Protective Chemistry: Sensitive Cell Control

A cell's defense against viruses can switch on at the prod of a single molecule. That biochemical armor, a protein called interferon, protects the cell from certain death. No one knows just how interferon works, but because its protective action confounds a wide range of viruses, the protein is being investigated clinically as a possible "pan-vaccine" (SN: 2/28/76, p. 130).

The most potent substance so far discovered for turning on production of interferon is described in the April 28 NATURE. Although all viruses will stimulate interferon synthesis, Philip I. Marcus and Margaret J. Sekellick of the University of Connecticut demonstrate that a single short segment of double-stranded RNA from a defective virus works best.

Defective viruses arise naturally when viruses are grown in cells in a laboratory. These agents consist of the same protein coat as the normal virus, but they contain only a fraction of the genetic material. This defect prevents them from successfully infecting cells alone, but they can reproduce in the presence of normal viruses. Virologists call these viruses defective interfering (DI) particles because they eventually interfere with the normal viruses' reproduction.

Defective interfering particles are likely to play a role in persistent infections. Alice S. Huang and David Baltimore suggested in 1970 that a balance of normal and DI viruses could explain infections that don't immediately either spread or heal. Marcus and Sekellick now propose that for a certain group of DI particles, interferon is involved in preventing viruses from killing cells.

Marcus and Sekellick studied DI particles that arise from vesicular stomatitis virus, which causes a cattle disease. The genetic material in that virus is a single strand of RNA, and most of the DI particles contain shorter pieces of that RNA. One set of DI particles, however, contains RNA consisting of two regions that can bind together into a double-stranded structure.

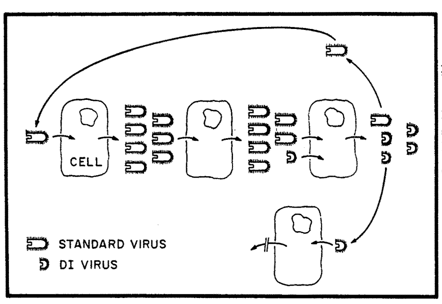
DI viruses with the single-stranded RNA have no measurable effect on a cell's interferon production, Marcus and Sekellick report. DI viruses with the double-stranded RNA, however, stimulate a burst of interferon production in the experimental cells, chick embryo cells grown in the laboratory. The double-stranded RNA did not need to be functional for reproducing or making protein in the cells. It could stimulate interferon production even if its other functions were destroyed by heat or ultraviolet light. After the double-stranded RNA enters a cell, it seems that a cellular gene for interferon is activated. New cellular RNA and protein appear to then be required for interferon production.

This action of double-stranded RNA fits well with experiments showing that interferon production can be stimulated, but less effectively, by an artificial double-stranded RNA. The difference in efficiency can be explained by the packaging. The RNA molecule in a DI particle is designed to be delivered into a cell, and the viral coat is designed to deliver its contents. The artificial RNA, on the other hand, has to find its own way through the cell membrane and is susceptible to various destructive enzymes. Researchers have to treat cells with thousands of artificial molecules in order to get just a few in, but the DI particle successfully delivers a single molecule, Andrew Ball, a colleague of Marcus and Sekellick explained to SCIENCE NEWS.

Treatment with DI particles that produces interferon allows laboratory-grown chicken and human cells to survive an otherwise lethal dose of the parent vesicular stomatitis virus. The researchers report that it also protects cells against a dose of the unrelated virus that causes Newcastle disease. Laboratory cells derived from the kidneys of green monkeys are a type of cell that does not respond to any inducers of interferon and was not protected by the DI particles.

There are currently no plans to use these defective viruses clinically, although trials have been run using the artificial double-stranded RNA. The toxicity of that material should make new approaches to stimulating human interferon production welcome.

To the scientists the most striking aspect of these experiments is the sensitivity of the cells. "This is the most dramatic demonstration that we've got yet that a single molecule of anything can affect a cell," says Ball. "When you compare the size of a molecule and the size of a cell, it's like a pea up against the Cathedral of Notre Dame." □



Alice S. Huang and David Baltimore/Nature

Balance of defective and normal viruses may produce persistent infections.

The big apple: Better for your psyche

Fifteen years ago, the results of the now-famous Midtown Manhattan Study shocked behavioral scientists and laymen alike by reporting that 23 percent of New York City's East Side residents were in need of psychiatric treatment. At the time, the report was greeted by some "with skepticism, flat disbelief or questions about the mental competence of the study's scientists," recalls Columbia University's Leo Srole, the sociological researcher who directed the study. Since then, the figure has come to be accepted as realistic for New York and other cities, and has added fuel to the argument that big cities are indeed unhealthy "jungles" for the human psyche.

Now, in a 20-year follow-up of 695 original interviewees (the 1962 report was based on data from 1,660 persons interviewed in 1954), Srole reports that the mental health of New Yorkers is about twice as good as it was in 1954. Moreover, in combining these latest results with survey data from the United States, Canada and elsewhere, Srole concludes that big city residents appear to have substantially fewer mental health problems than their rural and small town counterparts. "Mental health overall," he states, "is more favorable in big population centers, including New York as the biggest, than in smaller ones." The results, he emphasizes, "offer no support whatsoever to the antique presupposition of the superiority of rural mental health."

Srole presented his findings at the annual meeting of the American Psychiatric Association last week in Toronto.

In the 1974 reinterviews, the Manhattan follow-up subjects answered the almost identical battery of 92 symptom items they had answered 20 years before. Srole compared the results of persons from 40 to 60 years old with those of respondents in the same age ranges in 1954. In the original and follow-up studies, he notes, the samples are representative of both rich and poor persons living in the predominantly white population area.

Over the two-decade period, the percentage of those with "impaired" mental health in the 40 to 49 age category dropped from 16 to 8.4 percent. Persons between 50 and 59 went from 21.7 percent impaired to 10.3 percent. Srole attributes much of the improvement to changes in upbringing that occurred years ago. In the original survey, for example, the respondents in their 50s were brought up by parents who grew up in the late 1800s, Srole notes, whose attitudes and socio-economic histories were far different from the parents of the 1974 counterparts. Also critical were differences in the educational, occupational and environmental settings of each generation.

While improvements occurred in all demographic subgroups during the 20-year period, Srole reports that some groups gained more than others: Native-born improved more than foreign-born subjects; "middle-rung" educated persons improved more than the college graduates above them and those below with 10 years or less of schooling; women improved more, proportionately, than men. "Surfacing here for the first time," suggests Srole, may be the "cumulative positive mental health effects" of the growing independence of women that began around the turn of the century, highlighted by the right to vote in 1920.

To support his findings that the urban mental picture is healthier than that in rural areas, Srole combines several pieces of data, including a previously unpublished Health Examination Survey conducted in 1960 to 62 by the U.S. National Center for Health Statistics (NCHS). Compiling perhaps the most comprehensive nationwide set of symptomatic data in recent years, NCHS surveyed some 6,700 adults in areas ranging from rural pockets (less than 2,500 population) to metropolitan areas inhabited by more than 3 million people.

The study found that persons who lived in rural areas and in cities with populations of fewer than 50,000 had symptom scores nearly 20 percent higher than people who lived in cities of more than 50,000. The scores were based on 12 self-reported symptoms, such as sleeping difficulties, the feeling that "everyone is against me" and that a nervous breakdown is imminent.

Srole also contrasts the Midtown Manhattan data with a similar survey in Stirling county, Nova Scotia, where the average density is 20 per square mile, compared with Manhattan's 75,000. Srole drew demographically matching subsamples from each study and concludes that "Stirling's estimated mental morbidity rate is higher than Midtown's by a wide and highly significant statistical margin."

Finally, he cites a survey of all pharmacists in New Zealand. That unpublished data—which covers population concentrations from under 1,000 to over 100,000—reveals that "per capita psychotropic drug prescription rate varies inversely with the size of locality, the rural rate being over twice that of the biggest cities," Srole says.

He suggests that such findings may serve as input "into national policy-making that may have long-range promotive and preventive implications for both social and psychological well-being in the generations of our children and grandchildren." □

Giving cosmic rays their bounce

The existence of cosmic rays has been known for about 60 years. They are mostly protons and electrons with some mixture of heavier atomic nuclei. They come at the earth from all directions and with extremely high energies, much higher than terrestrial laboratories can produce. In fact, many of the weirder subatomic particles were first found in the debris produced when cosmic rays strike the earth's atmosphere.

In all these years, the source of that great energy has been a mystery. There have been a number of suggestions, but on examination they have seemed perhaps not quite sufficient. At the recent meeting of the American Physical Society in Washington, John S. Scott of the University of Maryland presented a theory for their energy that appears to fit and also has some independent observational support. It would accelerate the cosmic-ray particles by repeated bouncing off moving magnetic fields in supernova explosions.

A supernova is an extremely violent explosion that ends the life of a star. It throws a huge amount of gaseous matter into the surrounding space. Such a supernova remnant contains many patches of extremely hot ionized gas that carries magnetic fields "frozen" into it. Thus, in a supernova remnant, which, like the Crab nebula, can continue to glow for a thousand years, there are many turbulently moving patches of magnetic field.

In a supernova remnant are also the raw materials of cosmic rays: protons and electrons flying loose as well as the heavier nuclei, which, according to astrophysical theory, can be synthesized only in an environment as violent as a supernova explosion. All these particles are electrically charged, and therefore, when they encounter a moving patch of magnetic field, they are likely to be bounced off it. If the particle happens to hit a field patch that is receding from it, it will lose energy in the bounce; if it hits an approaching one it will gain energy.

A turbulent situation like a supernova remnant is statistically likely to have as many patches of magnetic field going one way as another. However, Scott argues, because the cosmic-ray particles are moving out from the explosion, it takes them longer to catch up with receding fields than it does for them to meet approaching ones, so there is a net excess of energy-gaining hits. Over the thousand years the supernova remnant lasts, the excess is enough to give the cosmic rays their immense energies.

The first question is one of numbers. Are there enough supernovas to supply the observed flux of cosmic rays? Supernova students figure an average of one per 25 years in our galaxy, which, according to Scott's figures is enough. Scott cites as a further support a study also reported at the APS meeting by Floyd W. Stecker of the NASA/Goddard Space Flight Center.

Stecker was studying the distribution of cosmic rays in the galaxy. Because the charged cosmic-ray particles suffer many bendings of their paths on the way to earth by interstellar magnetic fields, observers can't tell where they came from. However, satellites can observe gamma rays that result from the radioactive decay of pi mesons produced as cosmic rays strike interstellar gas near their points of origin. Gamma rays, being uncharged, come straight through. Stecker's observations indicate that the thickest source of cosmic-ray-produced gamma rays tends to lie in the densest parts of the galaxy, the spiral arms. He describes the galaxy as a kind of bagel shape as far as cosmic-ray production is concerned. Scott says this fits neatly with a theory of supernova origin because it is the dense parts of the galaxy where the hot young stars that become supernovas are more likely to form.

There is also independent evidence for the moving patches of magnetic field in known supernova remnants. Charged particles that happen to get trapped by the magnetic fields are induced to emit electromagnetic waves of a particular character called synchrotron radiation. The British radio astronomer A. R. Bell has observed synchrotron radiation coming from moving patches in known supernova remnants. So the whole thing seems to be falling together. □

Short-wavelength laser: A new record

Lasers began at long wavelengths. There the stimulated emission and multiple reflection required to produce their coherent high-power beams are easier to achieve. From the infrared, where the first laser functioned, they have been steadily marching toward shorter wavelengths. The ultimate goal is an X-ray laser. An X-ray laser, especially if it could make X-ray holograms, would have many applications in medicine and materials science. It is also interesting from a pure-science point of view, just to show that it can be done.

The shortwave laser limit is now in the ultraviolet, and according to a recent report by the U.S. Naval Research Laboratory, it has just made a significant leap downward. A group led by John F. Reintjes has produced laser radiation at a wavelength of 380 angstroms. The previous record was 532.2 angstroms achieved by the same group last September. The boundary between ultraviolet and X-rays is a little elastic, but it falls not far under 100 angstroms. □