Soc. Div. Fuel Chem. Prepr. **13**(4), 30 (September 1969)
34. W. B. Behnke, Jr., paper presented at AAAS meeting, Boston (28 December 1969).
35. F. W. Theodore, "Low Sulfur Boiler Fuel Using the Consol CO_2 Acceptor Process: A Feasibility Study" (report from Consolidation Coal Company to OCR, November 1967).
36. J. F. Jones, M. R. Schmid, M. E. Sacks, Y. Chen, C. A. Gray, R. T. Eddinger, "Char Oil Energy Development" [report from FMC Corporation to OCR (January 1967)]; C L. Tsaros, *Amer. Chem. Soc. Div. Fuel Chem. Prepr.* **12**(3), 95 (September 1968); R. T. Eddinger, J. F. Jones, F. E. Blanc, *Chem. Eng. Progr.* **64**(10), 33 (October 1968); C. L. Tsaros, J. L. Arora, W. W. Bodle, *Amer. Chem. Soc. Div. Fuel Chem. Prepr.* **13**(4), 252 (September 1969); N. P. Cochran, *NEREM Rec.* **11**, 134 (1969).
37. E. Gorin, G. P. Curran, J. D. Batchelor, Patent 2,824,047 (18 February 1958); J. D. Batchelor, E. Gorin, C. W. Zielke, *Ind. Eng. Chem.* **52**, 161 (1960).
38. C. A. Gray, M. E. Sacks, R. T. Eddinger, *Amer. Chem. Soc. Div. Fuel Chem. Prepr.* **13**(4), 270 (September 1969).
39. M. L. Vestal and W. H. Johnston, *ibid.* **14**(1), 1 (May 1970).
40. D. E. Elliott, "Can Coal Compete? The Struggle for Power," inaugural lecture, University of Aston in Birmingham, England (20 November 1969).
41. M. Benedict, *NEREM Rec.* **11**, 130 (1969).
42. A. Rozinek, *Feuerungstechnik Leipzig* **30**, 153 (1942); R. H. Essenhigh and J. M. Beér, *J. Inst. Fuel* **33**, 206 (1960).
43. C. H. Secord, U.S. Patent 3,253,906 (31 May 1966); H. R. Hoy, A. G. Roberts, D. M. Wilkins, *Inst. Gas Eng. J.* **5**, 444 (1965).
44. B. von Portatius, *Freiberg. Forschungsh. Reihe A* **69**, 5 (1957); A. M. Squires, *Chem. Eng. Progr.* **58**(4), 66 (April 1962).
45. W. Peters and H. Bertling, *Amer. Chem. Soc. Div. Fuel Chem. Prepr.* **8**(3), 77 (August 1964); R. Rammler, *Erdoel Kohle Erdgas Petrochem.* **19**, 117 (1966).
46. M. Gomez, W. S. Landers, E. O. Wagner, *U.S. Bur. Mines Rep. Invest.* **7141** (1968).
47. There are positive factors in the situation. Many of the present student generation have a bent toward service, and engineering students are growing sensitive to career stability. Word of layoffs from space or military programs reaches campuses quickly, and I predict that enrollments will drop precipitately in non-real-world engineering activities. The space effort attracted thousands of first-class minds whose loss to the real world's business the nation can ill afford. It will be important to decision makers of the future that they possess good data on the degree to which these minds succeed in obtaining retreads and again finding responsible work.
48. Work at the City College on desulfurization of fuels by calcined dolomite is supported by Research Grant No. AP-00945 from the National Air Pollution Control Administration, Consumer Protection and Environmental Health Service. This article is adapted from a paper presented 28 December 1969 at the Boston meeting of the AAAS in the symposium entitled "Power Generation and Environmental Change," arranged by the AAAS Committee on Environmental Alteration.

Cancer Viruses in Primates

Newborn simians are inoculated with viruses and neoplastic cells in an attempt to induce leukemia.

Roy Kinard

In 1962 the National Cancer Institute assigned high priority to the inoculation of newborn simians with oncogenic viruses as a part of the intramural viral oncology program. Gordon Zubrod, then the Institute's director of intramural research, introduced the concept of establishing breeding colonies in the United States to supply newborn simians for this purpose. Zubrod and Ray Bryan insisted that a reliable source of newborn simians would be necessary, and argued that, even if the search for human cancer viruses failed, the animals would be a valuable asset to other National Institutes of Health programs. Contracts to begin production and inoculation of newborn rhesus monkeys, baboons, and marmosets were arranged in 1962 and 1963. In 1964, the Special Virus-Leukemia Program, headed by Frank Rauscher, took over the support and direction of the existing contract projects.

In 1968 the program was renamed the Special Virus Cancer Program and was expanded to include the study of other neoplasms, but the projects described here are still directed mainly toward induction of leukemia in simians. The administrative functions of the program are to plan and coordinate projects so that the total effort will converge toward attaining the objectives listed below. This article is written in an effort to prevent unnecessary duplication of effort and to solicit the cooperation of individuals who may be considering similar work (*1*). Some general background and rationale is presented, then the work of the various collaborative projects is described.

The author is primate projects coordinator, Special Virus Cancer Program, National Cancer Institute, Bethesda, Maryland 20014. This article is written on behalf of the National Cancer Institute Primate Study Group. Other members of the group are Robert Cooper, Friedrich Deinhardt, Maurice Hilleman, Robert Holdenried, Joseph Melnick, and Frank Rauscher, Jr.

Program Rationale

The original program was based on the convictions that at least one virus is essential for the induction of human leukemia and that sufficient knowledge and technical competence was then available to achieve the following objectives: (i) induce leukemia in an experimental primate host; (ii) recover the responsible virus; (iii) establish laboratory passage strains of the isolated virus in animals or tissue cultures; (iv) confirm the pathogenicity of the virus for humans by seroepidemiological survey of leukemia patients and their contacts, whether human or animal; and (v) develop an effective vaccine or other control measure.

The knowledge underlying the convictions, and the techniques that can be used to attain these objectives, have been recently reviewed in detail (*2–4*). Viruses are known to be the primary cause of several forms of leukosis in chickens, mice, and cats (*5*). Viruses are probably responsible for various forms of leukemia in dogs and cattle, as well as for many transmissible and transplantable neoplasms of other vertebrates. Most viral leukemias in mice are preventable by vaccines. The leukosis viruses of chickens are a complex of related viruses one of which, the Rous sarcoma virus, causes malignant sarcoma in *Saguinus nigricollis* (a marmoset) and benign fibroma in the rhesus monkey. Simians of the family Cercopithecidae (macaques, baboons, and some other African monkeys) are susceptible to many cytolytic viruses of humans and have been used for experimental work, including the production and testing of vaccines, on many

of the acute diseases caused by these viruses. Comparative studies of susceptibility to viruses and of molecular homology of proteins and nucleic acids in mammals, including primates and man, tend to reinforce taxonomic and phylogenetic relationships previously established by anatomical and reproductive criteria. Kuru, a slow, lethal, neurotropic infection of man, was recently transmitted to chimpanzees and spider monkeys but not to other animals, including other primates tested (*6*). Several of the mouse leukemia viruses will cause leukemia in rats but not in any other common laboratory or domestic animal tested; the common mouse and rat used in the studies belong to the same family but not to the same genus.

Not only are primates likely experimental hosts for human viruses but discovery of a human virus that causes leukemia in a simian would be sufficiently convincing and encouraging to allow us to proceed to the next intermediate step, seroepidemiologic survey for the antigen in the human population, and perhaps even vaccine trials, either in simians or in humans. (Techniques for these steps are being developed in other projects of the program and are not discussed here.) Therefore, it is imperative that efforts be made to induce leukemia in man's nearest phylogenetic relatives, and that certain steps be taken to increase the probability of success.

First, the animals are inoculated with a great variety of known viruses or malignant cells presumed to contain viruses. Blood and bone marrow from untreated human leukemia patients are used when available. Tissues from patients with Burkitt's lymphoma and infectious mononucleosis also have high priority. Tissues from a rhesus monkey with myeloid leukemia have also been used (*7*). But we are not necessarily looking for a new specific virus of which leukemia is the sole or major manifestation. It is possible that human leukemia is induced directly or indirectly by common ubiquitous viruses, alone or in combination with other oncogenic factors. Therefore, Rous virus, Rauscher and Moloney murine viruses, cytomegalovirus, and many other known viruses are also being tested. Herpes-type and type C particles, often seen by electron microscopy in neoplastic cells of man and domestic animals, are used (*8*). Other examples of the kinds of viruses tested are given below in the discussion of specific projects.

The dose of virus or presumed virus-containing material must be as large as possible. The chance of inducing disease in an unnatural host and the chance of recovering virus from the induced disease is greatly enhanced when the dose of virus inoculated is large. (Several contract projects are concerned with the concentration or production of viruses by biological and physical methods.) Then, the resistance of the inoculated animal should be as low as possible. Only very young animals, fetal or newborn, are inoculated; x-irradiation and radiomimetic drugs are given before and after inoculation.

Adequate time must be allowed for incubation and pathogenesis. The optimum observation time has been arbitrarily set at 7 years, mainly because acute leukemia and Burkitt's lymphoma in children reach their peak incidence at or before the age of 7 years. Even in mice inoculated at birth with known mouse leukemia virus, the latent period can be as long as 2 years if the dose of virus is low and the mice are not of a highly susceptible strain. In the current program, the oldest primate inoculated at birth is now 7 years old, but most are still under 2 years old. Leukemia has not yet been diagnosed in an inoculated primate.

Finally, the variety of species and the number of individual animals inoculated must be as high as possible. Each contractor has had to obtain breeding stock and begin producing newborn animals before inoculation could begin. Several species are now breeding well; others are being tried, as space and breeding stock become available.

Because of the variety and concentration of the viral inocula used, personnel and uninoculated animals must be protected from contamination. The methods and degree of protection vary, but, in general, each contractor (i) removes the infant from its dam at birth and places it in a separate nursery for inoculation, (ii) provides protective clothing for personnel and plastic isolation cages for inoculated infants, and (iii) keeps inoculated animals in individual cages, as well protected from outside contact as facilities will allow.

Collaborative Projects

The most general and extensive project for inoculation of newborn primates is at Bionetics Research Laboratories in Kensington, Maryland. The project was developed by Arthur Pallotta and is now directed by John Landon and David Valerio. This commercial contractor is prepared to inoculate available primates with any inoculum approved by the National Cancer Institute. Their most notable accomplishment has been the development of breeding colonies and nursery with an annual production rate of over 600 newborn, artificially fed primates, mostly *Macaca mulatta*, and *M. irus* (*9*). Other species which have been inoculated at the laboratories, but not necessarily produced there, are *M. nemestrina, M. radiata, Papio cynocephalus, Cercopithecus aethiops, C. albogularis, Erythrocebus patas, Saguinus oedipus, Callithrix jacchus, Galago crassicaudatus*, and *Pan troglodytes*.

Newborn primates at Bionetics Research Laboratories are placed in clear plastic isolators for inoculation and nursing. They are handled only through gloves and sleeves in the isolator wall. After weaning at the age of about 4 months, they are kept in cages within individual plastic enclosures. Air enters and leaves each isolator or holding-cage enclosure through filters under negative pressure. All animal waste, including air, is decontaminated as it leaves the building. Over 1400 animals, about 1100 of them inoculated and the remainder uninoculated controls, are now in the holding colony under observation. Production reached its peak of over 600 per year in 1967. Due to recent budget reductions, production has been reduced to 300 per year.

Over 70 investigators in 50 different laboratories throughout the world have provided inocula for this project. These inocula are accepted with the understanding that they contain specific viruses or virus-like particles, or that they have special relevance to the objectives of the program. Of the nearly 1000 inocula given at birth to the animals, the most numerous have been the following.

1) Viruses or virus particles: adenovirus 12, simian virus 40, echovirus 9, reovirus 1, reovirus from Burkitt lymphoma, Rous sarcoma virus, Moloney sarcoma virus, rubella virus, herpes genitalis virus, and herpes-type particles in chimpanzee leukocyte culture.

2) Tissues or cells from patients with myelogenous leukemia (acute and chronic), lymphocytic leukemia (acute and chronic), Hodgkin's disease, Burkitt's lymphoma, polycythemia, rhabdomyosarcoma, epidermoid carcinoma, warts, infectious mononucleosis, and myelogenous leukemia, rhesus.

During 1968 and 1969, emphasis was placed on the inoculation of rhesus monkeys and chimpanzees with fresh blood or bone marrow from human leukemia patients at NIH. Over 100 newborn rhesus and five chimpanzees were inoculated with tissues and cells from a monkey with myeloid leukemia, contributed by Brooks Air Force Base (*7*). Inoculation of fetal rhesus in utero, at about 80 days or the middle of the gestation period, is beginning and will probably be emphasized in the future.

The Bionetics Research Laboratories also uses simian tissue culture to search for indigenous virus-like particles and to test these and other viruses for oncogenic potential or cytopathic effect in tissue culture. Cell cultures have been established from tissues and blood cells of rhesus, chimpanzees, and baboons. Many of these cultures contain herpes-virus-like particles and have been inoculated into newborn rhesus.

The department of virology and epidemiology of the Baylor College of Medicine at Houston, Texas, directed by Joseph Melnick, has a contract with the Special Virus Cancer Program for the comprehensive study of viruses as related to human cancer, which includes inoculation of newborn and fetal baboons (*4*). Newborn and pregnant baboons, *Papio anubis* and *P. cynocephalus*, are provided by the Southwest Foundation for Research and Education at San Antonio, Texas. The newborn animals are sent to Houston by direct commercial air express in small padded boxes. Losses attributed to transport have been negligible, apparently because employees of the research institutions at both locations attend the animals at all times except while the plane is closed for flight.

Over 500 baboons have been inoculated at Baylor, and over 400 remain under observation. The oldest was inoculated at birth in 1963, but most are less than 2 years old. Forty were inoculated in utero at the mid-point of the gestation period, and over half of these fetuses were delivered alive at term by cesarean section. Current production is about 100 per year, but the number is being reduced due to recent budget reductions. The inoculated baboons are kept in individual stainless steel isolators in small glass-enclosed rooms, ten per room. At weaning, they are placed in individual cages in similar rooms, where they stay until they are a year old. The entire area is restricted; all personnel in the area wear clean protective clothing, including disposable masks and shoe covers. At 1 year of age the baboons are removed to nearby buildings, where they are kept in ordinary large double-deck primate cages.

For inocula, fresh plasma or bone marrow cells from children with acute leukemia are preferred, if they are available. Other inocula often used are human wart suspension; lymphoblastoid cell cultures from patients with leukemia, Burkitt's lymphoma, or infectious mononucleosis; and various mixtures of these. Several human viruses that have been used, some of them known to cause tumors in experimental animals, are adenoviruses 2, 7, and 12; reoviruses 1 and 3; echovirus 9; simian adenovirus 7; rubella viruses (three strains); cytomegalovirus; and herpes simplex virus. Most of these viruses are also sent to Bionetics Research Laboratories and inoculated into rhesus monkeys there.

Many of the inoculated baboons are treated with one or more of the following immunosuppressants or carcinogens: x-ray, Imuran, prednisone, rabbit antiserum to baboon lymphocytes, urethane, or benzpyrene. The various inocula and other treatments have been given in combinations too numerous to list here. For example, 44 newborn baboons received inocula from leukemic children plus Imuran and prednisone; two baboons were inoculated in utero with a mixture of cells from patients with leukemia and patients with infectious mononucleosis. About 50 of the oldest inoculated baboons have been placed in a radiation field at the Delta Regional Primate Research Center of Tulane University, where they receive a dose of about 1.4 rad per day for an indefinite period.

Besides the work with baboons, this contract covers extensive laboratory work involving the techniques of immunology, cytogenetics, biophysics, electron microscopy, and inoculation of rodents in the search for viruses causing human cancer. The Baylor staff is especially interested and active in applying these techniques to study of the lymphoblastoid cell lines mentioned above, to human wart virus, and to certain herpes viruses believed to be associated with Burkitt's lymphoma and cervical carcinoma.

The third contract provides for the testing of tumor viruses in newborn marmosets at Presbyterian–St. Luke's Hospital in Chicago. This project is directed by Friedrich Deinhardt, chairman of their department of microbiology. The animals used are *Saguinus nigricollis* and *S. fuscicollis* (white-lip marmosets). The breeders are kept as monogamous pairs, 60 pairs in the hospital and 60 pairs in an auxiliary colony at Lincoln Park Zoo, directed by Lester Fisher. The total production of the two colonies is now about 200 live births per year; this rate will improve because proved breeding pairs are averaging three offspring per year. Many of the infant marmosets are isolated in small plastic boxes and nursed artificially, especially those inoculated at birth. The protective procedures are similar to those at Baylor.

The most important success of this project has been the induction of fatal metastasizing fibrosarcomas in marmosets by inoculation with the Schmidt-Ruppin strain of Rous sarcoma virus (*10*). Marmosets inoculated subcutaneously or intramuscularly at ages up to 7 months regularly have tumors at the site of inoculation, and metastases within 30 days after inoculation. Cells from the induced tumors have been cultured by standard tissue culture methods, and several cell lines have been developed. Current experimental work in which this virus-tumor system is used includes isolation of virus and detection of complement fixing antigen in cell cultures, reinoculation of the virus so isolated, reinoculation of marmosets previously inoculated with inactive virus, aerosol inoculation of young marmosets, and inoculation of other primate species. Other accomplishments of this project have been the recent induction of tumors in marmosets with cat sarcoma virus (*11*), the discovery of viral hepatitis of human origin in marmosets (*12*), and the isolation of an important lethal herpes virus of marmosets (*13*).

Since most of the work done in the past has resulted in relatively acute illness and quick death, no long-term holding and observation of inoculated animals has been possible. Space for long-term holding has recently been provided. Animals are now being held there after receiving inocula of the following origins: Bryan strain Rous sarcoma virus, mouse sarcoma virus (Moloney), DiGuglielmo's syndrome (erythroleukemia), human papilloma, Burkitt lymphoma (Epstein-Barr virus), Kaposi sarcoma, and cat leukemia.

Immunosuppressants and in utero inoculation have not yet been used in this project.

The fourth and last contract of this

group provides for evaluation of the reproductive potential, in captivity, of several species of small primates. This project is under the direction of Robert Cooper at the Institute for Comparative Biology of the Zoological Society of San Diego. Primates of species whose adult members weigh about 1 kilogram or less may be much cheaper than macaques or baboons to buy and maintain, and may reproduce faster. Representatives of all families of primates with the exception of Pongidae and Hominidae were considered, and, since the beginning of this project in 1962, 13 species of four families have been tried. The principal criteria for success have been high reproductive rates and survival of infants. Only four of these species failed to produce viable offspring in reasonable numbers. These species are *Saguinus oedipus* (cotton-top marmoset), *Aotus trivirgatus* (night or owl monkey), *Cebuella pygmaea* (pygmy marmoset), and *Galago senegalensis* (lesser bush baby). Evaluation of the reproductive potential of *Saguinus nigricollis* and *S. fuscicollis* (white-lip marmosets) was discontinued because these species are reproducing well in one of the other projects. Evaluation of *Leontideus rosalia* (golden marmoset) was discontinued because of impending extinction of the species and lack of breeding stock. The species that are breeding successfully and in which study is continuing are *Cercopithecus aethiops* (African green monkey), *Cercopithecus (Miopithecus) talapoin* (talapoin monkey), *Saimiri sciureus* (squirrel monkey), *Callithrix jacchus* (common marmoset), *Saguinus mystax* (moustached marmoset), and *Galago crassicaudatus* (bush baby). The total production of newborns is about 60 per year, but the number varies because of the experimental nature of the project. All these animals are kept outdoors in galvanized wire cages above a concrete floor. Each cage has a small fiberglass box with a 150-watt electric heater in the floor. The outstanding successes of the project have been the excellent reproduction of *Galago crassicaudatus* and *Cercopithecus aethiops*. The latter species is too large for the purposes of this contract, but the offspring are needed for inoculation with oncogenic viruses in studies at Bionetics Research Laboratories. The females are sent there in late pregnancy and returned to San Diego for breeding. Offspring of the galagos and other species have been used in several collaborative projects which include administration, through inhalation and parenteral inoculation, of Rous sarcoma virus (by F. Deinhardt); administration, through inhalation and parenteral inoculation, of benzpyrene; and treatment with thalidomide.

References and Notes

1. Virologists, pathologists, and clinical physicians having further interest in this program or materials to contribute should get in touch with Roy Kinard, National Cancer Institute, Bethesda, Md. 20014 (phone: 301-496-3323) either directly or through one of the collaborators. A list of information and materials needed by other segments of the overall virus cancer program has already been published [see F. J. Rauscher, *Hosp. Pract.* (April 1967)].
2. W. R. Bryan, *Proceedings of the International Conference on Leukemia-Lymphoma* (Lea and Febiger, Philadelphia, 1968), pp. 73–83; ———, *Perspectives in Leukemia* (Grune and Stratton, New York, 1968), pp. 94–109; ———, A. J. Dalton, F. J. Rauscher, *Progr. Hematol.* **5**, 137 (1967).
3. F. J. Rauscher, *Hosp. Pract.* (April 1967).
4. J. L. Melnick, M. Benyesh-Melnick, D. J. Fernbach, C. F. Phillips, R. R. Mirkovic, *Baboon Med. Res.* **2**, 669 (1967).
5. C. Rickard, in *Experimental Leukemia*, M. A. Rich, Ed. (Appleton-Century-Crofts, New York, 1968), pp. 173–189.
6. D. C. Gajdusek, C. J. Gibbs, Jr., D. M. Asher, E. David, *Science* **162**, 693 (1968).
7. M. Valerio, J. C. Landon, J. R. M. Innes, *J. Nat. Cancer Inst.* **40**, 751 (1968).
8. F. J. Rauscher, *Cancer Res.* **28**, 1311 (1968).
9. D. A. Valerio, K. D. Courtney, R. L. Miller, A. J. Pallotta, *Lab. Anim. Care* **18**, 589 (1968).
10. F. Deinhardt, *Perspect. Virol.* **5**, 183 (1967).
11. ———, L. Wolfe, G. Theilen, S. Snyder, *Science* **167**, 881 (1970).
12. F. Deinhardt, A. W. Holmes, R. B. Capps, H. Popper, *J. Exp. Med.* **125**, 673 (1967).
13. A. W. Holmes, J. A. Devine, E. Nowakowski, F. Deinhardt, *J. Immunol.* **96**, 668 (1966); J. L. Melnick, M. Midulla, I. Wimberly, J. G. Barrera-Oro, B. M. Levy, *ibid.* **92**, 596 (1964).

Medical Literature: The Campus without Tumult

Many medical journals would benefit from a clearer definition and more active pursuit of their goals.

Franz J. Ingelfinger

About 3 years ago, when I was privileged to succeed Dr. Joseph Garland as editor of the *New England Journal of Medicine*, some doubts were raised concerning the wisdom of a move from a professor's to an editor's chair. The doubters, being professors of medicine themselves, held that the duties of a full-time medical editor were not as rewarding as those of a professorial personage. But they were wrong, I hope. Indeed, in my well-rationalized imagination, I had become a dean, and a dean not only of the campus of the usual medical school, but of the unseen campus of a mighty multiversity to which right now 120,000 students pay tuition. The amount of this tuition, I admit, is a scandalous pittance. In addition, before anyone objects that a medical school deanship these days hardly warrants the word "promotion," let me emphasize the unique advantages of my deanship. Whatever happens to me, it is quite unlikely that my rambunctious students will break down my doors, smoke my cigars, deposit dejecta in the corners of my office, and—on top of it all—throw me physically downstairs.

The comparison of the general medical journal with a medical school is not farfetched. For the primary purpose of the *New England Journal of Medicine*, as an example, is certainly educational, and, like the medical school, the *Journal* has a pedagogic philosophy and a curriculum. It also has its teachers (the authors), its stu-

The author is the editor of the *New England Journal of Medicine*, Boston, Massachusetts 02115.