THE CANCER LETTER
RESEARCH EDUCATION CONTROL

1411 ALDENHAM LANE RESTON, VIRGINIA TELEPHONE 703-471-9695

Vol. 1 No. 31

Aug. 1, 1975

Subscription $100 per year

WHEN IS A CANCER CURED? NCI SUGGESTS ONE-YEAR SURVIVAL RATES USEFUL IN DETERMINING ADVANCES

The five-year survival rate yardstick for measuring the results of cancer treatment is being questioned by NCI statisticians who feel there may be other time intervals of greater significance in various forms of the disease.

The historic use of five-year survival rates as an indication of the cure rate "is an intellectual carryover" from the days when much less data were available than at present, said Marvin Schneiderman, who heads NCI's Field Studies & Statistics Branch.

"Five-year survival is not a five-year cure," Schneiderman said. "Time of survival after diagnosis varies with the different forms of cancer." NCI's End Results Program is in the process of developing survival curves for each form of the disease which may help determine the significant survival times.

"Where the curve becomes flat (that is, when the death rate levels off), I think we can say patients who survive to that time have been cured," Schneiderman said. "For some cancers that will be early, perhaps less than five years. For others, it will be later."

Schneiderman presented to the National Cancer Advisory Board the

(Continued to page 2)

In Brief

MATHEWS COULD HELP IN FIGHTING OMB OBSTRUCTION OF CANCER PROGRAM; EASILY WINS SENATE APPROVAL

DAVID MATHEWS' confirmation as HEW secretary breezed through the Senate with practically no opposition. General impression is that he's an intelligent guy, will leave most department-level decisions regarding health to Ted Cooper, his asst. secretary for health. Unlike his predecessor, Mathews isn't tied to the old Nixon-OMB policies aimed at limiting growth of the cancer program and could be helpful in fighting the OMB diehards on such matters as NCI's budget and personnel ceiling, construction grants, number of comprehensive centers, etc. . . . **ROSWELL PARK** investigators Claude Merrin, Tin Han, Edmund Klein, Zew Wajsman and Gerald Murphy reported on their use of BCG in treating carcinoma of the prostate. Seventy percent of the patients, all in the final stage of the disease, had a decrease in the size of the primary tumor after weekly injection of BCG for four weeks. Merrin said that immunostimulation with BCG could improve prognosis in conjunction with other therapeutic measures. . . . **NIH HAS** backed down and will accept for review the grant application of Nobelist Albert Szent-Gyorgyi *(The Cancer Letter,* June 27). NIH previously had asked for more information on Szent-Gyorgyi's proposal to pursue his "electromagnetic theory of cancer" before sending it on to a study section. The 82-year-old biochemist explained his theory in a paper presented at a meeting of Nobel laureates in Germany June 26.

FIVE-YEAR SURVIVAL RATES PARALLEL BUT DON'T KEEP UP WITH ONE-YEAR

(Continued from page 1)

results of a study comparing one-year and five-year survival data. He contended the study shows that one-year data could be extrapolated to determine what the approximate five-year survival rate would be.

"My point was that one-year information can be useful in evaluating a program," Schneiderman said. "As an example, take a cancer which has had a one-year survival rate of 50% and a five-year rate of 20%. That represents a potential gain of 50% with one-year survival and 80% with the five. Suppose that with a new therapy you achieve a gain of 5% in one-year survival. That is 10% of the total possible gain of 50%. The five-year gain, if the 10% improvement applied, would be 10% of 80%, or a gain of 8%."

The study showed that "we are not doing quite that well," Schneiderman said. "We are not getting the full percentage gain in five years that we did in one year, but only two-thirds to three-fourths of it." Other causes of death were taken out of the study, so that was not a factor.

It was suggested during the Board discussion that the first-year rates were higher because of "heroic efforts" to "prop up" cancer patients, efforts that could not keep them alive for five years. Schneiderman agreed this could be a factor in the drop off, but was not responsible for the entire gain in first-year rates. If it were, there would be no gain after five years.

In fact, the study, which used three calendar periods—1960-64, 1965-69 and 1970-71—did show a parallel between trends in one and five-year rates. An increase in the one-year rate suggested that the five-year rate is likely to increase.

Results of the study were published in a paper by Sidney Cutler, chief of NCI's Biometry Branch, and his colleagues, Max Myers and Sylvan Green. It appeared in a July issue of the *New England Journal of Medicine.*

"The data presented indicate that the picture is neither as dull nor as bright as some have claimed," they wrote. "The improvement in patient survival observed during the 1940s and 1950s has generally slowed since. However, continuing improvement in survival rates took place during the 1960s and is continuing into the 1970s for a substantial segment of cancers. In fact, prognosis for more than half of all cancer patients is better now than it was 10 years ago. The recent upward trend is less dramatic, but it is nonetheless real and consequential. . .

"The improvements that have been observed are due to a variety of factors. Among these are an increase in the proportion of cancers diagnosed in a controllable stage of development; improvement in surgical and supportive techniques, making possible the surgical treatment of a larger proportion of patients with cancer; improvements in diagnostic techniques, leading to more knowledgeable planning of treatment strategy; and improvements in radiotherapy, endocrine therapy and chemotherapy. Many scientists, physicians, institutions and programs have contributed to this forward movement.

"In recent years, scientists and physicians have arrived at a clearer understanding of the systemic nature of the disease processes known as cancer and of the tumor-host relationship. New treatment strategies have been and continue to be developed based on this new knowledge. Continued collection of information on the experience of a broad spectrum of patients treated in a wide variety of institutions, will reveal the extent of the payoff.

"Effective control of cancer will be achieved through a variety of approaches including prevention and prophylactic treatment of premalignant disease in addition to more effective screening for and treatment of invasive cancer. The marked decrease in the incidence of invasive cancer of the uterine cervix in large part reflects the benefits of cytologic screening for preinvasive cancer. The sharp and continuing decrease in the incidence of cancer of the stomach undoubtedly reflects changes in exposure to dietary and possibly other environmental factors. The National Cancer Institute is increasing support for a variety of epidemiologic studies that in time should provide information on which to base effective control programs."

NCI executives, NCAB members and the President's Cancer Panel are more than a little sensitive about survival statistics as the result of critical publications which used 1969 data in an attempt to show the Cancer Program has failed. They feel frustrated in attempts to answer the unfair criticism by the fact that there is a minimum time lag of 10-12 years before new therapeutic regimens introduced now can be expected to be reflected in improvement of overall national survival and mortality figures.

Guy Newell, NCI deputy director, is one of the more outraged by the statistical attacks.

"Do these improvements (cited in Cutler's paper), interpreted by some as being meaningless and insignificant, represent a dramatic breakthrough in cancer research and application?" Newell asked. "Some would say not. On the other hand, the many millions of Americans alive today who collectively make up these percentages would probably say differently."

Newell pointed out that the greatest improvement in survival has occurred among patients with relatively rare forms of cancer, notably leukemia and some types of lymphoma particularly Hodgkin's disease.

"These improvements have occurred due to the introduction of new treatment methods for these diseases during the mid-1960s," Newell said. "Additional improvement can be expected for patients with reticulum cell sarcoma based on a recent report by DeVita et al in early 1975 of actual cures in 40%

of patients with advanced reticulum cell sarcoma using combination chemotherapy. Before this, this disease was thought to be invariably fatal and only temporarily responsive to chemotherapy. Marked improvement in survival of children with osteogenic sarcoma is expected to be achieved by the use of high dose methotrexate with citrovorum factor rescue administered immediately following initial surgery.

"Knowledge gained from the research that went into these successes has quickly been transferred to treatment regimens for several of the more common types of cancer which have been those more resistant to treatment in the past."

RFPs AVAILABLE

Requests for proposal described here pertain to contracts planned for award by the National Cancer Institute, unless otherwise noted. Write to the Contracting Officer or Contract Specialist for copies of the RFP. Some listings will show the phone number of the Contract Specialist, who will respond to questions about the RFP. Contract Sections for the Cause & Prevention and Biology & Diagnosis Divisions are located at: NCI, Landow Bldg. NIH, Bethesda, Md. 20014; for the Treatment and Control Divisions at NCI, Blair Bldg., 8300 Colesville Rd., Silver Spring, Md. 20910. All requests for copies of RFPs should cite the RFP number. The deadline date shown for each listing is the final day for receipt of the completed proposal unless otherwise indicated.

RFP NCI-CM-67002

Title: *The isolation of antineoplastic agents from plants*

Deadline: *Sept. 19*

NCI's Drug Development Branch in the Div. of Cancer Treatment is seeking organizations having capabilities and facilities for (1) the franctionation and isolation of antineoplastic agents from plants; (2) the determination of chemical structures of the antineoplastic agent from plants.

Objectives of this project are to prepare by isolation enough of each compound to test for antitumor activity, to identify chemically, and to prove the structure if necessary and to prepare additional quantities, usually a few grams, of those compounds that require more biological testing to determine interest to NCI.

NCI will provide the plant materials and in-vivo tumor bioassays. The contractor may or may not elect to use in-house in-vitro bioawways. The facility must have the capacity for grinding plants ranging from 1-100 lbs. prior to extracting them, for performing all types of organic chemistry, and for carrying out organic structure and identification work.

A well instrumented analysis laboratory and an adequate library must be available. The principal investigator must be trained in organic natural products chemistry, preferably at the PhD level from an accredited school and must have extensive experience in isolating pure compounds from natural products and in organic chemical structure determination.

It is anticipated that the total project will require a minimum of 22 technical man-years of effort per year. The government will consider multiple awards of four or seven technical man-years (without in-house in-vitro bioawway capability) and five or eight technical man-years (with in-house in-vitro bioassay capability). The proposal may be at any or all levels of effort and should clearly indicate levels being proposed. The number of awards to be made and the level of effort of each will be at the discretion of the government.

Contract Specialist: Stephen Gane
Cancer Treatment
301-427-7470

VIRUS CANCER PROGRAM REPORT ON SCIENTIFIC ACTIVITIES CONTINUES

A portion of the report presented to the National Cancer Advisory Board on scientific activities of the Virus Cancer Program appeared last week in ***The Cancer Letter****, starting with a discussion of RNA viruses. That report, still dealing with RNA viruses, continues:*

Exogenous and endogenous viruses. Both type C and type B viruses can be either exogenous or endogenous in origin. Exogenous viruses are transmitted horizontally or by artificial infection. The most intensively studied laboratory strains, e.g., the mouse leukemia viruses, are of this type. They were especially selected to be virulent, easy to grow, and to produce cancer readily on injection into animals. It now appears that most wild type viruses as they are found in natural animal populations are not of this variety but are endogenous in origin. This means that these viruses can exist as an integral, heritable component of the cell genome. The viral genome is normally present in the cell in an unexpressed state from which it can be activated spontaneously, or by a variety of artificial means.

Neither the endogenous nor the exogenous RNA viruses are contagious in the usual sense. However, recent experiments with the feline leukemia virus (FeLV) have shown that this virus can spread from animal to animal especially when the animals live in crowded conditions. Gibbon ape leukemia virus also appears to be able to spread in laboratory colonies as does avian myeloblastosis virus. The mechanism of transfer of viruses between animals is not known, but it should be pointed out that the rate of spread observed is extremely low and rare as compared to diseases normally described as contagious.

Endogenous viruses have been recovered from cells of mice, rats, hamsters, cats, chickens and baboons; all clones from apparently virus-free cultured cells of these species can be induced to yield complete or partial expressions of type C viruses. Some endogenous

viruses have difficulty in replicating efficiently in the cells of the species of origin, but preferentially replicate in cells of other animal species; thus a subclass of endogenous viruses now called xenotropic has been recognized. The fact that endogenous viruses are at least partially expressed when the cells which harbor them become malignant indicates that their study is important. Many investigators now accept as a working hypothesis that natural RNA tumor agents are of endogenous origin.

Much of the recent evidence that RNA tumor viruses exist in unexpressed form is derived from studies in inbred mouse strains. Genetic and biochemical evidence indicates that multiple copies of the viral information are integrated within the DNA of the cell. Endogenous viruses are activated spontaneously during long-term passage of cells in tissue culture and by cocultivation with cells of a different species. The induction rate can be increased 1000-fold by treatment with carcinogenic chemicals, x-irradiation, or infection by exogenous type C viruses. Halogenated thymidine analogs (IudR, BudR) and protein synthesis inhibitors (actinomycin D) are extremely efficient inducers, increasing the rate of expression by more than 1 millionfold. Endogenous viruses can also be induced by passage of tumor material from one animal species into another. This is especially true when the recipient species has been immunosuppressed. An example of this method was the recovery of the RD-114 virus after injection of human sarcoma cells into the brain of a fetal cat. Although this virus has antigens distinct from those of known feline type C viruses, hybridization studies revealed that the virus was a feline endogenous virus.

Several independent endogenous murine type C viruses have been isolated. Each appears to be of mouse origin as determined by the antigenicity of its major virion polypeptide, p30. Although at first these virus isolates were indistinguishable from each other in serologic and host range properties, newer findings have shown that they differ considerably in the immunologic type-specificity of their p12 polypeptide. Furthermore, some grow preferentially in cell lines of another strain. For example, a virus inducible from BALB/c cells grows to markedly higher titer in NIH Swiss than in BALB/c cell lines. It is thus possible to distinguish different subgroups of endogenous viruses from the same species of origin. As these studies continue, it is quite likely that many subclasses of endogenous type C viruses will be discovered.

The role of endogenous viruses in naturally occurring malignancies has yet to be elucidated but certain suggestive facts are known. One class of type C virus that is chemically inducible from virus-negative mouse cells in tissue culture can induce lymphatic leukemia in vivo. The type B mouse mammary tumor virus sometimes transmitted through the milk, as well as genetically, is an endogenous virus that causes mammary cancer. In high cancer incidence mouse strains the titer of endogenous virus in the serum early in life correlates exremely well with the frequency of malignancies in that strain. In addition to their role in cancer, there is evidence that endogenous viruses may be responsible for certain autoimmune diseases such as glomerulonephritis.

Ubiquity of RNA tumor viruses. Viral DNA sequences related to those of RNA tumor viruses have now been demonstrated in the moral cells of many vertebrate species including primates and man. Indeed, it is generally believed that viral genes can be found in all normal vertebrate cells where they probably have an important, though as yet unknown, function in normal development. By means of a series of hybridization experiments it was shown that these ubiquitous viral sequences have probably become part of the animal genomes many millions of years ago and have evolved with their host species during the course of evolution. Today the relationship of the endogenous viral genes with each other parallels closely the taxonomic relationship of the animals in which they reside.

Control of RNA tumor virus expression. The presence of an RNA tumor virus in an animal does not necessarily lead to the development of malignant disease. Numerous genetic and environmental factors influence the expression of the virus; both viral and host genes are known to be involved.

The genetic effects of the host have been intensively studied in inbred strains of mice. During the last few years several host genes affecting viral function have been identified and the chromosomal location of some of them determined. A better knowledge of the mechanism of action of these genes may provide us with a means for controlling tumor viruses artificially.

The genetic makeup of the virus also influences the rate of tumor formation. This clearly follows from the observation that different viral strains produce different types and degrees of disease in the same animal. Many investigators are attempting to identify the viral gene or the viral product that will cause a susceptible cell to become malignant. Better tools for attacking this problem are becoming avilable all the time. We know now that viruses can lose the ability to cause malignant transformation by mutation, but the biochemical nature of the "transforming principle" is still a mystery. Knowledge of the nature of this "transforming principle" may be a key to the understanding of transformation of cells to malignancy.

Structure of RNA viruses. The RNA tumor viruses consist of a core of RNA and some proteins, including the enzyme RDDP, and an envelope composed of a variety of proteins and glycoproteins with which the virus becomes coated as it passes through the cell membrane. Basically the type C and type B viruses are quite similar in composition. The following discussion will, therefore, be mainly about type C viruses with reference to type B viruses where these differ significantly.

Viral RNA. When RNA is extracted from type C viruses the major components sediment at 60-70S and at 4-5S. The 60-70S RNA can be denatured into subunits sedimenting at 30-40S. From the molecular weight of the subunits one can estimate that between 2 and 4 such units make up the 60-70S viral RNA. When examined under the electron microscope, two subunits appear to be linked together by multiple bonds. According to the latest experiments the subunits found in one virus are all identical and have a molecular size of about 3×10^6 daltons. Comparison of the RNA subunits of leukemia and sarcoma viruses shows that they are of different length but have certain sequences in common. It appears that avian sarsarcoma virus RNA consists of complete leukemia virus RNA molecules which have picked up additional RNA sequences that presumably give the virus the ability to transform cells. In the case of murine sarcoma viruses, which are replication-defective, both a loss of some leukemia virus RNA sequences and a gain of new RNA sequences appears to have occurred.

The small RNA components found in the virus are probably of cellular origin. One of them acts as the primer necessary for transcription of viral RNA into DNA by RDDP.

Viral RDDP. One of the most characteristic properties of RNA tumor viruses is that they contain an enzyme which specifically transcribes viral RNA into DNA. The enzyme is clearly different from cellular DNA polymerases in its properties and in genetic experiments has been shown to be coded for by an viral gene. Type B viruses have a polymerase that differs in cation requirement from that of type C viruses and can, therefore, be readily distinguished biochemically.

RDDP of avian RNA tumor viruses has a molecular weight of 70,000 and consists of two subunits; one has the enzymatic activities associated with the enzyme and the other appears to be required for binding to the template. Since the product of the synthetic reaction catalyzed by RDDP is small pieces of DNA, other enzymes are needed in addition to RDDP to form the high molecular weight DNA that is the final product in the cell.

It is not clear how mature viruses are produced from the DNA copies made by the viral polymerase, but it is believed that DNA synthesis is an obligatory intermediate step. The DNA copies are also necessary for the integration of the viral genome into the host genome: this may be another obligatory intermediate step in viral replication. Although the mechanism of viral integration is not known, it has been shown that transformed cells contain more viral DNA copies than untransformed cells. Viral genomes can thus become part of the host cell genome, as well as become independent of it again.

Viral, virus-associated and tumor-specific antigens. In recent years several structural proteins of RNA tumor viruses have been isolated and characterized. The purified proteins and glycoproteins have been used to produce highly specific antisera and to develop radioimmunoassays which are more sensitive than standard serologic tests. These reagents have proven valuable for the characterization of new viral isolates, for the study of viral gene expression, and in the search for possible oncogenic viruses in human neoplasia.

A new nomenclature has been adopted describing the proteins by their molecular weight and indicating whether they are proteins (p) or glycoproteins (gp). Three of the known proteins are located in the core of the virus particle and three in the envelope. All the proteins have several kinds of immunologically reactive sites: type-specific determinants that do not crossreact with those of any other virus; group-specific determinants common to all viruses of one species of host animal; interspecies determinants common to viruses from many different host species. Some viral proteins have mainly group-specific determinants which are useful for classifying the virus according to species of origin. Other proteins have mainly type-specific determinants and are, therefore, useful for differentiating between the viruses of one species. The two type C components most prominent in the virus structure are the major envelope glycoprotein gp70 (5%) and the major core protein p30 (30%). Both possess interspecies determinants which crossreact with viral proteins of different species. Antisera produced against gp70 possess strong virus neutralizing activity.

Type C virus-induced tumors contain three major groups of virus-related antigens: viral structural antigens, antigens coded by the viral genome but not structural (virus-associated), and cellular genome-coded antigens expressed as a result of malignant transformation (tumor-specific). A variety of cellular control mechanisms determine which of these antigens (and to what extent) are expressed in each cell harboring a virus. Antigens of each group can be expressed on the surface of the cell, a fact which is important to any consideration of viral control because the immunological defense mechanisms of the host readily attack cell surfaces.

There is now considerable evidence that gp70 is a virus gene product and is expressed on the surface of transformed cells even in the absence of other virus expression. Its accessibility to antibody at this site has been demonstrated by a variety of immunologic techniques. Cell surface determinants resembling those of gp70 have also been identified on nonmalignant and leukemic lymphocytes and thymocytes of certain mouse strains and in normal and neoplastic human cells.

The evidence for the surface expression of other viral antigens is not as convincing. The recent demonstration that antiserum to p30 is cytotoxic in the presence of complement for cultured mouse tumor cells suggests that this antigen is also on the cell surface. A similar finding has been reported for p10. The presence of these internal components at this cell site is someqhat surprising since p30 has only rarely been

detected on the surface of mouse lymphoma cells which contain large amounts of this antigen. A distinct possibility is that p30 and p10 are adsorbed to certain cells as the result of disruption of other cells and/or virus disintegration. As yet, there are no reports that the other less prominent structural antigens of the virus are found on the cell membrane.

The most striking feature of virus-associated cell surface antigens (CSA) is that the tumors induced by a given virus, even in different species, share a common CSA. Different viruses, however, induce CSA with different specificities. This feature of common CSA specificity is of great advantage to immunotherapy of virus-induced tumors. Virus-induced tumors also appear to have tumor-specific antigens.

The difficulty in disentangling the nature of all the cell surface antigens on malignant cells stems partly from the fact that all cells harbor endogenous viruses. These may be producing some proteins that appear on the cell surface but since in most cases the endogenous viruses have not been fully characterized, the characteristics of their proteins are also unknown.

An important aspect of the study of viral proteins is the knowledge of how the host responds to the antigenic stimulus of these proteins. Immune responses to virus and/or virus-associated antigens, especially to those found on the cell surface, could affect the fate of the host.

In the mouse systems there are many reports on the natural occurrence of antibodies to internal and envelope components of type C viruses. Because of antigen excess, the antibodies were found mainly in the form of immune complexes in the glomeruli of the kidney. More recent studies show that mouse strains with low incidences of spontaneous lymphoma produce antibodies to murine leukemia viruses. Free antibodies in the sera of these mice recognize proteins of the viral envelope.

In the cat, infection with feline leukemia virus (FeLV) appears to be fairly common and neutralizing antibodies to gp70 can be detected in the sera. A similar result has been reported for infections by murine leukemia virus (MuLV) and gibbon leukemia virus (GaLV) systems. The findings correlate well with the proposed horizontal spread of FeLV, MuLV and GaLV. Cats, gibbons and mice also produce antibodies to their homologous p30 antigens.

Thus, despite the persistence of these viruses throughout the animal's lifetimes, most species seem to be able to respond immunologically to type C virus antigens. As yet there is little information to determine whether these natural antibodies benefit the host, i.e., control virus expression or oncogenesis.

(The rest of this report on VCP scientific activities will appear in subsequent issues of ***The Cancer Letter****)*

CONTRACT AWARDS

Title: Epidemiologic research on cancer
Contractor: National Academy of Sciences, $166,270.

Title: Molecular studies of cancer, with emphasis on breast cancer
Contractor: Meloy Laboratories, $721,731.

Title: Studies on the interrelationship of viruses, genetics and immunity in the etiology of cancer
Contractor: UCLA, $285,000.

Title: Therapy of patients with pancreatic carcinoma
Contractor: Univ. of Miami, $199,771.

Title: Development of methods of bowel preparation preparatory to barium enema or colonoscopy
Contractor: Univ. of Rochester, $74,267.

Title: Logistical and managerial support for scientific conferences for the Div. of Cancer Research Resources & Centers
Contractor: Courtesy Associates Inc., Washington D.C., $477,656.

Title: Develop new techniques for preparing and staining clinical gynecologic cytopathologic specimens for automated pre-screening
Contractor: Papanicolaou Cancer Research Institute, $150,000.

Title: Development of a computerized transaxial x-ray reconstruction
Contractor: American Science & Engineering, Inc., Cambridge, Mass., $1,092,700.

Title: A pilot study of the uptake of ^{67}Ga by cells from the human uterine cervix
Contractor: American Science & Engineering, Inc., Cambridge, Mass., $49,633.

Title: Construction of a projection data base for testing algorithms for computerized transaxial reconstruction
Contractor: Mayo Foundation, $58,126.

Title: Algorithms for computerized transaxial x-ray reconstruction
Contractor: State Univ. of New York, $54,402.

Title: Algorithms for computerized transaxial nuclide reconstruction
Contractor: Univ. of Pennsylvania, $71,825.

Title: Fabrication and evaluation of a computerized transaxial x-ray reconstruction system
Contractor: Presbyterian Hospital (NYC), $426,388.

Title: Algorithms for computerized transaxial nuclide reconstruction
Contractor: Massachusetts General Hospital, $69,135.

The Cancer Newsletter—*Editor* JERRY D. BOYD

Published fifty times a year by The Cancer Letter, Inc., 1411 Aldenham Ln., Reston, Va. 22090.