First Parvovirus Linked to Human Disease

Parvovirus B19 causes a shutdown of red blood cell production in children with sickle cell anemia and also a common infectious rash of childhood

Parvovirus B19, which was first discovered in human blood in 1975, has until recently been an etiology in search of a disease. Although surveys showed that human populations were widely exposed to the virus, it could not be associated with any specific condition until 1981 when it was linked to aplastic crises in patients with sickle cell anemia. The crisis results from the virtually complete shutdown of red blood cell production and causes an extremely severe, although transient, anemia in persons who are already anemic. The shutdown, investigators have now found, is caused by the parvovirus infecting and destroying immature red blood cells in the bone marrow. Within the past year, parvovirus B19 has also been shown to be the cause of erythema infectiosum, a common, but apparently innocuous, infectious rash of childhood.

The discovery of parvovirus B19 was serendipitous. It was found by Yvonne Cossart at the Central Public Health Laboratory in London in the mid-1970's during screening of donated blood for the hepatitis B virus.

During the next 5 years, there were occasional identifications of parvovirus B19 in patients with such nonspecific symptoms as fever; but the virus was not linked to any particular disease even though it appeared to be widespread. "It was shown to be a common infection in human populations, but we weren't able to associate it with human disease," says Philip Mortimer of the Central Public Health Laboratory.

In 1981, however, John Pattison and his colleagues at King's College Hospital Medical School, obtained the first epidemiological clue linking parvovirus B19 to aplastic crisis in sickle cell anemia. During the routine screening of serums of children between the ages of 2 and 15 years, they found the viral antigen in blood from a child who was suffering from such a crisis. Further work by the Pattison group alone and in conjunction with Graham Serjeant of the Medical Research Council Laboratories in Kingston, Jamaica, confirmed the strong link between evidence of parvovirus infection and aplastic crises.

During aplastic crisis, the hemoglobin content of the patient's blood may fall—becoming as low as 2 to 3 grams per 100 milliliters. Hemoglobin concentrations in individuals with sickle cell anemia usually range from about 8 to 10 grams per 100 milliliters, whereas the corresponding value for people who are not anemic is 12 to 15. Very few of the immature cells that develop into red blood cells can be found in the patient's blood or bone marrow during a crisis.

Parvoviruses generally have stringent requirements regarding the type of differentiated cells they can infect, says Peter Tattersall of Yale University School of Medicine. Moreover, they normally replicate only in cells that are actively dividing, probably because the viruses must depend on the dividing cell to provide them with the enzymes needed for replication.

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Parvovirus B19 infects immature red blood cells in the bone marrow. Neal Young, and his colleagues at the National Heart, Lung, and Blood Institute (NHLBI), Jeffrey Moore, Maria Harrison, and R. Keith Humphries, in collaboration with Mortimer, showed that blood serums that contain the virus inhibit the formation of red blood cell precursors by bone marrow cells in culture.

By tediously isolating individual colonies of immature red blood cell precursors and showing that parvovirus-containing serum inhibited the formation of more differentiated colonies, the Young group identified the late erythroid progenitor cell as the target of the virus. Eventually, using electron microscopy and an immunofluorescent staining technique, the investigators demonstrated the presence of the parvovirus in the target cells. The virus, by replicating in the cells, kills them and causes the plunge in the number of red cells in the blood.

Individuals who have one or another of the hemolytic anemias may be especially susceptible to the virus infection. Because their bone marrow must produce red cells at an accelerated rate to replace those that are lost prematurely it contains more of the rapidly dividing red cell precursors that are the viral targets. The investigators have linked parvovirus to aplastic crises in a number of hemolytic anemias in addition to sickle cell disease. These include hereditary spherocytosis, pyruvate kinase deficiency, and certain forms of thalassemia, although in the United States sickle cell anemia is by far the most common of the hemolytic anemias. According to NHLBI estimates, 50,000 to 60,000 blacks in this country have the disease.

Infection by parvovirus B19 apparently does not cause serious—or even noticeable—anemias in people who do not already have a hemolytic anemia. The duration of the infection is relatively short—perhaps a week to 10 days—because the virus elicits an active immune response that brings it under control. The half-life of red blood cells is usually 120 days and the temporary loss of their production is not a problem for normal individuals. But it is for patients with hemolytic anemias, such as sickle cell disease, in which the red cell half-life is only a few days. However, the severe anemia of aplastic crisis can be treated with transfusions until the patient regains the ability to produce red blood cells. Efforts to link the virus to the more prolonged, often fatal, aplastic anemias of unknown origin, have so far turned up no connection, according to Young and Mortimer.

Within the past year, Mary Anderson of the Pattison group, in collaboration with Mortimer and his colleagues, found that parvovirus B19 also causes erythema infectiosum, or fifth disease, the name given to it at the turn of the century because it was the fifth rash disease of childhood (after scarlet fever, rubeola, rubella, and epidemic pseudoscarlatina). In the spring of 1983, there was an out-

break of the disease, which is highly contagious and characterized by a flush-like rash on the cheeks, in two schools in North London. "We did find in that outbreak incontrovertible evidence that the [parvo]virus caused the disease," Mortimer says. Serums from 39 of the 41 patients tested had antibody against the virus, whereas those of people who had been in contact with the patients, but remained well, did not.

So far, no one has been able to grow parvovirus B19 in culture. The epidemiological and biochemical studies have had to be carried out with the small amounts of viral material isolated from blood. Nonetheless, Jesse Summers of the Institute for Cancer Research in Philadelphia, with Anderson, has characterized the viral DNA, showing, among other things, that it is about 5.5 kilobases long, the right length for the DNA of an independently replicating parvovirus.

Moreover, Tattersall, in collaboration with the group at the Central Public Health Laboratory, has cloned the viral DNA. The cloned DNA is about 5.3 kilobases in length and codes for four proteins. Its sequence, Tattersall says, is distantly related to those of the DNA's of the murine and porcine parvoviruses.

The cloning might make possible a vaccine against parvovirus infection, although this does not appear necessary, as fifth disease is apparently innocuous and aplastic crisis is readily treatable. According to Tattersall, the cloning should be most useful because it will make available the more abundant quantities of viral antigen that are needed for further epidemiological studies.

The parvoviruses that infect animals frequently cause severe birth defects if the infection occurs during pregnancy. So far, there is no evidence that parvovirus B19 does the same, although only very limited studies have been performed because of the lack of the viral antigen needed to screen for signs of infection. If parvovirus B19 should ever be linked to birth defects, then a vaccine would be warranted. The virus is widely spread. Its distribution is probably worldwide and, according to Mortimer's most recent data, about 60 percent of the blood donors in England have been infected at some time in their lives.

Moreover, Tattersall points out, it might be worthwhile to look for involvement of the virus in additional diseases thought to be of viral origin but for which no specific virus has been implicated. "The two diseases identified so far may be the tip of the iceberg," Tattersall says, "although the iceberg may be relatively small."—**JEAN L. MARX**

The Fine Points of Cloud Seeding

As part of a return to basics in the field of weather modification, chemists are taking a closer look at how ice forms around submicrometer particles, the first step toward wringing more precipitation from reluctant clouds. Seeding of clouds created in laboratory chambers is showing that processes on the smallest scales do not always work in the ways or at the rates that researchers had assumed. Although not yet confirmed in the field, the new information about old standby seeding agents like dry ice may eventually help to explain some past successes and failures.

The problem with some clouds is their tendency to hold back water they might release as rain or snow. The unused water is in the form of vapor or tiny cloud drops, a million of which would make one raindrop. Despite subzero temperatures, these cloud drops need not freeze, and they are too small to fall through the cloud. Some of them can be started on their way to becoming precipitation by natural ice-forming nuclei, usually micrometer-sized bits of clay that catalyze ice crystallization. A cloud drop can turn to ice about the clay nucleant and grow at the expense of water vapor evaporated from surrounding drops until the new ice crystal is heavy enough to fall. Still, there are often not enough natural ice-forming nuclei to go around.

Meteorologists' first solution was to toss dry ice into the cloud. That cooled some of the water vapor to below −40°C, where water must freeze with or without a nucleant. Chemists in a Colorado State University (CSU) group headed by William Finnegan have reexamined dry ice seeding in a laboratory cloud chamber and found it to be 10 to 50 times more effective than generally reported (*1*)—1 gram of it can create 5 trillion ice crystals at −10°C. The unsuspected efficiency of dry ice seeding could have been a problem for some past weather modification experiments, Finnegan speculates. If there are too many new ice crystals and not enough water drops left to feed them, the crystals will never grow large enough to fall.

The unexpected efficiency of another seeding agent may have aided two other experiments. Silver iodide and related compounds have become popular seeding agents because of the resemblance of their crystal structures to that of ice—they catalyze ice formation by providing an icelike template for the initiation of ice formation. The CSU group found that a 2:1 mixture of silver iodide and sodium iodide worked about as expected under normal cloud chamber conditions (*2*). But when the relative humidity slightly exceeded 100 percent, as can happen when natural clouds are forced over mountains, the rate at which water condensed onto the particles and froze soared by a factor of 30 and the number of ice particles per gram of nucleant increased about 100-fold. The same rate and efficiency increases could have played a role in the success of the experiments at Climax, Colorado, and in Israel, suggests Finnegan.

Another nucleant, silver iodide–silver chloride, may have been too slow for the good of the Florida Area Cumulus Experiment (FACE). The CSU group found that this nucleant, being less hygroscopic, must collide with a cloud drop rather than have water condense on it (*3*). This far slower collision process might have reduced the effectiveness of seeding during FACE, speculates Finnegan, where opportunities for effective seeding were brief. Feng DaXiong and Finnegan redesigned this nucleant by adding sodium chloride. That allowed direct condensation on the particles and accelerated the process by a factor of 10 or more.

So far, the significance of the mechanism and rate of reaction of submicrometer nucleants has only been demonstrated in the cloud chamber. Their roles in real clouds will remain speculative until their importance relative to the large natural variability of weather modification experiments can be determined. Most cloud physicists agree, however, that weather modification experimenters should no longer neglect even these smallest of details.—**RICHARD A. KERR**

References

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