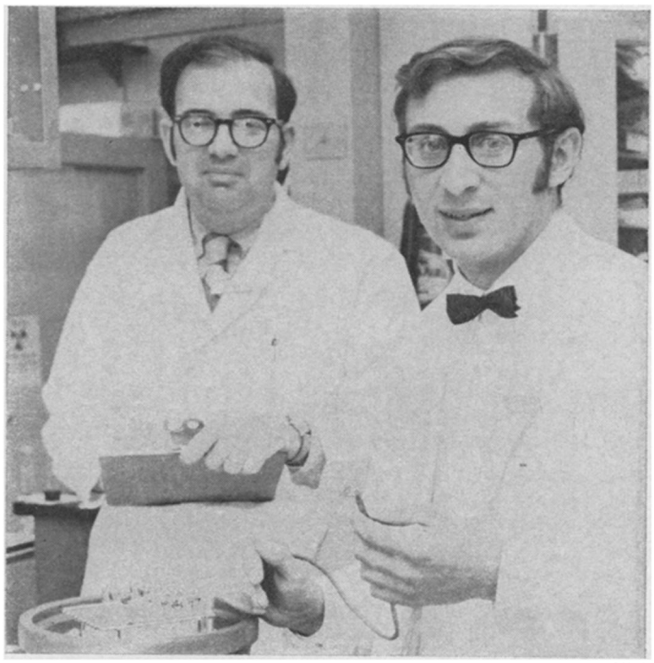
Poly I:C moves into a new arena: immunity

Synthetic RNA triggers a reversal of the self-destructive process of making antibodies to nucleic acids

by Barbara J. Culliton



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Drs. Talal (left) and Steinberg: New use for poly I:C.

The immune system protects life by recognizing and destroying foreign microbes and cells in the body. At times, as is the case with the rejection of organ transplants, this normally protective system can become life-threatening.

In addition, it sometimes threatens survival by turning on itself, mistakenly identifying certain of its host's own cells as foreign and rejecting them. Rheumatoid arthritis recently has been classed as such an autoimmune disorder. Systemic lupus erythematosus is another disease of autoimmunity, afflicting approximately a quarter of a million individuals in the United States.

Lupus patients make antibodies to their own deoxyribonucleic acid in a process that is almost invariably fatal if it affects the kidneys. Says Dr. Normal Talal of the National Institutes of Health in Bethesda, Md., "Once the kidneys become involved, the prognosis is about two years." What happens is that immunoglobulins, or immune cells, identify native DNA as foreign, and produce anti-DNA antibodies, which form complexes that lodge in the tubules of the kidney. Standard therapy revolves around the use of corticosteroids and other immunosuppressive drugs that block the formation of anti-DNA antibodies. But this handicaps the entire immune system, leaving patients dangerously susceptible to a wide range of infections.

Ideal therapy would involve subtle alterations in the patient's immune response, inducing tolerance to DNA without obliterating the system's ability to respond to genuinely foreign invaders. From experiments with mice, Dr. Talal, with Dr. Alfred D. Steinberg and Gerald G. Daley, have evidence that poly I:C (polyinosinic-polycytidylic acid) can induce just such a condition of specific tolerance. "This is the first experimental induction of tolerance to a nucleic acid antigen," Dr. Talal reports.

Poly I:C, a synthetic chemical that mimics double-stranded ribonucleic acid, first came into biological research when Dr. Maurice R. Hilleman of the Merck Institute for Therapeutic Research in West Point, Pa., discovered in 1967 that it induces antiviral interferon, the body's natural virus-fighting protein (SN: 8/19/67, p. 173). Since then it has also shown promise in destroying certain types of tumors by a mechanism unrelated to its ability to induce interferon (SN: 1/18/69, p. 60). According to Dr. Talal, the mechanism by which poly I:C induces immune tolerance to nucleic acids is also unrelated to its interferon stimulation.

Dr. Talal and his colleagues tested the synthetic nucleic acid in New Zealand mice, a strain that spontaneously develops a disease similar to lupus in humans. In both the animal and human diseases, formation of antibodies to DNA is a unique characteristic.

When poly I:C was injected into animals that were making anti-DNA antibodies, they experienced an acceleration of disease, recognizing the synthetic RNA as a foreign antigen and producing high levels of antibody both to it and to native DNA and RNA.

Following their injection of poly I:C into the diseased animals, the scientists gave injections of Cytoxan, an immunosuppressive agent that knocks out immune cells. Though the effects of Cytoxan itself are not specific—it acts against all types of immune cells—in this case it was particularly active against those immunoglobulins that produce antibodies to nucleic acids, because the challenge dose of poly I:C had triggered most of them into action. These cells are most susceptible to the effects of immunosuppressives when they are in an active state of cell division.

As a result of this regimen of poly I:C followed by Cytoxan, the level of antinucleic acid antibody production was cut up to 90 percent in some animals. Yet when these same animals were challenged by doses of other antigens, such as sheep red cells, they had a normal immune response. The conclusion is that they had developed immune tolerance to nucleic acids, but had not developed a dangerous tolerance to other substances.

"The idea," Talal explains, "is to wipe out the population of immunoglobulins that have the specific capability of reacting to nucleic acids, without destroying the rest." The next step is to test the effects of poly I:C in patients. Though the drug is known to have some toxic effects, Dr. Talal speculates that this will not present a problem in the doses that will be used.

For purposes of inducing specific immune tolerance, poly I:C appears to be potentially useful to lupus alone. But, says Dr. Talal, "This technique may have widespread application in various autoimmune diseases as well as in the field of transplantation." □