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FDA TO TIGHTEN UP REGULATIONS ON ANTICANCER DRUG COMBINATIONS, STOP "PERMISSIVENESS"

The Food & Drug Administration's Div. of Oncologic & Radiopharmaceutical Drugs has served notice it intends to tighten up regulations on drug combinations. In some cases, proposed combinations will be considered new drugs, requiring the same process for approval before they may be used by investigators or made available for general practice.

Robert Young, FDA oncology group leader, told the division's advisory committee last week that "FDA has been permissive" regarding combinations in the past. "We haven't really looked at combinations

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In Brief

SHINGLETON CHAIRS CANCER CONTROL COMMITTEE; JOFTES, PRICE HEAD REVIEW, ORGAN SITE BRANCHES

WILLIAM SHINGLETON, director of the Duke Univ. Comprehensive Cancer Center, has agreed to serve as chairman of the Cancer Control & Rehabilitation Advisory Committee. He replaces Gerald Murphy, director of the Roswell Park Comprehensive Cancer Center, whose term expired. Oliver Beahrs, head of general surgery at Mayo Clinic, will be the vice chairman. Next meeting is Sept. 23-24. . . .

DAVID JOFTES, who has been chief of the National Organ Site Programs Branch in NCI's Div. of Cancer Research Resources & Centers, is now chief of the Review & Referral Branch. Mordecai Gordon held that job until he retired earlier this year. Samuel Price, special assistant to division Director Thomas King, will continue with that job while serving as chief of the Organ Site Branch. . . . **IN LISTING** members of the NCI intrainstitute committee on centers, ***The Cancer Letter*** (Aug. 20) failed to include DCRRC members: King, Deputy Director and Centers Program Chief William Walter, and Bernard Keele, special assistant to Walter. . . . **JAMES DONOVAN**, chief organizer and first president of the Assn. of Community Cancer Centers, has left the staff of the West Coast Cancer Foundation to accept a position with the Whittaker Corp. The new job will keep him out of the country much of the time, so Donovan has resigned from the ACCC Board of Trustees. . . . **ROSWELL PARK** has established a Center for Light Research, to focus on the relationship between light and cancer. Cora Saltarelli is executive director. Studies have indicated that some wavelengths of light may promote animal tumor growth, others inhibit it. . . . **NEW MEDICAL** Devices Act enacted earlier this year requires FDA to establish classification panels for each device category, including one for radiological devices. Panels will advise FDA on safety and effectiveness of existing devices, recommend whether or not premarket approval is required for new ones, review premarket approval applications, and advise on the necessity of banning devices. The new panels replace the old device review panels which had more restricted responsibilities.

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CONTROLS ON INVESTIGATOR USE OF NEW DRUG COMBINATIONS TO BE TIGHTENED

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very carefully. Looking at some of the protocols that have been coming in for combinations, I'm not sure a permissive attitude is justified," Young said.

The reaction from committee members caused Young to attempt to distinguish between medical practice and clinical research involving drug combinations.

"Why should FDA get into this?" asked Chairman Michael Shimkin. "If a physician wants to take three bottles off the shelf, bottles with drugs you have approved, and give them to his patient, FDA has no business saying he can't do that . . . FDA has a vital role, in keeping bad drugs off the market. Beyond that, you are regulating medical practice."

Young acknowledged that FDA has no authority to prevent physicians from using drugs approved as single agents for specific types of cancer in combination with other approved drugs when that is done in medical practice. "But we can regulate investigational testing of new drugs," he said.

In other words, physicians treating patients not involved in any research protocol, may prescribe drug combinations as they see fit, even when the drugs as single agents may not be indicated for the specific disease for which the patient is being treated. But a clinical investigator who wants to try a new combination of approved drugs must submit an investigational new drug application (IND) to FDA before proceeding with the same treatment.

Before a new combination may be distributed in fixed doses for general practice, it must go through the new drug application (NDA) process, just like any new single agent, Young said.

Young argued, "When a drug approved for use as a single agent for certain indications is combined with another drug or drugs, even when approved for similar indications, the fact that you put them together makes them a new drug and they are subject to new drug regulations." He cited FDA regulations on that point.

Young said FDA would limit its concern, at least for now, to combinations administered simultaneously, rather than sequentially.

He listed four requirements that would be applied to INDs for combinations:

- There must be a reasonable rationale for the combination. Each agent in the combination will have to make a contribution, although not necessarily a direct contribution if it enhances the principal component.
- Where preclinical toxicology seems necessary or helpful, it should be done.
- Where combinations have never been tested before in humans, careful phase I type studies should be done.
- Investigators should provide for orderly acquisition and reporting of data to permit FDA to build a data base for use in considering future drug combination INDs. Awareness of combinations that have been determined ineffective would be especially helpful, Young said.

Franco Muggia, director of the Cancer Therapy Evaluation Program in NCI's Div. of Cancer Treatment, pointed out that the division's journal, *Cancer Treatment Report,* formerly *Chemotherapy Report,* has reported extensively on ineffective combinations.

Committee members and NCI representatives doubted that preclinical toxicology studies of antitumor drug combinations in animals provide much useful information.

"We've got 20 years of negative data," said Philip Schein, Georgetown Univ. "It's unlikely that animal studies will prove a combination is ineffective against a human cancer."

"It doesn't work that way," said Charles Moertel, Mayo Clinic. "There's no representative model system for many cancers. I thoroughly agree that a rationale must be there, but that can be derived from clinical experience."

John Vendetti, chief of NCI's Drug Evaluation Branch, agreed that "you can't use animal data to negate a prospective combination when the rationale for that combination is there."

Muggia said that "general rules are impossible and unnecessary. Successful combinations are designed by clinicians using specific rules for specific diseases."

Schein said that there is no specific species which correlates to man in toxicity "even for a single drug."

Only Melvin Krant, Tufts, Univ., who is a consultant to the committee, supported a stronger FDA role in regulating drug combinations.

"I think it is ridiculous when you say FDA does not regulate the practice of medicine," Krant said. "When you keep a drug off the shelf of pharmacies, you are regulating the practice of medicine. When you order pharmaceutical firms to list the dosages and indications on package labels, you are regulating the practice of medicine . . . I see regulation, education and the enhancement of medical practice as going together."

Shimkin was not convinced. "If three drugs are each approved for the treatment of neoplastic disease and all are mentioned as of some use against mammary tumors, where is the role of FDA in approving the three combined for breast cancer? FDA is not supposed to regulate the physician in the practice of medicine."

"If approved for mammary tumors and if used in private practice, FDA has no regulatory authority," Young said.

"That's too many ifs," Shimkin said, "If NCI or Sloan-Kettering wants to try two drugs with radiotherapy, you're saying they can't without FDA approval?"

"No, they can't," Young answered.

Vendetti asked how FDA could make the distinction between a "physician who makes a treatment decision, then writes it up. How can you then go back and make a regulatory decision?"

The discussion wandered into the use of drugs for non-approved indications. Young admitted that FDA cannot prevent a physician from using a drug or combination of drugs for non-approved indications. Controls in that regard include various quality review mechanisms and the spectre of malpractice. Although the law states that physicians may deviate from FDA-approved label instructions, they still have been brought into malpractice suits.

Krant said he favors "some controls by FDA. I don't want to go back to the time when a physician could do anything he wishes. If the role of FDA is to control material entering into general use as far as efficacy and safety are concerned, there has to be ongoing monitoring. The agency must have the power to determine if the original requirements are still being met."

COMMITTEE DENIES NDA APPROVAL FOR MeCCNU; NO SURVIVAL INCREASE SHOWN

Shimkin's committee jolted FDA staff, NCI drug development executives and representatives of Bristol Laboratories when it voted to deny approval of the NDA for Methyl-CCNU.

MeCCNU is the third nitrosurea to come out of NCI's Drug Development Program for which Bristol has filed an NDA under contract from NCI. FDA has just approved the NDA for CCNU, although that has not yet been announced; and approval for BCNU is coming up soon. CCNU and BCNU thus will soon be available for general practice, from the pharmacist's shelf, for a variety of antitumor indications. Since they cross the blood-brain barrier, they are expected to have significant impact on treatment of brain tumors.

Bristol asked approval of MeCCNU only for use against colorectal cancer. Although it did show activity against other tumors, the response rate was less than that from other drugs, according to Stanley Crooke of Bristol, who made the presentation to the committee.

Crooke referred to studies in which MeCCNU combined with 5-fluorouracil obtained a response in 32% colorectal patients, and combined with vincristine obtained a response in 43%. The NDA would limit MeCCNU's use to the combination with 5-FU, since the vincristine study was more limited.

But Moertel, who directs a study at Mayo involving MeCCNU, injected a new element—what Shimkin called "a breath of fresh air"—into the consideration of an anticancer drug's effectiveness: the survival rate. After Bristol's presentation, Shimkin asked, "Okay, is there enough evidence presented to recommend its use as requested?"

"None whatsoever," Moertel replied. "The prime interest of the American public in supporting cancer research is the lengthening of survival. The evidence is crystal clear, there is no increase in longevity with MeCCNU. There is toxicity, with carcinogenesis as a possibility. The fact that you may get 40% vs. 20% tumor shrinkage is not important. There are better pain relievers than MeCCNU."

Committee member Stanley Balcerzak, Ohio State Univ., asked if the survival rate in Moertel's studies was affected by the possibility that the studies have not been going on long enough.

"No, the studies are in, and there is no increase in survival," Moertel said.

"That's our feeling, too," Schein added.

"Both the Southwest Cooperative Group and ours conducted randomized, controlled studies," Moertel said. "There was zilch increase in survival."

Schein said that in his study at Georgetown, MeCCNU produced "unpredictable toxicity. I'm concerned about letting it out" into the hands of physicians less experienced with antineoplastic drugs.

"Even in experienced hands it was difficult to manage," Moertel said.

Shimkin asked if the toxicity problems also did not apply to BCNU and CCNU.

"At least with those drugs you have some increase in longevity," Moertel said.

"We've been too loosey-goosey in releasing drugs," Shimkin said. "The measure has been that the shrinkage of the tumor produced a better clinical situation."

"It does no good if the patient still dies in four months," Moertel said.

FDA's position has been, Young pointed out, that "If you can show a meaningful biological response even without increasing survival, we'll approve it as a palliative agent."

"Are we looking for something tangible?" Moertel argued. "Are we meeting the expectation of the patient when he pays for a drug? His expectation is that he will live longer." Moertel suggested that if the NDA is approved, "we will be taking a chance that this drug will be abused. It's abused now."

"I can't argue with you," Shimkin said. "You did the biggest study. But this does represent a change in our thinking."

Krant commented, "It would be a crime to discard this drug if the patient felt better, if it improved the quality of life. Is there any data from the studies on that?"

It's very difficult to get that out of a cooperative group study. It involves a lot of subjectivity," Moertel said. He emphasized that studies with MeCCNU are continuing, using it in various two and three drug combinations. "As an investigative drug, okay. For routine use now, no," Moertel insisted.

The committee first voted 4-2 to approve the NDA, with Moertel and Balcerzak against. After Margaret Sullivan, M.D. Anderson; John Whitaker,

Capital Medical Clinic of Austin, Texas, and Schein voted to approve, Shimkin said he would cast his vote for approval to go along with the majority.

But Schein had second thoughts. "My vote was a soft one," he said, and then asked to change it to the negative. Shimkin withdrew his vote, letting it stand at 3-2 against approval.

Crooke argued that NCI's distribution of the drug to investigators "already is liberal, and the distribution is increasing." Milan Slavik, chief of NCI's Investigational Drug Branch, replied that physicians who request the drug are given a common protocol to follow. "That's a lot different than making it available from pharmacies," Moertel said.

Schein summed up the discussion. "I think there are adequate controlled trials now. In a couple of years we may get some answers."

"This is music to my ears," Shimkin said. "I never thought that 21% vs. 17% tumor shrinkage was enough evidence to justify putting out another poison."

Whitaker, who as a private practitioner conducts investigational studies and thus is able to obtain experimental drugs from NCI, said that he has had some problems in getting those drugs in recent months. Muggia suggested that those problems have been more or less overcome, with the agreement between FDA and NCI relating to distribution of experimental drugs.

Krant was not satisfied. "If there is a demand for it, it is clearly because there is a feeling that it is useful. The response rate was good. In fact, doubling the response rate over other drugs is phenomenal."

"When these results get reported and re-reported, when someone comes into a meeting and says Dr. Moertel is getting 43% response, everyone gets excited," Whitaker said. "Sometimes we even have patients who have heard about it and ask for it."

"But there's no replacement for how long the host lasts," Shimkin said.

Muggia was not discouraged by the committee's action. NCI will continue to develop MeCCNU, he told ***The Cancer Letter,*** especially for use against gastrointestinal cancer where it appears to be more effective than the other nitrosureas.

Muggia did not think that the survival rate would become the dominant factor over tumor response in the development and approval of a new drug. "What Moertel was saying was that we already have drugs just as effective, as far as survival is concerned, and that are less toxic than MeCCNU, so why approve it for general use now? I think that is reasonable."

The committee's vote is an advisory one, and FDA is not required to follow the recommendation in deciding whether or not to approve the NDA. It could be weeks or months before Young and his superiors in the Bureau of Drugs reach a decision.

The committee went on to chop down another NDA. Hoffman-LaRoche had submitted an NDA for fluorouracil capsules to be given to patients who for one reason or another could not receive it intravenously.

Edward Miller, making the presentation for Hoffman-LaRoche, said that it is common practice for physicians to break open the vials in which the drug is distributed and mix it with a liquid to be taken orally. He said his company felt that providing the drug in stable form, in capsules, would offer a better alternative than mixing it with liquids. He said that bioavailability studies showed there is equivalent absorption to IV administration.

Moertel, referring to "four or five studies" in which IV vs. oral administration were compared, said there was "significant inferior response" from the drug when given orally.

"How does the cell know where the drug comes from?" Miller asked.

"I don't know, " Moertel said. "I think we have to look at the end results, rather than a philosophical fine point." He suggested that for those relatively few patients who could not receive the drug intravenously, physicians could continue to break open the vials.

"Why talk about it?" Balcerzak asked. "You can talk about bioavailability all you want, but we have had four to five studies in which the patient was the assay system, and the results were inferior."

Four committee members—Balcerzak, Moertel, Schein and Whitaker—voted to disapprove the NDA; Sullivan abstained.

Angered, Miller charged that "hospitals are paying 75 cents for vials, and some are putting $15 for them on the patient's bill."

"Did I hear you correctly?" Shimkin asked.

Miller retreated somewhat. "Well, I know of one that does," he said.

SCHEPARTZ NEW DCT DEPUTY; DEVITA TO CONTINUE AS CLINICAL DIRECTOR

Saul Schepartz, who has headed NCI's Drug Development Program since 1964, has been named deputy director of the Div. of Cancer Treatment. The position was left vacant when Stephen Carter resigned to become director of the Northern California Cancer Program.

DCT Director Vincent DeVita completed the task of filling key positions on his staff with other actions which he said were the final steps in a two-year process of reorganizing the division:

- DeVita, who has been acting clinical director since George Canellos left last year, will take over that role permanently.
- The Drug Research & Development Program and the Experimental Therapeutics Program have been merged into a new Developmental Therapeutics Program. Vincent Oliverio, who was head of Experimental Therapeutics, will be director of the new program.

• John Ziegler, who has been deputy clinical director, will continue in that position and also will be associate director for clinical oncology.

• A new Clinical Pharmacology Branch has been established, headed by Bruce Chabner.

DeVita said he decided to keep the clinical director position because it includes cross-division responsibilities. DCT and the Div. of Cancer Biology & Diagnosis share the 108 beds at the NIH Clinical Center assigned to NCI (DCB&D has 22 of them). "It's easier for me to deal with Al Rabson (DCB&D director) than it would for someone one notch back," DeVita said.

Since the DCT director and clinical director have been full time jobs, DeVita said he will handle it by permitting Ziegler to have the responsibility for overseeing intramural clinical research and Schepartz will have complete responsibility for the division's committee review functions.

NCAB SUBCOMMITTEE CONSIDERS NINE REVISIONS FOR CANCER ACT RENEWAL

A National Cancer Advisory Board subcommittee is considering nine changes in the National Cancer Act for recommendation to the full Board at its Sept. 16-18 meeting.

When the Act was up for renewal in 1974, all changes recommended by the Board were accepted by Congress. It might be a different story next year, however; some of the changes the subcommittee is considering are controversial.

The nine changes:

1. Authorization levels of $1.073 billion for FY 1978, $1.139 billion for FY 1979, and $1.214 billion for FY 1980.
2. Permit cancer center core grants for five years (the limit now is three.)
3. Delete the $5 million limit on core grants.
4. Permit the distribution of chemicals by NCI to investigators other than NCI grantees and contractors, and permit distribution of animals other than as surplus property.
5. Increase the number of expert consultants NCI may hire from 100 to 200.
6. Authorize the collection of data from state registries and federal government sources.
7. Establish regulations making cancer a reportable disease.
8. Permit the support of basic and clinical research with core grants.
9. Exempt all NCI projects from Health Service Agency review and approval.

The $5 million limit on core grants is one major issue. At the present time, only one center, Memorial Sloan-Kettering, is at that level, but others are approaching it.

Another would be the exemption of NCI projects from HSA review. Under present law, local and regional HSAs can review and disapprove if they wish any federally-supported health project. All centers, and many others with NCI grants and contracts, could find themselves subject to lengthy delays in getting their money if they have to go through that process. The problem of giving chemicals to investigators arose earlier this year when HEW lawyers ruled that NCI could distribute them only to its contractors and grantees and to other government agencies. That's what the letter of the law in the Cancer Act says, but clearly was not what Congress intended. Efforts to get it changed administratively have failed, so the approach now is to change the Act.

When the Act was being reviewed in 1974, then-HEW Secretary Caspar Weinberger argued before the House and Senate Health Subcommittees that the Cancer Program would be better off if no authorization levels were established. Congress did not agree. HEW recently asked the White House if that attempt should be repeated, but this time, someone at the Office of Management & Budget remembered; HEW's request was turned down. However, the Administration still will request a flat authorization level of $1.073 billion for each of the three years.

ABSTRACTS OF PAPERS PRESENTED BY BREAST CANCER TASK FORCE

Following are abstracts of papers presented at the most recent meeting of Breast Cancer Task Force contractors. The papers describe ongoing research being performed by the Task Force and have not been published elsewhere.

URINARY STEROIDS AND BREAST CANCER RESPONSE TO ENDOCRINE ABLATION – Ihor Masnyk, NCI

A collaborative study was carried out aimed at the development of a prognostic index for assigning patients to ablative procedures of adrenalectomy. Two 24-hour urine specimens were collected prior to surgery and analyzed for steroid content. Clinical results were reviewed by two independent investigators.

A total of 121 adrenalectomies were analyzed. There were 28 remissions in this group for an overall remission rate of 23%. When used in its original form, Bulbrook's discriminant was found to be inapplicable as a predictive index for the patient population studied. With 88 positive discriminants only 21 were remissions (24% correctly classified cases); out of 33 negative discriminant cases 26 were classified as progressors (79% correctly classified).

When the base line was lifted to 500, the discriminant's performance improved substantially. Now there were 38 positive cases, 15 of which were actually in remission (39% correctly classified); the negative cases increased to 83, 70 of which were progressions (84% correctly classified).

Our own approach, based on multivariate analysis used the logistic regression model for relationship between concomitant information and probability of remission. Among the cases with individually calculated probability of remission of less than 0.1, the observed remission rate was .07; the group with probability from 0.2 to 0.3 showed actually a 0.21 remission rate, and those with probability of 0.4 to 0.5 showed a 0.48 actual remission rate.

URINARY STEROID PROFILES – E.C. Horning, Baylor College of Medicine

Urinary steroid profiles were obtained by the use of recently developed analytical technology based upon high resolution glass open tubular capillary column gas chromatography, and upon gas chromatograph-mass spectrometer-computer (GC-MS-COM) analytical systems. These methods represent the most advanced form of technology now available for studies of this kind.

The identification of major and minor steroids was carried out by

GC-MS-COM procedures. The derivatives employed were methoxime-trimethylsilyl ethers (for keto/hydroxy steroids) and trimethylsilyl ethers (for hydroxy steroids). Direct comparisons of profiles were made for major steroidal hormone metabolites through quantitative data obtained by gas chromatographic analysis. Two hydrolytic procedures were used; enzymic hydrolysis (Glusulase) was employed for glucuronides and sulfates (except 3a-ol-5a sulfates) and solvolysis was used for sulfates.

Profile variations indicate variations in biosynthetic and metabolic pathways. Comparisons of profiles were made for postmenopausal patients with breast cancer, postmenopausal patients with benign breast lesions, premenopausal patients with benign breast lesions, normal post- and premenopausal females, and adult males. The results indicate that three types of profiles can be defined for females. These are (A) a typical pattern found for about two-thirds of adult females, (B) a typical pattern found for about one-third of adult females, which is not distinguishable from male patterns, and (C) a pattern found for about 20% of postmenopausal patients (cancer and benign lesions) but not for normal females, premenopausal patients with benign lesions, or males. It is believed that these differences are due to imprinting as a consequence of the hormonal environment existing during the fetal or neonatal period. Pattern (C) may represent high risk.

EVALUATION OF THERMOGRAPHY IN MASS SCREENING OF BREAST CANCER — Gary Shaber, Thomas Jefferson Univ.

17,526 patients have been initially screened with clinical examination, x-ray mammography and thermography. 4,237 patients have been placed on a 6-month followup program because of a suspicious clinical or mammographic finding or a positive thermogram; they will remain on a 6-month followup routine as long as their findings remain suspicious. 639 biopsies have been requested and 456 biopsies have been performed. There have been 156 proven tumors (8.9/1000) from the performed biopsy group, a favorable 1 tumor for every 3 biopsies. Less than 25% of the patients with proven tumors had metastatic nodes at the time of discovery.

Since the beginning of the project, two and one half years ago, thermography has been positive in 45% of the proven tumor cases. 18% of the total screened population have had a positive thermogram. However, there has been a vastly improved thermographic performance in the last year of screening. Thermography alone has been positive in 75% of the 51 cases of cancer discovered in 5,336 women in this period. 26% of all patients in the population had a positive thermogram during this period of time.

When thermography is combined with clinical examination 88% of the proven carcinomas were detected; this improvement can be attributed to better performance of readers and close quality control of technique and film processing. These results would lead us to believe that thermography may be a viable technique for breast cancer screening and further evaluation should continue.

XEROGRAPHY VERSUS FILM MAMMOGRAPHY: COMPARATIVE STUDY — Gerald Dodd, Richard Lester, Philip Strax

Both film mammography and xeromammography have gained widespread acceptance in the radiologic community. Additionally, as the result of publicity, xerography is demanded by many members of the laity. However, despite its widespread use, considerable controversy exists as to the relative merits of xerography and film mammography. These differences are of importance in view of the widespread screening procedures now being undertaken. Not only is the comparative accuracy of the methods in question, but the dose delivered to the patient has assumed considerable importance due to the implications of the BIER report. Recently a variant of the film-molybdenum target technique has become available which substantially reduces dose to the patient. Essentially this involves a relatively fine grain film enclosed in a vacuum cassette which contains a single intensifying screen. The manufacturers contend that films of this type, while inferior in resolving power to standard M or AA industrial films, offset the detail loss by enhanced contrast and low exposure rate.

Although the present study incorporates physical comparisons of the individual image receptors, many believe that there is no useful relationship between clinical adequacy and physical measurements. Therefore a clinical comparison has been included which involves 500 high risk patients from each of three cooperating institutions. Three cephalocaudad views of each breast are obtained on AA industrial film, LoDose vacuum cassette film and xerographic plates respectively. All films are interpreted by each institution. Each reading is recorded on a form designed for the purpose. The resulting information is intended to answer the following questions:

1. Is the performance of any modality "superior" with all examiners?
2. Is any modality "superior" for any examiner?
3. Are the results of the readings of each examiner very similar?

Following the accumulation of the data, the physical results will be compared with the clinical results in an attempt to determine whether any of the physical parameters are valid in judging the relative merits of a receptor system. If so, these may be applied to future systems.

At the present time, 5,208 images derived from 868 patients have been entered into the study.

EVALUATION OF THERMOGRAPHY IN MASS SCREENING FOR BREAST CANCER — Raymond Fink, Philip Strax, Louis Venet

The Health Insurance Plan of Greater New York is conducting research aimed at determining the role of thermography in mass screening for breast cancer. About 18,500 women age 45-64 have received initial breast examinations including thermography, mammography and clinical examinations of the breast. Thermograms and mammograms are each read twice independently and differences resolved by a third reader. Among the screened women, 32% are black; 44% had not completed high school, and 41% had annual incomes below $11,000.

Among the 17,370 women screened through December, 1975, 68.4% were negative on thermography, mammography and clinical examinations and advised to return for routine reexamination in two years, 31.6% were recommended for early follow-up, including 3.4% recommended for biopsy and/or aspiration. Positive thermograms accounted for 60% of the early recall recommendations, while nearly a third of the early recalls were based only on positive clinical or radiologic findings (or both).

Among the first 5,360 women screened, 1,644 were recommended for early recall, generally within six months of screening and 80.2% of these have been reexamined. Among the 1,033 women reexamined on the basis of positive thermograms alone, recommendations for early recall were again made for 55.2%. In addition, 2.7% of these women were recommended for biopsy/aspiration. Also, among the 62 women recommended for early recall because of positive thermograms and clinical examination, about one-fourth were recommended for biopsy/aspirations.

Among the first 15,496 women screened 53 had confirmed cancers, a rate of 3.4 per 1000. Among these, 14 or 26.4% had positive thermograms. The number of women with positive thermograms and/or positive clinical findings was 43.

PROGNOSTIC INDICES FOR BREAST CANCER RECURRENCE — G.H. Friedell

Clinical, pathological and biochemical variables were studied in 381 patients in an attempt to develop a prognostic index which could be utilized to predict with a high degree of probability for individual women the recurrence or metastasis of breast cancer within 24 months after radical mastectomy. In this report the term recurrence also covers metastasis. The investigation has involved six institutions contributing clinical patient material, a Central Pathology Laboratory, a Urinary Steroid Laboratory and a Statistical Center. This report will be concerned with the interaction between selected clinical and pathologic variables.

The most important of the latter are four pathologic characteristics of the primary tumor—tumor size, histologic type, degree of tumor differentiation, and blood vessel invasion—and the presence and number of axillary node metastases. In this report we discuss only one clinical factor, namely menstrual status, since the prognostic importance of the pathologic features listed is related to the menstrual status of the patient. Thus, if the patient is premenopausal, cases with one positive lymph node have a similar likelihood of recurrence at 2 years as patients with zero positive nodes, patients with two or three positive nodes have a less good prognosis, and patients with four or more positive nodes have the worst prognosis.

In the postmenopausal group patients with zero positive nodes have a prognosis comparable to that for patients with one, two or three positive nodes at the two year time. Cases with four to nine or 10 plus positive nodes have recurrence-free curves that are significantly less good at two years than those for cases with zero to three positive nodes. It is obvious, therefore, that the major difference between pre and postmenopausal women is in the patient group having two or three positive nodes. For this group of patients there is a statistically significant difference in the curves for premenopausal and postmenopausal women. Tumor size determined by pathologic examination appears to have an important relationship with recurrence; those tumors over 4.0 cm in maximum dimension are particularly meaningful in premenopausal women. Well differentiated infiltrating ductal carcinoma com-

prised 47% and poorly differentiated cancer of this type was 33% of the cases in both premenopausal and postmenopausal women.

In premenopausal women there is a highly significant difference between recurrence-free curves at two years for cases of moderately well differentiated and cases of poorly differentiated cancer. A difference in this direction is also present in the postmenopausal group, but it is not statistically significant. There is a relationship in both premenopausal and postmenopausal groups between degree of tumor differentiation and lymph node status. Blood vessel invasion was less common but of greater prognostic importance in the premenopausal group. Of 342 cases analyzedfor this factor 43% had blood vessel invasion identified at the primary site. In 140 premenopausal cases 39% had BVI; in 202 postmenopausal cases 46% had BVI. Two year recurrence-free rates differed significantly between BVI-positive and BVI negative groups of premenopausal women. Difference in the same direction was present in postmenopausal women between BVI-positive and negative cases but was not statistically significant.

COMPUTERIZED TOMOGRAPHIC MAMMOGRAPHY – Philip Karsell, Mayo Clinic

In view of the impact computerized tomography had in neuroradiology, following a suggestion from David Reese of the Mayo Clinic, the General Electric Co. developed and built a computerized tomographic device (CTM) to evaluate the female breast. This device has been undergoing clinical evaluation at the Mayo Clinic since October, 1975.

The hypothesis on which the machine was developed is that breast cancers almost always consist of tissue which is more dense than surrounding breast tissue. The ability of computerized tomography to differentiate subtle tissue density changes suggests that this modality might play a significant role in the early detection of malignancies of the breast.

To date, we have scanned close to 200 selected patients with CTM. Early experience showed CTM to be only approximately 70% accurate in the diagnosis of breast cancer. In later phases of our protocol, and after planned step-by-step modifications, of the machine, our more recent experience appears more promising.

POSSIBLE RELATION BETWEEN FIBROCYSTIC DISEASE AND BREAST CANCER – David Page, and Roger Vander Zwaag, Vanderbilt Univ.

The relationship between cystic disease of the female breast and subsequent development of malignant neoplasms of that organ remains controversial. The practical goal of this study is to estimate a predictive parameter for each type of fibrocystic disease allowing us to assign relative risks to individual patients concerning the likelihood of the development of carcinoma.

Benign breast biopsies performed at Vanderbilt Hospital between Jan. 1, 1952 and July 1, 1959 have been histologically reviewed and characterized as to individual component types of fibrocystic disease. At the present time followup data with relevant epidemiologic information by way of questionnaires is complete on 77% of the subjects. The relation of types of cystic disease to the subsequent development of carcinoma has been analyzed in 685 women giving a minimal followup of 17 years. Excluding women who had breast carcinoma preceeding their benign biopsy, 24 patients have developed breast carcinoma in the followup period.

As predicted in previous studies, epithelial proliferative lesions are found more often in women who later develop carcinoma. No other changes show any relation to subsequent malignancy (i.e., cysts, apocrine change, sclerosing adenosis, duct ectasia and fibroadenoma). Atypical lobular hyperplasia has a greater predictive value than atypical ductal hyperplasia with the former occurring three times as often in prior biopsies of carcinoma patients than in women free of carcinoma in the followup interval.

THE BIOCHEMISTRY OF BREAST CYST FLUID – Morton Schwartz, Sloan-Kettering

The objective of the study is to determine the biochemical composition of breast cyst fluid (BCF) and then to establish if the assay of any one or a combination of these constituents can help define the formation of breast cysts; predict the clinical course of patients with cystic mastopathy and/or elucidate the significance of the biochemical composition of BCF in the possible transformation of a precancerous lesion to a frank cancer. In addition, an objective is to establish through long term followup, the relationship of cystic mastopathy to the occurrence of breast carcinoma.

During the first 11 months of the project (through June 11, 1976) 269 BCF specimens from 231 patients have been received. The analyses performed were divided into broad categories and included are those assays available in the laboratories of the principal investigator and his subcontractor, the Steroid Institute of Montefiore Hospital & Medical Center.

Specimens were analyzed for their concentration of testosterone, cortisol, progesterone, estrogen, prolactin, leuteinizing hormone and follicle stimulating hormone. All of these were present in BCF at levels which ranged from somewhat below plasma level to a maximum of twice plasma levels.

Triglyceride concentration has been extremely low in BCF but total cholesterol values have been variable and ranged up to 1600 mg/dl. There was no conjugated cholesterol in the fluid.

The total protein in the BCF specimens is usually about 2g/dl with the majority (85%) in the globulin region. The albumin concentration is in the range of 0.2 to 0.3 g/dl. IgM is not detected and IgG and IA are present in concentrations much less than that measured in the serum of this same patient. Estrogen receptor protein (ERP) was determined and in some specimens there was a significant amount of a nonspecific hormone binding but in no instance was there significant inhibition by a specific ERP inhibitor.

The relationship of these various constituents to each other will be discussed and the possible significance of the mechanisms of the elevations considered. In addition the variation of the concentrations in different specimens from the same patient will be evaluated.

IMMUNODIAGNOSIS OF BREAST CANCER – Ronald Herberman, NCI

A variety of immunological approaches are potentially applicable to the detection or diagnosis of breast cancer or monitoring of breast cancer patients. The current status of several of these approaches will be reviewed. Several circulating markers have been associated with breast cancer: carcinoembryonic antigen (CEA), ferritin, casein, human chorionic gonadotrophin (HCG). Each of these markers can be detected by sensitive radioimmunoassays.

Cell-mediated immune reactions can be detected in many patients with breast cancer against breast tumor associated antigens. Assays of leukocyte migration inhibition (LMI), leukocyte adherence inhibition, and lymphocyte proliferation have been used to study these reactions. Antigens can be detected on some established cell lines derived from breast cancer, which provide apotentially standard source of antigens for large scale testing. Reactions in LMI have also been observed with mouse mammary tumor virus and the gp52 from the virus, and initial data suggest a possible place of these reactions in immunodiagnosis.

ANALYSIS OF BREAST FLUID – Nicholas Petrakis, and Eileen King, Univ. of California (San Francisco)

The purpose of these studies is to evaluate the use of nipple aspirates of breast fluid in the diagnosis of breast cancer or the detection of women at risk for breast cancer. Data to be reported relate to cytology, immunoglobulin and ferritin content of nipple aspirates of breast fluid. Breast fluids were obtained from women attending the Univ. of California Surgical Clinics and the Northern California Breast Screening Center.

Cytopathology of abnormal mammary duct epithelium

Cellular abnormalities occurred in nipple aspirate specimens from 197 breasts, 11% of a total of 1,779 breasts with satisfactory cytology. Abnormal cells were distinctive and easily recognized by their larger size and disproportionate nuclear enlargement as compared with normal duct cells. The nuclei contained fine or coarse granular chromatin and varied from hyperchromatic to hypochromatic. These changes were categorized according to their severity and correlated with clinical and pathological findings.

Tissue from breast biopsy or mastectomy was available for comparison with cytology for 122 breasts. The tissue contained benign lesions in 99 breasts, of which 28 had abnormal cytology, and contained carcinoma in 23, of which 14 had abnormal cytology. Within the duct epithelium were changes that appeared significant in relation to cellular findings, whether or not invasive breast cancer was found. These ductal changes were evaluated with regard to their anatomic location and cla ssified according to the degree of severity as hyperplasia, atypical hyperplasia, dysplasia and carcinoma in situ. They appear to provide the most probable source of the cellular abnormalities observed in nipple aspirates.

Total cellularity was found to be elevated in patients with breast disease and had a significant relationship to age in normal women. Analysis of differential cell counts revealed an inverse relationship between numbers of foam cells and histiocytes. The percentage of histiocytes within a specimen was found to be significantly increased in patients with abnormal cytology and/or malignant pathology, a finding that may be an indication of tumor host response.

Immunoglobulin levels in breast fluids of women with breast cancer

Because in several recent reports authors have suggested that immune disturbances may be present in women with breast cancer, we studied the immunoglobulin levels in breast fluid and serum from women with normal breasts, benign breast disease, and breast cancer using rocket immunoelectrophoresis. Concentrations of IgM were markedly increased in breast fluids of many women with breast cancer and prior mastectomy (33%), but in few women with normal and benign-disease breasts (5%). In addition, many women with breast cancer (33%) lacked IgA in their breast fluids. At present we can only speculate about the meaning of these findings, but in view of numerous reports of immune disturbances associated with breast cancer, the present findings may have diagnostic and etiologic significance. Prospective studies of women at the breast screening center and following mastectomy may provide information on the clinical significance of the observed variations in immunoglobulin content of human breast secretions.

Detection of ferritin in breast secretions

A variety of clinical studies have reported that the serum and tissue concentrations of ferritin proteins are increased in cancer patients. Recently, Marcus and Zinberg reported elevations of serum ferritins in women with localized and recurrent breast cancer (J. Nat'l. Cancer Inst. 55: 791-95, 1975). Because our studies indicate that the breast fluids contain increased concentrations of many serum constituents, it was considered of interest to determine if ferritin is present in breast fluids of women with cancer, benign disease and normal breasts.

Antisera to ferritin were supplied to us by Peter Dallman, Dept. of Pediatrics, UCSF. Since April 1976, 44 breast fluid and serum samples have been tested with antiferritin antibody employing the Mancini radical immunoprecipitin technique. Eight breast fluid samples and one serum sample gave positive tests for ferritin: Breast fluids from three of three cancer patients were positive, with only one of the three serum samples positive. Breast fluids from two women considered to have highly suspicious mammograms were positive. No diagnosis is yet available on these women. Breast fluid in one of 11 women with fibrocystic disease gave a positive ferritin test. Two of 38 fluids in women with clinically normal breasts were positive for ferritin. These highly encouraging findings have led us to measure ferritin levels in breast fluid and serum by radioimmunoassay. We hope to determine if ferritin levels can be employed in the diagnosis and screening for breast cancer.

CONTRACT AWARDS

Title: Study of effectiveness of interferon in combination with chemoimmunotherapy in controlling MULV induced spontaneous leukemia in AKR mice
Contractor: Mount Sinai School of Medicine, $1,162,862.

Title: Studies of latent virus infection and transmission
Contractor: Southwest Foundation, $49,730.

Title: Japan-Hawaii cancer study
Contractor: Kuakini Medical Center, Honolulu, $477,591.

Title: Preparation and purification of viral components
Contractor: Pfizer, $121,923.

Title: In vitro sensitization of human lymphocytes
Contractor: Weizmann Institute of Science, Rehovot, Israel, $81,375.

Title: Detect circulating antigen-antibody complexes
Contractor: Washington State Univ., $58,528.

Title: Improvement of assays for cell-mediated immunity
Contractor: Sidney Farber Cancer Center, $44,649.

Title: Mechanisms by which tumors avoid destruction by the immune system
Contractors: Weizmann Institute of Science, Rehovot, Israel, $80,625; Univ. of Hawaii, $75,467.

Title: Clinical chemotherapy program in cancer control
Contractor: Children's Hospital, Denver, $25,000.

RFPs AVAILABLE

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

RFP NO1-CO-65350

Title: *Analytical support services for DCRRC cancer centers program*
Deadline: *Oct. 15*

The proposed procurement listed herein is totally set aside for small business. NCI is soliciting proposals from small businesses to provide continuing analytical support services for the Cancer Centers Program of the Div. of Cancer Research Resources & Centers. The tasks to be performed will vary according to the needs of the Cancer Centers Program and are expected to include both short-term (less than three months) and long term (more than six months) efforts.

Programs supported by the Cancer Centers Program which are expected to generate the need for analytical support include core activities, clinical research, outreach, exploratory studies; and facilities construction. Analytical support services will consist of budget and financial analysis, resource analysis, program and project analysis, and special analytical support.

Contracting Officer: David M. Keefer
Control & Rehabilitation
301-427-7984

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