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RHOADS PRESSES FOR GREATER EMPHASIS ON ETIOLOGY IN DNCP; WORKSHOPS DEVELOP NEW RESEARCH LEADS

When the Diet, Nutrition & Cancer Program got under way last year, NCI's newly-marshalled advisors for the program immediately involved themselves in a hassle over emphasis–therapy vs. etiology.

That argument was resolved, for the moment at least, when the DNCP Advisory Committee recommended that the budget be divided 55% for therapy, 35% for etiology and 10% for program management and support.

But it was revived when National Cancer Advisory Board Chairman Jonathan Rhoads, meeting recently with the DNCP Advisory Committee, noted that in the priority ranking of proposed projects approved by the committee, the top nine were either in therapy or management and support.

"What was in the minds of members of the congressional committees

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In Brief

INTRA-NCI SCRAMBLE FOR FUNDS INVOLVES "TRICKS, MACHINATIONS, DAY TO DAY BATTLE"

"I CAN'T TELL you all the tricks and machinations one has to do to get funds. It's a day to day battle, planning strategy, with the head to impress those who make the decisions and decide among competing priorities." That was Gio Gori talking to the Diet & Nutrition Advisory Committee after surviving the latest reprogramming scramble at NCI, when Director Frank Rauscher required the divisions to shave previous budget estimates, making funds available for reallocation to high priority projects. As a division deputy director and head of the Diet & Nutrition and Smoking & Health Programs, Gori had more than his share of budget defenses to make. . . . IF NALSI, the organization of private firms in the life sciences field, does get an injunction against CREG awards while suing to open up grants to industry, NCI would consider readvertising as contracts previously announced CREGs. That probably will not happen. . . . CORRECTION: *The Cancer Letter* reported (May 21) that four members from the phased out cooperative group, the Western Cancer Study Group, had joined the Southwest Oncology Group. Actually, only one Western member transferred to Southwest. . . . CANCER CONTROL contracts to cooperative groups for expanding clinical studies into community hospitals will be awarded to two groups. Proposals from three more groups were returned for resubmission to meet the requirements of the RFP. Three more proposals are being reviewed. . . . RESEARCH CONTRACTS supported by NCI reached their high point in fiscal 1974, when $95 million awarded through that mechanism was 16.3% of the NCI budget. The preliminary mid-level budget for fiscal 1978 lists $136.3 million for research contracts, 14.3% of the budget.

RHOADS PRESSES DNCP FOR EMPHASIS ON ETIOLOGY; NEW RESEARCH SUGGESTED

(Continued from page 1)

when they wrote the diet and nutrition mandate into the Cancer Act revisions was not made clear," Rhoads said. "I had supposed it was an interest in etiology, stimulated by such information as that which we have about the stomach and colon cancer rate differences between Orientals and Occidentals, the changing incidences of migrant populations. These are critical questions. What factors account for these differences? We have little information on diet analysis of large groups of people. But your rankings indicate a low priority for etiology studies. Why did the priorities fall out this way?"

Gio Gori, director of the program, said that the congressional mandate did indicate a need for etiology studies, but the prime mover was therapy. "It was a dual mandate, but you're right. There is a great deal of concern about etiology."

Gori said that the epidemiological clues Rhoads was referring to "all point to a variety of factors. They identify too many things. There is some consensus that the epidemiological approach to the etiology of cancer may be slow and difficult. Dietary surveys, unless in controlled studies, will be of limited value. It is difficult to identify former diets by recall. It may be desirable to study the effects of altered diets in both animals and man, and perhaps to define what people should eat in the first place."

"What you've said is that it's a tough problem," Rhoads said. "But that's why you have $6 million."

Gori pointed out that eight of the projects ranked 10 through 20 are in etiology. All probably will not be funded with FY 1976 money, because the estimated cost is pushing up close to $6 million, and the program is unlikely to get more than $5.5 million. The quality of proposals still in review also could affect the funding schedule. Gori said some of the Cancer Research Emphasis Grant proposals were not responsive to NCI's announcement. Those will be processed through the regular grant mechanism and if competitive, would be funded elsewhere.

Committee member Stanley Dudrick suggested that the emphasis was placed on therapy because quicker results could be obtained. "We could quickly use up $6 million in etiology, and it would be years before we could show progress. The legislators might become discouraged. It might be best to show some rapid progress in therapy, with a greater margin of effectiveness."

Dudrick said that the series of workshops sponsored by DNCP generated "many more promising ideas in therapy than in etiology."

Gori said he considered the decision to spend 35% on etiology as mandatory, regardless of the priorities.

"That's encouraging," Rhoads said.

"It is and it isn't," Gori said. "I would like to see it reversed. That would be the best for the long range. But this (the 55-35 split) reflects the immediate necessities of the program."

DNCP workshops held in recent weeks have delved into three rather sophisticated aspects of nutrition—in vivo quantification of body nitrogen, direct calorimetry, and total parenteral nutrition. In addition, two separate editorial boards have met to develop nutrition handbooks for pediatric and adult cancer patients.

The workshops generated a number of suggestions for research which may turn up in the next round of RFPs or CREG announcements. Summaries of their reports follow:

In Vivo Quantification of Body Nitrogen Workshop

Accurately assessing lean body mass changes in cancer patients will require an improved quantitative method of nitrogen balance compared to the classical input/output method with its inherent problems. In an effort to explore alternative methods of nitrogen balance, this workshop discussed the possibility of applying neutron activation analysis methods. The major methods discussed are as follows:

Prompt Gamma Rays

This method was regarded as the most promising of the options. Presently there are some problems in uniformity of activation, but the workshop considered the uniformity problem to be resolvable.

n, 2n $\rightarrow N^{13}$

Workshop participants regarded this method as a possibility that warranted further exploration. One determinant of the method, however, is the inflated values due to isotope contamination. Since most of this extraneous contamination decays during the first 20 minutes after irradiation of the subject, the problem can be controlled and the predicted error rate is less than 1%.

$p\alpha \rightarrow C^{11}$

This method is accurate in small animals, but it was not considered to be adaptable to humans primarily because of problems related to the transfer of the isotopic CO_2.

μ Mesonic X-Rays

The mesonic x-ray technique, although perhaps the superior technique from a theoretical standpoint, has not as yet been adapted to whole body determinations. In discussing potential neutron activation analysis techniques, the workshop felt that the methodology would need to be correlated with K^{40} determinations of lean body mass, which presently is probably one of the most accurate methods of assessment.

Workshop participants recommended that, in studying neutron activation analysis as a method of N balance determinations, the first year's work should entail primarily assessing the feasibility of the method and secondly, patient testing. The second year of the study should be devoted to clinical testing.

Chairman was Thomas Mitchell, Johns Hopkins.

Other participants were Stanton Cohn, Brookhaven National Laboratory; Brian Murray, MIT; William Nelp, Univ. of Washington; Earl Palmer, Battelle Pacific Northwest; and Donald Pettersen, Los Alamos Science Laboratory.

Direct Calorimetry Workshop

Calorimetry has been suggested as a useful, necessary research tool for any study on metabolism. The workshop was asked to advise DNCP as to the practicality, desirability and/or necessity of using direct calorimetry methods in the following research environments.

Normal Volunteers

Very few direct data are available on the energy conversion process in normal volunteers either under baseline resting conditions or under conditions of moderate, prolonged work. Little is known about the influence on these processes of many factors that will characterize future patient populations (e.g., age, sex, nationality; cyclic processes—diurnal, monthly, etc.; or emotional state). This information must provide the control data base for future studies on cancer patients.

The exact design of such a study should be the subject of another workshop. There do not appear to be any insurmountable technical difficulties with devising a calorimeter for either test method. There are several calorimeters in the United Kingdom that are functional and could be used for pilot studies.

Cancer Patients

There was considerable discussion of this subject because of the participants' concern that the calorimetry methodology follow a definition of the goals of such studies. It was concluded that at the present time there is no evidence to suggest that the efficiency of metabolic energy conversion processes will be altered by the presence of cancer. It was felt that indirect methods, especially the use of hoods, may be adequate under present conditions for monitoring energy processes in patient populations where malnourishment is being treated experimentally. When indirect methods of calorimetry are coupled with nutritional monitoring, controlled work in controlled environments, and local thermal mapping, one can obtain most of the required information. When direct measurements using animal cancer models show specific problems, then direct studies should also be undertaken.

Animal Calorimetry

The workshop agreed that more direct calorimetry studies of tumor-bearing small animals are needed. Such studies need to search for alterations in the energy conversion processes resulting from the presence of tumors and/or the associated treatments for the resulting malnutrition. Studies on the energetics of artificial alimentation are also needed to screen temporal patterns that could be used to treat malnutrition.

It was agreed that new calorimeters could be built in about one year, but that their constructions should be carefully directed by experts who also have experience in building their own chambers.

Workshop chairman was Richard Bucles, Alza Co. Other participants were Gilbert Bradham, Univ. of South Carolina; James Gessamen, Utah State Univ.; John Kinney, Columbia Univ.; Seoras Morrison, NCI; and Norman Scott, Cornell Univ.

Total Parenteral Nutrition Workshop

Cancer research projects dealing with total parenteral nutrition (TPN) are designed to test the efficacy of TPN as an adjunct to cancer treatment. The purpose of this workshop, however, was to delineate research projects as a next step to studying specific aspects of TPN.

Metabolic Characterization

A need was expressed to characterize the metabolic response of cancer patients. Examples of altered metabolism in cancer noted by the workshop participants include increased anaerobic oxidation of glucose, increased GH levels by cancer cells, increased amino acid excretion, increased production of polyamines, inability to use the reduced form of folic acid, and decreased utilization of folic acid.

Minerals

Interest was expressed in magnesium and potassium requirements, since decreased intake of these nutrients has recently been reported to decrease tumor growth. The recommendation was made that deficiency solutions should first be tested in animals.

Linoleic Acid

Study of the relationship of linoleic acid to decreased immune competency was suggested, particularly in light of intralipid usage. Those studies involving fat, particularly linoleic acid, could be part of a broader study to examine the ability of specific substrates to preserve immune competence. Suggestions also included the usage of intralipid as a caloric source with amino acids.

Protein Dynamics

Studies were suggested that would determine not only intake and output products but also protein compartment levels. Amino acids could be labeled for dynamic studies. These parameters are undoubtedly altered under various cancer treatments. A suggestion was also made to develop a data bank of amino acid profiles of tumors.

pH

The ability to influence tumor growth by altering extracellular pH was discussed. This could perhaps be done by manipulating in vivo intravascular pH by altering glucose availability.

Workshop chairman was Murray Brennan, NCI. Other participants were Joseph Ansley, Emory Univ.; George Blackburn, Boston City Hospital; Edward Copeland, Univ. of Texas (Houston); Leon Prosky, FDA; Belding Scribner, Univ. of Washington; Maurice Shils, Memorial Hospital (NYC); and Norman Yoshimura, McGaw Laboratories.

Grace Monaco, a member of the pediatric handbook editorial board, reported on the status of that project.

"The proposed handbook is intended to guide parents in the nutritional management of children with cancer. The medical management of children is an area over which parents have little control. In contrast the nutrition of their child is something the parents can control, and by exercising this control can present a well-nourished child better able to withstand the rigors of the disease and its treatment.

"Although the handbook had been conceived primarily for the use of parents, it was agreed that it would have a potentially much wider distribution as a useful tool for the medical community in general and for pediatricians, clinicians and the nurses in particular.

"The editorial board discussion emphasis was on presenting a complete source book, well indexed, possibly with visual aids, e.g., nutrition charts which could be stuck on a refrigerator. Discussion also concerned the possibility of a loose-leaf format for ease in update.

"Participants agreed that introductory materials including a general discussion of cancer types, characteristics and treatment modalities; a treatment of the nutritional, physiological and psychological management of the child in remission as opposed to the child in relapse; an introduction to types of nutritional supplementation and a basic guide to good nutrition were indicated. A glossary of terms was considered a must.

"It became obvious to the members of the editorial board that there is a wealth of experience in the medical community that needs to be tapped for inclusion in this project. For this reason we would strongly request that the advisory committee offer suggestions of helpful personnel, for example pediatric pharmacologists, to advise the editorial board. This is a very exciting project particularly to parents. It will provide information that we have needed for a very long time, information which would permit us to be more full partners in the treatment and management of our children with cancer. The impact of this program will have a direct and positive effect on the lives of children with cancer and their families."

Other members of the pediatric handbook editorial board are Annette Gormican, Univ. of Wisconsin; Myron Winich, Columbia Univ.; Sarah Donaldson, Stanford Univ.; and Kathryn Smith, Illinois State Univ.

Joanna Dwyer, New England Medical Center, reported on the meeting of the adult handbook editorial board.

Recognizing that nutrition and cancer literature is limited, workshop participants discussed subjects to be included and the best method of presenting comprehensive nutritional information to the adult cancer patient and his family. It was decided that the handbook should be usable by the lay public and should contain simple and practical, yet comprehensive, information on nutritional management.

Preparation of the handbook will incorporate information generated both by current literature reviews and by recommendations and suggestions from professional personnel. It was decided to initiate a literature survey of current dietic practices and procedures, including patient weight loss and cancer treatment.

Utilizing professional resources will involve the following:

- Contacting recognized experts and interested persons in diet, nutrition, and cancer areas and ascertaining their current procedures.
- Determining the approximately 20 major cancer hospitals and consulting with the diet and nutrition personnel regarding procedures used.
- Gathering information for and from conferences in these areas to supplement planning and content of the handbook.

Through the implementation of the above methodology, the introduction and guidelines to be used in the handbook will be developed.

The handbook is intended for those patients having a particular nutritional problem related to certain characteristics. Therefore, it is necessary to consider these characteristics and how the cancer patient is affected by them. Characteristics of diseases called cancer will be dealt with, and nutrition management guidelines relating to them will be formulated. These characteristics are weight loss, anorexia, altered food preferences, nausea and vomiting, altered taste sensation, malabsorption, change in route of administration, water balance, diarrhea, reduced eating pleasure, life priorities, and pain.

The workshop participants agreed that the cancer patients' physical, environmental, social, and psychological needs should be dealt with and included in the handbook. Possible subjects for discussion include calorie and protein requirements, oral nutrient solution information, food consumption, food as food versus food as drug, description of defined and specific formulas, and frequency of food intake.

Gori said that over the next six months, the following list of topical areas will be utilized as the basis for formulating specific workshops:

Research directors and priorities for IV and oral solutions (including animal models); feasibility of using ultrasonic camera and scanning x-ray systems for evaluating tumor growth with nutritional therapy in laboratory animals and humans; optimal design of animal feeding studies to evaluate the effect of nutrition on cancer development, whole body human calorimeter studies.

Applicability of various stable isotope quantification procedures for clinical and laboratory use; specific hardware needs for ambulatory IV and oral alimentation; preferred approaches for determination

of body compartments; biological and metabolic markers; enhancement of ongoing epidemiology studies; DNCP information transfer to clinicians and dietitians; DNCP information transfer to cancer patients and parents of cancer patients; relationship of comparative physiology and dietary adaptation in assessment of cancer risk; small laboratory animal models for diet, nutrition and cancer studies.

Dietary fiber research: potential animal, clinical and laboratory studies; intestinal microflora: potential animal, clinical, and laboratory studies; sugar, carbohydrate, and sweeteners: dietary intake and cancer relationship; protein intake and its relationship to cancer; dietary fat and its relationship to cancer; dietary antioxidants and their relationship to cancer; esophagus and mouth research projects; stomach and upper GI tract research projects; lower GI tract and colon research projects.

Liver and pancreas research projects; breast research projects; problems in nitrogen metabolism of the cancer patient; evaluation of anthropology projects; evaluation of preliminary data for animal studies; problems in lipid metabolism of the cancer patient; problems in trace element metabolism of the cancer patient; animal studies–design considerations; metabolic epidemiology; artificial hyperalimentation clinical trials; anorexia–future projects; and host-protein metabolism.

DEVITA RELATES PROBLEMS IN GETTING NEW THERAPEUTIC RESEARCH STARTED

Difficulties encountered in obtaining funds for new therapeutic research were described at a recent meeting of the President's Cancer Panel in an exchange between Vincent DeVita, director of the Div. of Cancer Treatment, and Panel Chairman Benno Schmidt.

DeVita and Schmidt also discussed the capabilities of private physicians in community hospitals in treating cancer patients.

The discussion follows, with some editing out of remarks not pertinent to the primary topics:

DeVita: It is harder to get starter funds for therapeutic research than it is for any other research type activity, that is, going into a laboratory, setting up a laboratory and requesting a grant to support this. It is harder to get funds for therapeutic research, because it requires a certain amount of demonstrated success. You can't get the success unless you get the funds, and you have a Catch 22 built into it.

I calculated that the mock program that we worked on in NCI really cost, if you want to look at cost over and above patient care, only about $26,000 to get the first 43 patients off the ground. I tried to think of how I might have applied for grant support for that. I doubt whether I would have been able to get grant support. I would have had to be dependent on private funds with a great deal of discretion to use them any way you want. I think that is what [center directors] are really getting at. They want discretionary funds to be able to move them in therapeutic research, back and forth within the disease areas. It is very difficult. I don't know how you do it, because you can't account for them. It is a difficult accounting problem, to say here is a couple of hundred thousand dollars. Use it at your discretion to develop treatment.

Schmidt: Can't you write an application for that kind of research?

DeVita: You can. A CREG might be one way of doing it.

Schmidt: Isn't there a source of medical research money that could support that?

Rauscher: Yes, but for some reason or other many of them get turned down. They can't start up.

DeVita: They don't fare well. I think it is a more difficult problem to understand than laboratory research, and it doesn't fare well in the review process.

Schmidt: Well, it certainly doesn't fare well with your peers, because they all already know the best way.

DeVita: Well, I think it is just difficult. I think it is a poorly appreciated cultural gap, if you will, in terms of the difficulties in going clinical therapeutic research, and it doesn't fare well in the peer review process. The cooperative groups do have this kind of discretion. They get a grant to do this kind of work, and I think the center directors are feeling the pains of watching one program grow while the other one is not growing to their satisfaction with the same flexibility.

Schmidt: Peer review groups of clinicians may be tougher going than peer review groups of scientists. There is just as much room for good fundamental research in clinical medicine as there is in non-clinical.

DeVita: Laboratory research doesn't have to involve a social worker, and doesn't have to involve five other doctors, and worry about transportation of the experimental animal into the center, and so forth. When you get these complexities added on it adds a new dimension to peer review that gets confused. I think that hurts a lot of clinical research efforts. They say it is expensive when you add all these things on, and then it is not science, it is the ancillary support to get the fundamental question you are asking answered. That is what suffers in peer review.

Schmidt: Well, I think that is something, maybe, that we can try to figure out how to better serve. I kind of agree that the answer is not a block of discretionary funds in the hands of the director, just here it is, but on the other hand, there ought to be a way to get those things that Vince is talking about started.

Schmidt brought up the question of how best to get the latest clinical research advances into the hands of practicing physicians.

Schmidt: You and I have discussed before the dangers, problems and difficulties of trying to have a

sort of NCI summary and point of view of the best therapy in an area where the best therapy for most of our diseases hasn't been discovered yet.

DeVita: We would be taking a little flak in a couple of areas. One is in breast cancer where there is a great deal of controversy still about how fast we ought to be going.

The other is this article that came out in Parade on second opinions, and how to use second opinions, where our position was not correctly perceived by the reporter. We do think that one of the cheapest things you can do right now for cancer patients is to advise that when they are given a negative response, that is, you have cancer and there is nothing to do for it, they ought to get a second opinion. An independent second opinion at that, because of the fixed type of referral practice. In doing that I think a lot of people can avail themselves of treatments that are, as Louis Thomas would describe, half-way technology, but nontheless effective. There is a problem of making that kind of treatment available. Now, when you get to breast cancer it becomes a problem, but we have been spending a lot of time on breast cancer, and surprisingly, I think, in spite of the advances recently, there is still a great deal of feeling that we should pretty much stay with the way we are operating in breast cancer.

Schmidt: There is certainly a force at work in medical practice. How strong it is is a matter of difference of opinion, and most doctors will deny it, but doctors are like other human beings and they don't like to admit they are over their heads. They don't like to regard something as beyond their competence, and so they don't like to turn loose a case until it is sort of demonstrably beyond their competence, and by that time it is usually pretty well beyond the competence of anyone else. I don't know how you deal with that problem effectively.

DeVita: Well, one of the problems is that there are many private physicians who are as capable or more capable of taking care of cancer patients with the best available treatment as physicians in centers. I think the only difference between the two in some cases is that in one place you collect the data and you make a conclusion. In the other place you just deliver the therapy. I mean, you can talk about the different types of operations for breast cancer, and that is absolutely true. The private doctors can do all the variations on the mastectomy anybody in a center can do. But if they are done in a center the data can be collected and conclusions can be drawn that could influence practice. I think that the private physicians get very upset. They recognize some people don't know when they are over their heads. They also recognize that some of them have a great deal of competence.

Schmidt: That is right, and I think it is a great oversimplication to say if you have got a serious cancer problem get to a center. I know many doctors that aren't in centers that I would just as soon have as many who are in centers. You know even more. But when you think of people like Henry Kaplan in radiation therapy, and Jim Holland in chemotherapy and so forth who aren't in centers, you are talking about people who are at the very top of the heap.

DeVita: My definition of a center for a disease, in terms of therapy, differs a little bit. I think a collection of physicians with an interest and experience in a disease can frequently do very well, even if they are in what we would consider a private, community hospital. I mean for some of our very, very important diseases like breast and colon cancer where a great bulk of the surgery is done at the private level, they are able to do the basic ingredients of the experiment, the operation, as well as anybody. The real problem is mixing them in to get the data out. We have stood still for 50 years, it seems to me, because we didn't know how to make this mix. The tools that we are now using have all been available for a very long period of time. That is a very interesting thing to really sit back and think about.

Schmidt: The question is how many of those surgeons want to become involved in the combined modality that probably is involved in the best therapy.

DeVita: Some do, and others will resist it, kicking and screaming forever.

Schmidt: Of course, not all that resistance is among private physicians outside centers.

Rauscher: That is right.

Schmidt: On the other hand, it is overcome more effectively when he is a part of a center community than it is when he is his own master.

ABSTRACTS OF PAPERS PRESENTED BY BREAST CANCER TASK FORCE

Following are additional abstracts from papers presented by Breast Cancer Task Force contractors at recent meetings. Other abstracts appeared in ***The Cancer Letter*** *last week.*

GENETIC STUDIES IN HIGH RISK BREAST CANCER FAMILIES — Frans Cleton

Several observations indicate that hereditary factors may be of importance in human breast cancer. The risk for first degree relatives of patients with breast cancer is 2-3 times that of the general population. Also there is an aggregation of breast cancer in certain families. Studies of association of certain genetic markers with breast cancer have given inconclusive results.

The genetics of breast cancer have been studies extensively in the mouse. The resistance to infection with the mammary tumor virus appears to be determined by a gene that is closely linked to the major histocompatibility system (H-2). Studies were carried out to determine a possible association of breast cancer with antigens of the human histocompatibility system (HL-A).

Frequencies of known antigens of HL-A were determined in 200 patients with breast cancer and 200 matched controls. There were no significant differences between the two groups. These negative findings did not exclude linkage of a hypothetical gene determining susceptibility for breast cancer and the HL-A haplotype. Such investigations can only be carried out in families with a high incidence of breast cancer, in more than one generation. Fourteen high risk breast cancer families were investigated for HL-A haplotypes and a battery of gen-

etic markers including blood groups, serum groups, chromosome bands and red cell iso-enzymes.

The pattern of breast cancer in these families showed the special characteristics usually found in the familial type; a relatively large number of early onset patients, a high incidence of bilateral tumors and tumors of the medullary type. A total of 49 breast cancers all confirmed by histology were included in these studies. Levels of plasma prolactin in the unaffected female members of these families showed an abnormal distribution pattern. The average level of plasma prolactin was increased, indicating a possible endocrine dysregulation.

INVESTIGATION OF GENETIC POLYMORPHISMS IN HIGH AND LOW RISK BREAST CANCER FAMILIES – David Anderson

Three groups of pedigrees have been identified which differ in their clinical characteristics and risks for breast cancer. In the highest risk group, the disease has premenopausal onset and is bilateral more frequently than expected, age at onset is highly correlated among affected sisters, and the life-time probability of breast cancer development is about 35%. The moderate risk group is characterized by a later-occurring disease, no correlation in age at onset, bilaterality no higher than expected, and a 12% lifetime probability. Another group at low risk has a lifetime probability comparable to that of women in the general population.

These pedigree groups are being compared with one another and with controls in an attempt to determine if they differ with regard to various polymorphic blood group and enzyme markers, as well as chromosome abnormalities and/or variants. ABO and clinical Rh blood types are available on 404 patients. Other blood groups, haptoglobin, phosphoglucomutase 1 and acid phosphatase types are available on about 190 patients, 250 unaffected female, 140 unaffected male relatives, and 100 controls. Chromosome studies have been completed on 40 of 90 patients, controls, and unaffected sisters.

The only differences presently in evidence pertain to the ABO blood group system. Patients in the low and high risk groups have distributions similar to control distributions, while the moderate risk group has a noticeable deficiency of type O and an excess of type A. When the patients are classified according to their age at diagnosis, the differences become more pronounced. The moderate risk group continues to show a deficiency of type O and an excess of type A, whether onset is early or late, while the high risk group shows a marked excess of type O and a deficit of type A when onset is early, and the opposite when onset is late, i.e., the same as that observed in the moderate risk pedigrees. The chromosome analyses have disclosed no differences among patients, unaffected sisters, or controls in the mitotic rate, polyploidy, endoreduplication, breaks, rearrangements, sister chromatid exchanges, or G-band variants, but C-band variants are significantly increased in patients and their unaffected sisters compared with controls.

GENETIC MARKERS AS TOOLS TO IDENTIFY HIGH AND LOW RISK CANCER FAMILIES: BREAST CANCER FAMILY RESOURCE – Henry Lynch, Randall Harris, Nicholas Petrakis, Mary-Claire King, Gabriel Mulcahy, Rudolph Platt, Paul Terasaki, Kathleen Maloney, Laurie Rankin, Hoda Guirgas, Jane Lynch

Our familial breast cancer resource is comprised of 75 kindreds, each ascertained by two first degree relatives with verified breast cancer. These families reflect a variety of putative breast-cancer-prone genotypes (viz. site-specific breast cancer, breast and ovarian cancer, breast and gastro-intestinal tract cancer, breast and prostate cancer, and the complex of breast cancer in association with sarcoma, leukemia, brain tumors, and laryngeal and adrenal cortical carcinoma), we therefore suggest that genetic heterogeneity accounts for much of the tumor variability in familial breast cancer (Lynch, H.T. et al, JAMA, 222: 1631, 1972).

A remarkable subset of kindreds from the resource consists of 10 families with one or more cases of ovarian cancer in first- or second-degree relatives(s) of a breast-cancer proband. Notably, the cumulative cancer risk (all anatomic sites) to female relatives of these families is 44% for the age interval from 30-70 years. This is significantly higher ($P<.001$) than the corresponding cancer risk (29%) to female relatives of the remaining 65 families, and the estimate is also conservative in that one case of ovarian cancer plus the two original breast-cancer probands of each kindred are excluded from results to correct for ascertainment bias. Evidently, the presence of breast and ovarian cancer in close relatives provides a good indication that other females of the family are at high genetic risk for cancer of multiple sites.

Proband pairs of the 75 kindreds were analyzed as a separate group. Thirty-three of these pairs contained an affected mother and daughter, and interestingly, the daughters were typically diagnosed at a much younger age (44 years) than their mothers (57 years). This constitutes a 13-year mean intra-pair difference in breast cancer detection between mothers and their daughters which is highly significant ($P<.01$). Possible causative factors for the difference will be discussed.

The likelihood of genetic heterogeneity in familial breast cancer harbors major implications for future investigations of linkage and early cancer detection utilizing a variety of biological markers. Specifically, should multiple genotypes account for observed familial tumor variations, it would then be reasonable to assume that each different breast-cancer-prone genotype is characterized by its own particular array of biological markers.

POSSIBLE CORRELATIONS BETWEEN MORPHOLOGY AND FAMILIALITY IN BREAST CANCER – H. Stephen Gallager

A pedigree study has shown that the risk of developing breast cancer is far greater among women whose mothers or sisters have had the disease than among those with negative family histories. Furthermore, patients in the familial group show a strong tendency to develop their carcinomas at a relatively early age and to have bilateral tumors. These facts suggest that familial breast cancer may be a specific subtype of mammary neoplasia. If so, it is possible that it differs morphologically from the nonfamilial disease. The identification of any such difference would have multiple values. It would increase understanding of the basic process of breast cancer development and indicate directions for further investigations. At a clinical level, it would permit, even in the absence of a clear history, the identification of women in need of close surveillance or prophylactic treatment.

In an attempt to find such a marker, a pathologic study has been undertaken of the mastectomy sections from a group of over 300 patients with positive family histories. These patients are those included in Anderson's genetic study and the specific breast cancer pedigree is known for each woman. Specimens from affected relatives of the patients in this group will also be studied. The findings will be compared with those from a control series of nonfamilial breast cancers.

A set of specific criteria for evaluation has been developed. These relate to the histologic appearance of the neoplasm itself, the extent of disease and evidences of tumor-host interaction. Included are such items as the neoplastic cell type, the degree of differentiation, the pattern of infiltration, the pattern and extent of axillary nodal involvement, the intensity of lymphocytic response in the tumor and the degree of sinus histiocytosis in regional nodes. Associated non-neoplastic changes in uninvolved mammary tissue are also recorded. Each case is reviewed independently by three pathologists without foreknowledge of the family history. The data generated are analyzed by computer programs capable of making correlations between pedigree types and individual histologic characteristics or selected combinations of characteristics.

Results of this study are incomplete, but preliminary data indicate that familial breast cancer is more likely than nonfamilial to be of small-celled type or to include a small-celled component. The familial cases are frequently associated with a background of severe epithelial dysplasia in unaffected mammary tissue.

BREAST CANCER RISK IN RELATION TO ESTROGENS – Jack Fishman

The goal of this study is to evaluate whether genetic factors in hormone production and metabolism play a role in breast cancer. Premenopausal women from families of high incidence of breast cancer (high risk) and age matched control women from families with no histories of breast cancer (low risk) are being studied. A variety of endocrine assays is being done on plasma and urine collected throughout the mentrual cycle in each subject.

Mean plasma E_1 and E_2 concentrations during the follicular and luteal phases and during the entire cycle in 15 high risk and 17 control subjects will be presented. Mean urinary E_1, E_2 and E_3 excretion in 15 high risk and 17 control subjects during the follicular and luteal phases and during the entire menstrual cycle have been obtained. From these, "estriol ratio" (E_3/E_1+E_2) and "estriol proportion" ($E_3/E_1+E_2+E_3$) have been calculated. This preliminary report is concerned only with the estrogens and prolactin since the other hormones studied are presently being evaluated.

DIET AND EXOGENOUS ESTROGEN IN THREE POPULATIONS AT DIFFERENT LEVELS OF RISK FOR BREAST CANCER – Tomio Hirohata, Abraham Nomura, Lawrence Kolonel, Jean Hankin, Grant Stemmerman

A case-control study is being conducted to determine if there is an

association of breast cancer with the use of non-contraceptive estrogens and with specific dietary factors. Breast cancer cases from the selected populations (age 45-74) are identified: 1) the Caucasians in Hawaii who are at high risk for breast cancer; 2) the Japanese in Hawaii who are at intermediate risk; and 3) the Japanese in Fukuoka, Japan, representing a low-risk population. For each case, a neighborhood control and a hospital control matched by race and age within five years, is interviewed by trained interviewers to collect information on past drug usage and usual weekly dietary intake, Drug history is verified by checking doctors' records by nurse interviewers. Pathological slides of the breast cancer cases are reviewed by three consulting pathologists to confirm cancer diagnosis and to identify possible histological difference in the three populations.

The study is in its first year of operation. Two hundred cases and their 400 controls will be interviewed for each of the three populations during the study period of three years in Fukuoka and five years in Hawaii.

ASPECTS OF THE EPIDEMIOLOGY OF BREAST CANCER IN ICELAND – N.E. Day and H. Tulinius

The main purpose of the study is to determine the familial risk for breast cancer among different classes of relatives after taking account of risk factors associated with reproductive history for breast cancer risk. In Iceland, age at first full term pregnancy is a sufficient summary of reproductive history, in line with the findings of other workers. Using the data from the cervical cancer screening clinic and from the pedigrees that have been determined, a risk function has been constructed applicable to all Icelandic women for age specific risks of breast cancer, given year of birth and age at first pregnancy. This function clearly shows that the large increase in risk for successive years of both cohorts is not explicable in terms of changes in reproductive history. This presentation shows how a risk function of this type can be incorporated in an extension of Weimberg's general proband method for estimating familial risk.

NUTRITIONAL FACTORS IN THE ETIOLOGY OF BREAST CANCER – F. DeWaard

International differences in breast cancer incidence cannot be explained satisfactorily by reproductive factors, because

A. Postulated factors failed to stand the test of case-control comparisons (lactation);

B. Factors associated with risk are not sifficiently different in their distribution among populations in various countries (age at first pregnancy).

The nutritional hypothesis which we have advanced assumes the existence of (at least) two etiologies of breast cancer. One of the causes is thought to be of a nutritional nature: nutritional status as defined by weight and height has been shown to affect breast cancer risk.

The biological mechanisms involved are not yet clear but may be related to extraglandular steroid metabolism.

The present contract deals with the issue to what extent variations in body weight and height can explain differences in level and shape of age-specific incidence curves observed in international statistics.

Results are presented of population-based case-control comparisons in the province of Friesland and the cities of Rotterdam and the Hague. These studies suggest that part of the international variation in incidence can be explained by differences in nutritional status. Total body size seems to be a factor rather than overweight (Quetelet index).

Nutritional factors through their effect on hormone metabolism may be promotors of breast cancer growth. Ways of testing this hypothesis are being sought within the frame of a periodic population screening project.

INVESTIGATION OF POSSIBLE CORRELATIONS BETWEEN MORPHOLOGICAL AND EPIDEMIOLOGICAL CHARACTERISTICS OF BREAST CANCER – Bjorn Stenkvist

Most epidemiological studies of breast cancer have treated the disease as an entity although it is well-known that there are a number of morphological sub-groups of mammary carcinoma. In order to elucidate if there are different epidemiological characteristics correlated to different morphological groups of breast cancer, we are conducting a case-control prospective study on 183 breast cancer patients registered in four Swedish counties during the period October 1975 – March 1976. These patients as well as 183 controls matched by age being analyzed with respect to heredity, social and environmental factors, hormonal status (TSH, thyroxin, triiodothyronin, estron, estriol, estradiol, FSH) and other diseases.

Morphologically the cancers are being classified histologically according to WHO, AFIP and Ackerman and graded cytologically according to Black, WHO and Hartviet. In addition the cancer cell populations are graded via photometric measurement of DNA + RNA content of nuclei and such descriptors as size, shape, density, structure and averages, variations, coveriances, skewness, kurtosis and entropy of the parameter distributions.

The histologic typing and the cytologic grading will be used to subdivide the carcinomas into groups. The defined groups will be correlated to the epidemiological descriptors and later to prognosis.

A DIETARY STUDY OF BREAST CANCER – Baruch Modan

The rationale for studying dietary factors in the etiology of breast cancer is based on the following:

a. Laboratory experiments demonstrating a higher yield of tumors of the breast on certain diets, particularly high fat, and a lower induction rate by caloric restriction.

b. Correlation between the consumption of certain food constituents (e.g. fats and proteins) in individual countries and the disease incidence in those countries.

c. The observation that body weight is a risk factor in breast cancer.

d. The fact that the incidence of breast cancer varies markedly over the world, and that diet constitutes one of the major differential environmental factors between populations.

e. The correlation between the incidence of breast and colon cancer in many population groups.

The methodology of an ongoing three year dietary case control study in Israel follows closely the one established by our group in a previously undertaken dietary study of colon cancer. The study will include 500 newly diagnosed breast cancer cases, 300 belonging to a high risk population group (European born) and 200 to a low risk group (Asian and African). For each cancer case two controls—one a non-malignant, nonintestinal surgical case, and one a person living in the same neighborhood, both matched to the cancer case on age, sex, country of origin and period of residence in Israel—are selected. A specially designated nurse screens the surgical departments in the area for breast cancer cases and surgical controls. Neighborhood controls are identified through the Central Population Registry. The questionnaire includes over 200 questions referring to all food items consumed by the various ethnic groups in Israel. Consumption frequency of food items and food groups will be compared between cancer cases and controls. The effect of ethnic origin and pre- versus post menopausal status will be evaluated.

CHRONIC MASTOPATHY AND BREAST CANCER. A FOLLOW-UP STUDY – Dankward Kodlin

2,900 cases of benign breast lesions diagnosed by biopsy between 1948 and 1973 in the department of pathology, Kaiser Foundation Hospital, Oakland, were followed up for breast cancer development over an average period of seven years.

When classified according to traditional diagnostic categories, the cancer incidence per 1,000 person-years varies between 2.7 and 7.9 and appears to be elevated in comparison to expectations obtained from the Third National Cancer Survey, San Francisco Bay Area.

2,400 biopsies were also scored by the Black-Chabon method. There is an upward trend in the breast cancer incidence as the atypia score rises, a finding which confirms conclusions from a retrospective case-control study by Black et al.

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