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OPENING SHOTS FIRED IN 10 YEAR DEFENSE OF CANCER PROGRAM, LAUNCHING OF EFFORT TO CONTINUE, EXPAND IT

"Then and now the American public and Congress want the Cancer Program to be a priority program. Priority does not mean it is the same as everything else. Priority means favored treatment. We got it, and we need to continue getting top priority for the Cancer Program if we are going to continue to make progress."

Frank Rauscher, senior vice president of the American Cancer Society and former NCI director, fired that opening shot in what is shaping up as a defense of the National Cancer Program's first 10 years and a

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In Brief

DCBD BOARD ADDS CONCEPT REVIEW TO DUTIES, RABSON SEEKS FOUR ADDITIONAL MEMBERS

NCI'S DIV. of Cancer Biology & Diagnosis will start using its Board of Scientific Counselors for concept review of some of the division's extramural programs at the Board's October meeting. The Board has been limited to reviewing the DCBD intramural laboratories, while the Diagnostic Research Advisory Group and Breast Cancer Task Force have performed concept review in their respective areas. DRAG and BCTF will continue their roles, with the Board of Scientific Counselors taking on concept review of other DCBD supported research and of the division's resources contracts while continuing to provide the peer review of the division's intramural scientists. David Korn, chairman of the pathology department at Stanford, is chairman of the Board. Other members are Lee Leak, chairman of the anatomy department at Howard Univ.; Edmond Lin, professor of microbiology and molecular genetics at Harvard; Renata Cathou, professor of biochemistry and pharmacology at Tufts Univ.; Lisa Steiner, professor of biology at MIT; and Barbara Bowman, chairman of the department of human biological chemistry and genetics at the Univ. of Texas (Galveston). There are two vacancies to be filled, and DCBD Director Alan Rabson has asked that four additional members be authorized to help carry out the Board's expanded role. The Board will meet Oct. 9-10. . . . **JOHN BOICE**, a member of NCI's Environmental Epidemiology Branch, has received the J.D. Lane Award from the PHS Professional Assn. for an epidemiological study he conducted with George Hutchison of Harvard. The study showed no increase in the incidence of leukemia among women who received high doses of radiation for treatment of cervical cancer. . . . **"MANAGEMENT OF PATIENTS** with Cancer Pain" is the topic of a symposium Oct. 17 sponsored by the Northwest Ohio Cancer Network. Contact the program chairman, Roland Skeel, M.D., Director, Cancer Program, Medical College of Ohio, C.S. 10008, Toledo 43699.

LIFESTYLE MORE IMPORTANT THAN WORK EXPOSURES IN ETIOLOGY, SYMPOSIUM HEARS

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simultaneous launching of an offensive to continue and expand the program through the 1980s. Rauscher and former President's Cancer Panel Chairman Benno Schmidt were the opening speakers at "Cancer 1980: Achievements, Challenges, Prospects," the International Symposium on Cancer in New York this week sponsored by Memorial Sloan-Kettering Cancer Center, ACS and NCI.

Symposium speakers summarized progress over the past 10 years, although it has been only a little more than eight years since the first major increase in funds went to NCI. The National Cancer Act of 1971 was passed in December of that year, and NCI received a $100 million supplement to its FY 1972 budget several months later. In any accounting of the program's 10 year accomplishments, there are still two more years of achievements to come.

Relating the history of the Act and the early years of its implementation, Rauscher said Congress considers cancer control "the single most important part of the program. Congress is concerned with what you are doing for sick people. Things that are regarded as ivory tower stuff will be the first to go in times of tight budgets. We must convince the public of the importance of continuing strong support for basic research. . . . Basic researchers ought to kiss a clinician once a week. They are doing things that people see. Our critics say that breast cancer patients have no better chance for survival now than they did 35 years ago. That's nonsense. We have made very important progress in treating breast cancer, but it will take 10-12 years before we see an impact on survival.

"Efforts are being made to deprive NCI of some of its uniqueness," Rauscher continued, "particularly the budget bypass authority. It is very important that NCI continue to have that authority to go directly to the White House and Congress with its budget, rather than through four levels. Should that ever appear threatened, we should arise to protect it."

Rauscher mentioned as other important aspects of the Cancer Program which recieved major impetus from the National Cancer Act the development of centers, the International Cancer Research Data Bank and the international program.

Schmidt noted that it has been 20 years since he was asked by Sen. Ralph Yarborough to serve on the Panel of Consultants which was being asked to make recommendations regarding cancer research. Those recommendations were incorporated into the Act.

"I have had a rare opportunity to see the problems and controversies that have been a part of the cancer research picture for the past 10 years, both in the scientific community and the broader arenas of the Congress, the media and the public," Schmidt said. "These issues have dealt with some very important questions and their resolution has vitally affected our cancer research programs. . . . First, was Congress wise in passing the National Cancer Act and in stepping up the appropriations in support of cancer research? I believe that the answer is an unequivocal yes. The money has, on the whole, been well spent and I know of no federal dollars which have been put to better use than these. . . .

"It has also been charged that the Cancer Act and the increased expenditures were obtained by overpromise, and that the results have not lived up to the expectations. There was some overpromise, both from a few of those who testified and from some members of Congress, and much has been made of those quotations, but the overwhelming burden of the testimony and the overwhelming sense of Congress was not a promise of miraculous results but rather of good research, money well spent, and progress.

"Secondly, it was charged that good basic research would suffer under an expanded and revitalized Cancer Program. Why on earth would an expanded research budget hurt basic research? Because, it was said, the people running the Cancer Program didn't understand basic research. They would try to plan where planning was inappropriate; to program research that couldn't be programmed; they would try to target research that couldn't be targeted; they would use contracts when only grants would attract to the program the best of the basic scientists.

"Well, it hasn't happened that way. Investigator initiated, peer reviewed, grant supported basic research was funded by the National Cancer Institute at unprecedented levels and the proper atmosphere for fundamental basic research was guarded more zealously than perhaps any aspect of the cancer effort. Good basic scientists were always more than adequately represented on the National Cancer Advisory Board and the President's Cancer Panel. Of course, not everyone who wanted support got it, and few, if any, got all the support they wanted, but one of the outstanding attributes of NCI's support of cancer research during the past 10 years has been the high level of support of excellent basic research. . . .

"Third, there has been much talk of an inordinately high level of support for clinical research," Schmidt continued, "or as it is more popularly put: spending all the money on a fruitless search for a cancer cure when it could be better spent on something else. That something else might be basic research, prevention research, research in chemical carcinogenesis, epidemiology, nutrition research, or whatever happens to be the special interest of the critic. Incidentally, I have not heard any clinicians or clinical researchers who think we are spending too much on clinical research. Nor do I. We have made great progress in our clinical research programs, and

we must do our best for the 25 percent of our people who have cancer or are destined to have cancer in the years to come.

"I do not believe we are neglecting prevention research, research on chemical carcinogenesis, epidemiology, or nutrition research, all of which are vitally important. One of the most frequently voiced criticisms of the Cancer Program has been that we are not doing enough about chemical carcinogenesis. This is frequently combined with the criticism that NCI is lavishly backing the study of a possible viral cause for cancer, while many scientists have come to believe that the real urgency is now the study of environmental causes of cancer. Actually, both areas are extremely important and both areas are being supported in a substantial way, as they must be.

"The big mistake about the support of virology that continuously occurs in our press is that money is being spent in the search for a human cancer virus. The fact of the matter is that this money is being spent in the area called virology because that area has turned out to be the focal area for much of the productive research in molecular biology. It is in the area that we call virology that much of the progress in our basic understanding of the transformation of normal cells to cancer cells is taking place. It is this area of research that has produced our understanding of reverse transcriptase, recombinant DNA, gene structure and function, and surface antigens. The new technique that is provided by recombinant DNA is already leading to a deeper understanding of how genes act in both normal and cancer cells. Virology is a most important area of basic research which no knowledgeable scientist ridicules and substantial research in this area must continue to be supported.

"However, this in no way detracts from the importance of environmental carcinogenesis and that area of research is also receiving important support. In my opinion, virology and environmental carcinogenesis are not an either/or proposition. They are both important and they are both being importantly supported under the Cancer Program. The single most important discovery in environmental carcinogenesis may well come when we understand through basic research the mechanism of action of chemical and environmental carcinogens. This may prove to be the real key to elimination of this source of cancer."

Schmidt defended the cancer centers and cancer control programs.

"The centers have been in the forefront of combining surgery, radiation therapy and chemotherapy in such a way as to produce the best possible results for the cancer patient. . . . I think there are good ways in which the control dollars can and are being spent—dissemination of lay and professional information, training programs, and clinical cooperative groups for bona fide clinical research—but I believe we delude ourselves when we assume that in a short time frame we can, by the expenditure of control dollars, make available nationwide the excellence that exists in the best centers. That takes time, and it cannot be pushed as fast as we would like to think."

As for the criticism expressed in 1970 and 1971 (and presently by the uninformed) that increases in NCI's budget would be at the expense of the other NIH institutes, Schmidt pointed out that during the 70s, the total NIH budget increased from $1 billion in 1970 to $3.4 billion in 1980. "I am particularly pleased that the non-cancer portion of the NIH budget was over $1.5 billion higher at the end of the decade than at the beginning."

Two scientists renowned for their expertise in cancer etiology opened the scientific portion of the symposium by agreeing in general that lifestyle and personal habits probably play a more important role in causing cancer than exposure to industrial carcinogens.

John Higginson, director of the International Agency for Research on Cancer, said, "Contrary to misconceptions among the public, progress in environmental cancer has been considerable since 1950, as improved data on geographical distribution and temporal and migrant variations in cancer patterns have become available, high and low risk populations identified, and a better understanding of the carcinogenic process has increased collaboration between laboratory and field research workers.

"Further, it should be emphasized that epidemiological studies have not only identified specific causal factors for certain tumors but have also provided background data from which etiological hypotheses can be postulated for others. Progress, however, has been as much dependent on exclusion of hypotheses as on development of new concepts. Thus, geographical and temporal differences in cancer patterns and changes in migrants early indicated that most cancers are not predominantly racial or hereditary in origin, but rather are directly or indirectly modulated by the exogenous environment."

Higginson said that cancers can be divided into those of defined origin and those for which etiological hypotheses can only be deduced. Cancers caused by defined exogenous factors, he said, are predominantly tumors in adults arising in the skin, respiratory tract, upper digestive tract, liver, pancreas and bladder. It also includes some tumors of the endometrium and blood forming organs.

"Personal habits, notably cigarette smoking, alcoholic beverage consumption, betel quid chewing and sunbathing are by far the most important stimuli identified, causing from 25 to 50 percent of all cancers in males in different populations. All studies increasingly emphasize the overwhelming role of cigarette smoking in human cancer, not only per se but also as enhancing the effects of other agents, e.g.

asbestos and alcohol. A smaller proportion is related to occupational and iatrogenic exposures."

Lack of epidemiological data prevents adequate evaluation of the more than 500 chemicals identified by the IARC as potentially hazardous, Higginson said. Certain other cancers in this category include primary liver cancer in Africa and Asia, related to hepatitis B virus and aflatoxin; Epstein-Barr virus and Burkitt's lymphoma in Africa and nasopharyngeal cancer in China.

Cancers of probable environmental origin, Higginson said, include predominantly tumors of the GI tract, stomach, large intestine, endocrine related organs (prostate, ovary, breast, uterus, cervix) and some tumors of the genito-urinary system. This group forms about 40 percent of cancers in males and 60-70 percent in females.

Higginson challenged the concept that exposure to industrial/occupational chemicals is responsible for significant increases in cancer incidence. "No consistent relationships have been shown between overall cancer patterns or individual sites and probable indices of ambient environmental pollution, such as industrialization and urbanization. No significant effect can be demonstrated even for lung cancer, if correction is made for other variables, notably cigarette smoking and occupational exposures. On the other hand, the overall effect of occupations which tend to be located in towns can be partially evaluated. However, the demonstration of localized cancer 'hot spots' within a country requires analysis as to whether they reflect localized high exposures, e.g. mesothelioma in shipyard workers, or lifestyle factors, as distinct from general environmental pollution.

"Overall cancer patterns have been relatively stable in most western societies over the last 70 to 80 years, most changes being largely explicable by cigarette smoking, alcohol consumption or lifestyle changes. Available epidemiological data do not indicate a significant increase related to ambient pollution, e.g. water. . . . It has been argued that the increase in synthetic organic chemicals is too recent to permit any evaluation of their long term effects. It should be noted, however, that many were already produced in considerable quantities by 1950. Further, since no accurate measurements exist of the total carcinogen burden before then, and which is reflected in present cancer patterns, the increase in this burden can only be assumed. Further, in many countries, control of the escape of chemicals into the general environment has increased, so that greater production does not necessarily imply an increase in the total burden of a carcinogen exposure."

Higginson emphasized, however, that "a failure to demonstrate an effect does not mean that present levels of ambient environmental effect cannot be demonstrated in relation to other factors. Moreover, there are other excellent health and ecological reasons for the control of general air and water pollution."

On the significance of occupational studies, Higginson said, "There has been a tendency to associate occupational epidemiological studies only with the identification of discrete carcinogens. Recent occupational studies from the United Kingdom and elsewhere have also produced strong supportive evidence for the role of lifestyle factors in influencing cancer patterns in different occupations. Since individual occupations are recruited from specific segments of the community, the health patterns in such occupations also reflect the community experience. It has been calculated that most of the differences in cancer patterns between occupational groups are likely to be due to lifestyle and not to workplace exposures. Thus, distinction should be made between tumors due to industrialization per se and cancers occurring within an industrialized society."

Higginson concluded that many of the problems, especially in regard to lifestyle and extrapolation from animals, will probably require at least a decade for solution. "Developments will take place slowly by trial and error. Attempts by managers, politicians, etc. to make research more efficient are unlikely to be more effective than a system governed by a responsible scientific community, in which the public has trust. As Passmore has pointed out, the reputation of biomedical science in terms of honesty and incorruptibility is consistently high. There have been few instances of personal abuse of public money. The fact that certain work has been pedestrian and nonproductive must be regretted but it certainly does not mean that scientists have tried to distort research priorities for personal gain. To assume, however, that all scientists are objective in terms of research priorities is naive, as each has his own bias as to what is important. However, we must guard against raising false hopes and making promises about prevention. . . . The public seldom forgives twice. There has been a tendency in certain government and scientific circles to constantly present a pessimistic approach to developments in environmental carcinogenesis and prevention. Such an approach cannot but be detrimental to the image of the scientist as seen by the public and is unfair to the past accomplishments of epidemiology. It certainly leads to the belief that little has been done and that past support and effort have been wasted. The public must learn that our present optimism is based on an ever growing body of scientific fact, which will permit better intellectual approaches to future research and cancer control strategy."

Michael Shimkin, professor of community medicine and oncology at the Univ. of California (San Diego) suggested that "If there is anything clear about carcinogenesis, it is that the exposure is almost always intense and prolonged.

"The process takes seven to 20 years to eventuate

in cancer. During such a length of time, alterations occur in the host, nutritionally, hormonally, and immunologically. All such alterations influence the development and the growth of the neoplasm.

"The first question of a putative carcinogen for man should be whether man indeed is exposed to it at all," Shimkin continued. "In California we plant oleanders along the highways. Oleanders are poisonous plants, but we do not use them in salads and consider that their beauty is of no danger to us. The second question should be, how much of the chemical does indeed get on or into man. The third should be what happens metabolically to the chemical. This is undoubtedly the most important area for future research on carcinogenesis, to define the enzymatic and other metabolic mechanisms devised by our body to guard against the perils of the environment. In fact, the definition of such measures and their effectiveness will lead to the understanding of individual susceptibility, probably the next large step to be achieved in the clinical sciences."

Shimkin pointed out, as did Higginson, that if the increase in production of chemicals over the past 30 years was related to cancer, the occurrence of cancer should have increased. However, "when adjusted for age, no remarkable increases are observed during the past four decades. In fact, there has been a decline in mortality rates under 45 in the United States, interpreted by some as being due to therapeutic improvements, especially chemotherapy. Increased mortality among men has been attributed to the pandemic of lung cancer due to cigarette smoking, and the male rates show no increase when lung cancer is removed from the calculations. . . . Studies on the incidence and mortality in human populations do not support an important role for industrial carcinogens in the total cancer occurrence. By far the most important single carcinogen is our old enemy, tobacco smoking. . . .

"I am devoted to preventive medicine, but its limitations are only too obvious. Redemption of sins is closer to the human condition than a blameless life. Redemption is quick and visible; a blameless life, alas, only promissory. So is prevention as apposed to treatment. But it is an error to compare or to appose treatment and prevention. Both are necessary and desirable. The choice between the two depends upon their relative ease and effectiveness rather than upon any cosmic considerations. . . .

"When measures of primary prevention of cancer available to us at present are analyzed, it soon becomes obvious that the recommendations are not limited to cancer, but represent measures of general health protection. Cancer prevention is health protection, and should not be separated from it. Such separation is encouraged by health agencies bearing the label of cancer. They jealously guard their budgets and their turf, and are careful not to impinge upon the turf of other categorical prerogatives. It is high time they got together. Preventive oncology is but a part of preventive medicine, which in turn is but a part of medicine, a part of society. Control of cancer will be achieved by new knowledge acquired through research on causes and on cures. Special units propounding and applying the limited knowledge available to us at present are useful as an interim device.

"The final goal of all cancer research is cancer control, and in this we are not doing badly, unless we overpromise and raise anticipations beyond realistic levels."

TASK FORCE HEARS UPDATES ON CLINICAL, DIAGNOSTIC, ETIOLOGIC RESEARCH

The Breast Cancer Task Force heard reports at its summer meeting from a number of projects it is supporting, including clinical trials, diagnostic and etiologic studies.

Charles Hubay, Case Western Reserve Univ., reported on the study testing tamoxifen, chemotherapy and BCG with 318 stage 2 patients. At a mean followup of 48 months postmastectomy, Hubay said these conclusions can be made:

1. Stage 2 breast cancer patients with estrogen receptor negative tumors recur more rapidly than patients with estrogen receptor positive tumors following mastectomy, allowing identification of poor risk group.
2. Estrogen receptor negative patients have a higher mortality rate than similarly treated estrogen receptor positive patients at this point of follow-up ($p = .000$).
3. The addition of tamoxifen to cytoxan, methotrexate, 5-fluorouracil therapy was more effective than CMF alone in delaying recurrence of stage 2 estrogen receptor positive breast cancer ($p = 0.0202$).
4. In estrogen receptor negative stage 2 breast cancer patients there appeared to be no difference in the recurrence rate for any of the three treatments used in the study.
5. With CMF treatment, premenopausal estrogen receptor positive patients recurred less often than premenopausal estrogen receptor negative patients. It was postulated that the benefit may reflect suppression of ovarian function.
6. Anti-estrogen therapy appeared to offer benefit in the treatment of stage 2 estrogen receptor positive breast cancer patients in both pre- and postmenopausal women.
7. Any conclusion regarding the effects of BCG immunotherapy could not be made at this time (48 months followup) owing to the brief followup period in the BCG groups.

A parallel study of 509 stage 1 breast cancer patients, treated by mastectomy alone, was presented. In this group, premenopausal women recurred more rapidly than postmenopausal patients ($p = .006$). Estrogen receptor negative stage 1 patients appear to be recurring more rapidly than ER+ patients ($p = .049$). Comparison of ER values in pre- and postmenopausal patients shows no significant difference in recurrence or survival at 60 months followup. In the ER+ patients, however, the premenopausal group is recurring more rapidly than the postmenopausal patients ($p = .0246$).

A study headed by David Ahmann at the Mayo Clinic (presented at the meeting by Edward Scanlon of Evanston, Ill.) compared L-PAM alone with a combination of 5-FU, cyclophosphamide and prednisone with or without radiation. The results with 295 patients:

Recurrence rates per thousand weeks of observation are 4.63 on L-PAM versus 2.913 on CFP and 2.442 on CFP plus radiation therapy. Without question premenopausal patients did not do as well when they received L-PAM as treatment option compared to the two treatment programs involving CFP with or without radiation therapy. For the postmenopausal group of patients no statistically significant treatment differences are presently shown between the three treatment arms chosen.

Myelosuppression was almost universal with 97 to 99 percent of the patients achieving some degree of myelosuppression. Analysis of the data revealed that the only discriminants found to influence disease free interval and survival in the postmenopausal group of patients were tumor size and number of nodes involved. Treatment employed does not exert a statistically significant influence thus far.

With respect to the premenopausal group of patients, the age of the patient, the existence of unfavorable local signs, the number of lymph nodes involved, the body weight of the patients, and the treatment employed all influence disease free interval and recurrence rates. Treatment influence, however, is restricted to the markedly inferior performance of L-PAM in this treatment setting.

Thus far no subset of patients, pre- or postmenopausal, seems to benefit from the addition of radiation therapy to the polychemotherapy treatment program employed.

Recurrence rates specifically were not related to the amount of myelosuppression obtained; however, they were related to the absence or presence of continued menstrual function.

Morbidity with respect to the use of radiation therapy included increase in the incidence and amount of lymphedema, and several adverse sequalae which are unique to radiation therapy including radiation pneumonitis, esophagitis, pericarditis, radionecrosis and brachial plexopathy.

Edward Wilkinson, Medical College of Wisconsin, discussed occult breast cancer metastases in axillary lymph nodes:

The presently employed non optimum methods of sectioning lymph nodes removed at the time of mastectomy have been estimated, by optimum sectioning methods and lymph node sectioning probability studies, to miss 22 to 30 percent of occult metastases. The purpose of this study was primarily directed toward determining the frequency and significance, in relation to survival of occult lymph node metastases.

Six hundred and seventy-seven patients who had undergone radical or modified mastectomy for breast carcinoma and were initially found to have negative axillary lymph nodes by conventional histopathology were identified. Patients selected for study had five or more years followup and their original histopathologic slides as well as paraffin blocks were examined. From the original 677 cases, 525 cases were acceptable for the study. These cases were obtained from five primary care hospitals in the greater Milwaukee area affiliated with the Medical College of Wisconsin. In our initial review of the original slides of these 677 cases, we identified 18 cases with tumor identifiable in the original slides. These "overlooked" tumors made up 2.7 percent of the cases reviewed. A total of 525 cases were resectioned, which includes the 18 overlooked tumor cases.

A pilot study was carried out on the first 57 cases, which were serially sectioned at 6 micron spacing. This pilot study determined that optimal section spacing which gives positive identification of occult metastasis was 48 micron spacing of 6 micron sections. Subsequently, cases 58 through 207 were cut and read at 24 micron spacing and cases 208 to 525 were cut at 24 micron spacing and read at 48 micron spacing. All cases were examined by board certified pathologists and all occult tumor cases were reviewed by two or more pathologists.

On reexamination of the lymph node sections from the 525 cases a total of 89 occult tumor cases were identified (17 percent). No significant difference in the percent of occult tumors from hospital to hospital was detected. The average number of nodes studied was 13.8 per patient with approximately 7,245 nodes studied. A total of 121,772 slides were prepared with 176,057 sections made. A total of 1,156 blocks were resectioned.

All patients included within the study had five or more years followup. No significant overall difference in survival could be identified in patients with occult lymph node metastases as compared to those patients without such metastases. Our patient population is similar to other breast cancer series in mortality. Twenty-one of the 89 patients with occult lymph metastases had two or more nodes involved. Two patients had three nodes involved and one patient had four nodes involved by occult tumor. No significant differences in survival were noted between patients with one or with more than one node involved with occult tumor. The size or the volume of occult tumor in the lymph nodes studied did not correlate recurrence or survival. The presence or absence of infiltration of the occult metastasis into the lymph node did not influence survival. There was a substantially lower survival in patients that had the primary breast tumor in the inner hemisphere of the breast ($P < .001$). This was true whether or not occult tumor in the lymph nodes was present.

Elwood Jensen, Univ. of Chicago, reported on improved procedures for determination of estrogen receptors:

As a guide to prognosis and therapy, quantitative determination of the estrogen receptor (estrophilin) content of excised specimens of primary as well as metastatic breast cancers has become standard medical practice. Current assay procedures that depend on the binding of radioactive hormone as a marker for the receptor protein have the disadvantages of high cost, loss of binding capacity during sample processing or storage, and masking of receptor by endogenous estrogen.

We have developed two approaches to simplified receptor assay that promise to eliminate some or all of the foregoing difficulties. In the first procedure, unoccupied receptor is determined in tumor cytosols or nuclear extracts by treatment of the receptor protein with tritiated estradiol while it is adsorbed within the interstices of Controlled Pore Glass (CPG) beads; unbound and non-specifically bound hormone is readily washed away, and the receptor-bound estradiol eluted with ethanol for counting. Receptor occupied by endogenous estrogen is conveniently estimated by adsorption of the complex on CPG beads, release of the bound hormone by treatment with silver nitrate, removal of silver ions with dithiothreitol, and saturation of the regenerated receptor with tritiated estradiol, which is then eluted with ethanol for counting.

The second approach is immunoradiometric assay, making use of radioactive monoclonal antibodies to human estrophilin. Splenic lymphocytes from a Lewis rat, immunized with cytosol receptor from MCF-7 breast cancer cells after purification by a novel affinity chromatography technique, were fused with mouse myeloma cells of a nonimmunoglobulin-producing line. Cloning by limiting dilution furnished a hybridoma cell line that grows well either in suspension culture or as ascites tumor in athymic mice to produce milligram quantities of monoclonal antiestrophilin antibody. By growing the hybridoma cells in medium containing [^{35}S] methionine, radiolabeled antibody is produced biosynthetically, whereas radiodinated monoclonal antibody is readily obtained by standard chemical procedures.

These radiolabeled antibodies offer promise as reagents for the rapid, inexpensive measurement of estrophilin in breast

cancers, independent of whether or not the receptor is bound to estrogenic hormone.

William McGuire, Univ. of Texas (San Antonio) discussed whether histochemical methods for estrogen receptor determination are valid:

Because of the great usefulness of estrogen receptor determinations in selecting therapy for breast cancer patients, a number of histochemical and immunohistochemical methods for visualizing bound estrogen in cells and tissue sections have been proposed. All of these histochemical methods were discussed in the light of the known properties of the estrogen receptor and other estrogen binders, and some criteria were considered which must be met if such methods are to be considered valid for receptor. In spite of the great potential value of histochemical methods, it must be concluded that, in their present form, none of them is likely as yet to be detecting estrogen receptor.

A study headed by Gary Friedman (presented by Robert Hiatt) of the Kaiser Foundation Research Institute looked at serum cholesterol and breast cancer incidence in members of the Kaiser Foundation Health Plan:

Recent studies have suggested a role for dietary fat in the etiology of breast cancer. We investigated the relation of serum cholesterol and other serum lipid measures to breast cancer in a cohort of 95,179 women who took a multiphasic health checkup (MHC) from 1964 through 1972. Pertinent data on known risk factors were abstracted from each woman's first MHC in that period.

Up to the end of 1977, 1,035 breast cancer cases subsequently occurred in this cohort. Length of followup totalled 752,000 person-years. Age-adjusted breast cancer incidence rates were 1.41, 1.43, 1.31, and 1.37 per 1,000 person-years at risk from the lowest to the highest quartile of serum cholesterol level, respectively. Similarly, no relation was detected between β-lipoprotein or total lipids and breast cancer.

The validity of this lack of association was strenghened by the presence of the expected relation of breast cancer to established risk factors such as ages at menarche and menopause, parity, and educational level. These data suggest that the postulated causal relation between dietary fat and breast cancer does not act via an effect on circulating lipid levels.

Effects of obesity and diet on androgen-estrogen metabolism in women were reported by Marvin Kirschner, Newark Beth Israel Medical Center:

Obesity and dietary factors are under active investigation as possible promoters of human breast cancer. The current study was initiated to explore whether obesity and/or diet might alter hormone production and metabolism providing the link to breast cancer.

Androgen and estrogen production rates have been determined to date in 19 reproductive-age women with varying degrees of obesity. Androstenedione production rates averaged 3.34 mgm/day vs. 2.26 in a group of 23 non-obese controls ($p<0.05$). Extragonadal metabolism of Δ to estrone (E_1) was increased at 2.69 vs. 1.54 percent in controls ($p<.05$), confirming similar observations in obese men and postmenopausal women. Urinary E_1 production rates performed day 5-8 of cycle average 201 μg/day in obese women vs. 102 in lean controls. These values are not significant yet due to large variance in the obese group.

Metabolic clearance rates of androgens are accelerated in obese women. Whereas increased MCR of testosterone can be explained by lower levels of SHBG noted in obese subjects, a different mechanism must be evoked to account for the increased MCR of androstenedione (2898 L/day in obese women vs. 2140 in normals, $p<0.05$), since this latter androgen is not bound to SHBG.

Final conversion of androgens to their urinary metabolites, androstenedione and etiocholanolone appears to be no different in obese vs. normal women, although excretion of etio in obese women is elevated at 2.05 mgm/day vs. 1.34 in normals ($p<0.05$), probably reflecting increased overall androgen production.

The above androgen-estrogen parameters have also been compared in 16 normal female volunteers after one month periods of dietary manipulations, including normal diet, high protein diet and high carbohydrate diet. We cannot, to date, appreciate any significant changes in Δ production and peripheral metabolism nor estrogen production after these dietary changes.

Our studies to date indicate that obese young women exhibit differences in both gonadal and extragonadal production of androgens and estrogens, as well as differences in metabolism of the sex hormones. In normal women, isocaloric manipulation of dietary components does not seem to alter sex hormone metabolism.

Diagnosis of breast adenocarcinoma by use of Thomsen-Friedenreich antigen and antibody was discussed by G.F. Springer, Northwestern Univ.:

Thomsen-Friedenreich (T) antigenic specificity as determined with human serum anti-T was found in reactive form in 94 percent of 54 breast adenocarcinomata but not in healthy and generally not in benign breast tissues. T-antigenic specificity was also present in adeno- and squamous cell carcinomata from other organs; it was not found in any of the four melanomata, one glioblastoma and seven benign non-breast tumors tested. T antigen can be readily prepared from healthy human erythrocytes via isolated MN antigens in uncontaminated form and free of HL-A and Australia antigens. Breast carcinoma patients but not healthy people showed cellular immunity to T antigen in vivo and in vitro. Most striking was the delayed type cutaneous hypersensitivity reaction that was positive in 87 percent of the 83 patients with ductal breast carcinoma tested, negative in 96 percent of 144 benign breast disease patients (5 of 6 positive ones had hyperplastic disease and one developed breast carcinoma) and in all 52 presumably healthy individuals investigated. Results were not as clear cut in patients with lobular carcinoma.

In vitro determination of leukocyte migration inhibition due to T antigen showed a positive reaction in 49 percent of 89 patients with stages 2-4 breast carcinoma, while 34 percent of 64 with stage 1 (invasive and non-invasive) cancer reacted positively. The leukocytes of 14 percent of 142 persons with benign disease and none of 112 healthy ones showed a positive reaction to T antigen. MN antigens did not inhibit leukocyte migration.

We have begun to improve the sensitivity and specificity of this in vitro assay and are defining the active area on the T antigen. A substantial part of the activity was found in the desialized α-1 glycopeptide which appears to be a more sensitive indicator of carcinoma-induced T-specific cell-mediated immunity.

Because all humans have anti-T antibodies, we investigated whether or not there was any difference in anti-T agglutinin levels between patients with breast carcinoma, patients with benign breast disease and healthy persons. Agglutinating anti-T was severely depressed in 21 percent of 189 breast carcinoma patients, while only 5 percent of 270 patients with benign disease had a significant depression; at least three of the patients diagnosed histologically as having benign breast disease but with depressed anti-T subsequently had also histologically verified breast carcinoma (2 patients ductal, 1 lobular carcinoma). Among 200 control persons who had neither be-

nign breast disease nor carcinoma and who were either healthy or sick, there were 1.5 percent with severely depressed anti-T. These differences are statistically significant ($p<0.001$). Occasionally breast carcinoma patients had a substantial increase of anti-T agglutinins. Surgical removal of the bulk of carcinoma resulted in strong rebound or overshoot of anti-T.

We are now studying anti-T not only by semiquantitative tube agglutination but also Ig subclasses by strictly quantitative means. So far a significant majority of breast carcinoma patients but not of the other persons studied shows extensive changes (decreases or increases) of anti-T IgM from the norm. A lesser percentage of breast cancer patients shows less extensive changes of anti-T IgG.

The use of ultrasound in the diagnosis of breast cancer was discussed by Barry Goldberg, Thomas Jefferson Univ.:

The goals of the project were to develop characteristic ultrasound patterns of benign and malignant breast pathology in order to evaluate the efficacy of high resolution ultrasonic equipment in the detection of early breast cancers.

Two different ultrasonic machines, the Octoson B-scan and the Johnson & Johnson real time scanner, were clinically evaluated. Patients coming to surgery for suspected breast carcinomas had a preoperative x-ray mammogram, physical examination and ultrasonic examination. There were repeat examinations of any excised breasts. In addition, 8 to 10 cases per week recommended for biopsy or aspiration of suspected cysts were similarly examined. There were 250 asymptomatic patients enrolled in the program. Ultrasonic patterns were correlated with histopathology and x-ray mammograms in both in vitro and intact breast tissues. The Octoson ultrasound machine was also modified to obtain wave forms and ultrasonic wave form signal analysis and acoustic signaling techniques in a computer learning procedure were performed.

A total of 1,664 patients were enrolled in the research protocol. The evaluation of the first 1,029 patients has been completed. Seventy percent of these patients had an x-ray mammogram (705). There have been 278 biopsies performed to date on this subpopulation of 1,029 patients with 79 proven cancers, 24 under 2 cm and 53 over 2 cm in diameter. Fifty-eight of the cancer cases had both the ultrasound examination and x-ray mammography.

The ultrasound mammogram was interpreted at two different sessions, the first "blind" without benefit of other clinical information, and the second with all the clinical information available to the interpreter including x-ray mammographic results. The results of all of the examinations including physical and history were encoded on optically readable computer scan sheets.

Ultrasound's sensitivity for breast cancer in the entire evaluated population was .71 and its specificity was .80 for breast cancer. In the 705 patients who had both the x-ray and the ultrasound examination, the sensitivity of ultrasound for breast cancer was .69 and x-ray mammography was .74. If the clinical information was included in the ultrasound interpretation, the sensitivity rose to .79. The specificity of the true positive rate for ultrasound was .03, compared to .41 for x-ray mammography. In all cancer cases (79), ultrasound's sensitivity and specificity using the clinical information was .80 and .82 respectively.

Goldberg added the comment that "ultrasound is not ready for use in screening at this point. More work needs to be done."

NOTICE OF INTENT

NCI intends to recompete the work and services presently being performed by Litton Bionetics Inc. under Contract N01-CO-75380 calling for the operation and maintenance of the Frederick Cancer Research Center, Frederick, Md.

It is contemplated that the present contract will be divided into two distinct parts, specifically for the management and conduct of the (1) scientific research, and (2) research resources and support services. Offerors will have the prerogative of submitting proposals on one or both parts. Potential for a small business set aside exists for a portion of the support services.

Anticipated beginning date of new contract(s) is Sept. 26, 1982. Further notice will be published on or about June 1981. Estimated term of the new contract(s) is five years. Present contractor has indicated its intention to participate in the recompetition.

Current annual operating budget of this cost-plus-award-fee/cost-plus-fixed-fee contract is approximately $24 million. This announcement is intended to apprise all interested organizations of this future competitive opportunity.

NCI Contracting Officer: Ron Defelice
301-663-7148

CONTRACT AWARDS

Title: Bioassay of retinoid activity of tracheal organ culture system
Contractor: IIT Research Institute, $402,114.

Title: Carcinogenicity studies in rodents
Contractor: International Research & Development Corp., Mattawan, Mich., $323,913.

Title: Synthesis of new retinoids for the chemoprevention of epithelial cancer by retinoids
Contractors: SRI International, $444,287; Univ. of California (Riverside), $273,894; and Cornell Univ., $348,524.

Title: Endocrine events at the time of first pregnancy, continuation
Contractor: Emory Univ., $138,939.

Title: Breast Cancer Detection Demonstration Project
Contractor: Univ. of Arizona Medical Center, $139,520.

The Cancer Letter _Editor Jerry D. Boyd

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