# Stop that clot: Proteins uncovered

Two proteins with previously unknown roles in the complex series of chemical reactions that result in blood clotting are slowly revealing their workings to researchers. Deficiencies in these proteins have now been found to cause excess clotting, and further work with them may result in a way to prevent blood clots where they're not wanted, Charles T. Esmon of the University of Oklahoma in Oklahoma City said at last week's American Heart Association Science Writers Forum in Monterey, Calif.

The body suffers minute internal rips and tears on a daily basis, and usually seals them up quietly with small clots. But in some people an out-of-kilter clotting mechanism forms clots that break off. A wandering clot can cause great pain if it lodges in a leg, and it can cause death if it lodges in the lung. Esmon and Oklahoma co-worker Philip C. Comp have identified a series of such patients—about 50 so far—who are deficient in one of the two recently identified proteins, called protein C. And they have described another six people whose blood also clots too readily with a deficiency in a necessary cofactor of protein C called protein S.

Discovery of the functions of proteins C and S by observing their activity in animal organs explains a curious but vital phenomenon: While blood in a test tube becomes a solid clot within a few minutes, injured people form only enough of a clot to squelch bleeding. The reason, it turns out, lies in a factor missing in the test tube —the blood vessel wall.

"When blood is in contact with the blood vessel, part of the emphasis to form a clot is switched off," explains Esmon. The circulatory system uses its own complicated feedback system to shut down a long sequence of events called the clotting cascade that is set off when a blood vessel wall breaks. The last step in the cascade, the final "on switch," is the protein thrombin. And while thrombin causes clotting, it also flips on a second cascade that halts the process.

"Thrombin has a role in clotting but also serves as an anticoagulant," Esmon explains. It activates thrombomodulin, a protein on the blood vessel wall that turns on protein C, which, with the help of protein S, then shuts off clotting by interfering with previous steps in the process. Since without the blood vessel-linked thrombomodulin there is primarily *inactive* protein C in the test tube, that blood continues to clot unfettered, whereas it would be halted in the body.

Esmon isn't willing to predict how many unexplained cases of thrombosis are due to a deficiency in protein C or protein S, but he believes that the problem is "not uncommon." Blood drawn from healthy individuals contains no thrombomodulin and thus little or no activated protein C, making it appear no different from deficient blood. But knowing how the system works, the researchers can now test for the inactive form and thus identify people with anomalies.

Understanding the two proteins may have implications for people with normal levels of the substances as well. The tendency to "throw" blood clots is a common and occasionally fatal postsurgical problem, and the blood-thinning methods currently used to prevent it carry the threat of excessive bleeding. The clotting tendency may be due to the average reduction in protein C to 60 percent of normal, a level similar to that in people with disease-related deficiencies. As a result of surgery the protein may be used up faster than it is produced, or surgery may slow synthesis of the molecule. Whatever the cause, providing protein C postoperatively may safely prevent clot formation, Esmon says.

The gene for the protein has recently been cloned via genetic engineering, a feat that should speed up research. As for therapy, Esmon and Comp are working out a way to provide protein C to deficient patients; they expect to report on its use within three years. If all works out, Esmon says, "it may eventually provide a unique and much more specific approach to controlling coagulation." But, he says, given human-activated protein C's failure to dissolve clots in monkeys, the protein holds more promise as a clot preventer than as a clot buster. —*J. Silberner*

# IRAS satellite to be 'revived' for tests

The Infrared Astronomy Satellite (IRAS), which in 1983 performed the first survey of infrared sources across the entire sky before finally running out of its vital cooling fluid, is taking on a new job. It will make no more astronomical observations—loss of the cryogenic coolant that enabled its detectors to record faint heat emissions from stars, comets and even possible planetary systems in formation has left it effectively blind. Beginning in March, however, its still-operating computer and other systems are to be used in tests of several backup operating methods that might benefit future satellites but were never needed by the successful IRAS.

Soon after IRAS's launching on Jan. 25, 1983, for example, its controllers found that its fine-pointing sun sensor (which helped it maintain its orientation in space) was sending out spurious signals that the computer would interpret as evidence that the satellite was pointing in the wrong direction. Two such "glitches" per second could — and repeatedly did — cause the computer to switch over automatically from its programmable memory to a preprogrammed section containing safety instructions, but they would also render the changing astronomical observations impossible. The sensor was locating the sun correctly, but the glitches kept causing the memory switchover, and IRAS engineers worked around the problem by simply restocking the programmable part of the memory with instructions to ignore any such glitches that did not appear in a consecutive string of six or more.

Also helping the satellite hold its position, however, was a sensor that tracked the position of the earth's limb, or horizon, and which never necessitated any such problem solving. In the upcoming tests, the engineers will evaluate an automatic backup system that should come into play whenever the horizon sensor goes awry: IRAS carries a magnetometer that monitors the earth's magnetic field, including its direction, and the goal is to check out an algorithm in the computer that can automatically feed the magnetometer's directional measurements into the satellite's positioning system if the horizon sensor becomes unreliable.

The test series has been instigated by the European Space Agency (ESA), which was not responsible for IRAS but which is seeking experience in operating reprogrammable satellites such as its own planned Infrared Space Observatory. For the tests, ESA has contracted with Fokker B.V. in the Netherlands (IRAS's builder), the Dutch National Aerospace Laboratory (which wrote its computer software) and Britain's Rutherford Appleton Laboratory (which controls it from the ground).

In another malfunction that never actually appeared during IRAS's main mission, a "serious software failure," or programming error, will be deliberately loaded into the programmable memory so that the satellite starts to tumble. If the built-in safety provisions work as they are supposed to, the other ("read-only") memory will take over automatically to bring the craft to a safe orientation.

The other test in the series is more for use when everything is going right. To protect the mission against the possibility that IRAS's whole main computer might malfunction, it was provided with a spare, complete with programmable and read-only memories of its own. The test is merely to link electronically the programmable memories of both computers, producing twice the capacity for data storage and long sequences of computer commands.

IRAS ran out of coolant on Nov. 22, 1983, and for a while there was thought of resupplying it via the space shuttle. The idea was scrubbed largely because of cost, says U.S. IRAS project manager Gael Squibb of Jet Propulsion Laboratory in Pasadena, Calif., since the mission's all-sky survey was done, and selected targets for restudy would be better observed anyway by other facilities to come. —*J. Eberhart*



Science Service, Inc. is collaborating with JSTOR to digitize, preserve, and extend access to *Science News*. www.jstor.org