INTERFERON

Inducing the virus-fighter

In fighting off invading viruses the body is often in a race for time. If it can quickly muster enough antiviral interferon to protect cells from attacking viruses, infection will be thwarted. But if the interferon response is sluggish, viruses will gain an overwhelming advantage.

During the last decade, interferon, a native protein that forms the first line of defense against viruses of all types, has been the object of continually expanding research. Many investigators believe that eventually interferon will be to viral diseases what antibiotics are to bacteria infections. Their challenge is to find an effective and relatively simple way of artificially inducing interferon either to protect individuals against viral infections or to insure that the ones that do take hold are rapidly knocked out.

Recent work on a new inducer, the first to act orally, has excited interferon researchers. Says Dr. Thomas C. Merigan of Stanford University, "Experiments with this new compound, tilorone hydrochloride, provide an important opening, showing for the first time that a small, orally active molecule can induce interferon." Dr. Merigan, with his associate Dr. Erik DeClercq, has been testing the agent, which was developed by Drs. Russell Krueger, Gerald Mayer and their colleagues at the Wm. S. Merrell Co. in Cincinnati.

Tilorone hydrochloride, a fluorenone compound derived from coal tar, represents a new class of pharmacologic agents, and scientists predict that even if this initial chemical proves unsuitable for clinical use, similar agents produced by molecular tinkering may be valuable. From experiments with animals, the Merrell investigators first reported that tilorone hydrochloride appeared to be an interferon inducer. Studies by Drs. Merigan, DeClercq and others confirmed that finding, although its effect in man has yet to be demonstrated. According to Dr. Krueger, human trials of the new drug are under way but results are not yet available. Investigators are still working to determine doses needed to induce interferon in man, if, indeed, this drug is active in human beings.

Discussing tilorone hydrochloride, whose mechanism of interferon-induction is unknown, Dr Krueger points out that it is molecularly unlike previously identified inducers. By and large, these are polynucleotides, molecules that structurally mimic the nucleic acid core of viruses. Among them, poly I:C (polyriboinosinic-polynribocytidylic acid) is perhaps the most thoroughly studied. First developed in 1967 by Dr. Maurice R. Hilleman of the Merck Institute for Therapeutic Research in West Point, Pa. (SN: 8/19/67, p. 173), poly I:C has been shown to cure a potentially blinding eye infection (herpes simplex keratoconjunctivitis) in rabbits (SN: 1/18/69, p. 60). This year, Drs. Paul Fenje of the University of Toronto and Bosko Potic of the University of Pittsburgh used poly I:C successfully to induce protective and therapeutic levels of interferon in rabbits exposed to lethal doses of rabies virus. In limited cases, it is currently being tested in man.

But at least for the moment, poly I:C's uses are somewhat circumscribed. A large molecule with a molecular weight of upwards of 100,000, it has some toxicity and is active only when given by injection. Dr. Hilleman and others are exploring modifications of its structure which may enhance its effectiveness. Dr. Merigan observes that poly I:C may one day be useful for local therapy of virus infections by administering it specifically to the eye or respiratory tract, for example, and thereby avoiding systemic side effects.

To achieve high interferon levels throughout the system, however, tilorone hydrochloride or one of its descendants holds greater promise. In contrast to poly I:C, tilorone is a relatively small molecule with a molecular weight of 400. It is this feature that allows its absorption from the gastrointestinal tract. According to Dr. Merigan, whose work has shown it to be active in mice but not in chickens, tilorone is actually safer and more therapeutically active when given orally.

His experiments with mice demonstrate a 15-fold difference between the doses at which it is therapeutically effective as an interferon inducer and those at which it is highly toxic. Theoretically, at least, this provides a sufficiently wide margin of safety. Extrapolation of the mouse data to man, however, is risky, "We can't predict what will happen in man," Dr. Merigan declares. "We may find that therapeutic and toxic doses are very close or we may find an even greater margin than in the mouse."

Should tilorone become clinically available within the next few years, it could be put to work in a variety of circumstances. A pregnant woman exposed to rubella, for example, could be protected from infection. And in situations in which large numbers of persons were in danger of being exposed to a virus during an epidemic, the pill could be downs as a prophylactic.

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