of Being Eaten

Experiments on a western mountain herb, scarlet gilia, show that its fitness is enhanced after being partially browsed

WHAT advantage—if any—do plants gain from being eaten by grazing or browsing animals? This question has been debated vigorously by ecologists for more than a decade, with no clear consensus emerging. "The most common view," say Ken Paige of the University of Utah and Thomas Whitham of Northern Arizona University, "is that herbivory is detrimental to plants and represents a selective pressure for the evolution of plant defenses." The opposing view, which Paige and Whitham favor, is that "plants can benefit by overcompensating, ultimately achieving greater fitness."

When Joy Belsky of Cornell University last year reviewed some 40 papers that are often cited in support of the grazing-advantage hypothesis she concluded the following: "Although herbivores may benefit certain plants by reducing competition or removing senescent tissue, no convincing evidence supports the theory that herbivory benefits grazed plants." In other words, there is no sound evidence that plants' fitness can be enhanced through being eaten. Now, however, Paige and Whitham present what they consider to be the first clear-cut data—from natural and experimental observations—that plants can be fitter as a consequence of being eaten.

"Our studies are unique," they say, "because they represent a closer approximation of true plant fitness in that seed quality and subsequent survival were examined." David Inouye of the University of Maryland is impressed, though not surprised, by the results. "It makes a lot of sense that plants would respond like this," he says. "In fact, I've collected similar, though less detailed, data at the Rocky Mountain Biological Laboratory in Colorado."

Paige and Whitham studied scarlet gilia, a red-flowered herb that grows in the western mountains, and showed that compared with uncropped plants, cropped plants not only sprout more in what is termed overcompensation, but ultimately also produce more seeds of high viability. This measure of potential future reproduction is crucial in comparisons of fitness.

There are many examples in nature of what is known as coevolution, in which a pair of organisms become evolutionarily modified in concert as a result of their interaction. The adaptations of certain insects and the flowers they pollinate provide multiple examples of coevolution, for example. And so it is sometimes for plants and the animals that eat them.