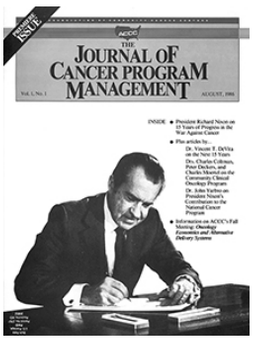

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THE NCCTG EXPERIENCE WITH CCOPs

Charles G. Moertel, M.D.
Chairman, North Central Cancer Treatment Group

I am very pleased to be allowed to participate in your commemoration of the 15th anniversary of the war on cancer. It has been one of the few good wars. Certainly, we haven't won, but we're making a good fight of it, and we will win. I think it is appropriate that we honor the man who was commander in chief when we began this war, and who signed the National Cancer Program into law. I happen to think this program is one of the most noble actions ever to be undertaken by a civilized society. I also think it's appropriate that the key speaker of this morning's meeting (Dr. Vincent DeVita) will be our five star general, or I suspect it's admiral. I think he's been a remarkably effective leader and spokesman. Although we disagree now and again, there is no one whose hand I would rather see on the helm. As does any good commander, he knows that wars aren't won by generals or in Pentagon buildings. From Sparta to Waterloo to Chateau Thierry to the Normandy beachheads, wars have been won by footsoldiers in the field. No cancer treatment research program, no cancer prevention research program will ultimately succeed unless you and those who you represent are strongly involved. It's been said so often that it's almost trite but it's worth saying again, over 85 percent of all cancer patients are treated in the community. And this figure is really an underestimate of the overall influence of the community physician on cancer patients in this country. Of the less than 15 percent who do show up at university centers, most are probably there because you referred them, you probably bear the responsibility of their sustained management, and you are probably caring for them when they die. Patients treated at university centers represent only a very small minority of the whole, and they are highly selected by mechanisms that defy identification. It's a rash and totally unproven assumption that clinical research results on this unique patient group directly apply to the totality of cancer patients. Clearly, applicability of new cancer management methodologies must be proven by research programs conducted in the community before these methodologies can be assumed to be of value to the overwhelming majority of cancer patients who are managed in the community. I feel it's prima facie that the community is the most ideal setting for clinical cancer research performed at a Phase III level. I also hope to demonstrate to you that it is in this setting where the highest quality clinical cancer research can be conducted and is being conducted. In addition to the advantages of scientific

Dr. Charles Moertel, head of the North Central Cancer Treatment Group, responds to questions following his remarks on community participation in clinical trials.

relevance and high standards of quality, clinical cancer research conducted in the community meets a clear mandate of the National Cancer Act, that is, that the technology of new and hopeful cancer management be expeditiously transferred from academic centers where they are developed to the community where cancer patients are diagnosed and treated. Both House and Senate reports accompanying the 1974 amendments to the Act left no room for doubt as to the intent of Congress as they reflected the expectations of the American public. It was specifically stated that no American cancer patient should be deprived of highest quality cancer care simply because of where he lives.

I hold firmly to the conviction that highest quality cancer care in no way equates with the best of standard treatment. For most cancer patients, regardless of stage, and for the overwhelming majority with advanced stage disease, the best of standard cancer treatment is bad cancer treatment. The evidence for this is crystal clear. Most cancer patients die of cancer. For this majority of cancer patients, the only hopeful cancer management is offered in a clinical research setting. If we are to respond to the mandate of Congress, this means that the highest quality clinical cancer research must be made available at the community level. Your organization has fought for this principle, and as you well know, Dr. Vincent DeVita has been fighting at your side and frequently in the face of some pretty stiff opposition. I feel certain that later on this morning Dr. DeVita will renew his commitment to you because you have shown that this commitment is fully justified. The CCOP program represents one of the most outstanding successes of the entire National Cancer Program, fulfilling in every respect its funded responsibilities and frequently exceeding expectations. The only significant problem I see with the CCOP program is that funding and charge have not been expanded to include cancer prevention and cancer control activities, and I very much hope that this deficiency will be corrected in the next RFA. I am going to present to you now what I feel is an outstandingly successful model for the conduct of scientifically important high quality clinical cancer research at the community level. Certainly, this isn't the only successful model, as you have learned from Dr. Coltman and Dr. Deckers, but we think it's a darn good one. And it's a model that met a clear national need.

In the mid-1970's, the resources of the National Cancer Program were distributed in a totally disproportionate manner. There were funded university cancer centers on the east coast, in the south, on the west coast, but the north central portion of our map was empty. With regard to funded cooperative group members, again literally every portion of the country was saturated except for the northern tier in that vast area between the Mississippi River and the Rocky Mountains. There were a lot of cancer patients out there, but unless they were willing to travel up to a thousand miles, they were completely deprived of any potential benefit from the National Cancer Program. Community oncologists in this area recognized this need. We were the closest Comprehensive Cancer Center to this region, and we felt that meeting this need was a responsibility of a comprehensive cancer center. We got together and we developed the concept of the North Central Cancer Treatment Group. Prior to that time, there was money available in com-

prehensive cancer center grants to meet this purpose, but as soon as our group was organized, this type of cancer control funding was struck from the cancer center guidelines. We went to the Division of Cancer Control asking for their assistance, but they said they couldn't help us because we planned on doing cancer research and that was forbidden to their division. Then we went to the Division of Cancer Treatment, and they said no, they couldn't help us because we were doing cancer control. Well, Dr. DeVita was very supportive of our purpose and sympathetic with our frustration. He was able to provide us with a small amount of funding from his Director's Fund. Dr. Dick Rauscher of the American Cancer Society also gave us a small amount of help but his ability to do this was also limited, and in the main we had to cut it on our own. But with all this, we did give birth to the North Central Cancer Treatment Group. We at the Mayo Clinic worked together with highly motivated surgeons, radiation therapists, medical oncologists, pathologists with the major community clinics in this region. We assisted them in recruiting any needed personnel, we helped train their oncology nurses and their data handlers, but they had to support themselves. A look at the cancer resource map today shows thirteen community cancer centers extending from Peoria to Billings, from Nebraska to Saskatchewan, a membership of some 300 community oncologists representing all disciplines who have been willing to push parochial interests aside and work together to produce something of value for the cancer patient.

The North Central Cancer Treatment Group

I think one of the most important ingredients of the success of the North Central Cancer Treatment Group has been our organizational pattern because it's built on trust and respect for each other. The governing body that holds the ultimate authority for group policies is the Executive Committee. Dr. Lloyd Everson of the Fargo Clinic, who will be talking to you in a while, chairs the Executive Committee. Voting members are the principal investigators of each community clinic group member as well as a representative elected by them of radiation oncology, surgical oncology, and pathology. The Mayo Clinic has no vote. As group chairman, I am responsible to the Executive Committee. If they don't like the way I am doing my job, they can fire me. Our function at the Mayo Clinic is to provide an Operations Office and a Statistical Center, to provide quality control, and to provide scientific coordination. More than 40 members of our professional doctorate level staff work at these functions.

We purposely kept our group relatively small so that everyone's voice can be heard and so that all community center members can have positions of either administrative or scientific responsibility. The nature of the group membership varies over the full range of oncology practice organizations. Some members are large, multispecialty group practices, some are consortiums built around a hospital base, and others are consortiums of oncologists in private practice. The Executive Committee has set certain absolute standards for group membership. These include a fully committed, multidisciplinary organization with representatives of at least medical oncology, surgical oncology, radiation oncology, and pathology. Each member must have the demonstrated capacity of entering at least 40 patients annually on group protocols. We feel this is essential so that a full-time data handler can be employed by the member and used cost effectively. We also require that each member be fully committed to the North Central Cancer Treatment Group. Group members, even if they are CCOPs, cannot shop around to other groups for protocols that they might consider more attractive. We do, however, have a close working relationship with the Eastern Cooperative Oncology Group (ECOG), and our group members do contribute patients to ECOG protocols but only under circumstances where this does not conflict with an active NCCTG protocol. Most of our protocols are conducted jointly by the Mayo Clinic and the NCCTG members, and in these instances about 25 percent of entries will come from Mayo, and about 75 percent from the group. In all instances, however, the protocol is chaired by an NCCTG member, and when multimodalities are involved in the protocol we will have a group co-chairman representing each of the modalities. When a new protocol is planned, possible concepts are discussed in the respective committees of our group. In the main, these are served up by Mayo scientific coordinators but certainly not exclusively. One of the important things that we at Mayo have learned in this group activity is that technology transfer is a two way street. The community oncologist works day by day with the patient and his family. They are very conscious of the impact of treatment procedures on quality of life for the cancer patient. They know what research treatment approaches will be feasible at the community level and what will not. They are very aware of the importance of cost containment in health care delivery. All of these considerations weigh very heavily on the success or failure of any given clinical research protocol. Once a protocol concept is agreed upon, the specific protocol procedures will then be developed by the group principal investigator working with one or more Mayo scientific coordinators. Procedures will be developed within each of the pertinent modality committees, and the final product will be accepted only after review and approval of all group members. What have we accomplished? Certainly, one measure of accomplishment is case accrual. In 1978, our first full year of activity, we put a total of 328 patients on protocol studies. Year by year, there has been a steady improvement reaching a total of 1,375 patients in 1985. With the addition of two new members, and hopefully with the activation of several new protocols, we anticipate this number will rise to well over 1,500 in 1986. I believe we have become the fifth largest cooperative group in the country from the standpoint of patient numbers. Among our 48 active protocols, the distribution according to primary site corresponds roughly to the frequency with which these cancers are encountered clinically, with the preponderance devoted to gastrointestinal, lung, and breast. We do have one cancer prevention protocol activated. This is secondary cancer prevention studying the comparative effectiveness of HemoQuant and Hemoccult assays in the diagnosis of colorectal cancer in high risk populations. We also have one cancer biology protocol active evaluating nuclear hormonal binding as a predictor of responsiveness in metastatic breast cancer. We soon hope to have a chemoprevention protocol activated involving preleukemic states. I think it's particularly important that almost 40 percent of our protocols are multidisciplinary in nature, 17 percent are surgical adjuvant trials. During 1985, medical oncology was involved in essentially all patient entries, radiation oncology was involved in 20 percent, surgical oncology in 24 percent, and pathology in 100 percent. Particularly with a new group made up of community oncologists, we thought it was exceedingly important that we developed uniform pathology standards and interpretations for our protocol conduct, and our group's pathologists wish to evaluate every case entry on every protocol. Whenever a new protocol is activated, one or more group pathologists together with one Mayo pathologist have been appointed as primary pathology reviewers. All cases in which their interpretation disagrees with that of the original pathology classification are brought to our Pathology Committee as a whole for a final decision, and they spend many hours at each group meeting reviewing these slides. Not only has this improved the quality control for individual protocols, but this mechanism has also served to develop a uniformity of classification and interpretation among the pathologists of

our group members. They now all speak the same language. We have gone through roughly the same procedure in surgical oncology developing common and frequently disease specific surgical reporting forms. Operative reporting has grown more and more uniform through the group so that we can now read an operative report which is submitted on all of our patients and get a pretty good idea exactly what the surgeon found and what he did.

Community oncology groups frequently have been bad-mouthed because of poor quality radiation therapy. We made a special effort there. When our group was founded, only five members had what we considered to be state-of-the-art personnel, equipment, and treatment planning facilities. Now they all do. Before a new member is allowed to participate in radiation therapy protocols, the facility is site visited by a Mayo radiation therapist and by a radiation therapist of one of the group members. Ours was the first group to have all members monitored by the Radiation Physics Center. We have also gone through similar procedures to ensure uniformity of interpretation of laboratory assays and specifically this does involve a formal quality control program for hormone receptor assays.

Well all of this is well and good, but in my opinion, the most important challenge that must be answered by any cooperative oncology group is can they produce a quality product. This is really the sine qua non for any Phase III study which makes up the bulk of cooperative group research. Our group began at a time when loud voices from ivory towers were blaring out the dogma that high quality clinical cancer research could not be performed by community oncologists. Well all that noise put a chip on the shoulder of our group members and they decided that not only were they going to be good, they were going to be the best.

Certainly, one of the most important standards for measuring quality in cooperative group trials is timeliness of form submission. You can have the best quality control apparatus in the world at your Operations Office and Statistical Center, but if those forms aren't reviewed until many months after a patient has been entered and treated, your protocol can be having disastrous problems that you won't recognize until the protocol is half completed and the damage is irreparable. We set much more rigid standards than other groups. All of our forms are due two weeks after patient entry and two weeks after the initiation of each treatment cycle. When the form arrives at our Statistical Center, it's promptly edited not only by an experienced data clerk but also by the Mayo scientific coordinator for that particular protocol. We don't batch them for weeks or months. If the forms are late, a vigorous bugging process begins, first by mail and then by phone. Our record during 1985 shows that among 1,819 onstudy forms and 2,725 flow sheets, only 12% were greater than a month overdue and one-half of one percent were greater than three months overdue. Nobody matches that performance.

Our greatest effort has been devoted towards obtaining highest possible quality in research protocol compliance. You can have a brilliant scientific idea, you can enter a thousand patients on a protocol, but if the quality of performance is bad, that protocol is meaningless and a waste of public funds. Certainly, the single problem that produces the greatest distortion of protocol results is a loss of randomized patients on entry due to cancellation or ineligibility. If we are looking for differences of 10%, 15%, 20%, as we usually are in Phase III studies, and if 10%, 15%, 20% of patients entered are lost to analysis because of quality problems, there is not a statistician in the world who can unravel the biases and distortions which may have been produced. Dr. Richard Simon has stated that if any protocol loses more than 10% of patients to analysis, the results of that protocol become unreliable. I think that he was really being very generous. Yet, if you look at recent publications of Phase III trials, you can see how very infrequently his standard is met. We have tried to handle this problem, first by taking great care at the vital time of patient entry, and we demand that data given to support entry eligibility criteria be stated specifically. We don't just ask if the white blood count is okay, we ask what was the patient's white blood count, and on what date was that white blood count obtained. The investigator just about has to be an out and out liar to enter an ineligible patient. We don't allow a patient to be randomized today and then treatment start two or three weeks later. That's the way you get the cancelled patient. In our group, the patient has to be started within 72 hours, otherwise he's ineligible.

A main portion of every one of our NCCTG's meeting is devoted to an open display and discussion of each member's quality problems. This gets very much like an AA meeting. The representative from Fargo will get up and say I'm Lloyd Everson and I have entered ineligible patients. And, then all his associates will gather around and say supportive things and they will give him their phone numbers so he can call in case he feels he might enter an ineligible patient again. Well, does it work? Yes, it works. We have had a total of 7,727 patients entered on our group protocols. Only 3½ percent have been ineligible, less than 1 percent cancelled, and that 4 percent total reflects some of our early developmental groping around. For the first nine months of 1985, all of our cases have now been reviewed including pathology review. We experienced a rate of loss of patients to analysis because of ineligibility or cancellation of only 1.8 percent. These figures are not the product of soft review. We are hard-nosed. This quality performance has been confirmed in site visit after site visit. Dr. Robert Wittes, whose job it should be to know things like this, has publicly stated that among cooperative groups, the NCCTG is "numero uno" in terms of quality of performance. And, we are proud to claim that title.

How about that difficult area for community oncologists, radiation therapy? Results of careful monitoring of port films and Radiation Physics Center review have shown a rate of major deviations of only 7 percent. Anyone familiar in this area knows just how good that is. So, by God, good clinical cancer research can be done by community oncologists.

Well, have our protocols just been easy to do, trivial waste baskets for maintaining case accrual? I don't think so. This year, the NCCTG sent 12 abstracts to ASCO or AACR. Ten were accepted for presentation, and in nine of these, a community oncologist will be standing on the podium. Dr. John Laurie of Grand Forks will present a positive surgical adjuvant trial in colorectal cancer involving over 400 patients. Dr. Jim Krook of Duluth will present a positive multidisciplinary surgical adjuvant trial in rectal cancer—recurrence rates literally cut in half—the first time chemotherapy has ever been proved to work in this setting. Dr. Lloyd Everson will be presenting fascinating early results in surgical adjuvant breast cancer, a study involving over 700 patients. Dr. Don Twito of Billings will present a positive hormonal study in advanced breast cancer. Dr. Roscoe Morton of Des Moines will display some striking and long lasting responses for advanced visceral melanoma in patients treated with a gentle regimen that did not involve LAK cells and IL2. Dr. Rob Marschke of Sioux Falls will present a study in small cell lung cancer demonstrating that a community oncology group can obtain therapeutic results comparable to university centers and strongly suggesting that VP16 makes a positive contribution to duration of response and patient survival.

We are proud of our group. But, I have heard it rumored, and Jerry Boyd has recently suggested in *The Cancer Letter*, that we are the last of a breed destined for total extinction. I think the rumors of our impending death, Jerry, have been greatly exaggerated. If anybody tries to shoot us down, they are going to be in for a fight. And, the first thing that they better be able to prove is that the institution or group that they represent has done a better job than our gang of community oncologists. ■