as ACDA inside the government, there would be no one to speak for arms control. Arms control lobbyists fear that the effective demise of ACDA, if this is what the White House plans, could fatally weaken the impetus for further arms control agreements.

It is of course possible that the White House does not wish to progress too hastily with SALT. The agreement negotiated last May runs for 5 years. And striking bargains with the Soviets, a former Kissinger aide observed recently, is only 60 percent of the problem; the rest is domestic politics. The so-called missile gap assisted Nixon's defeat in 1960. An instance that occurred early in the SALT talks was when, through fear of stirring up the hardliners, the White House reneged on an offer, already accepted by the Russians, to limit ABM systems to the sites of the national capitals. The White House, it may be surmized, does not consider ACDA the best place for keeping control over the domestic implications of such issues.—NICHOLAS WADE

Erratum: In "Metabolite distribution in cells," by R. H. Davis (24 November 1972), two errors occurred. On page 839, column 3, line 20, "CPS-A" should read "CPS-P". In Fig. 2, on page 837, parentheses enclosing "ureidosuccinate" and "uridylic acid" in the lower part of the figure should instead have enclosed the same words in the upper part of the figure.

RESEARCH NEWS

Perfluorochemical Emulsions: Promising Blood Substitutes

Blood is a highly complex liquid with many components and a variety of functions, the most important of which include transport of oxygen and metabolic substrates to tissues, removal of carbon dioxide and metabolic products, and maintenance of the concentration of ions and other solutes in extracellular fluids. Many widely used substitutes for blood serum perform some of these functions, but none provides adequate oxygen transport, which may be the most critical function since oxygen deprivation leads to rapid death.

Recently, however, a small number of investigators have begun to demonstrate that certain perfluorochemicals—organic compounds in which all hydrogen atoms have been replaced by fluorine—can supply oxygen transport and, in conjunction with a simulated blood serum, perform many functions of whole blood. These combinations have been used in several laboratories to maintain physiological function in isolated organs and to replace a substantial part of the blood of laboratory animals. One group has also used them for complete replacement of the blood of mice. Clinical trials have not yet been performed in humans, but a major barrier to such research, the propensity of perfluorochemicals to accumulate in body tissues with unpredictable effects, may have been overcome with the discovery of two perfluorochemicals that are rapidly eliminated from animals.

The need for a blood substitute was again made clear during the recent New Year's holidays when the reserves of blood banks in major areas of the country were nearly depleted. The annual seasonal decline in donations and increase in accidents forced hospitals in many cities to restrict or postpone elective surgery and to rely more heavily on commercial sources of blood, with a concomitant increase in the risk of hepatitis and other infections.

Even when adequate blood supplies are available, major problems abound. Blood is very expensive to collect, store, and administer. It is highly perishable, and thus cannot be used for routine treatment of accident victims at the site or stored for more than a short time. Incompatibility is a major problem: administration of blood of the wrong type can lead to an immune response far more serious than the condition being treated, and lifesaving transfusions may be perilously delayed during typing of the recipient's blood or during a search for a rare blood type. Blood supplies for animals are virtually nonexistent. Development of a universal blood substitute would ease or solve all of these problems and, in addition, provide a valuable tool for physiological research.

But obtaining a suitable oxygen carrier is difficult, both because of the scarcity of materials that can bind oxygen reversibly and because of the body's strong propensity for clearing foreign substances from the bloodstream. Even hemoglobin, when not incorporated in an erythrocyte, does not carry oxygen, and some scientists suggest that it is rapidly removed from circulation.

Oxygen is highly soluble in liquid perfluorochemicals, however. Whereas salt water or blood plasma dissolve about 3 percent oxygen (by volume) and whole blood about 20 percent, perfluorochemicals dissolve 40 percent or more; carbon dioxide is at least twice as soluble. In 1966, Leland C. Clark, Jr., of the University of Cincinnati College of Medicine demonstrated this high oxygen solubility by submerging mice in inert liquid perfluorochemicals for extended periods (Fig. 1). The animals were able to obtain sufficient oxygen by breathing the liquid and, upon removal, showed no apparent ill effects from the experience. Clark has also shown that breathing such liquids can

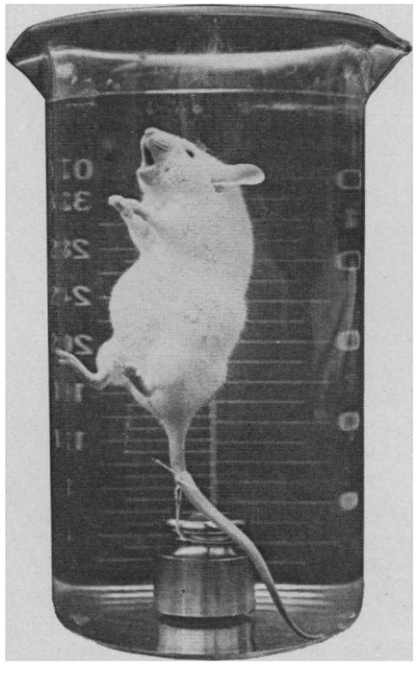

Fig. 1. A mouse breathing perfluorobutyltetrahydrofuran. After an hour's immersion, the mouse was inverted to drain the liquid from its lungs, and is now alive and well. [Source: Leland C. Clark, Jr., University of Cincinnati College of Medicine]

protect mice from the effects of rapid decompression, and he suggests that the liquids would be useful for such applications as escape from submarines and deep-sea diving.

Intravenously injected perfluorochemicals can be lethal because they are immiscible with blood and can thus produce embolisms (blood vessel obstructions). This problem can be overcome by dispersing the perfluorochemical into very small particles with the aid of a surfactant. About 5 years ago, Robert P. Geyer of the Harvard School of Public Health, Boston, Massachusetts, made the fortuitous discovery that members of a family of polyoxyethylene–polyoxypropylene polymers called Pluronics not only emulsify the organic phase, but also serve as plasma expanders to reproduce the oncotic pressure normally provided by blood proteins. A typical preparation, then, would contain about 15 to 30 percent perfluorochemical by weight and 2.5 to 10 percent surfactant in an aqueous solution with an ionic composition resembling that of blood.

The Pluronic polyols have molecular weights ranging from 8,000 to 14,000. They are nontoxic at low concentrations —for a typical Pluronic, the lethal dose for 50 percent of mice receiving it (LD_{50}) is 10 grams per kilogram— and, unlike all ionic and many nonionic surfactants, they do not cause

Speaking of Science

Physics and Astronomy in 1972: Progress with Fusion

Several years ago the discoveries of the "quark" and polymerized water were announced, but today few scientists think that new entities were found. The year 1972 was marked with the announcement of several "firsts" in physics and astronomy, some of which may become matters of record while others become matters of dispute.

Two big announcements were the purported discoveries of an x-ray laser and a "black hole" in our galaxy. The evidence for the x-ray laser is being hotly disputed, but the possibility that a black hole was really discovered seems to be accepted more readily. Other firsts, such as the first close-up pictures of Mars and the first beam of high-energy protons (400 billion electron volts) from the National Accelerator Laboratory, were not so much new discoveries as outstanding technical achievements which will almost certainly lead to new understanding about the evolution of the fourth planet and the interactions of the fundamental particles of nature.

Out of the many experiments reported during the past year, the American Institute of Physics has selected about 35 developments as being "interesting, exciting, and important activities" of *Physics in 1972* (*1*). Some of them were:

► The announcement that the source of erratic x-ray emissions called Cygnus X-1 is a black hole, that is, a burned-out star that has collapsed to become so dense that it would trap anything that came near, including light. Cygnus X-1 is only one of many unusual objects that have been discovered with Uhuru (Small Astronomy Satellite-A), the first U.S. satellite for observations of x-ray emissions from the stars.

► An experiment claimed as evidence for an x-ray laser was reported by physicists at the University of Utah earlier this year. They irradiated a sandwich of glass and copper-sulfate gel with a neodymium glass laser, and reported that a collimated x-ray beam emerged. No one has yet confirmed the experiment, but many researchers have made proposals for producing coherent x-ray emissions in aluminum ions, oxygen, and diamond. An extremely important instrument that would become feasible if x-ray lasers are developed would be a high-resolution x-ray microscope for studying the structure of biological molecules.

► The most spectacular outburst ever witnessed by radio astronomers occurred on 2 September in another recently discovered x-ray source, called Cygnus X-3. The radio outburst, which was at least 1000-fold greater than the normal radio signal, was observed by six radio telescopes, but neither the x-ray detectors on Uhuru nor the ultraviolet detector on the recently launched Copernicus (Orbiting Astronomical Observatory-C) recorded any outburst. It was probably one of the best-documented events in radio astronomy. All the evidence together suggests that the signals did not just come from a hot body, but from a cloud of relativistic electrons.

► Another result of studies of an object producing x-rays, this time the Crab Nebula, seems to indicate that cosmic rays may come from the Crab pulsar. Measurements of the polarization of x-rays from the Crab Nebula, made in a rocket-borne experiment, established that the x-rays are polarized in the same direction and to the same extent as radio and optical emissions. This indicated that very high energy electrons and protons may come from the pulsar in the nebula.

► A recent addition to the long list of molecules found in space is hydrogen sulfide (H_2S). With the 11-meter (36-foot) radio telescope of the National Radio Astronomy Observatory on Kitt Peak in Arizona, astronomers detected millimeter-wave radiation characteristic of certain molecular transition in H_2S in the extended regions of seven galactic clouds. It had not been previously detected in any astronomical sources, including the sun, stars, planets, and comets. Also in the last year, hydrogen isocyanide (HNC), a peculiar isomer of hydrogen cyanide (HCN) that does not exist on the earth, was tentatively identified in two sources. Methanol (CH_3OH) and nitrous oxide (N_2O) were found in the central region of the Milky Way.

► A new route was opened in the search for a controlled thermonuclear fusion reaction, as the Atomic Energy Commission revealed that fusion induced by a very high-powered laser is beginning to look much more promising. The idea of laser-induced fusion is to heat small pellets of fusion fuel (deuterium plus tritium) so rapidly with a laser pulse that the fusion conditions will be reached before the heat is dissipated. Thus, the "magnetic bottle" that confines the fuel during fusion in the traditional schemes is not needed. The new idea in laser fusion is that many properly shaped pulses hitting the fuel pellet from all directions will produce an implosion. The imploding pellet is

hemolysis of erythrocytes. Clark has also had success with similar surfactants to which a fluorinated aliphatic chain has been attached. Because this chain has a higher affinity for the liquid perfluorochemical, he argues, the fluorinated surfactant is able to disperse the organic phase into smaller particles.

The size of the particles is apparently very important. Particles much larger than erythrocytes, which are about 10 micrometers in diameter, will not pass through small capillaries, and thus increase the risk of embolism. Furthermore, Geyer says, large particles are removed from the bloodstream more quickly than smaller ones. Decreasing the particle size, however, increases the viscosity of the emulsion for most perfluorochemicals, but this can be partially overcome by reducing the concentration of the organic phase. Geyer has also had great success with hydroxyethyl-starch as a viscosity reducer. The best preparations now in use have particle diameters less than 0.2 micrometer—a size that makes them colloidal suspensions rather than emulsions—and can remain in the bloodstream for as long as 7 days.

Preliminary experiments with perfluorochemical emulsions have shown much promise. Henry A. Sloviter of the University of Pennsylvania Medical School, Philadelphia, has shown, for example, that isolated rat brains per-

and Lasers, and New Discoveries with an X-ray Satellite

expected to reach fusion conditions with much less energy than needed in the simple laser heating approach.

► A significant advance was made along one of the old routes to a controlled fusion reaction, as a new method of heating fusion fuel in a toroidal magnetic bottle proved successful. The device is a variation of the tokamak design called the Adiabatic Toroidal Compressor (ATC). The ATC demonstrated that compression of the radius of the plasma by means of a magnetic field is a viable method of heating. The plasma pressure achieved in the ATC is several times higher than the best previous values which were reported by Soviet tokamak experimenters.

► The world's largest particle accelerator succeeded in producing a beam at the energy specified in the original design, 200 billion electron volts (Gev), in March, then reached 300 Gev in July and 400 Gev in December. The first experiment from the National Accelerator Laboratory in Batavia, Illinois, was completed in August.

► A new theory that attempts to unite two of the four basic forces of nature has been hailed as one of the most important developments in weak-interaction theory in the last 15 years. On a scale in which the nuclear force (the strongest) is 1, the electromagnetic force has a relative strength of 10^{-2}, the weak-interaction force is in the range 10^{-5} to 10^{-13}, and the gravitational force has a relative strength of 10^{-40}. The theory of Steven Weinberg of M.I.T. is a possible unification of the weak and electromagnetic forces. The theory predicts the existence of a charged intermediate vector boson with a mass greater than 37.3 Gev.

► The measurements of the number of neutrinos coming from the sun seem to have cast serious doubt on the current models of the sun. The neutrino is the only fundamental particle that can emerge unscathed from the middle of the dense sun and, in principle, bring information directly to the earth. It has no mass or charge, and interacts only by the weak interaction. A neutrino experiment conducted deep in the Homestake Gold Mine in South Dakota by Raymond Davis of the Brookhaven National Laboratory has found five to ten times fewer neutrinos than expected.

► A new type of laser that appears to be a reality is a semiconductor laser that emits visible light at room temperatures. Before 1970 semiconductor lasers (first demonstrated in 1962) operated only at low temperatures, and before 1972 the room-temperature lasers emitted only infrared radiation. A group at the University of Illinois, Urbana, reported laser action in the visible region of the spectrum for a semiconducting alloy of indium, gallium, and phosphorus. A group at RCA laboratories in Princeton, New Jersey, reported visible laser action from a cooled junction diode of the same materials. Junction diodes promise to be very inexpensive and simple lasers.

► With an extremely well-stabilized helium-neon gas laser, scientists at the National Bureau of Standards in Boulder, Colorado, simultaneously measured the frequency and wavelength of an infrared emission line, and thereby established an improved value for the speed of light. The new value is 299,792.4562 ± 0.0011 km/sec, with an error of only 1 part in 300 million. The accuracy with which the speed of light is known is important for a number of applications, such as the laser ranging measurements to determine the distance from the earth to the moon. At the National Bureau of Standards in Gaithersburg, Maryland, the frequency of a visible red emission line from a helium-neon laser was measured as $(473{,}612{,}166 \pm 29) \times 10^6$ hertz. This is the highest frequency ever measured absolutely.

The year 1972 was also marked by the publication by the National Academy of Sciences of a massive report, *Physics in Perspective*, on the past and future of physics, and by the awarding of the Nobel Prize in physics to the men responsible for the Bardeen-Cooper-Schrieffer (BCS) theory of superconductivity.

In outline, the theory shows how the interactions of electrons with the vibrations of the atoms in a crystal lattice result in an attraction between electrons that is greater than the mutual electrostatic repulsion. Because of the net attraction, electrons tend to form pairs, and this pairing is ultimately responsible for superconductivity. The BCS theory has been called the most important development in theoretical physics since quantum mechanics.

All in all, 1972 seems to have been a year for striking discoveries in astronomy, with the x-ray detecting satellite Uhuru, and notable progress in fusion, and lasers, while most of the rest of physics proceeded at a moderate steady pace.—WILLIAM D. METZ

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fused with such emulsions retain their electrical activity as well as or better than they do when perfused with a suspension of erythrocytes. He has obtained similar results using the emulsions to maintain normal function in isolated canine kidneys, and has also shown that a substantial portion of the blood of mice and frogs can be replaced by such an emulsion with no apparent ill effects.

William H. Rosenblum of the Medical College of Virginia, Richmond, has replaced as much as 75 percent of the blood of mice with a perfluorochemical emulsion and measured several parameters of brain function. He finds that all such measurements are within normal limits for large numbers of mice and, since the brain is the organ most sensitive to oxygen deprivation, concludes that the emulsion is fulfilling its purpose. These mice also respond to the stress of oxygen starvation in the same manner as control animals, an indication that the presence of the perfluorochemical has not itself stressed the brain.

Clark has replaced as much as 90 percent of the blood of dogs with emulsions, and has observed no ill effects: some of these dogs are still alive and well almost 4 years after the replacement. Using an oxygen electrode implanted in the brain of these dogs, he has shown that the partial pressure of oxygen in the bloodstream is at least three times as high under conditions of 90 percent replacement as it is in control animals. The pressure is also well above that at which the remaining hemoglobin releases oxygen, indicating that all oxygen transport is provided by the emulsion.

Geyer has recently successfully replaced all of the blood of rats with a perfluorochemical emulsion. These animals show no apparent ill effects from infusion of the blood substitute, and immediately begin producing erythrocytes and blood proteins. By the time most of the perfluorochemical has been cleared from circulation, generally within about a week, the animals have regenerated nearly all their erythrocytes. And the mice have a normal life-span after the replacement. This success, Geyer says, relies on development of the proper flow characteristics of the emulsion, particularly a reduction in its viscosity, and is the result of 5 years' work in refining the preparations.

Good results have been obtained in several laboratories with the use of perfluorotributylamine and perfluorobutyltetrahydrofuran, but many other perfluorochemicals have been examined. Most others have been found unsatisfactory either because they do not form good emulsions or because their high vapor pressure causes tissue damage in the lungs. The primary limitation of most of the perfluorochemicals is their accumulation in body tissues. Perfluorochemicals in crude preparations tend to accumulate in the liver and spleen, but there is some evidence that the accumulated chemicals become more widely dispersed as the particle size of the emulsions is decreased. The perfluorochemicals are, however, highly inert (much more so than polychlorinated biphenyls and DDT, for example), and there is some evidence—such as the absence of fluorinated products in the urine or of fluoride in macerated tissues—that they are not metabolized. More definitive evidence of their fate has not been obtained because of the lack of isotopically labeled perfluorochemicals that can be traced through the body more easily.

Accumulation a Major Problem

Accumulation of perfluorochemicals in various organs and lack of knowledge of their long-term effects could be a major impediment to the use of the blood substitutes in humans, but most investigators are confident that nonaccumulating compounds will be developed. Clark has just discovered two new compounds—perfluorodecalin and perfluoromethyldecalin—that are completely eliminated from animals in 1 to 3 weeks and that provide a tenfold decrease in viscosity of the emulsion. More such compounds seem certain to be found when a greater number of perfluorochemicals are available for screening.

Many other problems must also be overcome before clinical testing in humans can be attempted. Some other investigators, for example, have been unable to duplicate Clark's and Geyer's survival rates, and it now seems likely that this is a result of variability of the preparations. One source of this variability occurs in formation of the emulsion, which requires a great amount of energy. This energy has frequently been provided by sonication (ultrasonic vibration) of a crude emulsion, but it is now apparent that, under some conditions, sonication breaks down the perfluorochemicals, thereby releasing toxic quantities of fluoride ion. Mechanical homogenization is generally inadequate in producing sufficiently small particles, and a better method of emulsification would be very useful.

Other variables could include the presence of toxic impurities in both the perfluorochemicals and the surfactants, as well as the use of nonoptimum concentrations. The research effort would be greatly speeded, Geyer contends, if there were a centralized source of high quality materials and emulsions so that experimenters could simply test the emulsions for physiological effects rather than waste time learning how to produce them. Such a source, he adds, would also increase the limited supplies of high purity perfluorochemicals now available.

The ultimate bridge to be crossed before clinical testing can proceed is experimentation with primates or other animals to simulate more closely conditions in humans. Geyer has already replaced as much as 80 percent of the blood of monkeys with emulsions, but it is obvious that a much more extensive demonstration of both efficiency and safety in such animals will be necessary before the Food and Drug Administration will allow any use in humans. This testing will require much greater quantities of the emulsions and a large infusion of research funds.

Even when perfluorochemical emulsions have been proved safe and effective, they will still be only an erythrocyte substitute. Perhaps the most critical deficiency of such preparations will be the absence of a clotting system, but other problems could include the absence of the globulins and leukocytes that comprise the body's immune defense system and lack of the buffering capacity and enzymatic activity normally provided by erythrocytes. Nonetheless, these synthetic materials offer a very real possibility of functioning as blood for at least a few hours, long enough perhaps to explore the physiology of other blood components in experimental animals, long enough to save the prize animal in the zoo, long enough to get an accident victim to a hospital, or long enough to perform an open-heart surgical procedure.

—THOMAS H. MAUGH II

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