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P.O. BOX 2370 RESTON, VIRGINIA TELEPHONE 703-620-4646

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SIX PATIENTS APPARENTLY RESPONDED TO LAETRILE, NCI REVIEW FINDS; DCT CONSIDERS CLINICAL TRIAL

Six cases out of 67 in which patients were treated with laetrile were determined to have had a response, according to a panel of 12 oncologists who reviewed records collected in response to a nationwide appeal by NCI for evidence of beneficial responses to the substance.

Two of the six showed complete disappearance of all evidence of cancer, and four showed shrinkage of measurable tumor by 50% or more. In addition, three other patients were judged to show a longer

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In Brief

CONGRESSIONAL ACTION IMMINENT ON CANCER ACT RENEWAL, HEW MONEY BILLS; VETO THREATENED

CONGRESS SHOULD act any day, now that it is back in session, on two major pieces of legislation vital to the Cancer Program—renewal of the National Cancer Act and HEW appropriations for the 1979 fiscal year, which starts Oct. 1. The House has passed its version of the appropriations bill, and the Senate has approved renewal of the Cancer Act (and other biomedical research authority); each now has to act on the other. Neither bill was scheduled for floor action this week (by *The Cancer Letter* press time). With major differences between the two bodies on both bills, early action now is imperative if they are to be completed before both renewal and spending authorities expire Sept. 30. Another hangup over abortion in the appropriations measure could delay it for months. Still another complication was a threat by the White House that President Carter might veto the bill unless it is trimmed substantially. Big difference in the renewal legislation is that the House bill would extend the Cancer Act for three years, the Senate for one. Senate conferees probably will go along with increased responsibilities and funding authorizations for cancer control that are in the House bill. . . . **"QUANTITATIVE ASPECTS"** of cancer prevention is the subject of a meeting sponsored by NCI Sept. 25-28 at the Sheraton Hotel in Reston, Va. The meeting, open to the public, will attempt to estimate the relative impact of various causes of cancer, "with reconciliation of divergent estimates," according to NCI's announcement of the meeting. It also will attempt "to estimate the probable impact of various preventive measures, and to assess probable degrees of uncertainty to these estimates." The meeting is being organized by John Bailar, editor of the *Journal of NCI.* Contact him at Blair Bldg 2A09A, Bethesda, Md. 20014, phone 301-427-7923. . . . **PRACTICAL ASPECTS** of cancer management is the topic of a continuing education course offered by the Medical College of Virginia, Virginia Commonwealth Univ. and the American Cancer Society Nov. 5-7 at Williamsburg. Subjects include advances in diagnostic tools, treatment of Hodgkin's disease and management of early breast cancer.

DECISION NETWORK TO CONSIDER CLINICAL STUDY OF LAETRILE AT SEPT. 25 MEETING

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survival than would normally be expected for their form of cancer, although their cases were considered nonevaluable in terms of a measurable tumor response because laetrile was used when no definite sign of disease was present.

NCI undertook the survey and review in an effort to determine if sufficient evidence of beneficial effect existed to justify clinical trials. The evidence will be presented to the Div. of Cancer Treatment Decision Network Committee Sept. 25. The meeting, open to the public, in Wilson Hall, located in Building 1 on the NIH campus, will start at 9 a.m.

The Decision Network is part of the process in DCT's Drug Development Program by which compounds are selected for clinical trial. The program previously has found laetrile to be inactive in its various animal screens and has not approved it for further tests. With the clinical data provided by the NCI review, the Decision Network Committee could recommend it for clinical trials.

NCI Director Arthur Upton will make the final decision on whether or not an IND application will be submitted to the Food & Drug Administration. FDA's approval is by no means assured, considering the long history of animal tests which have demonstrated the drug's inactivity.

Normally at this stage in drug development, DCT would have to wait for large scale production to be set up and for large animal toxicity studies. However, NCI has already obtained sufficient quantitites of laetrile, and there is enough toxicological data. Clinical studies could start as soon as IND approval is obtained.

The Decision Network Committee consists of 29 DCT staff members, chaired by Vincent Oliverio, who heads the Developmental Therapeutics Program.

The NCI survey started with an analysis of 93 case records of cancer patients who claimed to have benefitted from the use of laetrile. Those records were submitted in response to a nationwide appeal for evidence of beneficial responses made to U.S. physicians, groups supporting the use of laetrile, and an estimated 70,000 laetrile users. A report of the findings is published in the Sept. 7 issue of the *New England Journal of Medicine.*

Of the 93 case records obtained by NCI, 67 were considered to contain enough information to be presented to the panel of 12 oncologists for evaluation. The 12 were Irwin Krakoff, Vermont Regional Cancer Center (chairman); Laurence Baker, Wayne State Univ. School of Medicine; Lawrence Davis, Jefferson Medical College; Rose Ruth Ellison, Columbia Univ. College of Physicians & Surgeons; George Escher, Albert Einstein College of Medicine; Robert Golbey, Memorial Sloan-Kettering Hospital; Rita Kelley, Massachusetts General Hospital; Louis Leone, Rhode Island Hospital; Virgil Loeb, Washington Univ. School of Medicine; Gerald Murphy, Roswell Park Memorial Institute; Kenneth Olson, New Smyrna Beach, Fla., and Manuel Valdiviéso, M.D. Anderson Hospital & Tumor Institute.

NCI's summary of the report:

"It is impossible to tell from these results whether laetrile was responsible for the improvement in (the six) patients. The review was not designed to prove the anticancer activity of laetrile or to measure its efficacy but merely to determine how much evidence there was suggestive of activity. The following features of the review preclude making any conclusions about the anticancer activity of laetrile:

- "Only patients thought to have had positive responses to laetrile were asked to submit their records. No attempt was made to review the effects of laetrile in all the other cancer patients in whom the agent has been used, since such a review was judged not to be feasible.
- "The analysis provided no way to distinguish between a response to laetrile and spontaneous variability in the course of cancer or the occurrence of spontaneous remissions.
- "There were no assurances that the clinical data submitted were complete.

"For the remaining 58 cases presented to the panel, a total of 59 courses of laetrile treatment were evaluated. (One patient was treated at two different times with laetrile, and each course of treatment was evaluated separately.) Eleven of these treatment courses were judged as having insufficient data for evaluation, 32 as nonevaluable (either because the patient did not have cancer at the time laetrile was given or because anticancer drugs were given along with laetrile), nine as showing stable disease, and seven as showing progressive disease.

"The panel also conducted a separate review of 11 cases submitted by Mario Soto de Leon, medical director of the Clinica Cydel in Tijuana, Mexico. One case was judged as having insufficient information for evaluation, nine as nonevaluable (either because the patient did not have cancer at the time laetrile was given or because anticancer drugs were given along with laetrile). One case was judged as showing progressive disease.

"Laetrile is an extract derived from apricot seeds. Numerous animal studies supported by NCI and others have failed to show convincing anticancer activity for the substance. Furthermore, the safety of laetrile has been questioned; vials of laetrile have been shown to be contaminated and subpotent. Several people have died of cyanide poisoning after ingesting laetrile, and others have been hospitalized because of allergic reactions to injections of laetrile.

"Despite these findings, more than 70,000 cancer patients in the United States reportedly use laetrile,

17 states have passed bills legalizing the substance, and the U.S. Court of Appeals has ruled that terminally ill cancer patients can legally procure the injectable form of laetrile for their use.

"Last January, NCI launched a nationwide search for cancer patients whose case records could be used to document anticancer activity of laetrile with or without concomitant "metabolic therapy" (special diet, vitamins, minerals, enzymes, and chelating agents). The following information was requested for each case: written consent of patient or next of kin (if deceased), slides to confirm a diagnosis of cancer, a palpable tumor or x-ray evidence of tumor, adequately documented medical history, use of laetrile with or without metabolic therapy for a period of at least 30 days with a preceding period of at least 30 days in which no conventional treatment was given, and records written in English.

"Two hundred to 300 such cases were sought through national publicity, contact with groups supporting the use of laetrile, and a direct mailing of 385,000 letters to U.S. physicians and 70,000 other health professionals. Assurances were given that the Food & Drug Administration would not use information submitted to the institute to initiate any legal action against either patients or physicians.

"Despite these efforts, only 93 patients signed consent forms authorizing NCI to collect information from their medical records. For 67 of these patients, enough information was obtained to allow review.

"Summaries of the 67 laetrile-treated cases containing all pertinent data were mixed with 26 similarly prepared summaries from the NCI file of cases treated by conventional chemotherapy. A panel of 12 oncologists was asked to evaluate the results. Panel members were not informed of the actual treatment given to prevent any biases about laetrile from influencing their clinical decisions.

"The confirmed diagnoses for the two patients judged as showing a complete response to laetrile were nodular, well-differentiated lymphoma and squamous cell lung cancer. The four patients judged as showing a partial response were diagnosed as having Hodgkin's disease, metastatic carcinoid (a rare cancer arising from the serotonin-secreting epithelial cells that line primarily the gastrointestinal tract), an adenocarcinoma in the abdomen, and an adenocarcinoma in the chest. Three patients judged to show increased lifespan had testicular cancer, ovarian cancer and a malignant tumor in a lymph node."

The panel summarized its review in the *NEJM* article:

"Despite widespread publicity and intensive efforts, the 67 laetrile treated cases presented to the review panel were far fewer than the 200 to 300 that we had hoped to obtain. We have no way of knowing whether reluctance to submit cases, paucity of objective antitumor responses to laetrile, or other reasons explain our difficulty in collecting cases. Since only 81% of those individuals contacted supplied information our findings should be interpreted with caution.

"The judgment that many cases had insufficient information or were not evaluable should in no way be taken as criticism of the management of these patients, since in treating patients, one often uses several treatments together in the desire to help the patient rather than to evaluate the effects of a single therapy. Also, it should not be construed that these patients showed neither improvement nor progression of disease—they were simply not evaluable for our specific purposes. The lack of unanimous agreement in judging responses is not surprising. Universal agreement about criteria for responses does not exist, especially when a variety of tumor types are considered and clinical experience varies.

"The objective of this retrospective analysis was to see if it would be possible to document beneficial objective anticancer responses to laetrile.

"We cannot dismiss the possibility that the six patients responded to laetrile, but the design of this study in no way allows us to draw this conclusion. Submission of incorrect clinical interpretations, falsified data, intentional or unintentional omission of data (for example, concurrent conventional therapy), the possibility that we were unaware of some physicians treating these patients or non-response to our inquiries must all be considered in interpreting these findings. It should be emphasized that the 67 laetrile-treated cases analyzed in this report cannot be identified as the denominator for the six laetrile-treated patients that were judged to be responders. These 67 cases were submitted for review because they were thought to demonstrate laetrile's anticancer effects. Only patients showing a beneficial response were solicited, and no attempt was made to review the effects of laetrile in all the other 70,000 or more patients in whom this agent has been used.

"Other explanations for the six apparent responses to laetrile are, of course, possible. Spontaneous regressions of tumors, although rare, have been documented in at least 176 cases, with frequency varying by tumor type. Even in the absence of true spontaneous regression, the well documented variability in the natural history of some tumors may confuse interpretation, and, in fact, the panel judged by consensus that a partial response occurred in one case receiving no treatment during the course evaluated. The patients treated with laetrile were almost always given concomitant metabolic therapy, including substances that might be regarded as immune stimulants, as well as general supportive care measures such as improved diet, psychologic support, and the unmeasurable ingredient of hope. This fact makes it

difficult to attribute any tumor responses to laetrile alone.

"Despite the fact that the panel identified the correct treatment more often than would have been predicted by chance, a consensus guessed chemotherapy for those laetrile treatment courses judged as complete or partial responses and those judged as showing increased disease free interval. This finding can be interpreted as demonstrating that these treatment courses were in fact given a fair review. Although a more thorough evaluation might have been possible by allowing the panel to examine the records submitted to us, we felt that blinding was more important in order to avoid charges of anti-laetrile bias by the review panel.

"This retrospective analysis illustrates the difficulty of drawing inferences about therapeutic efficacy in the absence of properly designed randomized trials."

CLEARINGHOUSE SUBGROUP APPROVES TESTING OF CHEMOTHERAPEUTIC AGENTS

The Clearinghouse on Environmental Carcinogens Executive Subgroup approved "in principle" the desirability of testing anticancer drugs for carcinogenicity at the Subgroup's meeting last week.

The issue of whether or not chemotherapeutic agents should occupy some of the limited slots in NCI's Carcinogenesis Testing Program had been raised by the Clearinghouse Chemical Selection Subgroup (*The Cancer Letter*, June 16). Some subgroup members felt that in the case of drugs which provide the only effective treatment for catastrophic disease, it would make little difference whether or not they were found to be carcinogenic—they will be used in any event.

Div. of Cancer Treatment Deputy Director Saul Schepartz insisted that it would make a difference in the way in which a drug would be used, particularly if it were being considered for adjuvant therapy. Schepartz persuaded the Chemical Selection Subgroup to go along with testing anticancer drugs, specifically cis-platinum in that instance, despite declining an offer to allow DCT to pay for the test.

Clearinghouse Chairman Arnold Brown felt the issue of testing any or all anticancer drugs should be established as Clearinghouse policy, and presented the matter to the Executive Subgroup.

Executive Subgroup member Michael Shimkin suggested that chemotherapeutic agents which seem to be promising might be given a preliminary (and less expensive) test than the full bioassay, which requires at least two years and $200,000 per compound.

"Could a strategy evolve like this?" Shimkin asked. "At one point, if an agent looks promising, inject it subcutaneously in eight to 12 CT3H mice and 20 strain A mice, and put them aside. Watch them for six months. If there is carcinogenic potential, there would be some cutaneous response. Then you could go ahead with longer and more extensive tests."

The Subgroup agreed with the proposal in general and recommended that the Experimental Design Subgroup determine if some screen can be devised to see in a preliminary way if a compound has carcinogenic activity.

David Clayson, chairman of the Chemical Selection Subgroup, said his subgroup considered these factors in recommending testing of anticancer drugs:

- Bioassay may give some indication, if there are two therapies for the same disease, which may be safer.
- Selection for bioassay should be made both in light of a compound's chemotherapeutic potential and whatever else is waiting in line for testing.
- Testing might help protect against misuses of chemotherapeutic drugs ("This is a most important point," Clayson said. Misuse by the overbright clinician who gets hold of these drugs can lead to calamitous results").
- The Experimental Design Subgroup should investigate using less expensive tests for chemotherapeutic drugs, perhaps the Ames test or other in vitro methods.

"Would you feel comfortable with an in vitro screen?" Brown asked Schepartz.

"I would not feel very secure with in vitro tests," Schepartz responded. "But if your experts can come up with a less expensive in vivo test, that might be okay."

"This is a policy decision that is extremely important," Brown said. "Resources are finite, and the priority listing is important to Dr. (Richard) Griesemer (Carcinogenesis Testing Program director) and the program."

Schepartz suggested that an effort be made to get the drug manufacturer to carry out carcinogenesis studies, or to pay for them. "It might be easier to make a decision (on whether or not to test) if the manufacturer agrees to pay for it."

"That's not a requirement by FDA?" Brown asked.

"Not for anticancer drugs," Schepartz said.

"I would think it would be reasonable for FDA to require that," Brown said.

"Maybe it should be done concurrently, but it is not a requirement of the NDA (new drug application, which, when approved by FDA, permits the drug to go on the market)," Schepartz said.

NCI Director Arthur Upton, sitting in part of the meeting, asked if it were possible to make a generalized determination that all cytotoxic drugs are carcinogenic.

"You can certainly about the metabolites," Schepartz said. Brown added that all antitumor drugs "certainly are suspect."

Stanford Research Institute, under contract with the Carcinogenesis Testing Program, compiles data

on suspect compounds and those submitted for consideration by the regulatory agencies and others. SRI's report goes to the Chemical Selection Working Subgroup, made up entirely of government employees. In addition to NCI staff members, this group includes representatives of FDA, the Environmental Protection Agency, Consumer Product Safety Commission, Dept. of Defense, National Institute of Occupational Safety & Health, Occupational Safety & Health Administration, and National Institute of Environmental Health.

CSWG forwards its recommendations to the Clearinghouse Chemical Selection Subgroup which assigns priority rankings to each compound. Those recommendations then go to Griesemer, who makes the final decisions.

Herman Kraybill, scientific coordinator for environmental cancer in the Div. of Cancer Cause & Prevention, heads the Chemical Selection Working Group. The group two weeks ago agreed on a policy of assigning "moderate priority" to chemotherapeutic drugs in general, and a high priority to those used for childhood diseases. Kraybill summarized for the Executive Subgroup CSWG's arguments supporting the policy:

"1. Since many of the chemotherapeutics are the product of NCI, it is the obligation of NCI to test them. The animal bioassay is only a small part of the developmental costs of these drugs.

"2. The use of cancer therapies is increasing and has developed to the point where we are talking of regimens using drugs in combination and as adjuvants. As such, these agents warrant testing.

"3. The use of these drugs for other purposes, e.g., in the treatment of immune diseases, is increasing and therefore they should be tested.

"4. The testing of these drugs will provide the clinicians with a knowledge of the relative carcinogenic potency and target sites of various anticancer drugs. This information is valuable in cases where a choice of therapies is available, as it will enable the clinician to choose the therapy involving the least carcinogenic risk. There exists a need to identify target organs and the results of the testing would provide ways to increase the efficacy of treatment.

"5. The goal of chemotherapy is to cure tumors and every effort should be made to avoid giving the patient another tumor, if there is a choice.

"6. Testing a representative of each class of chemotherapeutic agents would provide some much needed information for structure-activity relationships."

The Clearinghouse Executive Subgroup urged NCI to proceed with use of in vitro tests to assist in the chemical selection process.

Subgroup member Verne Ray pointed out that the Clearinghouse had approved a formal resolution to that effect a year ago. "The program now has the capability to do these tests on a regular basis, and it should now be routine," Ray said. He said the Chemical Selection Subgroup asked that in vitro tests be utilized regularly in selection of chemicals for testing, and that the program "go back through those already tested and use the in vitro tests to provide an expansion of the data base."

Elizabeth Dunkel, who heads in vitro carcinogenesis testing research for NCI, said, "We do now have the capability to test four chemicals per month in the hamster embryo and eight per month in the salmonella mutagenesis (Ames) test."

"My feeling is we've talked about this too much," Kraybill said. "I would like to see a plan in writing."

Griesemer and Dunkel argued that there is a logistical problem, that it takes two to four months to get chemicals to the lab, once the decision is made to place them in the in vitro tests. But Griesemer agreed with the desirability of going ahead. "We have a mutual enthusiasm for this. I would suggest that we proceed more rapidly with selection, and have a waiting list of chemicals to go on (the bioassay) test. We could be working on that list with the in vitro tests."

Clayson objected. "We're told the program wants more and more selections submitted, so that it can build up a backlog, if I may use that infamous word." Clayson's point was that the selection should be based in part on data suppliedby in vitro tests, and thus those tests should be completed before priorities are assigned for the long term tests.

Carl Morris, EPA representative on the Chemical Selection Working Group, commented that "we need this short term data to help make these selections. EPA is looking at chemicals coming out of the NCI program, and it would be helpful to have the short term test data to supplement information from the long term tests."

"Can we assume that EPA might help pay for the tests?" Brown asked.

Morris' answer might well make the Bureaucratic Equivocation Hall of Fame. "If it seems appropriate and if we have the money, we might consider some financial participation," he said.

As for the "infamous" backlog of several hundred reports on chemicals tested in the program which had piled up over several years, Griesemer told the Executive Subgroup that "it is appropriate now to tell you that this will be the last day to kick the backlog around." Of the 21 reports still to be made, 14 are complete and seven are awaiting final reading. "Now we can start talking about the frontlog," Griesemer said, referring to reports coming through on tests started since the backlog accumulated.

"I hope that now we can dispose of that term, and all of its derivatives," Brown said.

GM OFFERS THREE $100,000 AWARDS FOR EXCELLENCE IN CANCER RESEARCH

General Motors has announced what may be the largest cash awards ever offered "for individual excellence in cancer research"—three awards a year of $100,000 each in basic science, diagnosis and treatment of cancer, and prevention of cancer.

GM said it has established the General Motors Cancer Research Foundation, a nonprofit organization, and funded it with a grant of $2 million to support the awards. Winners will be selected by peers "for demonstrated achievements in research directed at the discovery of the cause, prevention and treatment of cancer," according to Thomas Murphy, chairman of the company.

Murphy will be chairman of a seven member board of trustees of the foundation. Roger Smith, GM executive vice president, will be vice chairman. Joseph Fortner, director of the GM Surgical Research Laboratory at Memorial Sloan-Kettering Cancer Center and professor of surgery at Cornell, will be president.

The awards are named for three men associated with General Motors and noted for their philanthropic efforts—Alfred P. Sloan Jr., Charles F. "Boss" Kettering, and Charles S. Mott.

GM said the Sloan Medal and $100,000 award will be given "for the most outstanding recent basic science contribution to cancer particularly in etiology and pathogenesis; the Kettering Medal and $100,000 for the most outstanding recent contribution to the diagnosis or treatment of cancer; and the Mott Medal and $100,000 award for the most outstanding recent contribution in the prevention of cancer including environmental influences."

The first awards will be announced in March 1979. They will be made annually "provided that one or more nominees are considered to be prizeworthy by the Awards Assembly."

Jonathan Rhoads, chairman of the National Cancer Advisory Board and professor of surgery at the Univ. of Pennsylvania, is chairman of the Awards Assembly which is made up of 25 basic and clinical scientists. The assembly will choose from recommendations by selection committees established for each of the three prizes.

Members of the Foundation's board of trustees in addition to the three already named are William Baker, president of Bell Telephone Laboratories and a member of the National Cancer Advisory Board; Rhoads; Benno Schmidt, chairman of the President's Cancer Panel; and Charles Townes, professor of Physics at the Univ. of California (Berkeley).

Members of the Awards Assembly are Lauren Ackerman, SUNY (Stony Brook); Harold Amos, Harvard; Baruj Benacerraf, Harvard; Arnold Brown, Univ. of Wisconsin; Gilbert Fletcher, Univ. of Texas; Emil Frei, Harvard; Fernando Gentil, Sao Paulo, Brazil; Philip Handler, National Academy of Sciences; Charles Heidelberger, Univ. of Southern California; Werner Henle, Univ. of Pennsylvania; Shichiro Ishikawa, Tokyo; George Klein, Stockholm; LaSalle Lefall, American Cancer Society; Brian MacMahon, Harvard; Enrico Mihich, Roswell Park Memorial Institute; Gerald Murphy, Roswell Park; Gustav Nossal, Melbourne; Frederick Seitz, Rockefeller Univ.; William Shingleton, Duke Univ.; Lewis Thomas, Memorial Sloan-Kettering Cancer Center; Arthur Upton, NCI; and Umberto Veronesi, Milan.

Consultants will be used by the selection committees for in depth analyses of candidates and their contributions. Prize winners will be expected to deliver lectures on the subjects for which prizes are awarded. Candidates must be nominated on official forms submitted by invited proposers. These invitations will be sent on a rotational basis to provide a broad representation of countries, individuals, universities and cancer institutions, GM said.

NCI CONTRACT AWARDS

Title: Comprehensive cancer centers communications network, renewal
Contractor: Illinois Cancer Council, $395,913.

Title: Annotating of surplus cancer documents (ICRDB)
Contractor: SBA (Technassociates Inc., subcontractor), $19,020.

Title: Biochemical analysis of human breast cyst fluid and its correlation with development of human carcinoma, continuation
Contractor: Sloan-Kettering Institute, $48,000.

Title: Metabolism of PAH in the induction of mammary tumors
Contractor: Midwest Research Institute, $452,200.

Title: Isolate/characterize antibodies to collagen/-procollagen
Contractor: New York Univ. Medical Center, $212,600.

Title: Facility to provide and maintain subhuman primates for cancer research, continuation
Contractor: Litton Bionetics, $94,646.

Title: Application of animal virus model systems to human plasma, continuation
Contractor: Litton Bionetics, $49,839.

The Cancer Letter —*Editor* JERRY D. BOYD

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