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. ■

GINA KOLATA

ADDITIONAL READING

J. Eschbach *et al.*, "Correction of the anemia of end-stage renal disease with recombinant human erythropoietin, *N. Engl. J. Med.*, **316**, 73 (1987).

K. Welte *et al.*, "Recombinant human G-CSF: Effects on hematopoiesis in normal and cyclophosphamide treated primates," *J. Exp. Med.*, in press.

A. Cohen *et al.*, "In vivo stimulation of granulopoiesis by recombinant human granulocyte colony stimulating factor," *Proc. Natl. Acad. Sci. U.S.A.*, in press

D. Golde and J. Gasson, "Myeloid growth factors," in *Inflammation: Basic Principles and Clinical Correlates*, J. I. Gallin, *et al.*, Eds. (Raven, New York, in press).

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."

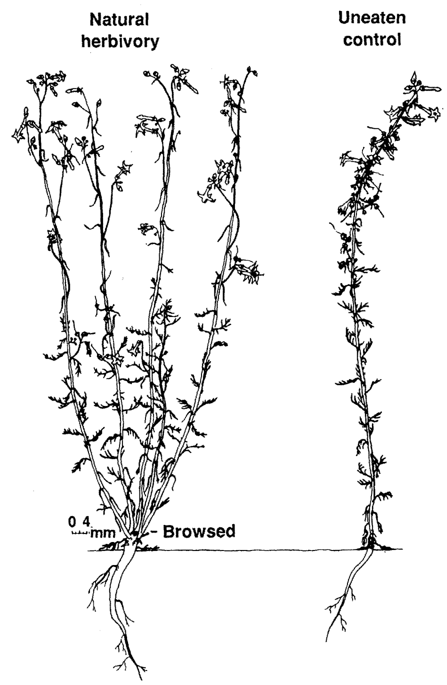
Paige and Whitham studied scarlet gilia, a red-flowered herb that grows in the western mountains, and showed that compared with uncropped plants, cropped plants not only sprout more in what is termed overcompensation, but ultimately also produce more seeds of high viability. This measure of potential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

The open grassland plains of the Old World are relatively recent in its natural history, having arisen somewhat haltingly over the past 15 million years or so. During the same time there evolved a range of grazing animals, the modern forms of which appeared within the past couple of million years. Part of the coevolution between grasses and grazers was the introduction of abrasive pieces of silica into the leaves and the development of bigger teeth equipped with thick enamel in the animals that ate the leaves.

This aspect of coevolution was a kind of arms race between grass and grazer, between defense and offense. A second consequence of the interaction, according to a proposal made a couple of years ago by Samuel McNaughton of Syracuse University, was a behavioral one for the grazers. He showed that the animals benefited if they ate in herds, because plants cropped in this systematic way, rather than by a scatter of lone animals, tended to be more productive, yielding about twice the normal biomass. The question addressed by Paige and Whitham was, do the plants benefit too, not just in increased biomass but in Darwinian fitness? Do grazed plants have the potential for leaving more offspring than ungrazed plants?

In preliminary observations on scarlet gilia in two locations in Arizona, Paige and Whitham noted that almost three-quarters of all plants were fed upon by their natural grazers—mule deer and elk—at some point during the flowering season, the immediate result of which was the loss of 95% of the plant above ground. Once cropped, the stub of the original single stalk rapidly regrows four replacements (see diagram), which bear 2.76 times as many flowers and 3.05 as many fruits as unbrowsed plants. This field observation led Paige and Whitham to suspect that "mammalian herbivory plays a beneficial role in the survival and reproductive success of scarlet gilia."



Consequence of being eaten. *Once cropped—either naturally or experimentally—the single stalk of scarlet gilia rapidly regrows four replacements, ultimately producing almost three times as many viable offspring as uncropped plants.*

The notion had to be tested experimentally, which was done by taking 40 plants into the laboratory and artificially cropping half of them. The result was that although experimentally cropped plants produced on average fewer flowers than naturally browsed plants, there were still 1.86 as many as on uncropped plants. The number of fruits produced, however, were rather similar for the naturally and experimentally cropped plants. Cropping therefore does seem to benefit scarlet gilia.

There are, however, many examples of plant growth increase following cropping, which is nevertheless accompanied by the production of poorer quality seeds. For instance, when Fraser fir is cropped naturally the weight of its seeds declines 39% and germination rate drops 43%. In the case of scarlet gilia, by contrast, neither seed weight nor germination success suffered from cropping. And once germinated, the seedlings derived from cropped plants thrived as well as those from noncropped plants. Paige and Whitham were therefore able to conclude that "Cumulative estimates of plant performance demonstrate that browsed plants achieve a 2.4-fold increase in relative fitness over uneaten control plants."

The mechanisms by which growth of cropped scarlet gilia is stimulated are still unclear, but Paige and Whitham say they can eliminate two popular proposals. The first is that overcompensation in above-ground growth is at the expense of root structure. In this case, however, cropping also enhances root growth, producing roots twice as big as in uncropped plants. The second idea is that saliva from the browsing animal acts as a form of growth-stimulating hormone. The fact that natural and experimental cropping produced similar growth promotion rules this out as being important in scarlet gilia.

Paige and Whitham's results do seem to imply an evolutionary response by scarlet gilia to herbivory. Although the plant does not absolutely depend on being cropped in order to reproduce—as has occasionally happened in some coevolutionary pairs—its fitness is apparently enhanced through being eaten.

The Northern Arizona and Utah researchers do not yet know how common a phenomenon this might be among cropped plants. According to Inouye, "it is likely to be common enough to make it worthwhile looking for in other species." Paige and Whitham urge that investigations with other plants must include analysis of seed quality so that fitness, not just the immediate growth response to being eaten, can be truly measured. ■ ROGER LEWIN

The eaters and the eaten: *An evolutionary interaction has occurred between many plants and herbivores that eat them. Whether plants actually benefit from herbivory has long been debated by ecologists.*

ADDITIONAL READING

A. J. Belsky, "Does herbivory benefit plants?" *Am. Nat.* **127**, 870 (1986).
K. N. Paige and T. G. Whitham, "Overcompensation in response to mammalian herbivory," *Am. Nat.* **129**, 407 (1987).