An Independent Approach to Science

Anachronistic style of research leads to possible blood test for multiple sclerosis

A provocative article describing a blood test for multiple sclerosis (MS) appears in this month's issue of the *Journal of Laboratory and Clinical Medicine*. The article is by John Angers and nine others. No institutional affiliation is given. Their only address is "New York, N.Y."

John Angers is a physician in private practice who does research on the side. He receives no government funds or large grants. His research is supported in part out of his own pocket and in part by donations that patients and friends make to the Human Immunology Foundation, which he runs. The co-authors on his paper include his wife, an English major who Angers says is a "frustrated doctor." They also include several students at nearby New York universities as well as an M.D.-Ph.D. researcher who recently emigrated from Leningrad. Angers' discovery of what may prove to be an important diagnostic aid and clue to the etiology of MS is a story of how original results may still come from a style of research that seems anachronistic in this day of "big" science, with its institution-affiliated laboratories supported by large grants.

Angers has two small laboratories, one at his office and one that was added onto his home through the support of a grateful MS patient. He says he spends five evenings a week and one day of each weekend doing research. His funds are limited, but so far he has not needed much money for his research. Last year, Angers spent $35,000 of his own money and $50,000 that was donated to his foundation. He has not applied for a grant because he realizes that a person working alone with no past history of significant results is unlikely to be given funds. William Reynolds of the Multiple Sclerosis Society agrees. "We don't fund fishing expeditions," he explains. Now that Angers does have promising results, he plans to apply for grants.

Those who know Angers respect him and say he is not a crank. Jack Dean, who is a cancer immunologist at Litton Bionetics in Bethesda, Maryland, admits to having been taken aback when he first met Angers and learned that "he was more or less doing research in his garage." But now he is convinced that "Angers is a unique guy. He seems very, very bright and has a lot of good ideas." James McCoy, a cancer immunologist at the National Cancer Institute, says that "Angers is very dedicated and his work looks sound."

Now that Angers' work has been published in a respected journal it gains credence. One of the referees of his paper, who prefers to remain anonymous, describes the paper as "a very interesting report, a highly original finding." Dale McFarlin of the National Institute of Neurological and Communicative Disorders and Stroke, who saw a preprint of the paper, plans to invite Angers to give a talk at the National Institutes of Health and hopes to send him some coded specimens of blood to verify the accuracy of his test. Both the anonymous referee and McFarlin caution, however, that there have been other blood tests for MS that looked promising but fell by the wayside. They feel it is important that others now try to confirm Angers' work.

Angers' test is similar to other proposed blood tests for MS in that it is phenomenological, not quantitative like a radioimmunoassy. But Angers' test is also different from previous tests, which generally were designed to detect putative antibodies that reacted with brain tissue or viruses. His test, in contrast, detects white blood cells with altered properties in the blood of MS patients. These white cells have presumably been sensitized to a substance present in the blood of these patients. Angers found that when an MS patient's white blood cells are exposed to an extract from blood of other MS patients, the white cells lose their ability to adhere to glass. The white cells of patients without MS, some of whom have other neurological disorders or cancer, do not exhibit this effect. Angers reports that the test was positive for 53 of 58 MS patients but for only 3 of 75 control patients. Moreover, one of the controls in whom the test was positive developed MS the following year.

The sort of test Angers uses was first developed in 1972 by William Holliday and Elizabeth Miller of the University of Queensland in Brisbane, Australia. They observed that the proportion of white blood cells that normally adheres to glass decreases substantially if the cells are exposed to a substance to which they have been immunologically sensitized. It is very common for all sorts of cells to adhere to glass or other surfaces. In fact, tissue cultures are carpets of cells adhering to plates. Thus what is suprising is that sensitized white blood cells lose this property when exposed to antigens.

The reasons for altered white cell properties, explains Arnold Powell of Case Western Reserve University, are still poorly understood. But the test seems to be specific for cell-mediated immunity and is currently of great interest to cancer researchers. Powell, Dean, and McCoy point out that the test has diagnostic potential for some kinds of cancers, as demonstrated by double-blind studies. McCoy adds, "Many people think that the test has more promise than any other cancer assay."

If Angers' results can be confirmed, it will mean that doctors who see young patients with various symptoms suggestive of MS—such as blurred vision, limps, or unexplained aches—will be able to determine whether they have the disease. Some of these patients, Angers says, are now sent to psychiatrists by doctors who do not suspect MS.

The results might also provide important clues to the etiology of MS. Angers says his results indicate that the blood of MS patients contains a substance that acts like an antigen, which is consistent with the hypothesis that MS is an immunological disease. The next step is to isolate this substance. "We get so few clues in MS that none can be ignored," says the referee of Angers' paper.

Angers decided to try the test on MS patients because he was familiar with the work with cancer patients and because of the hypothesis that MS is related to an immunological disorder. His primary interest has been in cancer immunology; he has relatively few MS patients, most of whom came to him because they were anxious to be treated with immunological techniques.

Angers is first and foremost concerned with treating patients. After being trained as a physician at McGill University, he did research on Hodgkin's disease for 8 years at St. Vincent's Hospital in New York and spent 1 year as a fellow in oncology at Sloan-Kettering Memorial Hospital. Then he went into private practice in cancer chemotherapy. He later began specializing in immunotherapy,

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all the while keeping up with the literature on cancer treatments, he says.

Arthur Levy of St. Vincent's Hospital worked with Angers when he was there and still is a close friend. He says Angers "has a huge drive to do good. He tries every tack available, often jumping ahead of investigators to try new methods on his patients. And he has the kind of patients who want that type of treatment."

Despite his independent style of research, Angers is not an Arrowsmith doing work in complete isolation. He regularly attends scientific meetings (at his own expense) and gets to know other researchers, whom he then calls upon for advice and exchange of ideas. But what is remarkable is that by investigating in his own way things that he thinks are important, he has produced results that may make the established research community sit up and take notice.

—GINA BARI KOLATA

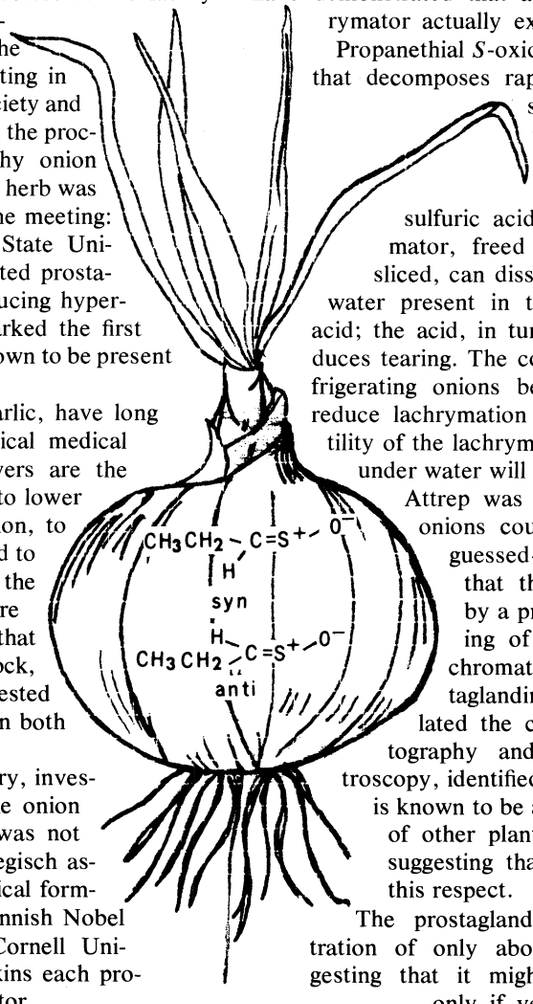
It's Nothing to Cry About . . .

The tears live in an onion that should water this sorrow.
—WM. SHAKESPEARE, Anthony and Cleopatra

It's nothing to cry about, says Eric Block of the University of Missouri at St. Louis, but previous investigators have assigned the wrong structure to the lachrymating agent in onions. Block presented the correct structure for the lachrymator at the recent joint meeting in Hawaii of the American Chemical Society and the Chemical Society of Japan and, in the process, offered an explanation for why onion fumes make one weep. The aromatic herb was also the focus of another paper at the meeting: Moses Attrep, Jr., of East Texas State University announced that he had isolated prostaglandin A_1, which is capable of reducing hypertension, from onions. His work marked the first time that a prostaglandin has been shown to be present in a plant.

Onions, and their close cousin garlic, have long been reputed to have almost mystical medical powers. Among those alleged powers are the ability to stimulate bile production, to lower blood sugar, to alleviate hypertension, to speed healing of gunshot wounds, and to cure scorpion bites, freckles, and the common cold. Both investigators were searching for chemicals in onions that might cause these reputed effects. Block, furthermore, is particularly interested in sulfur compounds and their role in both medicine and air pollution.

As long ago as the late 19th century, investigators had shown that oil from the onion (*Allium cepa*) is rich in sulfur. It was not until 1956, however, that W. D. Niegisch assigned to the lachrymator the empirical formula C_3H_6SO. In the early 1960's, Finnish Nobel laureate Arturo I. Virtanen and Cornell University graduate student W. F. Wilkins each proposed a structure for the lachrymator. The Nobelist's structure proved to be the wrong one. In 1971, M. H. Brodnitz of International Flavors and Fragrances Inc. confirmed Wilkin's proposal that the lachrymator is propanethial *S*-oxide. This compound can exist in two conformations, depending on whether the ethyl and oxygen moieties are on the same side of the double bond linking the central carbon and sulfur atoms (*syn*) or on opposite sides (*anti*). With no evidence to guide them, Wilkins and Brodnitz guessed that the compound existed in the *anti* conformation in onions. They were wrong. Using microwave spectroscopy, Block and Robert Penn of the University of Missouri have demonstrated that about 95 percent of the lachrymator actually exists in the *syn* conformation.



Drawing by Holly Bishop

Propanethial *S*-oxide is a very volatile compound that decomposes rapidly; Block thus had to use special techniques to isolate it at low temperatures. When the compound is dissolved in water, it hydrolyzes to form sulfuric acid. Block suggests that lachrymator, freed when onions are peeled or sliced, can dissolve in the small quantities of water present in the eye and produce sulfuric acid; the acid, in turn, acts as an irritant that induces tearing. The common kitchen practice of refrigerating onions before peeling them can thus reduce lachrymation because it reduces the volatility of the lachrymator. Similarly, peeling onions under water will dissolve the agent.

Attrep was intrigued by the reports that onions could lower blood pressure and guessed—correctly, it now appears—that this effect might be produced by a prostaglandin. An initial screening of onion extracts by thin-layer chromatography suggested that prostaglandins might be present. He isolated the compound by further chromatography and, primarily by mass spectroscopy, identified it as prostaglandin A_1, which is known to be an antihypertensive. Screening of other plants showed no prostaglandins, suggesting that onions might be unique in this respect.

The prostaglandin is present at a concentration of only about 1 part per million, suggesting that it might have a therapeutic effect only if very large quantities of onions are consumed—a regimen that might have some unpleasant social effects of its own. The concentration is probably not an economic one either, despite the fact that such prostaglandins sell for about $10 per milligram. It thus seems likely that the discovery of the compound in onions will remain little more than a botanical oddity.—THOMAS H. MAUGH II

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