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The promise of growth factors

Compounds that stimulate the growth of red and white blood cells may help in the war on cancer and AIDS.

One area which holds out the possibility of contributing to mankind's war against cancer and AIDS is the increasing knowledge of a group of substances known as hematopoietic growth factors. As the name implies, these compounds stimulate hematopoiesis, the technical term for the growth of red and white blood cells in the bone marrow, and occasionally in other locations.

In the April 7 issue of the *New England Journal of Medicine*, a group of researchers from the Duke University Medical Center in Durham, North Carolina reported on the use of one of these growth factors in the treatment of cancer patients on high-dose chemotherapy. The compound in question, known as Recombinant Human Granulocyte-Macrophage Colony Stimulating Factor (rHuGM-CSF), was given to cancer patients who had received transfusions of their own bone marrow after high-dose chemotherapy for their cancers.

Autologous bone marrow transplantation is a technique in which a patient's bone marrow is removed and preserved by freezing, and then the marrow cells are reinfused into the patient. The purpose is to allow the use of high doses of cancer chemotherapy and then to replace the bone marrow which otherwise would have been destroyed by the chemotherapy. The problem is that it takes a certain amount of time for the graft to produce enough white blood cells to control infection. As a result, many of these patients may have their tumor eradicated by the chemotherapy and then succumb to an infection.

The Duke study demonstrated that the use of rHuGM-CSF can speed up the production of two types of white blood cells, known as granulocytes and macrophages, which are important in fighting bacterial and fungal infections. The importance of accelerating production of these cells is underscored by the fact that morbidity and mortality are especially high during the three-week period required for the bone marrow graft to "take" and replenish the supply of white blood cells.

One unexpected finding was that patients receiving rHuGM-CSF had lower levels of toxic damage to the liver and kidneys than control patients. The most common cause of early death and disability among patients on high-dose chemotherapy is multiple organ failure, which frequently starts off as malfunction of the liver and kidneys. It is thought that this multiple organ failure is caused by bacteria circulating in the bloodstream, and the early recovery of white blood cell production may prevent this. In the Duke study patients receiving rHuGM-CSF had half the incidence of bacteremia (bacteria circulating in the bloodstream) of control patients.

In a previous study, researchers at Harvard Medical School used rHuGM-CSF in AIDS patients with leukopenia (decreased numbers of white blood cells) and were able to increase granulocytes and monocytes. Whether this will actually be beneficial to AIDS patients remains to be seen, since their major problems relate to a lack of T-lymphocytes, a cell type which is not stimulated by rHuGM-CSF. Also, the cell types which are increased, especially monocytes, may act as a reservoir for the HIV virus.

GM-CSF is one of a number of blood cell growth factors which have recently been identified and produced in large quantity by genetic engineering. Only the first of these compounds, known as erythropoietin, appears to act like a hormone in the sense that it is produced by one organ, the kidney, in response to a lack of oxygen, and exerts a general effect on the bone marrow to increase the supply of red blood cells.

The white blood cell growth factors, such as GM-CSF and the interleukins, are produced by the white blood cells themselves or by other cells such as those which line the blood vessels. These cells are distributed throughout the body, as opposed to forming a discrete organ such as the lung or the kidney. The growth factors' effect appears to be affected by local supporting tissues.

The mechanism by which overall coordination of the activities of the different growth factors takes place is unknown. It is postulated that the production of blood cells results from the integrated output of countless randomly occurring interactions between blood-cell producing cells and their local environments.

If the foregoing sounds like the invisible hand of Adam Smith's "free market," or a contemporary sociology textbook, it is not surprising. The weakness of today's biological science does not lie in its ability to discover and produce interesting biologically active compounds, such as the blood cell growth factors, but in grasping the lawful interactions of the life process mediated through these molecules. This lack of understanding poses the ultimate limitation to fully exploiting the early promising results in clinical trials of blood cell growth factors.