LETTER FROM JERUSALEM

Drug against a virus

A pine-tree fungus appears to work against the smallpox virus

by Hadassah Gillon

Conventional wisdom holds the best, and perhaps the only, way to fight virus disease is prophylactically, with a vaccine. However, a corps of scientists recently united in defense of the proposition that antiviral drugs are a valid approach to virus diseases. They presented evidence that progress to date, if properly explored, could initiate an era of antiviral agents equal to the antibiotic age (SN: 8/23, p. 148).

At present, the list of known antivirals is short, though potential agents are under study. One, IUdR, fights the herpes virus that causes eye disease in man. Symmetrel attacks certain strains of Asian flu viruses. Marboran, licensed in Europe but not in the United States, aborts smallpox viruses and has been used successfully in India.

A fourth compound, already known for its antibiotic activity in experimental situations, is the focus of extensive research, particularly abroad and may be added to the antiviral list. Called rifampicin, it is a semi-synthetic chemical produced from a fungus that grows in the pine forests of southern France. Discovered 10 years ago by P. T. Margalith, it is manufactured by the Lepetit Co., in Milan, Italy.

In bacteria, this antibiotic destroys the microorganisms by inhibiting the synthesis of ribonucleic acid. This occurs because the chemical interacts directly with RNA polymerase, an enzyme essential to the process of translating genetic information from deoxyribonucleic acid to the RNA that will carry it to organelles in the cell. In culture, however, it appears to have no inhibitory effect on mammalian RNA, therefore causing no damage to host cells in the process of eliminating bacteria.

Researchers at the Hebrew University-Hadassah Medical School in Jerusalem report that rifampicin not only acts against bacteria but that it inhibits the replication of certain viruses as well. A group headed by Dr. E. R. Heller has found that the drug selectively blocks replication of vaccinia viruses in mouse cells. It also inhibits DNA viruses and some RNA viruses including cowpox and adenoviruses, but appears to be ineffective against other RNA viruses, including polio and influenza strains. Vaccinia, which causes smallpox, is an RNA virus—that is, a core of RNA enclosed in a protein coat that is shed when the virus infects a cell. The genetic material is the infecting agent.

"The mechanism of the inhibition of vaccinia replication is not known," Dr. Heller says. But there is evidence enough to allow for some speculation.

Vaccinia is known to spread directly from cell to cell rather than through culture medium, indicating that the probable site of rifampicin action is within the cell. If indeed it hits RNA polymerase activity, it is possible that viral and bacterial RNA polymerase are similar and that the mechanisms of antiviral action and that of antibacterial action are the same.

Experiments reported from scientists at the University of Glasgow in Scotland support and extend the work from Israel. Dr. J. H. Subak-Sharpe and coworkers have isolated mutant strains of vaccinia that are resistant to the inhibitory effects of rifampicin, suggesting again that RNA polymerase may be the drug's target. Their experiments show that rifampicin inhibits viral RNA from incorporating an essential chemical, uridine, and therefore blocks its replication. In the mutant, a single change in RNA polymerase would change its mode of chemical behavior. This could render the mutant strain immune to the action of the antibiotic, which is highly specific. If scientists can show that the mutant does in fact have a modified polymerase enzyme—in other words, a single gene-ordered variation in the amino acid sequence—the point will be proved.

Rifampicin is one of a large family of closely related compounds, many of which were also tested for antiviral activity. Rifazine, rifamycin SV and rifamide all proved totally ineffective in this regard, the Scottish researchers found, even when vaccinia viruses were hit with extremely high concentrations of drug.

One of them, rifamycin SV, actually killed host cells—rifampicin, itself, selectively affects only viruses—but this action may have been due to contamination rather than the rifamycin SV. However, they say, there is no reason to suspect that rifampicin is the only, or even most potent, of this family of compounds in the inhibition of virus replication. Others must still be tested.

The implications of these reports for therapeutic use of rifampicin against vaccinia or other viruses are encouraging, though untested. Further work will have to precede its use as an antibiotic as well because of findings from the Glasgow group. Even samples of the drug that are more than 99 percent pure contain contaminants that will have to be removed before clinical application is possible.