THE CANCER LETTER

Vol. 6 No. 27

July 4, 1980

Subscription $125.00 per year

P.O. Box 2370 Reston, Virginia 22090 Telephone 703-620-4646

AUTOMATED THERMOGRAPHY SYSTEM SAID TO BE AS GOOD AS MAMMOGRAPHY DEVELOPED FOR MASS SCREENING

Mass screening for breast cancer by electronic infrared pattern recognition, a sophisticated thermography system, has been developed at the Oklahoma Univ. Health Sciences Center under contract with NCI using the 10,000 patient cohort of the center's Breast Cancer Detection Demonstration Project. JoAnn Haberman, the program's principal investigator, told the Diagnostic Research Advisory Group last week that the system is comparable to mammography in detecting breast tumors in asymptomatic women.

(Continued to page 2)

In Brief

ORVILLE KELLEY, MAKE TODAY COUNT FOUNDER, DIES; ELLI KOHEN HONORED BY PAP INSTITUTE

ORVILLE KELLEY, whose fight against cancer and its debilitating effects inspired cancer patients and their families around the world, died last week at age 49. Kelley founded Make Today Count, an international self help organization which grew to include 250 chapters in the U.S., West Germany, Australia, and Canada. . . . **ELLI KOHEN** has been named the first Papanicolaou Cancer Research Institute Distinguished Scientist by the organization's board of directors. He is credited with developing the microspectrofluorometry process which permits examination of chemical changes within single living cells without dissecting them. . . . **PIEDMONT ONCOLOGY** Assn. and Piedmont Oncology Nurses Assn., with the Oncology Research Center of Bowman Gray School of Medicine, will sponsor a conference Oct. 3-4 in Winston-Salem. The program for physicians will include discussions of new drug development and an appraisal of cancer therapy and management. The nursing program will include thanatology, legal implications of oncologic nursing, burnout, stress management for patients and nurses, assertiveness training and physical sexual adaptations necessary for the cancer patient. Contact Douglas White or Cheryl Lane, Oncology Research Center, Bowman Gray, 300 S. Hawthorne Rd., Winston-Salem N.C. 27103. . . . **NATIONAL CAPITAL** Area Branch of the American Assn. for Laboratory Animal Science will have its 10th annual seminar Sept. 3-4 at the Marriott Hunt Valley Inn, Hunt Valley, Md. The program will include sessions on animal models and their alternatives, biology and care, and energy conservation. Contact Harry Rozmiarek, Chief Animal Resources Div., USAMRIID, Ft. Detrick, Md. 21701. . . . **NEW APPROACHES** to Cancer Therapy will be the subject of an EORTC symposium in Madrid Oct. 2-3. Information requests and abstracts may be addressed to H. Cortes-Funes, Hospital "1 de Octubre," Carretera Andalucia km 5.5, Madrid 26, Spain.

NEW ATT THERMOGRAPHY SYSTEM READY FOR CONFIRMING MASS SCREENING TRIALS

(Continued from page 1)

The system was developed with the university as the prime contractor and the Honeywell Corp. as subcontractor. Total cost of the contract to date, since its inception in 1974, is slightly more than $1 million.

The system involves "a totally new concept in infrared diagnosis, absolute temperature measurement," Haberman said in the report submitted to NCI following completion of Phase II of the contract. Absolute temperature measurement, "combined with methods of pattern recognition and statistical classification permits a scientific and objective approach to be introduced—absolute temperature thermography (ATT)."

ATT utilizes computer techniques "to take thermography away from the art form and put it on an objective basis," Haberman said.

Not only has the study indicated that ATT is at least the equal of mammography in detecting tumors, but it may even be better in picking up very small cancers. Haberman and her colleagues found that it can locate tumors as small as .1 cm as well as it can those up to 3.5 cm.

The primary advantage of thermography over mammography is that it is a noninvasive procedure and is totally safe, while the safety of ionizing radiation is in question. The NCI recommendation now is that mammography should not be used as a routine screening procedure for asymptomatic women under age 50 (although still very much recommended for such women over 50 and as a diagnostic tool when symptoms are present).

Another factor could be the cost, although that has not yet been demonstrated in the Oklahoma project. Honeywell estimates that the ATT system will cost from $50,000 to $100,000 when fully developed and available. Haberman believes that the comparatively low initial investment plus the greater capacity and speed of the system will result in a much lower cost per screenee.

The BCDDP has demonstrated that screening will pick up tumors at earlier stages. Although some statisticians and others contend it has not been proven this will result in improved survival, evidence is strong that it will. Early detection also is more important as the feasibility of breast conserving techniques becomes more accepted.

Radiation doses have been drastically reduced in mammography, but the safety concerns persist. Haberman and her colleagues believe that ATT will be the answer. Excerpts from the report:

The use of infrared sensing for breast cancer detection has the obvious advantage of complete safety. It can be accomplished in a very short period of time and has the potential of low cost screening. However, thermography as practiced today is highly subjective, requiring extensive experience by the physician thermographer. Conventional thermograms permit only a relative indication of temperature differences. These temperatures are represented by varying shades of grey recorded on polaroid or 70 mm film. The evaluation of infrared images is based on a qualitative judgment of the symmetry of these shades of grey. Thermograms are obtained by technologists who adjust contrast and brightness, thus influencing apparent symmetry. The degree of adjustment varies from day to day for the same technologist and may vary greatly from one technologist to another. Consequently, the physician must make adjustments to compensate for these variations. This has contributed to a situation in which good results are limited to a small group of dedicated thermographers, and as a result qualitative thermography is regarded as a disappointment.

It must be emphasized that the present study represents a radical departure from state of the art qualitative thermography. A new concept in breast cancer diagnosis, that of absolute temperatures, is introduced and is the basis for the entire effort.

An absolute temperature digital map is the format of each breast thermal image recorded. This provides an objective baseline of temperature information for each subject examined. Absolute temperatures allow an assessment of the magnitude of temperature differences. For the first time, serial examinations on a given individual can be compared in an objective and meaningful manner. Group comparisons can be made objectively. There is now a standardized parameter or baseline that exists for each subject examined, i.e., the digital array of that individual's absolute temperature. With the introduction of absolute temperatures to breast thermography, subjectivity is eliminated, reproducibility is achievable and thermography has become a completely objective scientific modality.

[Honeywell previously had developed an infrared imaging system on contract with the Dept. of Defense. Haberman noted that at least $5 million in developmental costs, paid for by DOD, had been completed before any thought had been given to its medical application.]

The system developed and used in the Oklahoma project included the Honeywell medical infrared scanner, a Quantex digitizer and digital storage unit, a Pertec tape formatter and tape port, a Honeywell Level 6/43 computer system, and an International Image System M70/E image processor.

Honeywell is in the process of developing an improved scanner and a digitizer which can be displayed on conventional television sets for "real time" (instantaneous) observation.

The newer equipment will be delivered to Haberman for the Phase III study which she is recommend-

ing. Phase III would be a large data collection and analysis using this system before general clinical implementation. [Haberman feels that at least one other screening center should be established for the Phase III study, and that ideally, "if money were not a problem," a total of six such centers would be established.]

[NCI's Div. of Cancer Biology & Diagnosis probably will be asked to support a minimum of two Phase III studies, either through noncompetitive awards to Oklahoma Univ. and one other center, or through a competitive RFP.]

Haberman and several members of Honeywell's technical staff initiated the program in 1971 with a study of the requirements for a system for mass screening based on her extensive background in the application of thermography for breast cancer detection and Honeywell's background in infrared technology and systems design. This study revealed that the basic limitation in thermographic instruments could be overcome by the use of the unique infrared imaging system developed by Honeywell for DOD.

The system they put together was capable of producing calibrated absolute temperature signals compatible with commercially available television systems. It was envisioned that the specialized application would be as a screening device to identify women with a high probability of having breast cancer. Those women would be referred for mammography. This screening approach, if successful, would significantly reduce the number of women requiring mammography. Because of its broad scope, the program was designed and organized into three phases.

An unsolicited proposal for development of the system was submitted to NCI in 1972. A site visit and oral presentation before the Breast Cancer Task Force followed in 1973, and a contract was awarded in April 1974.

Phase I was concerned primarily with the construction of the absolute thermography system.

This system provides spatial and thermal resolution necessary for an accurate digital representation of the thermal image. The prototype instrument which provided the capability of displaying and recording absolute temperature images at conventional television frame rates was designed and assembled at the Honeywell Electro-Optics Center in Lexington, Mass. The instrument was delivered to the university in June 1975. During the next six months, the thermal uniformity, sensitivity, spatial resolution and reproducibility of the system were evaluated and subsequently improved.

After this testing and improvement stage, the clinical portion of Phase I was begun in February 1976. A number of paid female subjects, normal controls from the Oklahoma Breast Cancer Detection Demonstration Project, and patients recommended for biopsy were examined with the new mass screening system. Certain variables were examined as possible diagnostic indicators. An analysis was made of the early data on this limited number of cases. Preliminary results indicated the potential value of computed absolute temperature variables in correctly identifying women with breast cancer and signaled the successful completion of Phase I.

Phase II was to test the prototype instrument on a larger population sample. A two year program designed and initiated in October, 1976, followed site visit and committee approval.

The early months of phase II were devoted to system improvement with acquisition of a video digitizer which provides online digitization of the terminal image.

To date, over 25,000 patients, including 204 with cancer, have been examined. The digitized absolute temperature images have been characterized by a number of variables. The variables are based on diagnostic features as determined from thermographic interpretation experience or biological principles. These variables have been computed by software programs developed by Honeywell and are being utilized in the development of allocation rules which, when applied to the female population, will separate women with cancers from the normal population.

Absolute temperature thermography system: Principles and configuration

The thermal data being collected are the digital thermal images which are obtained from the continuum of thermal radiation emitted from the surface of the breasts. Since the skin acts essentially as a black body source, the infrared radiation from each minute area of the skin is proportional to the local skin temperature. Physiological and environmental factors transiently affect the skin temperature. These transient temperature effects can be of similar magnitude to the cancer caused temperature effects. Therefore, the thermal environment must be carefully controlled while the subject is cooling. This equilibration period (15 minutes) is to allow a stable temperature pattern before measurements are taken.

The body core temperature and the examining room temperature are obtained when the digital thermal imagery measurements are being collected. This makes it possible to account for these sources of variations in the measured temperature of the skin. Consideration for these extraneous variations is possible in this program because true skin temperature (radiation) in units of absolute (rather than relative) temperatures is measured.

The present research program is the first comprehensive study of breast cancer detection by thermography using calibrated absolute temperature images. This study is being conducted using the most ad-

vanced infrared technology available. Principles of heat transfer are being employed with the collection of the skin temperatures in a carefully controlled environment. This standardization enables reproducibility of methods and results. For the first time, it allows a scientific investigation of the role of skin temperatures in breast diagnosis.

Patient population and data collection

The population for this study consists of all subjects entering the BCDDP at the university since February 1977. The number of examinations to date is approximately 25,000. This includes 18,000 examinations of BCDDP screenees and 7,000 private referrals. The protocol required examining and collecting breast temperature data on 10,000 subject examinations. Routine data collection on the 10,000 was completed by July 1978. Thereafter, only designated subjects were included.

One hundred eighty-five cancer cases have been identified since the first subjects were examined. None of these subjects had a mastectomy prior to thermographic data collection. Presently, subjects with only a single breast are not included in the allocation rule development. February 1977 is the date of the last major system upgrade. Data collected before that date cannot be pooled with the later data and has been analyzed separately. Also, the data collected between February 1977 and July 18, 1977, were purged due to equipment failures. Only data collected after July 18, 1977, are included in the pattern recognition study reported in this document.

A group of 561 normal subjects was selected from the large number of examinations available for use in the allocation rule development and testing. This number of normal subjects is used because it ensures scientifically valid results. Altogether, 208 benign and 97 cancer subjects are used. Women examined after July 18, 1977, who had surgery resulting in a diagnosis of cancer or benign disease were candidates for the respective groups.

The normals were matched to the cancers by age and calendar time, i.e., the date the thermographic data were collected. This means the normal group has approximately the same age and calendar time distribution as the cancer group. Approximately five normals were chosen for each cancer case.

Data collected from each of the 25,000 examinations included digital thermal images; demographic, clinical and epidemiological information; and routine examination results by mammography, physical examination and conventional therapy. Pathology information on women undergoing biopsy subsequent to their visit also was obtained. In addition to the hospital pathologist reports, a consultant, Perry Lambird, also examined the slides on each case.

The cancers from the BCDDP group represent early cases. The women in this group had been enrolled in the screening program for a minimum of four years, during which the cancer did not manifest. These cancers therefore represent lesions which were detected as soon as possible by physical examination or mammography. In contrast, private referrals usually have a known mass or other symptoms which were the stimuli for having the examinations made. Cancers from this group generally represent more advanced lesions.

The sample of 97 cancers is composed of 34 cases obtained from the BCDDP and 63 cases obtained through private referrals. The ATT identification of tumors was equally as accurate with both groups.

Problems and conclusions

[Acknowledging deficiencies in the system and the study, the report suggested pertinent issues which require critical examination.]

* Does the method (new approach of absolute temperature measurements) in truth contain discriminating information in the emitted signal? In other words, does ATT detect breast cancer?

* Given that the method does contain information to discriminate cancer from normal subjects, how effective is it?

* How useful is the method compared to accepted techniques for breast cancer screening and detection?

* Has the research effort been successful?

The first issue to arise during the research program concerned itself with the ability of thermography to detect breast cancer. Thermography was considered a useful technique when introduced and during the first 15 years of application. Later, due to the very subjective nature of qualitative thermography, lack of interpretation and procedural standards and the absence of training programs, the method developed severe credibility problems during its use of the Breast Cancer Detection Demonstration Projects. An article was published in 1976 which concluded that in early cancer detection, thermography was no more effective than tossing a coin.

The first phase of this research program was under way at that time, and the prototype of the ATT system had just been delivered. Data collection during the first year was limited to four basic absolute temperature measurements per breast. The absolute temperature values were provided by an analog to digital device and were recorded manually. An analysis of the allocation rule performance was obtained on a sample of 180 normals and 45 cancers. The results indicated a sensitivity level of 70 percent at a 30 percent false positive rate. The initial results clearly demonstrated that the ATT signal contained information which discriminated cancer subjects from normals. It confirmed that diagnostic information existed in the absolute temperature measurements; demonstrated the feasibility of the method; demonstrated the potential of the automated approach.

The next critical issue was to determine ATT's level of performance. Efforts during this period of

the research have centered on data collection, development and testing of allocation rules (automatic classifiers) and determining performance level. An overall detection rate and an evaluation of performance level based on tumor staging, source of cancers, assocation with physical examination and mammography recommendations, benign disease and the younger than 50 age group was completed.

Of special interest is data indicating that this performance level remained the same for small cancers and was not associated with physical examination and mammography biopsy results. Other data suggesting the ulity of the approach concerns the performance of ATT on benign disease. Benign disease is assigned to the cancer class at the same rate as the normals. This implies that the technique could be useful in limiting the number of biopsies for benign lesions.

An analysis based on recorded data from the Oklahoma BCDDP and the HIP study (the study in New York which provided the rationale for the BCDDP) was used for the mammography and physical examination comparisons. The important point is that the estimated performance levels from these studies were obtained using techniques similar to those utilized in the ATT analysis.

The comparison reveals that on a rescreen population, ATT is performing at a level similar to mammography and physical examination. On advanced cancers, mammography and physical examination perform at considerably higher levels. There is a direct association between performance of these two methods and tumor size—the larger the tumor the higher the performance rate. It should be pointed out that the comparison between mammography and physical examination with ATT is optimistically biased in favor of the former, because only those two can initiate surgical intervention.

In summary, problems are inherent in all research, and this program was no exception. One situation concerning technology development in the field of video digitizers impacted the program both positively (improved automation) and negatively (additional sources of error). Throughout this study as problems were encountered, causes were identified and the necessary corrections made.

An important part of any investigation is the additional knowledge and insight attained as the program evolves. One of the most important aspects of Phase II was the determination of hardware modifications, calibration and procedural requirements necessary to collect adequate absolute temperature to collect adequate absolute temperature data. This information provided the design characteristics allowing the construction of a digital ATT system optimized for breast temperature evaluation. This new, computerized system to be utilized in Phase III is nearing completion.

FDA ADVISORY COMMITTEE APPROVES THC AS A GROUP C DRUG FOR ANTIEMETIC USE

The Food & Drug Adminstration Oncologic Drugs Advisory Committee last week recommended approval of NCI's request to make Delta-9-THC available to physicians through its Group C distribution mechanism.

If FDA accepts the recommendation, the substance—the active ingredient in marijuana—would be available at no charge through registered hospital pharmacies to any qualified physician for control of nausea and vomiting associated with anticancer chemotherapy. The indication would be limited to patients refractory to standard antiemetic agents.

The committee split 4-4 on the issue, permitting Chairman Philip Schein to cast the tie-breaking vote. The closeness of the vote and the fact that committee member Charles Moertel, who submitted a letter arguing against the request, did not attend the meeting led some observers to conclude that FDA might not accept the committee's recommendation. The agency is not required to comply with advisory committee findings.

The Cancer Letter has learned, however, that in this instance, FDA probably will accept the recommendation and approve THC as a Group C drug.

Vincent Bono, chief of the Investigational Drug Branch in the Div. of Cancer Treatment, and staff member Don Poster presented NCI's proposal to the committee. Earlier, NCI had invited 500 hospital pharmacies to participate in the program for THC distribution, which will be more tightly controlled than for other Group C drugs because of the fact that THC is a controlled substance under the Drug Enforcement Administration. The 500 institutions included the comprehensive cancer centers, 30 clinical cancer centers, five new drug study groups, and 400 institutions that are members of the Council of Teaching Hospitals. NCI received 91 affirmative replies and 19 additional expressions of interest. Most of the institutions which so far have indicated willingness to participate are in the East and Midwest.

The distribution system will consist of the following steps:

1. NCI will send copies of its guidelines for THC and the DEA registration forms to cooperating hospital pharmacies. The guidelines, in addition to serving as the protocol for THC use, will contain a patient consent form and a statement of investigator form (modified FDA-1573). This is the form used by all clinical investigators who are studying investigational drugs.

2. The pharmacy will register with the DEA in the researcher category requesting permission to handle Schedule I drugs. The central DEA coordinator will contact the DEA inspector closest to the hospital. The inspector will evaluate the pharmacy and inform

the central coordinator. For accepted pharmacies, drug request forms will be pre-printed and sent to the pharmacy.

3. After the pharmacy receives notification that the registration has been activated, the pharmacy can order drug from NCI by using the DEA Drug Request form and the NIH Clinical Drug Request Form (986).

4. Both of these forms are sent to the Drug Regulatory Affairs Section at NCI where the requested quantity of drug is verified and shipment is authorized.

5. The Drug Regulatory Affairs Section will then send the DEA form to the NCI Pharmaceutical Resources Branch for drug shipment to the hospital pharmacy, and for inventory adjustment.

6. The pharmacy will dispense THC upon presentation of a "Research Order for Medication" signed by a physician who:

a. Has a DEA license.

b. Is registered with the pharmacy on a modified FDA 1573.

c. Affirms that the patient consent form is signed.

d. Limits the use of the drug to the indications outlined in the guidelines.

e. Will report adverse drug reactions immediately to IDB.

7. The pharmacy will forward the modified FDA-1573 to the Drug Regulatory Affairs Section at NCI and retain a copy for its own use.

The Drug Enforcement Administration is aware of this distribution system. Distribution of THC will begin in the fall of 1980.

The guidelines submitted by NCI warn of possible adverse reactions with adolescents, epileptics and other patients with seizure disorders, pregnant females, schizophrenics and others with mental instabilities, patients with impaired liver functions, elderly patients, and patients with cardiovascular disease.

The guidelines call for administration at a starting dose of 5 mg/m_2 given six to eight hours prior to chemotherapy and every four to six hours thereafter as needed and tolerated for the duration of chemotherapy, and for 12 hours after. If the starting dose is ineffective and in the absence of significant side effects, the dose may be escalated to 10 mg/m_2.

Side effects include sedation, disorientation, dizziness, hallucinations, poor concentration, dysphoria, headache, sleep disturbances, cardiovascular changes, autonomic changes, decreased intraocular pressure, confuctival redness, and nausea and vomiting.

Poster told the committee that Solomon Garb, a leading investigator in the use of THC as an antiemetic, has estimated that five percent of curable cancer patients will not complete their chemotherapy courses because of severe nausea and vomiting "even though they know they are giving up their best chance for survival. Nausea and vomiting thus amounts to a fatal toxicity in many cases."

Poster cited a number of studies, by Sallan, Chang, Ekert, and Frytak and commented that none showed negative results for THC and only Chang's produced results which questioned its efficacy.

Garb briefly discussed his study in which high doses (up to 80 mg) of THC were combined with a phenothiazine (usually prochlorperazine). Phenothiazines block most of the undesirable cerebral effects of THC, except drowsiness, Garb said, which permitted the safe use of higher THC doses. He concluded that THC is a potent and useful antiemetic and is much more effective than prochlorperazine alone.

Committee member Charles Haskell, the discussion leader for the proposal, agreed "there is no question that with some patients, THC is efficacious and safe. . . and may be quite effective used with compazine (prochlorperazine)."

In his letter, Moertel said, "I can fully sympathize with those bearing the weight of the current political hysteria for general release of THC. I wonder if perhaps the weight of this political pressure does not exceed the scientific evidence justifying release. In my opinion it is premature to release THC to the cancer patient population at large by classifying it as a Group C drug. THC does not qualify as a Group C drug for the following reasons:

"1. Specific indications have not been established. There are a variety of mechanisms by which chemotherapeutic agents in current use can cause nausea and vomiting. In only three reported controlled studies is there sufficient patient volume treated with any specific chemotherapy regimen so that specificity can be established (Chang, Frytak, Neleman), and in two of these three unfavorable side effects overshadowed any favorable antiemetic effects (Frytak, Neleman). For regimens that are the biggest clinical problems, e.g. platinum, no controlled studies have been reported although these are the areas where we can anticipate most widespread clinical application.

"2. Specific populations of patients suitable for THC have not been established. The most favorable studies for THC have involved very young patients with a median age of about 30 years (Sallan, Sallan, Chang). Many of these patients were known THC users before study. Such patients are decidedly atypical when one considers the global population of cancer patients undergoing chemotherapy. In the largest study (Frytak) a typical cancer age group population without prior THC exposure found THC to produce greater disability than benefit. The guidelines simply warn against treating the elderly patient. How old does a patient have to be to be considered 'elderly' and what data do we have to support any specific age limit we might choose?

"3. Effective dosage schedules for THC have not been established. All of the randomized controlled studies demonstrating an antiemetic effect for THC

employed a substantially higher dose than that recommended in the Group C drug brochure prepared by NCI—usually a 100 percent greater dose. There is absolutely no controlled study establishing the effectiveness of the 5 mg/m2 dose recommended in the brochure. (We cannot use the Duke study because it was uncontrolled.) To throw out for general consumption a regimen that has never once been treated seems unconscionable. It is clear that considerably more dosage and schedule evaluation studies must be conducted and that we cannot at this time accept the arbitrary dosage schedule as originally recommended.

"4. The safety of treatment with THC at doses effective for antiemetic purposes remains in serious question. Two of the six randomized controlled studies of THC reported side effects that were sufficiently distressing and disabling so that in the opinion of the investigators the dosage schedule employed was not suitable for clinical use. An earlier study evaluating the analgesic properties of THC (Noyes et al) reported the same result. In addition to this quandary regarding THC per se, we also have no information regarding possible drug interactions. It is particularly disturbing that in the study of Neleman, involving only MOPP treated patients, there was a 36 percent incidence of hallucinations and one patient developed a psychosis requiring hospitalization. Could this have represented an adverse interaction with high dose prednisone or with procarbazine? The results of the additional studies currently in progress should enable us to provide reasonable answers to these questions so that this drug can be released with far more security.

"5. Reported, peer-reviewed experience with THC is contradictory and still very fragmentary. Two of the four favorable studies for THC involved only 15 and 20 patients, and only one of the four favorable studies involved enough patients on a given chemotherapeutic regimen to permit conclusions with regard to drug interactions to be drawn. The favorable studies also involved crossover design which produce some serious problems in interpretation of results. In each of these crossover studies there was a large patient dropout which must cloud analysis of the crossover comparison. This would seem to be a very shaky foundation on which to permit general release of any drug and would seem to set a very poor precedent.

"6. A large number of controlled trials are currently in progress that address vital questions with regard to THC. It would seem premature to permit general distribution of THC before these ongoing studies have been reported and subjected to critical review. This general release is proposed based on the results of only six randomized studies, the conclusions of which are contradictory. Uncertainty regarding effectiveness, safety, and proper dose of THC is indicated by the fact that 37 studies are currently in progress. These studies may provide vital information either encouraging or discouraging general distribution of THC. Certainly they will provide us with more specific information with regard to drug safety and drug interactions. It would seem appropriate to defer any consideration of general release until the results of more of these studies are in hand."

The California Research Advisory Panel, which is overseeing trials in that state on the safety and efficacy of cannabinoids as an antiemetic, objected in a letter to the committee to the NCI proposal. The letter incorrectly stated that the "Panel understands that NCI proposes . . . that (THC) be rescheduled and decontrolled." NCI did not propose that THC be decontrolled.

Garb commented that in his opinion 10 mg/m2 doses "will work with the average patients. I get the worst patients (at the AMC Cancer Research Center in Denver) who need the higher doses. . . . We have observed that it is quite easy to get 100 percent control of vomiting with patients on methotrexate or cytoxan. With adriamycin, it is not quite so easy. With DTIC, the best we can get is 50 percent improvement. With cis-platinum, it depends on the duration of cisplatinum administration. If it is bolus, we are not successful. If it is over many hours, we have been quite successful."

Robert Randell, a Washington free lance writer and glaucoma patient who has fought successfully for the legal right to smoke marijuana as therapy for his disease, argued against the NCI proposal. He contended that THC is an inferior product.

Committee member Brigid Leventhal agreed with Moertel, "that we don't have enough information on THC for it to go out as a Group C drug. Once it is out, we have no control in limiting its use to patients refractory to other antiemetics."

Poster and John MacDonald, director of NCI's Cancer Therapy Evaluation Program, disagreed. "All doses from five to 20 milligrams have been tested," MacDonald said. "No matter how many more studies we do, further studies to evaluate nuances in doses will not be that helpful."

Voting for the Group C recommendation were Haskell, Carol Portlock, Jack White and John Whitaker. Voting against were Leventhal, Leon Hellman, Sherman Kay and Richard McHugh. Valerie Miké abstained.

"This drug is probably no more toxic than many others we have approved," Schein said in breaking the tie. "It has a potential for abuse but so do many others, and this has been approved for studies in 26 states."

HARRIS FINALLY OKAYS REORGANIZATION; DIVISION NAMES NOW ARE DEA, DCCAR

The effort started by Arthur Upton two and a half years ago to reshape NCI was finally completed this

week when HHS Secretary Patricia Harris signed the order implementing the reorganization.

The order had been on Harris' desk for months after having worked its way through channels since NCI submitted it last year. Presumably, she had delayed approving it until Upton's successor as NCI director had been appointed by the President, permitting the new director to have something to say about the final shape of the reorganization.

At press time, President Carter still had not announced the appointment of Vincent DeVita, but that is expected momentarily.

With the reorganization now official, these changes are officially implemented:

* The Div. of Cancer Research Resources & Centers becomes the Div. of Extramural Activities. DEA is exclusively NCI's review division; all NCI contract and grant review committees are assigned to it. All of the grant programs formerly assigned to DCRRC are transferred to other divisions.

* The Div. of Cancer Control & Rehabilitation has ceased to exist. In its place is the new Div. of Centers, Community Activities & Resources. This division includes all of DCCR's control and rehabilitation programs, and in addition picks up the centers, construction, organ site and manpower training programs. The program project and R01 grants formerly in DCRRC had been assigned to the appropriate program divisions.

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, citing the RFP number. Some listings will show the phone number of the Contract Specialist, who will respond to questions. Listings identify the respective sections of the Research Contracts Branch which are issuing the RFPs. Address requests to the contract officer or contract specialist named, NCI Research Contracts Branch, the appropriate section, as follows:
Biology & Diagnosis Section and Biological Carcinogenesis & Field Studies Section—Landow Building, Bethesda, Md. 20205; Control & Rehabilitation Section, Chemical & Physical Carcinogenesis Section, Treatment Section, Office of the Director Section—Blair Building, Silver Spring, Md. 20910. Deadline date shown for each listing is the final day for receipt of the completed proposal unless otherwise indicated.

RFP N01-CP-05686-58

Title: *Laboratory rodent and rabbit facility as a resource to the Laboratory of Experimental Pathology*

Deadline: *Sept. 2*

Private laboratory logistically oeprated by a dependable contractor for the conduct of collaborative research programs emphasizing lifetime tumor induction studies in rodents and rabbits. This laboratory and its personnel must be available for immediate response capability to the requirements of the NCI Laboratory of Experimental Pathology (LEP), Carcinogenesis Program needs. This will involve contractor staff availability in Bethesda for scientific discussion with NCI staff.

The laboratory will be used chiefly for long term treatment, holding and observation of animals in carcinogenesis investigations emphasizing lifetime tumor induction in rodents and related activities. This animal facility must meet AAALAC certification requirements for housing of mice (including athymic nude mice), rats, Syrian hamsters, guinea pigs and rabbits, and must satisfy NCI guidelines for safety of personnel handling chemical carcinogens to be administered to animals by skin painting, gavage, parenteral injection, or intratracheal instillation.

It is expected that the following approximate numbers of animals will be housed per year in long term studies: 4000 mice, 1400 rats, 1500 hamsters, 20 rabbits and 500 nude mice. The animals will be purchased by NCI. The required facility shall provide approximately 10 rooms of animals holding space plus space for surgery, autopsy, and cage and bottle washing.

The principal investigator must be an experienced scientist manager who is capable of supervising a multi-task contract involving many personnel within his own institution as well as interacting with NCI personnel. There will be a single NCI project officer, but there are many individual investigators with whom projects are implemented.

The principal investigator should possess a doctorate in one of the relevant disciplines and be able to contribute between 50 and 100 percent of the time to the contract. The services of a DVM having demonstrated experience in laboratory animal medicine and the management of a large colony of experimental rodents is required, although this individual need not be assigned principally to this contract.

In addition, on an annual basis, 6,000 man hours of senior and junior technical personnel, 6,000 man hours of technical support personnel and 4,000 hours of laboratory aid personnel will be required.

Contract Specialist: Mary Armstead
Carcinogenesis
301-427-8764

The Cancer Letter _Editor Jerry D. Boyd

Published fifty times a year by The Cancer Letter, Inc., P.O. Box 2370, Reston, Virginia 22090. Also publisher of The Clinical Cancer Letter.