Tumor angiogenesis factor: A Dr. Jekyll and Mr. Hyde

A chemical that is deadly to the human body under certain conditions also seems to be its salvation under others, new research from England suggests.

It is a small molecule of yet undetermined chemical composition called tumor angiogenesis factor. Past research has shown that tumors make the molecule, and that it then entices blood vessels in the body to grow into the tumors—an action that nourishes them and allows them to ultimately kill the patient (SN: 3/22/80, p. 189). And now research from S. Kumar of Christie Hospital in Manchester, England, and colleagues suggests that hearts that have experienced heart attacks also make the factor. As in tumors, the factor induces new blood vessels to form, helping the damaged hearts to recover.

This finding was published in the Aug. 13 LANCET. Judah Folkman of Harvard Medical School in Boston and the discoverer of tumor angiogenesis factor told SCIENCE NEWS that he considers it "very exciting and important." Says Robert Langer of the Massachusetts Institute of Technology in Cambridge, who is studying a cartilage inhibitor of the factor: "I think it's an interesting and thorough piece of work." Adds Gerard Lutty of the Johns Hopkins Medical Institutions in Baltimore, who has been studying an inhibitor of the factor found in the eye: "It is very interesting and makes perfect sense" since infarcted hearts are well known to be repaired by the ingrowth of new blood vessels.

Kumar and his co-workers took tissue samples from eight human hearts that had experienced heart attacks (obstruction of blood to the heart, leading to death of tissue). They placed the samples in chromatography columns containing antibodies to tumor angiogenesis factor. Samples from five of the eight hearts contained material that bound to the antibodies, implying that it was tumor angiogenesis factor. (The reason samples from only five of the eight hearts contained the purported factor, the researchers suspect, was because the five had been infarcted long enough to start making the factor, whereas the remaining three had only been infarcted for a few hours at most.)

The investigators then took the material that seemed to be tumor angiogenesis factor and placed it in chicken egg tissue. Indeed, it made new blood vessels form and the vessels grew toward it, just as tumor angiogenesis factor does in the same system. Further, the material was found to weigh about the same as tumor angiogenesis factor. Finally, tissue from human hearts that had not experienced attacks was found to *not* make the purported factor, further bolstering the case that infarcted hearts make the factor, because they, and not healthy hearts, need new blood vessels to survive.

Thus, "human myocardial infarcts contain angiogenesis activity which is indistinguishable from tumor-associated angiogenesis factor," the investigators conclude. They also believe that their discovery might eventually benefit heart attack patients. If new blood vessels could be artificially stimulated to form in an infarcted heart (beyond those already stimulated there naturally), it might further a patient's chance of survival. And new blood vessel formation might be artificially stimulated by injection of heart-attack angiogenesis factor (alias tumor angiogenesis factor) into the patient's infarcted heart. The local delivery of drugs to an infarcted heart is already technically feasible. Before such strategy can be tested, though, the researchers point out, the cells that make the heart-attack angiogenesis factor have to be identified and the factor's chemistry resolved.

Meanwhile, the plot surrounding tumor angiogenesis factor made by tumors seems to be thickening rather than being solved. Lutty says that he and his colleagues still haven't purified the eye chemical that inhibits tumor angiogenesis factor, although they are sure that it's a large protein. Nor has the cartilage inhibitor of the factor been purified, Langer says, because "the assays are very cumbersome and make progress slow." And then Folkman and co-workers reported in the Aug. 19 SCIENCE that they have found still another inhibitor of the factor — the blood-thinning drug heparin combined with the steroid hormone cortisone.

This report, Lutty admits, "threw me for a loop. It's such a different thing from what they've been looking for and what we've been looking at. I really don't know what to say about it." —*J. A. Treichel*

Probing an elementary hydrogen reaction

The simplest known chemical reaction — the reaction of a hydrogen atom with a hydrogen molecule — seems almost too trivial to study, but powerful laser techniques are beginning to unveil intimate details about the reaction. These new data are sending theorists back to their computers to do calculations that they've hitherto neglected because they did not expect that chemists would ever succeed in providing an experimental check on their predictions.

At the American Chemical Society annual meeting, held last week in Washington, D.C., Richard N. Zare of Stanford University reported, "We finally can actually look, one collision at a time, at this simplest reaction...measure all the quantities ... and then compare them against theory."

Zare and his team are studying the reaction of a hydrogen atom, H, with a deuterium molecule, D_2. (Deuterium, a hydrogen atom with an extra neutron, is used so that the product, DH, can be distinguished from the starting material, D_2.) A powerful laser breaks up hydrogen iodide gas molecules to produce the needed "fast" hydrogen atoms. These atoms have enough energy to collide and react with the deuterium molecules.

After a delay just long enough for the chemical reaction to occur, a second, finely tuned, intense laser beam pumps ultraviolet light into the mixture so that individual molecules receive energy from three photons simultaneously. As a result, electrons are knocked out of the molecules. A mass spectrometer separates unreacted, ionized deuterium molecules from the ionized product, DH. The researchers then derive a spectrum of energies representing rotations and vibrations of the product molecules. This spectrum lies in an energy range that was not accessible to experimenters before.

Zare says the key step was finding that hydrogen molecules could be ionized by the simultaneous absorption of several photons. The "off-the-shelf," commercial equipment required is simple enough that any reasonably equipped laboratory can conduct similar studies, he notes.

Zare sees "years and years of work" ahead in exploring this simple chemical reaction. Questions to be answered from the study of the molecular motions as revealed by the spectra include the nature of the forces that govern the making and breaking of chemical bonds and the effect on the reaction of the angle at which atoms collide with molecules. Spectral data also provide estimates of how much molecules "bend."

"What we'll learn ultimately is what theoretical approximations we can get away with," says Zare, "because chemists aren't going to measure everything, despite what they say." The mathematical equations that represent even this simple hydrogen reaction are too complicated to solve exactly, and theorists have had to make approximations to come up with their answers. "We're going to develop the knowledge so that we have a base to draw upon to understand more complex processes," says Zare.

So far, Zare's results, and data from a group at the Los Alamos National Laboratory in New Mexico that is using a more complicated laser method, show close agreement with trends indicated by earlier theoretical calculations. "Whether they'll come together in detail, we have to wait to see," says Zare. Several groups of theorists are already at work computing the values needed for comparison with the preliminary experimental results. —*I. Peterson*