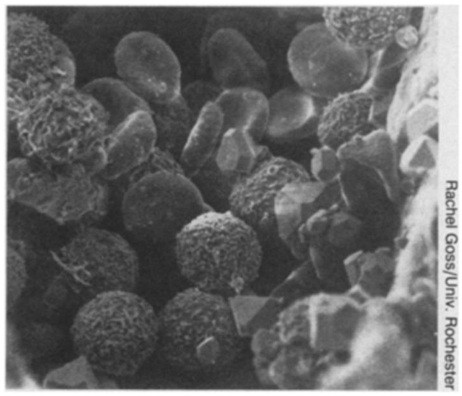
Bioreactor yields marrow-like cell mixture



Red (disk-shaped) and white (spheroidal) blood cells grow in bioreactor.

In the soft, gelatinous cores of breast, rib, arm, and leg bones toil the body's blood-producing factories. There, primitive stem cells divide, mature, and transform into a varied cast of cells that can clot, carry oxygen, and defend against foreign invaders. Researchers recently isolated the mysterious human stem cell (SN: 11/9/91, p.292), and they now hope to harness its blood-cell-building power.

A new report suggests that the secret of stem cell differentiation lies in the shape of its surroundings. Using a three-dimensional "bioreactor" for culturing bone marrow tissue, J.H. David Wu and his colleagues at the University of Rochester (N.Y.) have shown that they can produce almost all of the stages and subtypes of human blood cells – a significant improvement over the commonly used two-dimensional flask culture system, which produces only two cell types.

"This kind of culture is a better model of what goes on inside the body," says Wu, who described his team's work this week at a meeting of the American Chemical Society in Denver. Wu hypothesizes that bone marrow contains a rich variety of biochemical niches that coax stem cells to develop into diverse cell types. The bioreactor's three-dimensional scaffold creates a similar environment, making possible extensive cell-to-cell contact and exposure to growth factors.

Researchers hope someday to grow substantial quantities of bone marrow in laboratory bioreactors in order to boost the availability of the tissue for transplantation into patients with leukemia and other cancers and to reduce the need for donors, who at present must be anesthetized while a quart of marrow is removed by aspiration. Efficient bioreactors could also enable researchers to culture genetically engineered blood cells for transfusion back into patients with hereditary blood diseases.

To make a bioreactor that mimics the porous environment of real bone marrow, Wu's group packed a small plastic shell with several milliliters of spongy material such as animal collagen, a protein abundant in marrow. They inoculated the reactor with cells from whole human bone marrow. An automated "circulatory" system bathed the contents with a flow of nutrients and oxygen and removed the lactic acid and other waste products produced.

The reactor generated nearly all of the cells found in natural marrow, including red blood cells, megakaryocytes (which form platelets), and white blood cells such as lymphocytes, macrophages, and all three types of granulocytes, Wu says. The two-dimensional flask culture system produces only macrophages and one type of granulocyte.

"This is an important and interesting development," comments Ian Ponting, a stem cell biologist at Amgen, Inc., in Thousand Oaks, Calif. Now the race is on to build a commercial bone marrow bioreactor. Bernhard Palsson of the University of Michigan in Ann Arbor predicts that companies investigating such a bioreactor will develop a superior matrix that allows for easy harvesting of the blood cells.

Says Wu, "Our reactor is not very fancy and could have many different designs as long as the three-dimensional design is preserved, which appears to be the key."

– K.F. Schmidt

Wrapping carbon into superstrong tubes

What could one do with an ultrastrong tube only a few nanometers wide but hundreds of kilometers long? In his 1978 novel *The Fountains of Paradise,* Arthur C. Clarke imagined using such "hyperfilaments" to construct an elevator to a tethered space station in synchronous orbit around Earth.

Although Clarke's space elevator remains firmly embedded in the realm of science fiction, his notion of fabricating extremely tough, microscopically thin, flawless fibers from carbon gained credibility with the discovery that sheets of carbon atoms can wrap themselves into microscopic tubes (SN: 11/16/91, p.310). Produced in a high-voltage electric arc, the resulting nanotubes appear to have perfectly formed structures, consisting of networks of carbon atoms arranged in a hexagonal pattern.

"This is a new kind of crystal," says chemist Richard E. Smalley of Rice University in Houston. If it were possible to manufacture such tubes in meter lengths, "they would be the strongest fibers that we could ever make from anything."

Nanotubes normally form as a thick black deposit on the end of a carbon electrode. Close examination of this deposit reveals a fibrous interior and a hard outer shell of fused carbon.

The entire structure seems organized as a hierarchy of tubes, says Thomas W. Ebbesen of the NEC Fundamental Research Laboratories in Tsukuba, Japan. The visible fibers consist of bundles, which themselves consist of smaller bundles, and so on, down to the carbon nanotubes. Each nanotube, in turn, typically consists of two or more tubules nested within one another to form a layered assemblage. These multilayered tubes range from 1 to 20 nanometers wide and up to 3 microns long.

Smalley and his co-workers have now taken a tentative step toward growing such tubes as continuous fibers. Basing their approach on the assumption that high electric fields are largely responsible for keeping nanotubes growing in an orderly fashion, the researchers create a high voltage between a carbon electrode and a sharp, needle-like electrode. Then they introduce benzene vapor, or some other hydrocarbon, into the narrow gap between the electrodes.

Using a laser to heat the hydrocarbon molecules and gradually increasing the separation between the electrodes, the researchers create a carbon fiber just 50 nanometers wide and up to a centimeter long. The product, however, lacks the perfection of true nanotubes. Smaller structures branch off from the main fiber at various places along its length. Only tiny portions actually appear tubular.

"We're beginning, but it's still very crude," Smalley says. "It's not the fullerene fiber of our dreams."

The presence of hydrogen from the hydrocarbons may account for some of the defects, but there's no guarantee that this particular approach will ultimately lead anywhere, Smalley admits. He described this work at last week's American Physical Society meeting, held in Seattle.

Meanwhile, Ebbesen and his colleagues are exploring ways of stuffing carbon nanotubes with metal atoms to create microscopically thin wires. In earlier work, NEC researchers had managed to introduce lead into nanotubes (SN: 1/30/93, p.69). Because nanotubes normally form with capped ends, lead atoms had somehow broken the seals and entered the tubes.

"We [now] know how to open nanotubes in large quantities in a very simple way," Ebbesen reports. That makes it possible to fill tubes with metals other than lead. *– I. Peterson*