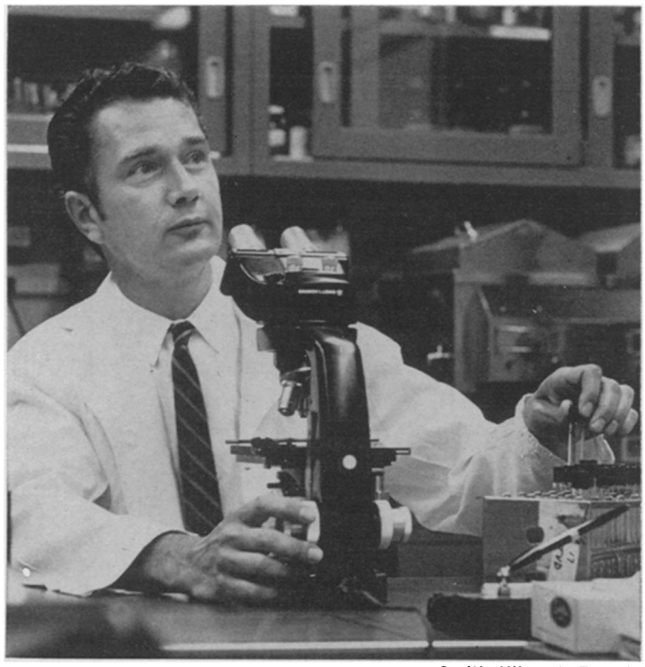
VIROLOGY

Mutiny over methods

A band of scientists call drugs the answer to diseases vaccines cannot prevent

by Barbara J. Culliton



Smith Kline & French

Dr. Boyle: Prospects for a common cold drug emerge.

Conventional wisdom holds that the best way to deal with a virus infection is not to get it, and that the best way to do that is to have a vaccine against it.

Those who hold this view in the civil war now stewing among virus researchers have in their favor:

- The initial premise that prevention is always preferable to a cure.
- An impressive history of success. Vaccinations have virtually obliterated smallpox, yellow fever, polio and measles, and are on the verge of dealing a death blow to rubella. By September, millions of doses of the newly licensed rubella vaccine will have been injected into schoolchildren (SN: 6/21, p. 597).
- The coffers of the United States Government. Indeed, much of the research that lead to the rubella vaccine was conducted in the laboratories of the National Institutes of Health in Bethesda, Md.
- A scientific idiom that says: A virus cannot reproduce without invading and usurping the genetic machinery of an infected cell—viruses have no such machinery of their own—so any agent that would kill a virus would inevitably kill the cell as well. Therefore, immunization by vaccine is the only answer.

Now, however, the vaccine men themselves have something going against them: a slowly organizing camp of rebels who contend, and who have demonstrated in principle at least, that antiviral drugs are as useful a route against viruses as vaccines and, in some cases, a better one. At an international meeting on antiviral substances, sponsored by the New York Academy of Sciences, the opposing factions gathered and, in the Starlight Roof of the Waldorf Astoria, bared their views with an openness uncommon among scientists who traditionally respectfully hide their criticism of colleagues from public scrutiny.

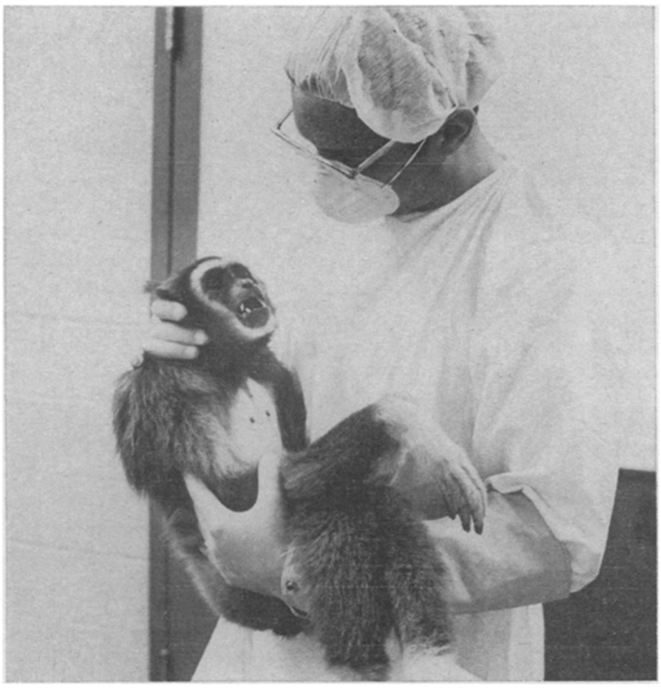
The emergence of three antiviral agents since 1960, it was contended, adequately defeats the argument that antiviral drugs are an impossibility. Experimental drugs now in the works appear to confirm this. Some, like vaccines, are prophylactic, preventing disease. Others may actually be therapeutic, curing them. "With a minimum of effort," Dr. Ernest Herrmann of the Mayo Clinic declares, "we could launch an era of antiviral drugs comparable to the antibiotic era, maybe more so.

"In 20 years of concentrated search for antibiotics, few more than a dozen compounds were found. The plethora of modern antibiotics essentially represents variations of a theme. In only nine years of far less rigorous effort, hundreds of potential antivirals have turned up from the laboratory screening. The question drug houses face—and most of the pioneering is in the drug industry—is which of the hundreds to pursue."

During the last 20 years, a number of compounds have been reported to block viral replication, but little came of such observations. That is probably because the antiviral effect really represented a toxic effect on all cells and did not seem worth pursuing. In 1960, however, techniques were devised for screening compounds in the laboratory for antiviral activity and care has been taken to distinguish between specific antiviral and toxic effects. Generally, scientists look for agents that inhibit synthesis of viral DNA or RNA, then selecting for further research those with the most specific action.

Some agents already in drug form are:

- A compound called IUdR, licensed by the U.S. Food and Drug Administration, treats herpes keratitis in man, a virus-caused corneal infection.
- Symmetrel (amantadine) is approved for A2 strain influenza viruses, with the exception of the Hong Kong strain (SN: 6/28, p. 613). It is a controversial product, but FDA acknowledges that it effectively prevents flu when taken prior to infection and may have a limiting effect on the disease afterwards, though U.S. Public Health officials challenge this.
- A sister compound, called rimantadine, a modification of molecularly diamond-shaped amantadine, appears to have some therapeutic, as well as prophylactic, effects against A2 flu viruses.
- A third recognized antiviral drug, approved abroad though not in the U.S., is Marboran (methisazone), extensively tested in Madras, India, and shown to abort smallpox in patients who take it during the incubation period of the disease. "It is now known that smallpox vaccine gives much more limited immunity than had been thought, causing death in a few cases," Dr. Herrmann reports, "and in all likelihood should not be used in the U.S. in a generalized vaccination program. If nothing else, it



Smith Kline & French

A white-handed gibbon—Less violent than a chimp.

would seem advisable that methisazone at least be available for the treatment of adverse reactions to smallpox vaccination if the present widespread use of this vaccination continues." There is no reason to expect that either suggestion will be taken soon.

But if there are drug pros, there are also cons.

In general, mechanisms of antiviral drug action are poorly understood—though one approach is to identify substances that will block virus-induced enzyme activity—and progress is on something of a hit-or-miss basis.

But with some empirical evidence that drugs can, in fact, inhibit viruses, bolstered by the determination that viruses induce enzymes in cells—enzymes that are either absent or inactive in normal cells—investigations of antiviral substances are growing.

Current research efforts are concentrated on viruses that cause colds and upper respiratory infections, on grounds that these diseases are caused by hundreds of viruses—at least 60 different cold-causing rhinoviruses are known—and thus that vaccine development is unlikely. An effective cold vaccine, for example, would have to include every rhinovirus in order to be effective. Nevertheless, Dr. Daniel Mullally of the Vaccine Board of the NIH suggests it may be possible to attenuate and make vaccines with rhinoviruses.

"One experimental vaccine, tested in about 25 persons, had some effectiveness," he observes.

Scientists from Smith Kline & French Laboratories in Philadelphia, a company that has heavy investments in vaccines, report some promises with a cold compound known as SK&F 30097. "One problem we've had to face," explains Dr. John J. Boyle, "is that while determining a compound's antiviral activity in a test tube is a fairly simple matter, animal studies and predictions of applicability to man are difficult."

Chimpanzees, for example, do not catch colds. At least, when exposed to rhinoviruses, they do not develop symptoms including a fever or runny nose. In 1968, however, Dr. Elliot Dick of the University of Wisconsin in Madison showed that chimps do develop a subclinical infection, with high levels of virus in blood. Tests by Dr. Dick, subsequently confirmed in SK&F laboratories, showed that Dr. Boyle's SK&F 30097 reduced virus levels when given prophylactically 24 hours before exposure to the virus. The effect lasted for eight and a half days after exposure.

Difficulties in handling chimps—it takes five or six men to hold one down—lead the scientists to look for another animal model. As a result, animal studies are now being performed on the white-handed gibbon, a good-natured native of Southeast Asia. "The gibbon," Dr. Boyle says with relief, "develops subclinical infections and requires much less heroic efforts."

Human trials of SK&F 30097 will be conducted soon by research teams in Virginia, Wisconsin and Illinois. Dr. Boyle predicts that the present compound will not prove so effective that it will ultimately be marketed, but suggests it as a promising step in the direction of finding a molecularly similar agent that will.

Other experimental compounds were reported to the New York meeting.

One, called DEHT, provided mice with complete protection against respiratory disease from Coxsackie A21 viruses, in studies by Dr. Donald C. DeLong of Eli Lilly and Company in Indianapolis. "The safety and metabolic fate of the drug are now being studied in human subjects preparatory to its trial against respiratory infections in man," Dr. DeLong announced.

A second, kethoxal, was described by Dr. H. E. Renis of the Upjohn Company in Kalamazoo, Mich. As cautious as Dr. Boyle, Dr. Renis does not suggest that kethoxal itself will be the answer to virus diseases, but reports that research with it was promising because it showed the possibility of attacking many different viruses with a single drug. In test-tube experiments it has demonstrated activity against Vesicular Stomatitis viruses, which cause trench mouth and skin infections; Newcastle viruses, which cause animal diseases and conjunctivitis in man; influenza and parainfluenza viruses; reoviruses which cause upper respiratory disease, and others, rhinoviruses not included.

While the antiviral drug camp pushes for greater support and tries to convince vaccine supporters to join their camp—many, they say, already have—and vaccine advocates continue on their established course, a third group of researchers is devoting its time to proving that interferon, the body's natural antiviral protein, is a productive route to success.

Split among themselves over whether interferon should be harvested from human volunteers and given directly to individuals or whether it should be induced indirectly by injecting chemicals that will trigger its production or release from cells (SN: 7/12, p. 21), they too are engaged in infighting, subject at the same time to skepticism and outright criticism from their colleagues in vaccine and drug camps.

Dr. Maurice Hilleman of the Merck Institute for Therapeutic Research in West Point, Pa., developer of poly I:C, one of the most widely used interferon inducers, Drs. Samuel Baron and Hilton Levy of NIH, and others, favor inducers. British and other European scientists have strong commitments to exogenous interferon and plan extensive clinical trials using human interferon which may resolve the question, or at least introduce strong new evidence.

In the end, chances are that neither vaccines nor drugs nor interferon will clearly win or lose. A reasonable bet is that eventually scientists will successfully fight viruses with all three. ◇