Hope to End Virus Disease

Body's defenses may be alerted in advance to conquer harmful invaders—animal tests successful.

Once upon a time—back in 1960—viruses attacked Flash Gordon and his crew as they traveled through space. One by one men aboard the spacecraft lapsed into comas and died.

Desperate, Gordon tried to arrest the epidemic by injecting his companions with interferon, a drug untried on humans.

Interferon worked; the crew was saved.

Interferon is no comic artist's dream. In fact, it may hold the key to the elimination of virus diseases in man—from the common cold to hepatitis to some forms of cancer.

It was first identified in 1957 by a British scientist, Alick Isaacs, who had been studying the action on influenza virus. It was through Dr. Isaacs that Dan Barry, author of the comic strip, learned about interferon.

Interferon is a protein the body manufactures in response to virus invasion. Viruses trigger interferon production by the cells and then interferon wipes out the invaders by interfering with their ability to reproduce.

If the body can be induced to make interferon even when no virus is present, it then has built-in immunity in event of viral attack. This, many scientists believe, is the best approach to eradicating virus diseases.

For the past seven or eight years, researchers have been looking for compounds that induce interferon production. Many such compounds were found, but all had harmful side effects.

Now, however, scientists at the Merck Institute for Therapeutic Research, West Point, Pa., report new insight into essential requirements for interferon induction; insight that represents a giant step toward the prevention of viral infections. From studies with three different inducers—a viral RNA, a penicillin extract and a synthetic—Dr. Maurice R. Hilleman and his coworkers identified two essential characteristics of interferon inducers. Interferon, they report, is induced by administering RNA or ribonucleic acid that is both double-stranded and free of an inhibitory protein coat.

Interferon inducers, which have never been tested on humans, have now reached the stage where clinical trials are being planned for the first time.

"Dr. Hilleman's work could be the breakthrough we've been waiting for," says Dr. Samuel Baron of the National Institutes of Health.

"By determining that double-stranded RNA is essential, we've discovered the natural basis for interferon induction," Dr. Hilleman says. "Now we have the approach to a practical way of getting this into man. Our hopes are especially high for preventing common colds."

Most natural RNA is single-stranded, scientists believe, with one major exception—viral RNA. When virus particles reproduce, there is a point at which their RNA takes a double-stranded configuration, and it is at this point that interferon is induced.

Dr. Hilleman joined two synthetic chemicals—polyinosinic acid and polycytidylic acid—to make a compound structurally like double-stranded viral RNA. Neither of the two synthetics worked alone, but joined together they induced interferon production and virus resistance in rabbits, mice and cell cultures, Dr. Hilleman says. The double-stranded synthetic is nontoxic.

A second experimental inducer, called helenine after the wife of its discoverer, Dr. Richard E. Shope of Rockefeller University, was extracted from 100-gallon batches of Penicillium funiculosum, a mold. Helenine RNA in double-stranded configuration triggered interferon manufacture; single-stranded did not.

For the conclusion of this desperate adventure in space medicine, turn page.

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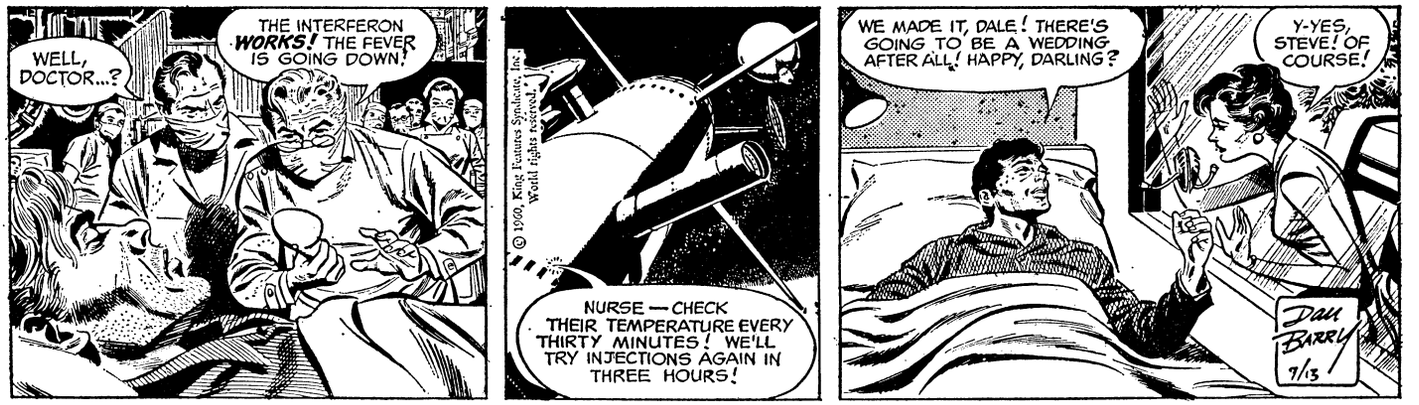

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The third test compound was double-stranded RNA from reovirus type 3, which commonly infects man with respiratory and intestinal disorders. Unlike whole reo-3 virus, reo-3 RNA caused no infection but did induce interferon and virus resistance in animals.

Dr. Hilleman and his colleagues will report their findings in three papers beginning in the August issue of the PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES.

Other scientists, including Nobelist John F. Enders of Harvard University and Dr. Robert M. Friedman of NIH, feel it is premature to say that only double-stranded RNA is effective, but agree that the finding that double-strandedness appears to always work is extremely important. "Interferon has a big future in studies of how cells work—how things get turned on and off," Dr. Friedman says.

Vaccinia, or smallpox virus, which has been considered a double-stranded DNA or deoxyribonucleic acid particle without any RNA at all, has been cited as an example of a non-RNA inducer, but Dr. Hilleman reports there has been some slight, though not established, evidence that vaccinia may contain RNA after all. "If this is true, we'll have to revise a lot of past thinking about vaccinia," he says.

The second essential requirement—that the double-stranded RNA must be free of its protein coat—in part accounts for the fact that interferon induced artificially works more quickly in attacking viruses than that induced naturally. It takes about five hours, for example, for viral RNA to shed its protein covering and begin inducing interferon. Dr. Hilleman's RNA, however, already free of its protein casing, did the job in a mouse in about one hour.

The inducers studied in Dr. Hilleman's laboratory, particularly the helenine, Dr. Enders says, offer a potentially inexpensive raw material for use in clinical trials and eventually by the public.

Of 20 mice treated with the helenine RNA, 18 or 90 percent survived normally lethal doses of pneumonia virus. All 30 controls died. Similarly, 86 percent of 21 mice protected with synthetic RNA survived lethal doses of pneumonia virus and all 17 control mice were killed.

Although scientists may now consider double-stranded RNA a key component of interferon induction, there still is much to learn about how it really works at the cellular level.

In the meantime, the promise of a drug that gives people wide-range immunity to viruses suggests that the whole nature of treatment and study of many garden variety ailments will be drastically changed. If the body could be made to keep a constant supply of interferon on hand, mankind could be spared much misery.

PERCEPTION

A Path in the Jungle

Some people furnish their homes in clean, stark lines; others go for clutter. Some like bright light; others dim. Some see detail in a picture; others see the whole.

There is no doubt that an individual's perceptual style exerts a powerful influence on his personality and life style. The problem in psychology has been to figure out just how different people do see the world.

The study of perception is usually a can of worms. Personal reports from those being tested may or may not be honest. Behavioral studies in the laboratory are often confused by extraneous influences, such as the temperature of the room or the scientist's personality.

Recently, however, researchers at Harvard University and the National Institute of Mental Health have begun to find a way into this perceptual jungle.

Harvard's Dr. Asenath Petrie set the course a few years ago when she discovered that perceptually, normal people fall into three equal categories: roughly a third exaggerate intense stimulation, a third block it and the rest are in the middle.

The exaggerators, whom Dr. Petrie called "augmenters," cannot stand pain, while the blockers, called "reducers," can.

Building on this base, Drs. Julian Silverman and Monte Bucksbaum, at NIMH, theorized that blockers were actually people with hypersensitive nervous systems. Their blocking at the higher levels of stimulation was a means of protecting themselves from sensory input they could not stand.

There were several reasons for believing this was the case, says Dr. Bucksbaum. For one thing, schizophrenic patients seemed to be reducing or blocking sensations. The easily distracted, nonparanoid schizophrenic is one who is very sensitive to marginal, minor stimulation, yet will let a cigarette burn into his fingers without the slightest reaction.

When tested, these schizophrenics turned out to be reducers, but more extreme than most normal people, with the exception of some women and persons under the influence of LSD.

Another clue came from the fact that the reducers couldn't take isolation and sensory deprivation. They seemed to have a need for continuous stimulation.

The NIMH team, however, wanted to find a neurophysiological basis for their theory directly in the brain's electrical activity.

Using a computer, they have located and amplified the brain's response to light flashes, and the pattern which emerges fits neatly into the hypersensitive-blocking theory.

The so-called reducers clearly react strongly to a dim night light, but block somewhat at a bright 150-watt light, while the opposite is true for augmenters.

Sexual differences between men and women have also appeared. "We can't say one sex is more sensitive than the other," says Dr. Bucksbaum, "but we