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Committee, BSC Recommend Against Continuing Women's Health Trial; Appeal To NCAB Seen

The Board of Scientific Counselors of NCI's Div. of Cancer Prevention & Control last week approved the recommendation of its Committee for the Women's Health Trial that the $90 million, 10 year trial not be continued. The Board also went

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In Brief

Kennedy To Hold Hearing On Mammography Reimbursement, Waxman On Reauthorization

SEN. EDWARD KENNEDY has scheduled a hearing on reimbursement by Medicare for mammography screening and on the quality of Pap tests. The hearing will be held Jan. 28 by the Senate Labor & Human Resources Committee, which Kennedy chairs. . . . **REP. HENRY WAXMAN** is planning information gathering hearings by the House Health Subcommittee which he chairs in February or March on biomedical research reauthorization, including renewal of the National Cancer Act. . . . **ANNUAL JOINT** meeting on cancer control research of the Assn. of Community Cancer Centers and the Assn. of American Cancer Institutes will be joined this year by the American Society for Preventive Oncology. The meeting is scheduled for March 16 at the J.W. Marriott Hotel in Washington DC, the day after ASPO's March 14-15 annual meeting and the first day of ACCC's annual meeting. The morning session will be on innovative approaches to cancer prevention control research, the afternoon on cancer control research evaluation. . . . **SUZANNE HAYNES** has been named chief of the Health Promotion Sciences Branch in the Div. of Cancer Prevention & Control by Lillian Gigliotti, director of the Cancer Control Science Program. Haynes, with a PhD in epidemiology and a background in economics, came from the National Center for Health Statistics. . . . **DCPC DIRECTOR** Peter Greenwald is still searching for a director of the Centers & Community Oncology Program, a position vacant since Jerome Yates left last October. Greenwald is also looking for someone to head the new Laboratory for Nutrition & Cancer Research. . . . **BARUCH BLUMBERG**, Nobel laureate and vice president for population oncology at Fox Chase Cancer Center, is host of a one hour television program titled, "Plagues," which will be shown Jan. 20 on WHYY-TV in Philadelphia and other PBS stations in May. Blumberg relates details of historic epidemics and the AIDS outbreak, which he says acts much the same as earlier epidemics.

Animal Studies Weaken Hypothesis, Committee Says; Limited Trial Asked

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along with the committee's recommendation to continue followup of the 1,700 women already enrolled in the study at three centers.

Investigators involved in the trial indicated that they will take their case again to the National Cancer Advisory Board. The final decision rests with NCI Director Vincent DeVita.

It does not seem likely at this point that either the NCAB or DeVita will reverse the DCPC Board's decision, since it came on an 11-1 vote with two abstentions. Also, the committee's recommendation was unanimous.

The proposed trial would be a decade long randomized controlled field trial intended to evaluate the hypethesis that a reduction in the proportion of dietary calories from fat, from about 40 percent to about 20 percent, will lower the incidence rate of breast cancer by 50 percent among women at increased risk of the disease. The trial would involve about 32,000 women, aged 45-69 at enrollment, drawn from about 20 collaborating centers. It was estimated to cost about $90 million in direct costs, expressed in 1987 dollars.

The trial was controversial from the time it was first proposed to DCPC about three years ago. Critics argued that accrual would be difficult, that women would not comply with such a major change in their diets over the required time, that monitoring compliance would not be possible. The Board approved a feasibility study at three participating centers in 1985 with a "vanguard" group of about 300 women. A Statistical Coordinating Unit and a Nutrition Coordinating Unit also were funded.

As it turned out, the feasibility study demonstrated conclusively that accrual, dietary modification and maintenance, and monitoring were indeed feasible. Approval was given to the three centers to continue accrual, and a total of about 1,700 women were enrolled.

However, the scientific basis for the hypothesis eroded somewhat in the intervening years. Animal studies which appeared to show increased risk with increased dietary fat were supplanted by studies which found that the increase risk may be due to higher caloric intake rather than fat. Also, the type of fats seemed to make a difference.

The most solid basis for the hypothesis, epidemiological studies, especially population differences in diet and incidence, was challenged. Other factors such as weight, exercise and age at menarche had to be considered in those differences.

The Policy Advisory Committee of the Board, established to oversee the trial and make recommendations to the Board, decided last September against proceeding with full implementation. The Board rejected that recommendation and voted to set up a new committee to look at the evidence and again. That committee met in October and again last month (**The Cancer Letter**, Jan. 1). Last week's recommendation was the result.

The committee was asked by DCPC Director Peter Greenwald to address these questions:

1. Is the hypothesis that dietary fat causes breast cancer among women sufficiently strong to justify a randomized trial?

2. Does the WHT, as currently designed, provide an adequate test of the hypothesis?

3. What data are necessary to assure that the women in the WHT are actually eating in the manner they report?

4. Are there other issues that warrant discussion?

Here is the committee's response:

Credibility of the hypothesis

A. Animal studies and implications for human beings

The frequency of cancer among experimental animals given an ad libitum diet is directly proportional to the level of fat in the diet. Both saturated and polyunsaturated fats contribute to the increase of mammary cancer. However, while high fat diets that contain limiting amounts of the essential fatty acids are effective enhancers of carcinogenesis, fish oils are not and may even be protective. Thus, at the ad libitum level of food consumption, with relatively high levels of fat intake, i.e. 40 percent of total calories, cancer incidence is influenced by the nature of the fat.

In contrast, even the moderate restriction of calories reduces the frequency of mammary neoplasms, even with a high fat diet. Therefore, animal experiments suggest that dietary fats increase mammary cancer risk only under circumstances of ad libitum feeding; under conditions of restricted feeding, the effect of fat is much less apparent. Animal studies raise questions about the validity of the dietary fat-breast cancer hypothesis among human beings. These questions may be especially relevant for the women in the

WHT's intervention group who may experience caloric restriction.

B. Epidemiological studies

The available case control studies show either no association of dietary fat intake with the risk of breast cancer or, at most, a slight positive association. Furthermore, the two published prospective followup studies show an inverse association between fat intake and breast cancer incidence. Finally, one retrospective followup study in nuns, with presumed low fat intake, found them to have average breast cancer mortality rates. On balance, then, analytic epidemiologic studies do not support the hypothesis. It has been suggested that the reason that analytic studies do not show a clear association is that the instruments used to assess fat intake have low validity, with a resulting measurement error sufficiently large to obscure any true association.

The major epidemiologic evidence in support of the hypothesis comes from studies relating variation in national breast cancer incidence or mortality rates to per capita fat "disappearance" data. Some of this relationship may be real, but much of it is probably attributable to correlates of fat intake. Such correlates include established breast cancer risk factors such as body weight among postmenopausal women; for example, evidence indicates that half the difference in risk between postmenopausal Dutch women and Japanese women is attributable to the heavier weight of Dutch women, As another correlate, it may be that the effect of diet is mediated, at least in part, through age at menarche. Other possible breast cancer risk factors such as physical activity may also be correlated with fat intake. Statistical control for these factors has been inadequate because of the unavailability or poor quality of the necessary data. Thus, the association between fat intake and breast cancer risk is likely to be weaker than it appears from plots of incidence or mortality rates against fat disappearance data.

Other epidemiologic data supporting the hypothesis are provided by studies of women who migrated from Italy or Poland to high risk countries. These data suggest that the migrants adopted relatively rapidly the life style and the breast cancer rates of the host country. However, the comparability of the incidence and mortality data in the countries of origin and of adoption is rather uncertain, making the results of these migrant studies difficult to interpret. Further, the breast cancer rates in migrants soon after migration may be inordinately low.

In summary, both the analytic epidemiologic studies with negative results and the correlation studies with positive results have serious limitations. Nonetheless, they provide no strong support for the hypothesis. Further, they suggest that if a positive association does exist, it is not as strong as has been represented. The suggestion has been that a reduction from 40 percent to 20 percent of calories from fat will reduce the incidence of breast cancer by 50 percent after 10 years. This prediction of a 50 percent decline in rates does not reflect the probable confounders already mentioned. In addition, the correlational studies should be considered to represent lifetime fat intake since any association between diet and breast cancer is likely to reflect lifetime eating patterns. Therefore, it is not likely that diet between ages 45 and 69 can explain all the differences among countries.

The committee judges that the available epidemiologic evidence does not support the proposal that the incidence of breast cancer can be reduced by 50 percent in women who change to a low fat diet after age 45. A reduction in risk of more than 25 percent is considered highly unlikely.

C. Conclusion

The hypothesis that dietary fat is a cause of breast cancer among women is plausible but only weakly supported at present. The two major detractors from the credibility of the hypothesis are: (1) The difficulties of generalizing to the human situation the controversial and restricted results from animals and, (2) the reliance on international comparisons and migrant studies among the epidemiologic studies. Such studies are susceptible to alternative explanations and do not offset the numerous available analytic investigations which are negative or only weakly positive. Furthermore, even if the dietary fat-breast cancer hypothesis is assumed to be correct the association should be viewed as considerably weaker than has been inferred in planning the WHT.

The Women's Health Trial

A. Power

As planned the trial has a power of 80 percent to detect a reduction (averaging 17 percent and becoming 50 percent in the 10th year) in breast cancer incidence in the fat

reduction intervention group. However, the power is 30 percent if the effect of the diet reduction is only one half that assumed by the investigators. That is, at the greatest reduction in risk that the committee considers reasonable, the WHT has a power of only 30 percent. If the true magnitude of the risk reduction is considered to be 25 percent, not 50 percent, the WHT study size would need to be increased four fold; alternatively, the trial would need to be continued for an additional six years (total of 16 years) to achieve 80 percent power.

B. Enrollment and compliance

The WHT calls for the randomization of 32,000 women (40 percent intervention, 60 percent control) aged 45-69 years, at increased risk of breast cancer and with a dietary fat intake estimated to be at or above 38 percent of calories. These women would be enrolled over a three year period. The three initial centers have enrolled about 1,500 women and are projected to recruit about 4,100 in total. Ten other centers were selected in response to an RFA and it is proposed that these would enroll about 18,300 women for the full scale trial. It is anticipated that seven more centers would be required in order to recruit the 32,000 subjects for the full scale trial. The three initial centers have recruited and retained subjects in accord with projections. Some problems have been encountered and resolved. Undoubtedly, further difficulties will develop, especially with the centers yet to be identified and added. Nevertheless, enrollment has improved with time and experience and the current projections are reasonable.

The women in the vanguard group have achieved a reduction in fat intake from about 76 to about 34 grams per day and from 39 percent to 23 percent of calories. There has been little change in the P:S ratio. This result was sustained for up to 24 months at all three centers. These data were collected using the usual instruments for dietary assessment and were verified by trained personnel who were not involved directly in counseling the subjects and who were unaware of the subject's status.

The intervention group's compliance with the study diet was evidenced by reductions in serum cholesterol from their own baseline and from the control group's level. These were, respectively, a decrease of 8 mg/dl (4%) and about 15 mg/dl (7%). The intervention group also reduced caloric intake by 21 percent and experienced a weight loss of 3 kg. Thus, the centers have achieved a sustained reduction in the fat content of the diet close to the target levels. This dietary modification was accompanied by a reduction in calories and by a modest change in body weight.

Attrition among vanguard women, over the two year study, was 7 percent in the intervention group and 6 percent in the controls. More dropouts may be anticipated in the full scale trial because of the length.

C. Markers

The data available from the vanguard women demonstrate that serum cholesterol can be used as a marker of group differences in dietary fat intake. At present there is no available biochemical marker of an individual's fat intake over time. Although desirable, such a marker is not required for the purposes of the trial.

D. Diet alteration by controls

The educational efforts of public and private groups such as the National Cholesterol Education Program and the National Academy of Sciences may significantly affect the WHT by causing a reduction in the fat content of the diet of the control group. Any reduction in the dietary fat of the control group, below the 36 percent of calories used in planning the WHT, will reduce the power of the trial.

E. Costs

The committee opines that the actual cost of the WHT will be higher than the current estimate. Major reasons for this view are that enrollment is likely to be protracted and that the observation period will need to be extended beyond 10 years.

Summary and Recommendations

It has been demonstrated for the first time that a group of free living adult Americans can be educated to reduce their dietary fat intake by about 40 percent over several years. The information concerning this achievement will be of great value to the scientific and to the public health community in planning clinical experiments and intervention programs. For this, the WHT investigative group and staffs have earned the respect and admiration of all.

The committee considers that the hypothesis under discussion has little support and is descriptive of an association that is weak at best. Furthermore, the WHT as proposed offers a relatively low power (80%) which, even so, has to be viewed as an overestimate

as it is based on an implausibly strong cause-effect relationship. An additional concern is the possible dietary fat reduction by controls as they and the American public are subjected to dietary health education by the mass media and as low fat foods become more diverse and available. The three limitations just mentioned pose the severe problem that if the WHT is done and produces a negative result, that result may be uninterpretable.

With respect to the specific charge given to the committee, the following responses are offered:

1. Is the hypothesis that dietary fat causes breast cancer among women sufficiently strong to justify a randomized trial?

In the committee's opinion, the hypothesis is not sufficiently strong.

2. Does the WHT as currently designed provide an adequate test of the hypothesis?

Because of age and time limitations and low power, the WHT does not provide an adequate test of the hypothesis.

3. What data are necessary to assure that the women in the WHT are actually eating in the manner they report?

The information to be gathered in the course of the trial is adequate to assess the extent to which women in the intervention group and in the control group have modified their diets.

4. Are there other issues that warrant discussion?

The committee believes that the charge as constituted and this report address all of the major issues.

The committee offers these recommendations to the BSC:

1. The WHT as currently proposed should not go forward.

2. At the discretion of NCI staff the WHT centers now active should be considered for continuing financial support in order that the education and followup of enrolled women, or a sample thereof, may continue and in order that scientific proposals based on the study groups can be generated and possibly implemented.

The report was signed by all members of the committee--chairman Philip Cole, chairman of epidemiology at the Univ. of Alabama (Birmingham); Edward Bresnick, director of Eppley Institute and with Cole the two BSC members on the committee; Roswell Boutwell, McArdle Laboratory and a member of the National Cancer Advisory Board; Wayne Calloway, senior science consultant on food and nutrition with the National Academy of Sciences; Elaine Feldman, chief of nutrition at the Medical College of Georgia; Jennifer Kelsey, head of epidemiology at Columbia Univ.; Malcolm Pike, Dept. of Preventive Medicine at the Univ. of Southern California; and Paul Engstrom, vice president for cancer control at Fox Chase Cancer Center and chairman of the DCPC BSC.

Greenwald, although thanking the committee for a "thorough and thoughtful report," disagreed with some of its conclusions. "My own view is that the epidemiological evidence on dietary fat and breast cancer is fairly strong and that it is important for this hypothesis to be tested. The error measurement of diet in the so called analytic epidemiology studies appears to be very large indeed, severely limiting the value of these studies."

Greenwald added he felt that "the epidemiology has changed. There's too much stock in case control."

Despite that disagreement, Greenwald does not intend to go against the Board's recommendation and ask DeVita for permission to go ahead with the trial. "But I do think that the hypothesis has to be tested some time," he said.

Greenwald paid tribute to the investigators involved in the study. They are "a superb group" which "thought through in depth and tested in the vanguard group and first stage participants the first large scale dietary intervention in cancer prevention. New information was provided or soon may be on achieving and maintaining dietary behavior change, monitoring dietary change, biochemical methods to better measure and document diet, and what happens at a 20 percent fat diet in biochemical/endocrine changes.

"The Statistical Coordinating Unit has done a more exquisite analysis of standard epidemiological studies of diet and cancer than previously seen. Their work indicates need for debate about currently accepted epidemiological 'hierarchy of evidence' with respect to diet and chronic disease."

The study has shown "the dynamic nature, excitement and importance of nutritional research in cancer prevention," Greenwald continued. "It illustrates the need for new scientists and new technologies to be attracted to this field. I hope some of our brightest young scientists will join in this

effort." The work of the investigators "paves the way for the development of future cancer prevention trials. It helped us to better define scientific and management processes for such a trial. It helps define further work that may lead us to a new trial based on refinements of the ideas for this one." He suggested a hypothesis "linked to type of fat and interaction with calories, energy expenditure and other factors (e.g. endocrine) which may merit testing in a trial. A genetic marker of very high risk and/or biochemical marker of fat intake might be achievable within two years and might make a trial proposal more attractive."

Greenwald accepted the recommendation for continued support of the existing participants and followup of women already enrolled, with some modification.

Any continuation would have to be approved by the NCI Executive Committee, would be limited to two more years and could not exceed the budgets already established for those units.

Also, "I would like to go beyond the scope of the RFA, if the investigators can come up with recommendations for further studies," Greenwald said. "Should we still be thinking toward a future trial?" He suggested that some new development, such as a biological test for documentation of diets, or a refinement of the hypothesis might make it more likely "that we can get a conclusive answer."

David Byar, chief of DCPC's Biometry Branch who has been an outspoken advocate of WHT, pointed out, "There are no established criteria for when evidence is strong enough to undertake a trial." He suggested that the cost of the study was a major factor in the decision not to go ahead with it. "How can we ever undertake a dietary trial (if the hypothesis has to be proven in advance)? That's like saying you will never bet on a horse unless he is rigged to win."

Cole responded that "the committee obviously was interest in the cost. But the recommendation not to go forward was not based on cost. If the cost were lowered 50 percent, the recommendation would be the same. If it were lowered 90 percent, then maybe.

"How credible does a hypothesis have to be?" Cole continued, responding to Byar's other point. "I don't know. There does have to be a window. You don't need to do a trial if the evidence is clear and strong. You can't do a trial to test every silly hypothesis. It needs to be somewhere in between."

Board member Donald Iverson, a supporter of the trial, asked, "If we don't do this kind of study, what can we do? Is there any other option?" No one ventured an answer.

"I went into this committee as a firm believer in the relationship of dietary fat to cancer," Bresnick said. "I came out as one of those unanimously opposed to continuing the trial. After a good look at the animal data, I eat humble pie from Dr. (James) Holland."

Holland argued at the September BSC meeting against continuing the trial, with one of his points being that animal studies show incidence is more closely related to caloric intake than to fat.

Board member Robert McKenna expressed concern over misinterpretation by the press of the committee's recommendation and the Board's action. "I would like to see a statement from the Board that this does not mean there is no relation of fat to cancer."

"If we can't recommend going ahead with this study, I don't see how we can pass a motion recommending to women that they reduce fat in their diet," Engstrom said.

Greenwald pointed out that NCI and the National Science Foundation have recommended that Americans cut down on fat in their diet, stay trim, reduce amount of calories they consume, reduce sodium and alcohol consumption and refrain from smoking.

"The basis of Dr. McKenna's motion is to endorse what Dr. Greenwald and NCI and the National Science Foundation has recommended," Engstrom ruled. The Board agreed unanimously, for whatever that might be worth in heading off misinterpretation by the press of the decision against proceeding with the WHT.

On the vote accepting the committee's recommendation, 11 voted for it, McKenna was opposed, and Iverson and Johanna Dwyer abstained. Dwyer said she abstained because she was an investigator in the trial, and Iverson said he abstained because he had been a member of the trial's Steering Committee.

William Insull, principal investigator for the WHT clinical unit at Baylor College of Medicine in Houston, told **The Cancer Letter** by phone after the Board meeting (which he did not attend) that the trial's Steering Committee would meet this week to determine what action to take. He said representatives of the trial would attend the NCAB Feb. 1-3 meeting, indicating they would ask that the trial be continued.

RFPs Available

Requests for proposals described here pertain to contracts planned for award by the National Cancer Institute unless otherwise noted. NCI listings will show the phone number of the Contracting Officer or Contract Specialist who will respond to questions. Address requests for NCI RFPs, citing the RFP number, to the individual named, the Blair building room number shown, National Cancer Institute, NIH, Bethesda MD 20892. Proposals may be hand delivered to the Blair building, 8300 Colesville Rd., Silver Spring MD, but the U.S. Postal Service will not deliver there. RFP announcements from other agencies will include the complete mailing address at the end of each.

RFP NCI-CN-85069-43

Title: Analysis of fiber components in food
Deadline: Approximately March 20

The major goal of this initiative is to support the analysis of dietary fiber components in foods. The major objectives of the procurement will be the following:

1. Design and execute a statistically valid food sampling plan of fiber containing foods which would be representative of foods in the U.S. diet by food type, geographical region and season.
2. Analyze these foods for total dietary fiber, soluble and insoluble fractions and the major fiber components, cellulose, hemicellulose, pectin and lignin.

It is anticipated that two awards will be made and that a three year incrementally funded cost reimbursement (completion) type contract will be awarded to each of the successful offerors.

Contract Specialist: Diana Wheeler
RCB Blair Bldg Rm 2A07
301/427-8745

RFAs Available

RFA 88-CA-02

Title: National collaborative diagnostic imaging trial projects
Application receipt date: March 11

The Div. of Cancer Treatment invites applications for cooperative agreements for participation in the the national collaborative diagnostic imaging trial projects. The objectives of the present proposal are to conceive new approaches for the development and implementation of national cooperative trials carried out by multiple institutions using this approach to develop new algorithms for the appropriate sequential use of the most advanced imaging procedures to diagnose, stage and monitor malignant disease.

The decades of the 1970s and 1980s have been characterized by spectacular technical advances in medical imaging, particularly those applied to tumor definition and characterization. These technologies have now been developed to the stage where a clear identification of the relative roles of each diagnostic modality in the diagnosis and staging of cancer is warranted. To date, most comparative studies evaluating imaging technologies have been based at a single institution and have involved small numbers of cases making their results often equivocal and not applicable in large scale patient care settings.

Diagnostic imaging procedures cost in excess of $10 billion annually, representing approximately three percent of the total health care monies expended in the U.S. It is also claimed that nearly 30 percent of thse imaging studies are inappropriately applied or unnecessary. In 1983, in excess of $2 billion was expended in capital equipment acquisition in the diagnostic field, not including supplies, service or replacement parts.

A multi-institutional collaborative clinical trials group was funded in 1987 by NCI to assess the relative role of each imaging modality in cancer management of carcinomas of the prostate and lung.

The objective of this RFA is to support multicenter cooperative clinical trials to determine the most effective imaging procedures required to stage and monitor pancreas and colorectal carcinomas. The successful applicants will join the ongoing collaborative institutions already funded by NCI as the Radiologic Diagnostic Oncology Group.

It is anticipated that approximately eight to 10 scientifically meritorious applications can be funded.

Copies of the complete RFA and further information may be obtained from Dr. Matti Al-Aish, Deputy Chief, Diagnostic Imaging Branch, Radiation Research Program, NCI, Landow Bldg Rm 8C09, Bethesda, MD 20892, phone 301/496-9531.

Program Announcements

Title: The role of growth regulatory factors in normal and neoplastic prostate
Application receipt dates: Feb. 1, June 1, Oct. 1

The Organ Systems Program of the Div. of Cancer Prevention & Control seeks applications for studies to identify and characterize growth regulatory factors produced by normal or neoplastic prostate cells, to determine their possible autocrine or paracrine functions in normal growth and neoplasia, and to define the role of growth regulatory factors in the pathogenesis and metastatic spread of prostate cancer.

The prostate displays a wide range and diversity for growth and metastatic potential. Prostate cancer is associated with an unusual and extremely high pevalence of latent or dormant cancer that is clearly identified on pathological examination, but which in most cases will never grow further to become clinically manifest. For unknown reasons growth is held in check in 90 percent of these latent prostate cancers and this is by totally unknown biological mechanisms. However, those latent cancers that are subsequently activated to grow, produce a mortality rate that makes prostate cancer the second leading cause of cancer deaths in the U.S. male.

The responsiveness of prostate tissue to androgens and the role of androgens in prostatic cancer makes the prostate amenable to studying a putative role for growth factors in mediating androgen action. In the absence of androgen, prostate cancer does not develop. For example, there are no reported cases of prostate cancer in individuals who have been castrated in early life. In advanced cases of prostate cancer, removal of androgens by castration or estradiol treatment results in a marked regression of the cancer. However, such regression is usually transitory and in the majority of cases there is a recurrence of cancerous growth at some time after endocrine ablation therapy. Thus, prostate cancer appears androgen dependent during the early stages of oncogenesis.

It is clear that the initial stimulation of prostate growth is mediated by androgenic steroids. It may be that under androgen regulation, growth factors are expressed at specific periods of development, thereby playing an important role in prostate growth and/or differentiation. Indeed, evidence suggests that growth factors, stimulated by estrogens in estrogen responsive cells, may serve as autocrine mediators of estrogen action. There is also evidence that differentiation of epithelial cells within the prostate is mediated by paracrine signals from stromal cells. Thus, it is reasonable to study growth factors in the prostate which may serve as paracrine and/or autocrine mediators of androgen stimulation.

A characteristic property of the prostate is that it contains a high concentration of androgen

receptors. Androgen receptors exhibit a high affinity and specificity for androgenic steroids and these steroid receptor complexes bind to DNA in androgen responsive genes. Recently the genes coding for two intranuclear steroid receptors, i.e., glucocorticoid and estrogen, have been cloned and sequenced. Interestingly, both have segments of nucleotide sequences very similar to a segment of the oncogene, vErb A, which codes for a nuclear protein. Other oncogeneic products have been demonstrated to have sequence homologies similar to proteins that are important mediators of hormone action on target cells. It is therefore likely that growth factors within the prostate may be related to oncogene products. There is also the possibility that androgen dependent cells within the prostate are transformed to an androgen independent state by alterations in growth factor regulation. Thus, studies on growth factors in the prostate may elucidate alternative mechanisms by which androgens regulate prostate function and may contribute to understanding how cancer cells become androgen independent.

As prostate growth regulatory factors are identified and purified, it becomes important to characterize the mechanisms by which they affect normal and malignant growth and their interactions with the different cellular elements of the prostate. Stromal elements can affect the growth of prostatic cancer cells. It has been reported that conditioned media from fibroblasts derived from the prostate, but not from the skin, contain a substance which inhibits the growth of an established prostatic cancer line in vitro. Defining the specificity of the stromal epithelial interaction of these paracrine factors may provide a better understanding of the wide variability of the malignant potential of prostatic cancer.

There are little data regarding autocrine factors involved in the growth of prostatic cancer. A prostatic epithelial cell growth medium has been formulated that contains cholera toxin, extract from either the pituitary or hypothalamus and epidermal growth factor. It is not known how these are related to endogenous endocrine, paracrine or autocrine factors that affect prostatic growth. Furthermore, these prostatic growth media are supplemented with glucocorticoids but not androgens. The lack of androgen effect on growth in vitro in contrast to in vivo is puzzling. The question is raised whether androgens block growth inhibitory factors in vivo, or whether cholera toxin, brain extract, and EGF provide growth stimulation that would otherwise be induced by androgens. The development of a spectrum of androgen dependent prostatic cancer cell lines would permit resolution of which autocrine factors are important in the progression of prostatic cancer.

Prostate cancer is a slow growing solid tumor. Since there is little evidence of increased mitotic activity in prostate cancer compared to normal tissue, it has been suggested that prostate tumor growth regulation may possible involve alterations in the tumor cell death rate, i.e., increased neoplastic growth reflects a shift in the balance between cell replication and the rate of cell death, such that a positive net accumulation of tumor cells occurs. To date, most investigators have focused on factors associated with increasing cell proliferation. Recently, it has been shown that androgen sensitive tumor growth in rats is mediated through androgens decreasing the rate of tumor cell death, while in other tumor models, androgens have been shown to increase cell replication. How growth regulatory factors might alter the balance between cell proliferation and death by either a positive increase in cell replication or through altering or inhibiting the rate of cell death is not known.

Observations described above suggest that autocrine, paracrine and endocrine factors are involved with the regulation of prostate growth. It is timely to encourage research efforts to understand how normal prostate growth is controlled and regulated, and how these controls are altered or uncoupled in both androgen sensitive and androgen insensitive autonomous prostate cancer growth and metastasis. This announcement is intended to stimulate research on prostate growth regulatory factors and address factors involved with stimulating DNA replication, and altering rates of cell death.

Possible approaches could include isolation and identification of prostate growth regulating factor(s) (stimulators and/or inhibitors) from normal and neoplastic neoplastic prostate. Development of new animal and human prostate stromal and/or epithelial assay systems is encouraged since growth factor effects on different cell types may vary and such assay systems are essential for the identification of prostate specific factors. Growth regulatory factors need to be characterized in comparison to the biological activities of other known growth factors and purified for partial sequencing and production of polyclonal or monoclonal antibodies. Further structural analysis by isolation of cDNA probes from animal and human prostate cDNA libraries is encouraged. Obtaining the full nucleotide sequence of prostate growth regulatory factor(s) will make it possible to derive the amino acide sequence for comparison with sequences of known growth factors and oncogenes.

Biological activity of growth factors in the prostate could be pursued by identifying the cell types responding to growth regulatory factors, whether stromal or epithelial, by identifying specific cell surface receptors and by measuring the growth responses of different prostate cell types. Other possible approaches include localizing the site of production of prostate derived growth factors, determining the patterns of hormonal regulation of these factors and investigating their role as hormones. It has long been recognized that prostate development and growth are regulated by the male hormone, dihydrotestosterone. It is becoming increasingly suspect, however, that this effect of androgen is not a direct action on DNA synthesis, but rather one mediated by other intracellular regulators. From what is known about cell cycle control, it is likely that growth regulatory factors mediate androgen control of prostate growth. Thus, it will be imporant not only to determine whether growth factors are responsive to androgen stimulation of normal and neoplastic prostate, but to learn also whether other hormones and growth factors stimulate prostate growth regulatory factors.

Those are examples of possible approaches. It is not implied that any single applicant should pursue all or any of those appraoches. Other approaches with appropriate rationales are also encouraged.

Research grant applications should be submitted to the NIH Div. of Research Grants. A copy of the face and summary pages should be sent to, and further information obtained from, Dr. Andrew Chiarodo, Organ Systems Section, Div. of Cancer Prevention & Control, NCI, Blair Bldg Rm 717, Bethesda, MD 20892, phone 301/427-8818.

The Cancer Letter _Editor Jerry D. Boyd Associate Editor Patricia Williams

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