THE CANCER LETTER

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DRAMATIC INCREASE IN THIRD WORLD CANCER RATES MAY FACE NATIONAL, INTERNATIONAL ORGANIZATIONS: MURPHY

National cancer organizations around the world must face the prospect that the significance of cancer will be "raised dramatically" in Africa, Asia and Latin America, where two thirds of the world's popu-

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In Brief

DURANT TO LEAVE ALABAMA, WILL BECOME PRESIDENT, CHIEF EXECUTIVE OFFICER AT FOX CHASE CANCER CENTER

JOHN DURANT, director of the Univ. of Alabama Comprehensive Cancer Center, will leave that position to become president of the Fox Chase Cancer Center, effective Oct. 1. He will replace Alfred Knudson, who has been Fox Chase president since 1980. Knudson, who had been director of the Institute for Cancer Research, one of the two components of Fox Chase, has continued to hold that position and will return to it full time. Durant, who has headed the highly successful Alabama center since it was founded, grew up in Philadelphia and was educated there. He worked in the Dept. of Medicine at Temple Univ. before he went to Alabama. He will be chief executive officer of the Fox Chase center and of both of its components (the other being the American Oncologic Hospital). He will act as director of the hospital until he can recruit a permanent director. He also is chairman of the Southeastern Oncology Group, but will give that up. A new chairman will be elected at the group's meeting in January . . . . **NCI EXECUTIVES** may resubmit the issue of withdrawing support for the Centralized Cancer Patient Data System to the Div. of Resources, Centers & Community Activities Board of Scientific Counselors. The Board voted earlier this year to end NCI's role in the program when the current grants (and one contract) expire. CCPDS officials met in Seattle last week with Jerome Yates, head of the Centers & Community Oncology Program, who told them that NCI staff might ask the Board to consider restoring at least part of the funding. CCPDS collects, stores and analyzes patient data at the comprehensive cancer centers. The Board's decision to end NCI support was based primarily on what reviewers said was the failure by centers to fully utilize that data, particularly for intercenter studies. CCPDS officials responded that the program had only recently reached the stage where cooperative studies are feasible . . . . **MARGARET EDWARDS** "is the mother of oncology," Tim Lee Carter said at the ceremony in which she was presented a certificate of appreciation by the Assn. of American Cancer Institutes. Carter noted that when Edwards first started her long career as head of NCI's clinical education programs, oncology was taught at only one institution in the U.S. Today, 68 institutions teach it. Edwards retired last May, now lives in Seattle where she participated in the International Cancer Congress . . .

NATIONAL GROUPS MUST STIMULATE INTERNATIONAL ONCOLOGY, MURPHY SAYS

(Continued from page 1)

ulation resides, Gerald Murphy, secretary general of the International Union Against Cancer, said in the plenary lecture at the 13th International Cancer Congress last week.

"These nations should anticipate that the control of communicable diseases, the projected increase in life expectancy, and the introduction of lifestyle changes, workplace exposures and environmental effluents associated with industrialization will raise dramatically the significance of cancer as a community health concern," Murphy said. "It has been noted that the transition from a preponderance of infectious diseases to a preponderance of noncommunicable diseases occurred in China and Singapore within a single generation. Unfortunately, few developing nations currently have either the total number of medical professionals needed or a sufficient cadre of committed community leaders to mount an effective national cancer campaign. The UICC, therefore, must remain committed to efforts that promote the establishment of cancer organizations at the national level in developing countries."

Murphy emphasized what he said was the "essential role that national organizations must play in stimulating and coordinating contributions to international oncology." He quoted A.O. Williams of Nigeria, who at a UICC meeting last year defined 10 UICC projects which could facilitate these national efforts:

- Establish close contacts with local, indigenous organizations in developing countries.
- Contact appropriate health authorities in developing countries without national associations with a view to stimulating their formation.
- Arrange consultative visits between established national organizations and groups in developing nations.
- Collaborate with other international and regional agencies in these endeavors.
- Stress the development of materials and audio visual aids relevant to programs of developing nations.
- Bring the discussion of national organizations to the agenda of international meetings and congresses.
- Encourage studies directed at the particular needs of developing countries.
- Raise funding support specifically for the development of national programs in developing countries.
- Organize within the UICC to give attention to priorities and policies regarding developing countries and assist in follow-up and implementation.
- Promote throughout the world an awareness of the significance of cancer control to the health of communities in developing nations.

"This agenda represents a major undertaking," Murphy said. "I have no doubt of the need for the effort and its merit. National organizations will play the key role in developing and coordinating the field of oncology on an international scope. With your assistance, an effective program can, will and has been mounted."

Murphy suggested that national efforts are concerned with three fundamental roles: Activities inherently requiring a national perspective; national strategies to stimulate local activities; and coordination of local resources and activities.

"Responsibilities inherently necessitating a national perspective include public health legislation, definition of standards of care, national data bases, and provisions for specialized services and an overall infrastructure," Murphy said. With regard to public health laws, this aspect is particularly relevant to developing countries. The pattern of disease, including cancer, in developing countries reflects primarily the economic and technological conditions of the countryside and urban centers. Although hospitals generally represent approximately 80% of health expenditures in developing nations, medical practitioners in developing countries readily confirm the need to enact public health measures that address community conditions. Given the tendency to focus upon major health institutions such as hospitals, national efforts may be appropriate to encourage these institutions to take on community outreach programs, particularly in the training of medical practitioners to undertake extramural commitments in the community setting. These steps are essential to achievement of the goal, established at the World Health Organization's conference at Alma Ata in 1978 on primary health care in developing countries, which called for "health for all by the year 2000".

"With regard to national standards of care, these criteria may apply to either the facilities available in local communities or their utilization. A small country such as Papua and New Guinea can report a national cancer control program based upon agreement on treatment protocols. In larger countries, such as Iran and Ireland, comprehensive cancer centers in capital cities maintain national centers for pathological diagnosis. In West Germany, screening services coordinated by the Deutsches Krebsforschung Zentrum in Heidelberg are mandated by law. And in India, regional comprehensive cancer

centers in Ahmedabad and Bangalore cite their operation of rural cancer diagnostic camps to screen for early disease. Developing nations need to consider to what extent they wish to define optimal, attainable standards for the provision of cancer services in the community.

"Maintenance of a centralized data registry should be a fundamental national responsibility. In the absence of data registration, identification of epidemiological patterns of disease and followup of patient cases become impossible. Such data registration must be supraregional to assure observation of rare tumors, comparison of etiological factors in different regions, and follow-up of referral patterns that encompass a large region. Countries that do not currently collect morality statistics, which may represent nearly 90% of developing nations, must be encouraged to establish cause of death reporting for all diseases. In carefully selected areas, the development of hospital and population-based registries should be encouraged for reliable estimates of cancer incidence. While cross-sectional reports from different countries are useful, time-series data from a single country usually are more revealing of disease mechanisms and the efficacy of cancer control interventions.

"A national perspective is necessary to review the availability of specialized cancer resources and provide a network of arrangements to assure accessibility to these referral facilities. In smaller countries, single institutions may establish a central facility, such as radiation therapy, as a regional service, as exemplified by the National Oncology Institute of Panama, which maintains the only radiation therapy facility in the country and arranges for the referral of approximately 90% of all cancer patients. Some countries, such as Colombia, have defined a national cancer plan, which in Colombia combines a commitment to central facilities at the Instituo Nacional de Cancerologia (Colombian National Cancer Institute) in Bobota with a plan or decentralized diagnostic capabilities at eight regional cancer units and a network of over 1,000 volunteers promoting cancer prevention interventions. Typically, many nations have developed a cancer center in the capital, collaborating with the Ministry of Public Health, to direct attention throughout the country to cancer control. Examples include the National Cancer Institute at Cairo University, the Instituto de Oncologia Luis Razetti (Luis Razetti Institute of Oncology) in Caracas, and the National Cancer Control Center of the Department of Health in Manilla.

"In larger countries, the network of specialized services and related infrastructure is dependent upon district or regional centers. Our neighbor Canada provides an excellent illustration, where each of the provinces has a designated comprehensive cancer center, such as the Princes Margaret Hospital of the Ontario Cancer Institute, and some such centers have designated subregional networks, such as units of the Ontario Cancer Foundation in Kingston, London, Ottawa, Thunder Bay and Windsor."

Murphy suggested strategies for national stimulation of local initiatives.

"Facilitation of local initiatives represents a second major role for national efforts. Areas in which national organizations can implement strategies to stimulate local activities include definition of national priorities, promotion of international exchanges, wide dissemination of new findings, and facilitation of regional collaborations.

"Priorities need to be established at the national level in order to highlight the specific concerns of significance to the local community. This consideration is particularly relevant to developing countries which may have public health issues quite different from the general goals of international oncology as formulated by agencies representing technologically advanced societies. These priorities should take into account not only the patterns of disease in the country and the opportunities for prevention and control programs, but a national program can incorporate consideration of the unique service resources available in that community, and the implication of national traditions, social, economic, or political conditions. Once priorities are identified, cancer leagues and societies play a critical role in bringing these issues to the attention of the government and the national media. Acceptance of these goals by these national agencies can provide local activities with a baseline credibility and authorization which builds receptivity in the community setting.

"Visits between workers in different countries remain one of the most effective mechanisms for establishing an international exchange on oncology. Within developing countries, these exchanges can stimulate collaborative efforts in the definition of priorities and interventions particularly suited to developing nations. Exchanges between technologically advanced countries and developing nations can expedite the dissemination of new techniques and research approaches. These exchanges should not be limited to scientific centers, for national voluntary leagues and associations similarly can benefit through visits which highlight the roles of these societies in different settings.

"The UICC has maintained three major travel

fellowship programs, the Yamagiwa-Yoshida Memorial International Studies under the auspices of the Japan National Committee, the Fellowships of the Cancer Research Campaign, and the Eleanor Roosevelt International Cancer Fellowships supported by the American Cancer Society. Several nations have sponsored scholarship programs to benefit directly their country. La Asociacion Argentina del Cancer together with the Foundation Alfredo Fortabat offered four fellowships to attend this Seattle Congress. The Ligue Nationale Francaise Contre le Cancer has awarded international fellowships to bring recognized foreign researchers who are willing to introduce a new technique or idea into a French cancer research laboratory. In many cases, bilateral agreements have fostered such exchanges. The Soviet Union has established such arrangements with France, Italy, and the United States. The United States has been most active in bilateral agreements through the NCI since 1972. U.S. bilateral agreements currently involve:

- USSR Agreement for Cooperation in the fields of Medical Science and Public Health.
- Japanese Society for the Promotion of Science.
- Polish People's Republic Agreement.
- French Institute National de la Sante et de la Recherche Medicale.
- Arab Republic of Egypt.
- Ministry of Science and Technology of the Federal Republic of Germany.
- People's Republic of China Accord for Cooperation in Science & Technology.
- National Cancer Institute of Milan.
- National Institute of Oncology (Hungarian People's Republic).

National agencies play a key role in these exchanges, which promote the coordination of international oncology.

National cancer congresses also have a valuable role to play in stimulating local cancer initiatives. For example, the Fourth Cancer Congress of Colombia, jointly sponsored by the Colombian National Cancer Institute, the Colombian League for the Control of Cancer, the Colombian Cancer Society and the Colombian Society of Radiotherapy, combined such valuable and diverse elements as a national congress, a major symposium on cancer research, refresher courses on cancer services, and seminars on education of the community in cancer control. Similar national meetings are hosted by cancer societies of Japan, Argentina and the Phillipines. Dissemination of information, then, on the current status of cancer research and services should be a commitment of a national organization in developing countries.

"The development of regional cancer centers should be encouraged at the national level. Comprehensive cancer centers at the regional level can stimulate interaction between bench scientists and practicing clinicians, foster multidisciplinary care, and serve as local points for dissemination of new developments in the field. Cancer centers should be selected on the basis of the excellence of their expertise and the role they can play for a given geographic region. In some countries, associations are dedicated to fostering the collaboration of cancer centers. These associations include French Federation of Anticancer Centers, Association of Italian Cancer Institutes, Scientific Council for Multidisciplinary Study of Malignant Neoplasms (USSR Academy of Medical Sciences), Swiss Working Group on Clinical Cancer Research, Turkish Federation of Oncology Centers, and Association of American Cancer Institutes. (AACI)

"Such centers need not be constrained by walls or institutional affiliations. At the level of particular research disciplines, scientific academies, professional societies, and those concerned with the publication of scientific and technical journals can provide a valuable resource through organization at the national level.

"The second major reason for developing coordinated programs in international oncology at the national level, is that organizations within developing countries can bring together incentives for local cancer control initiatives. Programs such as the definition of national priorities, promotion of international exchanges, forums for dissemination of findings, and encouragement of associations of centers and professionals can play a key role in stimulating cancer research and control endeavors throughout the country.

"One should also stress the role of national efforts to assist in the coordination of local resources and activities. A comprehensive cancer control program should integrate education, environmental monitoring, epidemiological data, screening and early diagnosis, interdisciplinary care, rehabilitation services and continuing care, community support, and research.

"Few local institutions can direct such a wide array of interventions without the support and assistance of regional and national organizations. With regard to education, many local institutions will need aid in the recruitment of medical and non-medical volunteers for projects to educate the general public on prevention and early detection of cancer. A major problem of many cancer leagues and societies is the difficulty experienced in getting health professionals to commit to roles in nonscientific activities of these organizations. Five Scandinavian cancer associations recently

sponsored a Scandinavian workshop on doctor involvement to identify means to involve general and community physicians in educating the public about cancer. Cancer societies were cited as key agents in securing the cooperation of groups such as health personnel and schoolteachers. The first step should be advocacy of national policies on undergraduate medical training that would emphasize coverage in the curricula of aspects such as prevention, screening, primary care, and psychological support for cancer patients. In many developing countries, however, perhaps only 10% of the rural population is served by physicians. In countries with a shortage of doctors, cancer societies must identify community health workers or nurses who can be utilized in public education, and regional workshops may be necessary to train relevant manpower. Some aids are available for the task. For example, a special UICC project produced a manual on cancer education in schools, which has been presented at regional implementation conferences.

"The variation in frequency of different types of cancer means that cancer leagues and societies should identify public education interventions aimed at the types of cancer most prevalent in their own country. Certainly the concern for exposure to cigarette smoke, the sun, and vinyl chlorides should be widespread, and one should emphasize particularly the importance of national antismoking campaigns. These campaigns are not futile, as evidenced by the sharp decrease in the number of smokers in the informed population of health professionals in Australia, Scandinavian countries, the United Kingdom, and the U.S. The Third European Symposium on Smoking Control held in Budapest in 1981 emphasized that patterns of tobacco consumption vary considerably from one nation to another, and thus an effort at the national level is imperative. In any public education campaign, a national society can play a key role in the development of audiovisual materials. The UICC must maintain its commitment to providing for developing countries publications, audiovisual materials, and expertise references in English, French, Spanish and Portuguese which can be adapted further for other nationalities.

"The need for national assistance to regional data repositories has been indicated previously. While hospital and local registries are important for achievement of complete cancer reporting, and can be targetted to data relevant to local studies of interest, coordination at the supraregional level is necessary to assure sufficient coverage of rare tumors, comparison of regional patterns of exposures and disease, and follow-up of treatment and survival results in a referral network.

"Cancer leagues and societies have a major role to play directly, or in aiding local institutions, in the promotion of cancer screening and early detection programs. These efforts are relevant particularly to sites of disease such as cervix, breast, lung, and colon/rectum. Many comprehensive cancer centers have established early detection clinics for assymptomatic patients, such as the unit at the Louvain Cancer Center in Belgium which screens 15,000 clients annually. An interesting collaborative effort is underway in Peru. Cervical screening is compulsory for all hospitals and health centers in Lima, and the slides are collected, processed and followed-up free of charge through a central service of the Instituto Nacional de Enfermedades Neoplasicas (Peruvian National Neoplastic Disease Institute), which also trains 10 cytotechnics annually. In Arequipa, the Goyeneche Hospital Tumor Unit reaches throughout the community through detection subcenters in Arequipa, Puno and Mollendo. At the national level, associations can define projects aimed at concerns particular to that community.

" . . . One should stress the need for national efforts to raise funding for cancer research. We must recognize that the private sector, great as its commitment to research and development may be, cannot adequately finance the necessary level of biomedical research desired. Although many cancers can be controlled and will be controlled in our lifetime through application of current knowledge, the key contributions to the long-term advance of medicine, enhancement of oncology services, and improvement of community health care will come from the clinical and preclinical research insights under development in pilot studies or still at the conceptual stage.

"A primary responsibility of cancer leagues and societies, therefore, must be to raise money for cancer research. Third world nations can benefit to a limited degree from the experience of successful voluntary associations. The Danish Cancer Society is funded in part by the national lottery. The Swedish Cancer Society has the support of the King Gustaf V. Jubilee Fund. The National Cancer Institute of Canada has awarded grants and fellowships since 1947. These resources are examples of an essential function which is necessary to support the advances in technological capabilities, the increasing research specialization, and the pace at which research insights are developing.

"In summary, national efforts are vital to the coordination of the diverse elements necessary to a comprehensive cancer control program. Voluntary societies and agencies, in particular, have a role to play in such areas as education, environmental monitoring, data exchange, screening and

early detection, confirmation of diagnosis, treatment collaboration, rehabilitation, community support and research.

"Oncology truly is an international field. One should apologize to those associations or organizations who have not been mentioned in this brief report who are conducting exemplary work in response to some of the responsibilities we have defined for national efforts. All are encouraged to review the "International Director of Specialized Cancer Research and Treatment establishments which provides a wealth of references to active and effective projects in diverse settings."

LITTON WINS FCRF RESEARCH CONTRACT, HARLAND GETS ANIMAL PRODUCTION

Litton Bionetics Inc., which had the entire contract for operation of the Frederick Cancer Research Facility for 10 years, kept the prestigious research program in the recompetition of the contract. Litton's opposition came from Johns Hopkins Univ., which put together a very strong proposal for the research contract, according to NCI executives.

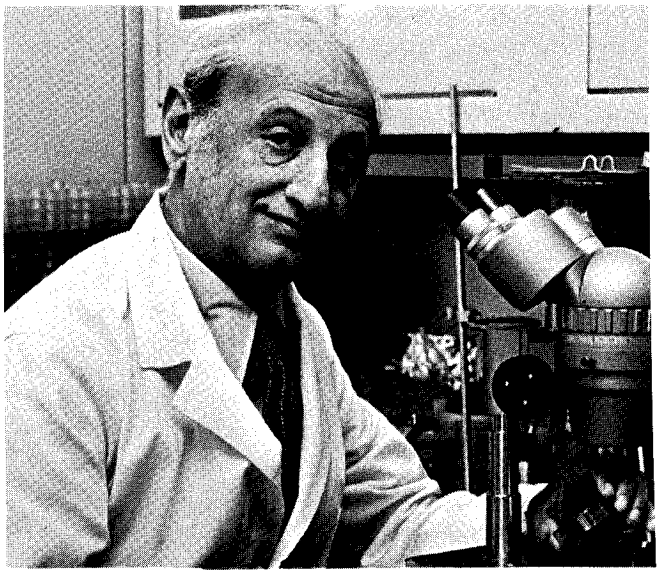
Litton thus managed to salvage one phase of the operations which the company had built up at Frederick since it was converted from an Army biological warfare development base in 1972. NCI split the recompetition into five contracts, two of them set aside for small business, to stimulate competition. Program Resources Inc. won the big management contract, for which Litton also competed (*The Cancer Letter,* Aug. 20).

Litton also went after the contract for animal production, but lost out to Harlan Sprague Dawley Laboratories of Indianapolis. Thomas Davis, who has headed animal production at Frederick as a Litton employee, will continue in that same capacity with Harlan. All other Litton employees in animal production were offered the opportunity to remain in their jobs, and most will do so.

One Litton employee who will not remain in his present position, although he will stay with the company, is the man who has headed the entire operation for the past five years and before that ran the research program—Michael Hanna. He will become director of the Litton Institute of Applied Biology, in Kensington, Md.

Litton has established a search committee to look for a new director of the research program. Its selection will be subject to NCI approval.

Winner of the contract for operation of the facility's library has yet to be announced. It was one of the small business set asides. The other, for operation of computer facilities, was awarded to Information Management Services Inc.



CHARLES HEIDELBERGER

. . . Two major contributions.

CHARLES HEIDELBERGER WINS FIRST ATHAYDE $100,000 CANCER AWARD

The first $100,000 Athayde prize for the most outstanding contribution to the fight against cancer has been awarded to Charles Heidelberger, director for basic research and distinguished professor of biochemistry and pathology at the Univ. of Southern California Comprehensive Cancer Center. The award was made last week at opening ceremonies of the 13th International Cancer Congress in Seattle.

Heidelberger was honored for his unique contributions in two major areas of cancer research—development of anticancer drugs and studies of the mechanism of chemical carcinogenesis. His best known achievement is the development of 5-fluorouracil while working at McArdle Laboratory at the Univ. of Wisconsin.

Heidelberger was unable to accept the award in person, due to illness, and it was presented to his wife, Patricia. He has been battling nasopharyngeal cancer for the past year. Surgery and radiotherapy had the disease under control until recently, when metastatic recurrence was found.

"It is rare enough when one individual can make one outstanding contribution against cancer in his lifetime," UICC Secretary General Gerald Murphy commented at a press conference announcing the award. "Dr. Heidelberger has made at least two." Murphy said that Heidelberger's basic research has uncovered the biochemical events which lead to abnormal growth of cells. "This has led us to believe that he has demonstrated how that process might be stopped or prevented."

Heidelberger was one of the pioneers in develop-

ment of antimetabolites. He changed the molecular composition of a natural metabolite, uracil, by introducing a fluorine atom into its structure. The resulting antimetabolite, 5-fluorouracil, has become one of the most effective and widely used anticancer drugs.

Heidelberger's contribution to cancer research also includes the introduction of elegant techniques for growing human cells in culture. His methodology on this difficult operation has provided an essential tool for cancer researchers trying to solve the mysteries of the carcinogenic process—how normal cells are converted into cancer cells.

The Athayde prize is funded by a foundation established by Brazilian millionaire real estate developer and attorney Mucio Athayde. It will be awarded each year, and Athayde asked UICC to administer it. A 13 member UICC committee made the selection. Educators, businessmen, and political figures may be considered along with scientists, researchers and physicians anywhere in the world.

Athayde told the press that the foundation has been funded with $20 million, and that award would be made in perpetuity. The foundation also will make a $20,000 award each year to a Brazilian scientist or physician for contributions to cancer research.

NEW DRUG RESISTANCE UNDERSTANDING "AN EXCITING REVOLUTION": DEVITA

Recent studies of tumor cell response to anticancer drugs have led to a new understanding of drug resistance and tumor mass, NCI Director Vincent DeVita told participants in the 13th International Cancer Congress. This could lead to new designs of chemotherapy adjuvant trials and development of more effective drug regimens, he said.

Reviewing development and use of chemotherapy in the 1970s, DeVita cited "puzzling observations"—only those combinations of drugs known to be effective individually worked; significant fractions of patients who had achieved complete remission relapsed and would fail to respond satisfactorily to further treatment; it was not possible usually to predict which patients would relapse; tumor volume itself was not as good a predictor of curability in the clinic as one would have expected on the basis of available cell kinetic data; some patients with massive amounts of certain kinds of cancer achieved permanent remission with drug combinations or even single agents; and in some cases, drug combinations as adjuvants to surgery or radiotherapy were no more effective than the same treatment in patients with advanced disease.

"An extraordinary observation had also been largely overlooked and unexplained: Normal target tissue never developed resistance to chemotherapy," DeVita said.

Referring to studies by J.H. Goldie, A.J. Coldman, and G.A. Gudauskas, DeVita noted their finding that the failure of bone marrow tissue to develop resistance to anticancer drugs suggests that most mammalian cells, perhaps including all cancer cells, start out sensitive to the toxic effects of these drugs. They also found that the "proportion resistant cells in any given mass is likely to be small and the initial response to a treatment should not be influenced by the number of resistant cells. In a clinic this means that a complete remission could be attained even if a resistant cell line were present. Failure to achieve a significant clinical response would occur only if the proportion of resistant cells exceeded 50% of the tumor mass. Failure to cure, (relapse from a complete remission) would, however, be directly dependent on the presence or absence of doubly resistant cell lines. . . .

"Recently, Goldie and Coldman have published on a computer-assisted program to develop strategies for managing treatable cancers with existing chemotherapy. Their basic assumption is that tumors are curable by chemotherapy if no permanently resistant cell lines are present. But curability diminishes rapidly with the appearance of a single resistant line, if only one effective therapy is available, or with the appearance of a doubly resistant line, if two equally effective therapies are available. Two equally effective therapies can be either two single agents or two equally effective combinations of noncross resistant drugs."

The Goldie-Coldman model, utilizing a number of assumptions, predicted a cure rate of 64%. To improve results of drug treatment at the clinical level using their model, it should be reemphasized that two equally effective combinations of drugs are required," DeVita said. These conditions are met clinically in only a few human tumors today such as acute lymphocytic leukemia, Hodgkin's disease and diffuse histiocytic lymphoma. In Hodgkin's disease, alternating cycles of MOPP and the non cross resistant combination ABVD appear superior to MOPP alone in some categories of disease, and in diffuse histiocytic lymphoma, alternating MOPP with the ProMACE combination may be superior to MOPP alone. All of these experiments were designed intuitively by clinicians. The Goldie-Coldman model, however, may provide a prospective way of designing their use in treatment protocols when other variables are added to the data set. Additional assumptions treatment protocols when other variables are added to the data set. Additional assumptoms of their model critical to the successful applica-

tion of this strategy may not be consistent with what actually happens under clinical circumstances, such as the requirement for similar growth characteristics in multiple metastatic sites of the same tumor in the same or in different patients, and equivalent log kill for each treatment program. These and other variables will make the actual development of such strategies more complicated.

"There are three major clinical implications of the Goldie-Coldman hypothesis: (a) First and foremost, these data suggest a reason why chemotherapy may not be much more effective in the adjuvant setting than in patients with clinically evident tumors, even though the growth characteristics of micrometa- vulnerable to drug treatment. Time to first drug treatment may be more important than had been appreciated previously. Thus, if a resistant line can develop spontaneously in weeks at a subclinical tumor cell number, adjuvant therapy should be started as soon as possible. Adjuvant studies with breast cancer suggest that even a short delay in starting chemotherapy may have an important negative influence on outcome. (b) Attempts to improve responses to chemotherapy by debulking operations to reduce tumor mass and favorably alter cell kinetic characteristics have not been successful in increasing cure rate and, according to the Goldie-Coldman hypothesis, could not be expected to be successful. Since mutation toward resistance is mass related, patients with large masses of cancer prior to debulking already have a high likelihood of having developed at least one and probably more than one resistant cell line. If these lines have metastasized widely prior to reductive surgery, reducing the mass, while it may improve response to chemotherapy, is not likely to improve curability unless the resistant lines in large tumor masses have little propensity to metastasize.

" . . . There are implications for the design of future chemotherapy adjuvant trials in these data: First, combination chemotherapy rather than single agent therapy is a likely requirement for adjuvant chemotherapy programs as it is for most of the successful treatment programs for patients with clinically evident disease. Second, adjuvant chemotherapy is not likely to be effective unless the intensity of treatment of micrometastases is at least commensurate with that used for clinically evident disease of the same tumor type. Third, drugs that produce partial responses in patients with clinically evident disease should not necessarily be expected to produce better results (cures) in the adjuvant setting, as has been shown by most studies of patients with colon cancer. Fourth, the duration of treatment may not need to be as lengthy as was thought in the past if the multiplicity of drugs and the intensity of their administration is sufficient to eradicate relatively small numbers of resistant tumor cells. In fact, a lengthy period of adjuvant therapy could accelerate the growth of a resistant population by enhancing its mutation rate. And finally, preoperative chemotherapy, as has been used in some studies in patients with head and neck cancer, may provide important clues to the usefulness of a drug program that is proposed for use in the post-surgical or post-radiotherapeutic phase of treatment."

DeVita moved on to what he called "A paralogical leap to a different paradigm."

"While this exciting revolution in our thinking about the development of drug resistance is taking place, a revolution of a different sort is in progress. Oncogenes identified in RNA tumor viruses over the past decade-and-a-half, have now been found to have normal cellular homologs in vertebrates. This is an extraordinary observation. Recent data from DNA transfection experiments (the transfer of DNA from one cell to another) has shown that fragments of DNA from human colon, bladder, and other types of cancer can transform NIH 3T3 fibroblast cell lines, and these DNA fragments are, in some cases, homologous to the viral oncogenes. Some 17 such oncogenes have now been identified. It is at least a reasonable hypothesis that cancer is caused by an overdose of these genes, probably working through an overdose of the gene product itself. Since these genes appear to exist in normal tissue, the gene product itself may have a normal function in the development of vertebrates. Great excitement surrounds research on the identification of the function of these gene products. A somewhat paralogical leap in thinking in the 1980s could be the convergence of diagnosis, prevention, and treatment focused exclusively on the action of these gene products.

"In conclusion, data generated by the expanded research effort in the Cancer Program indicate we have much to be optimistic about in our struggle against this dread disease during the coming decade. Cancers are, after all, chronic illnesses. Cancers, although frequently fatal, appear to be the most curable group of chronic diseases in the US today."

The Cancer Letter _Editor Jerry D. Boyd

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