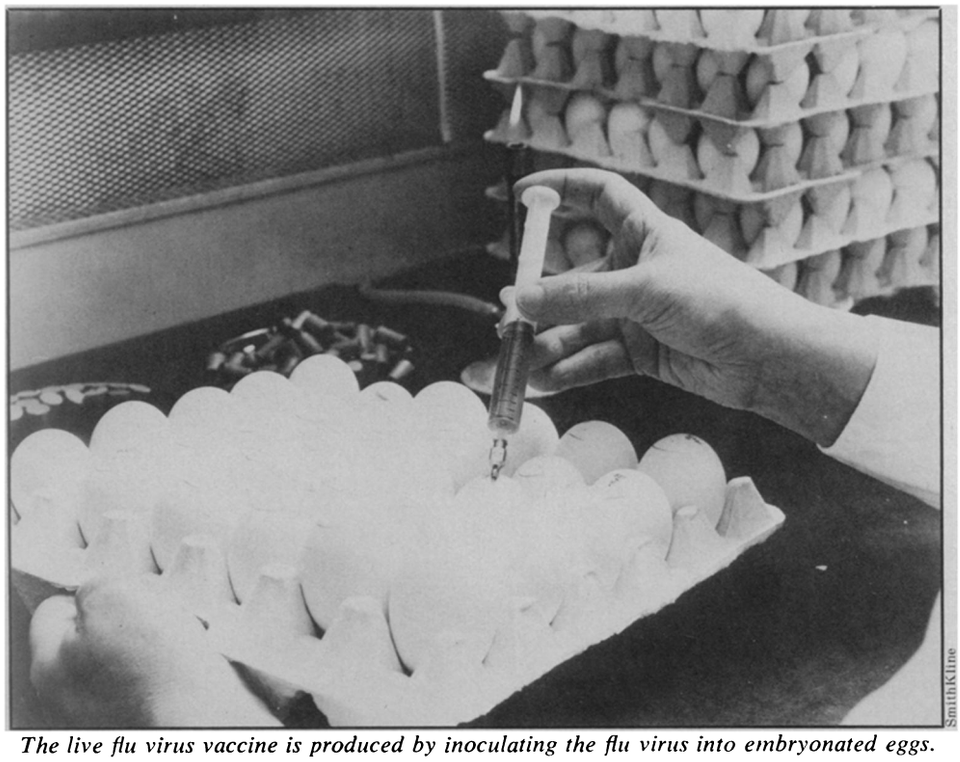
Vaccines On the Horizon

Improved vaccines and vaccine delivery are being sought

by Joan Arehart-Treichel



The live flu virus vaccine is produced by inoculating the flu virus into embryonated eggs.

One bright spring day in 1796, an English country physician named Edward Jenner chatted with a dairymaid. He learned that she, like many dairymaids and farmers, had been accidentally infected with cowpox. Cowpox is a mild disease. "For this reason," she told Jenner, "I cannot acquire the smallpox."

Smallpox was then the scourge of Europe, leaving thousands of young people dead or disfigured for life. The dairymaid's remark gave Jenner an idea. He took pus from a cowpox sore and inserted it under the skin of a healthy eight-year-old boy. Six weeks later Jenner exposed the boy to smallpox. And as Jenner hoped, the child was immune to this dread disease.

Thus the smallpox vaccine was born, and for the next 200 years it and other kinds of vaccines have had more impact on world health than any other measures, with the possible exception of sanitation and insect control.

Vaccines to prevent 20 diseases are now available in the United States. The diseases are smallpox, rabies, cholera, typhoid, whooping cough, diphtheria, scarlet fever, staph infection, tetanus, typhus, Rocky Mountain spotted fever, influenza, mumps, tuberculosis, yellow fever, polio, adenovirus infection, measles, and German measles. The diseases for which vaccines are available are increasing in number virtually every year now. Those probably coming in the next few years are strep throat, venereal diseases, hepatitis (SN: 4/21/73, p. 255), meningitis and pneumococcal pneumonia (the only infectious disease included among the 10 leading causes of death in the United States). Each new vaccine should prove of immense value to millions of people. But what is exciting, from a scientific view, is the increasing sophistication of vaccines.

The basic concept of vaccines, since Jenner's day, is that an infectious organism is injected into a person in such tiny amounts that it will prompt an antibody response but not give the person the disease. Then, if the person later comes into contact with the organism in the natural environment, he or she will have already made enough antibodies to fight off the organism and prevent disease. With the smallpox vaccine, of course, the benign cowpox virus is so closely related to the smallpox virus that it can be used instead to provoke cross-reacting antibodies against smallpox. Now scientists are expanding the vaccine concept by calling on advances in virology, bacteriology, chemistry and genetics.

They are experimenting with new modes of vaccine delivery. They are making vaccines from parts of infectious agents rather than using the whole agents. They are exploring the value of giving benign organisms to enhance vaccine effectiveness. They are genetically altering infectious agents so that they can be used as live, yet safe vaccines. They are even contemplating vaccines made totally of synthetic chemicals, so that many vaccines could be delivered together.

A promising new mode of vaccine delivery is by nose spray instead of by needle injection. Spray vaccines are being developed for strep throat and

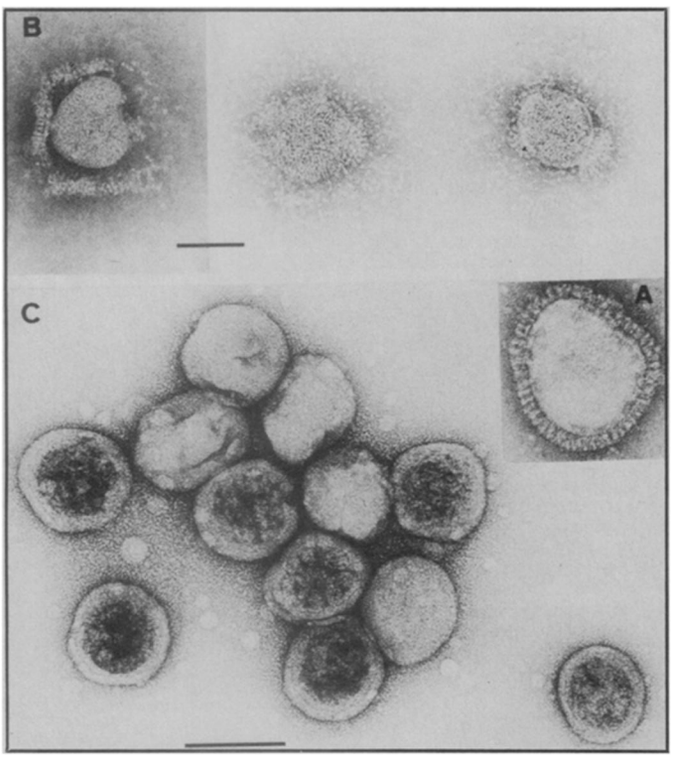
German measles (SN: 5/25/74, p. 358) —news that should make children of the world stand up and cheer. The Smith Kline & French Laboratories have received permission to market, in Belgium, a live flu vaccine that can be sprayed up the nose. The vaccine has been approved by authorities in Belgium and will be available to Belgians during the 1974-75 flu season. If it works well, it will probably be licensed in other countries as well.

neuraminidase—that prompt the immune reaction in a host. So Webster and his co-workers are trying to isolate only these protein antigens to use as a vaccine. That way they hope to trigger sharp immunity in a person, yet avoid any danger of the flu virus replicating itself and causing disease rather than disease protection.

"Whereas a bacterium is a big creature," Webster explains, "a virus is so tiny that to obtain pure antigens

fants are most threatened by the disease, and scientists are not yet sure that the vaccine protects them. There is a chance that it may not, because the human immune system doesn't reach maturity until age two.

If it turns out that the vaccine is not sufficiently protective in infants, there may be another way of making it work. And that is by giving infants benign bacteria along with the vaccine to step up the maturation of their im-



Flu virus as particle (A), with spikes (B), as cores (C).

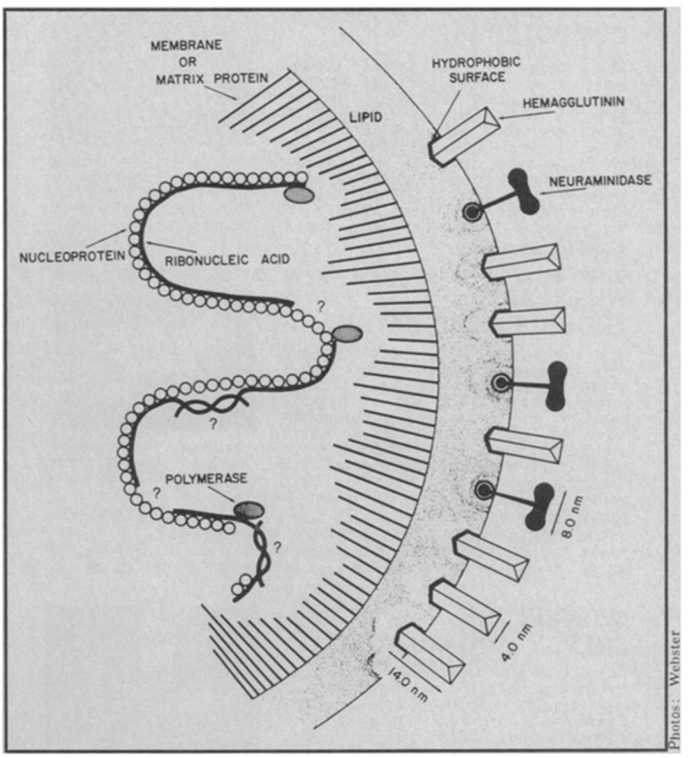


Diagram of flu virus protein spikes and how they're made.

Is the trend now toward live or dead vaccines? "It depends on which scientists you talk to," replies George Golasso, chief of the Infectious Disease Branch of the National Institute of Allergy and Infectious Diseases. "The live virus, of course, is the ideal one because it will result in more antigens, active immunization and therefore longer-lasting antibodies. But there is a possibility that it might replicate and cause disease—something that a dead virus cannot do. Thus there are some scientists who prefer inactive vaccines." As a result, Robert Webster and his virology team at St. Jude's Children's Research Hospital in Memphis are trying to devise a flu vaccine that would be potent, yet safe, by using only parts of the flu virus. (Licensed flu vaccines now used in the United States are all made from dead viruses.)

The flu virus is a tiny protein sac held together with lipid. Inside the sac is the genetic information that the virus needs to replicate itself. On the surface of the sac are little spikes—proteins known as hemagglutinin and

stretches the limits of our technology right now."

Unlike viral antigens, bacterial antigens have been used as vaccines since the 1940's. Nonetheless, such antigen use is becoming more sophisticated. For instance, some dozen related bacteria cause about 78 percent of the cases of pneumococcal pneumonia. Robert Austrian of the University of Pennsylvania and the Eli Lilly Co. have designed a pneumonia vaccine that contains polysaccharide antigens from all the crucial bacteria. Clinical trials with this vaccine started in 1972 and will end in 1975. So far the vaccine appears to be 80 percent effective.

Emil C. Gotschlich of Rockefeller University has helped develop a vaccine for meningococcal meningitis—a disease that can lead to neurological damage and death among infants. The vaccine consists of two polysaccharide antigens from the meningitis-causing bacterium. The vaccine has been tested since 1968 all over the world, and it has been found to work well in persons from school age on up. However, immune systems. One approach, Gotschlich suggests, "would be to take polysaccharide antigens from nonpathogenic bacteria and use those antigens along with a low level of meningitis bacteria antigens to sharpen babies' immune response to polysaccharide antigens."

In fact, John B. Robbins of the National Institute of Child Health and Human Development is exploring this approach for meningococcal meningitis, and especially for a similar disease caused by the bacterium *Hemophilus influenzae* type B. Meningitis caused by this bacterium is the leading cause of acquired mental retardation in the United States.

A particular strain of the bacterium *Escherichia coli* naturally lives in the gastrointestinal tract of a small percentage of persons of all ages. This *E. coli* strain is not pathogenic, yet shares polysaccharide antigens with *H. influenzae* type B. So Robbins asked: If *E. coli* were fed and colonized in the gastrointestinal tract, would it get the

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body to make antibodies against *H. influenzae* type B because of their shared antigens? He tested this hypothesis in rabbits. He fed them *E. coli;* the rabbits made more antibodies to *H. influenzae* type B than did control rabbits. He then fed *E. coli* to primates; they made more antibodies to *H. influenzae* type B than did control primates. He fed *E. coli* to eight human adult volunteers. They responded with limited colonization of *E. coli* and synthesis of antibodies to *H. influenzae* type B. Finally Robbins examined 4,000 infants and found that one percent of them had the *E. coli* strain that shares antigens with *H. influenzae* type B. And those infants with the *E. coli* made antibodies to *H. influenzae* type B earlier than control infants did.

So Robbins sees *E. coli* feeding or injection as a means of assisting infants in the acquisition of natural immunity against *H. influenzae* type B. "Perhaps a priming sensitization can be achieved," he says.

Meanwhile several other teams are working on altering the genetics of flu viruses so they can be used as effective, yet safe flu vaccines. Edwin D. Kilbourne and his virology team at the Mount Sinai School of Medicine in New York City crossed flu viruses with benign viruses in hopes of using the hybrid progeny as a vaccine. Such a vaccine would confer only partial immunity.

"The point of this," Kilbourne explains, "is to allow the individual to be infected by the wild flu virus, but not become diseased because the best immunity is that which follows natural infection. In other words, we're trying to blunt the effects of natural infection, but not completely prevent it because we want to get the immunizing effects of this infection."

The vaccine looked promising in experimental animals. Clinical trials will get under way this winter.

Fred M. Davenport of the University of Michigan School of Medicine, with the help of his group at the school and at the Public Health Laboratory in Lansing, Mich., have come up with mutant flu viruses that grow at lower temperatures than flu viruses usually do. They've made a flu vaccine out of these mutants and are now testing it on volunteers.

"The rationale," Davenport says, "is this: If the virus is able to resist high temperature when a patient's temperature is up to 103 or 104, that means that it's a virulent virus, one capable of causing disease. Otherwise, as soon as the temperature went up, it would kill the virus. Therefore, if you can get the reverse of that, get strains that will grow in cold but not at high temperature, then maybe these will be gentled, as it were."

Robert Chanock, Brian Murphy and their colleagues at the National Institute of Allergy and Infectious Diseases have been genetically crossing flu virus strains to come up with hybrids that will replicate in the cooler areas of a person's upper respiratory tract, where flu viruses strike, but will not replicate in delicate warm lung tissues. If these strains are made into a flu vaccine, they should offer protection in a strategic area of the body, yet not replicate in an area that might hurt the person who has been vaccinated.

The NIAID scientists have also come up with a temperature-sensitive mutant of the virus that causes mycoplasma pneumonia. As they report in the October PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, they gave the mutant by the intranasal route to 16 human volunteers. The mutant remained genetically stable throughout the course of infection and stimulated local and systemic antibody response.

New modes of vaccine delivery, vaccines made from selective antigens, giving benign organisms to make vaccines more effective in infants, breeding viruses into effective, yet safe vaccine material—these are some of the vaccine advances that may become available to the public during the next five years or so. In a decade we may well have access to vaccines made purely of synthetic chemicals.

Michael Sela and Ruth Arnon, chemical immunologists at the Weizmann Institute in Israel joined forces with Christian B. Anfinsen of the National Institutes of Health, a 1972 Nobel Prize winner in chemistry. The three cut a string of amino acids out of a large protein molecule and synthesized a string like it. They arranged the string into a loop and attached it to a synthetic chemical carrier and injected in into rabbits and goats. The animals made antibodies against the synthetic chemical loop, and the antibodies were precisely those deployed against the natural protein molecule.

Sela anticipates "that six, seven or more different loops from different antigens [proteins] can first be isolated, then synthesized and finally combined on a carrier molecule that will then be injected to produce immunization against a number of different diseases."

Asked what the advantage would be of having synthetic antigens packaged together into one vaccine, Sela replied: "Our children get immunized against so many things that one day they will reach a breaking point, and it won't be possible to use the present approach any longer. Synthetic vaccines, produced by molecular engineering, could be the answer, but it may take a decade or so to achieve it." □