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Dear Oley:

I am sorry to be so late in contacting you concerning the Miami MRFIT meeting (this is being dictated from a Florida Spa on February 16). There appear to be no urgent matters that required my calling you and I'm sure Dr. Kaelber has been in touch with you. I have asked that he expedite the minutes to both of us so that we can get caught up, and you have seen the current C.C. Newsletter.

Of course the most interesting and intricate aspect of the meeting was the formation of the new committees and their self-assumed responsibilities. In many instances these responsibilities overlap and the main question is whether there should be a small meeting between the leadership of the committees and yourself, NIH and the Coordinating Center to work out these problems, or whether they should be allowed to seek a natural resolution.

The report on recruitment experiences was routine and useful. It will be made far more useful if we can promptly get the material into written form. I would like to suggest that you take the occasion to speak to Hal Schnaper so that his promised format for reporting of recruitment procedure in the various centers be dispatched very soon to the principal investigators so that this information may be collected in a systematic fashion for the baseline publication, as well as for circulation among MRFIT investigators. This form has been promised since the November meeting of the Publications Committee and is not yet forthcoming. I believe pressure may be needed here. Clearly the editorial effort of taking individual PI reports of recruiting procedures and synthesizing them into a useful form would be a hopeless and thankless task. If Hal Schnaper appears to be too preoccupied to perform this function, I would suggest that it be reassigned by him to someone else on the Publications Committee. The Minnesota Center, which has already considered such a systematic proposal will be happy to assist in expediting this matter if you wish.

The experiences on obtaining high follow-up rates were much less detailed and systematic and any formal reporting of these should probably wait until annual exam follow-up data appear in the first MRFIT centers reporting. Much of a generally helpful nature was voiced however, and should appear in the minutes of the steering committee meeting. In addition, I and my staff are preparing a formulation of salient points from our past and present follow-up experience which we will circulate to principal investigators within the next period.

The report of the Design and Analysis Committee was adequately handled by Dr. Cohen as new chairman. Confidentially, he will need support, principally from the Coordination Center, and from Dr. Kjelsberg, and from the chairperson to present and discuss adequately some of the issues as many of us would need support for the more complicated actions of that critical committee.

For your information, the Minnesota Center has proposed as an ancillary study the performance of the exercise electrocardiogram at the first annual examination and this was approved by the Steering Committee. We chose this mechanism for expedient reasons to get prompt approval, though this is not the procedure that we would recommend for the study as a whole. I will send you a more definitive description of this study before long. Incidentally, having had an ancillary study passed by my center, Design and Analysis, the Steering Committee and funded by the Heart Association, I have a real concern about the posture of the Policy Board in denying such approval, based on inadequate evidence.

In regard to the exercise ECG at the 1st annual exam, it appears that at least one other center, Newark,has the funds and the interest to pursue this matter and we are suggesting that they also submit an ancillary proposal so that approval may be obtained promptly. My own feeling which I hope you might consider and share is that this is not properly an ancillary study. Rather, the gathering of such data is essential to future decisions in this study concerning the exercise electrocardiogram. Most principal investigators and others of the Steering Committee who spoke on this issue made the point that it seemed penny-wise and pound-foolish indeed to perform the exercise test at baseline without anticipating that it would be repeated at some time in the study. My greatest hope was that it be done at the first annual examination when the most information would be obtainable. I did not push this issue because of the clear signals I received from you and from Bethesda that the money would not be available and that there would be little support for it at the first year. However, you will recall that two prime issues other than the proper classification at baseline were to be considered in the use of the stress test. The first was whether there would be revealed Usual and Special Care differences in physical conditioning. This answer may be obtained readily from a small sample, probably the results from one center being sufficient. The second major question has to do with the determination of coronary events, that is the new appearance of distinct ischemic changes or dangerous arrhythmias at given work loads or not previously present on baseline examination.

Before imposing the considerable inconvenience and expense of this retesting on the study as a whole, it seems to be very appropriate that there be gathering of data which will allow intelligent decision making concerning its future use or not.

We are now in the process of making sample size estimates which would reveal new event rates and their confidence intervals. It is just conceivable that we might obtain useful rates if they vary between one-half percent and three percent of new positive exercise tests from a sample size of 1,000 people, possibly reached with two centers participating.

This is to let you know, therefore, that I will be submitting a formal proposal that MRFIT support this not as an ancillary study, for which external funds may not be available, but as a crucial gathering of information for the study as a whole, in one or two centers. I will discuss this with you and I hope that we will find some favorable reception to this idea. Of course, extra support may not be in the picture at all. In which case Minnesota and Newark will probably try to eek by without extra support for the performance of this test at the first annual exam.

I think it would be appropriate for the Steering Committee to send very promptly a letter, under your signature, of condolence to Jessie Marmorston for the loss of her husband.

A number of other important decisions were made including tentative closing dates for recruitment of September 1, for the first 15 centers and November 1, for the subsequent centers; encouragement of recruitment of more than 600 people with submission of cost estimates for negotiation with the contract office, but limiting any center to total randomization of 900 individuals. It was proposed and generally accepted that we seek a target date of December 31, 1975 for termination of randomization.

There continues to be considerable resentment on the part of the five latest centers that they would be penalized in their total award and their total staff function by such early termination dates and this question was not resolved satisfactorily. I think it will be necessary for the Coordinating Center and the leadership to present a strong argument for the target termination dates in terms of design, but this is likely to cause a real burden to Rutgers, Miama and Los Angeles who may end up with a significantly lower number of randomized participants. This picture should become very clear by the time of the June meeting and it might be appropriate to hold discussions about the matter between the April and June meetings.

With regard to the new committee organization I think we should have not only the quiet discussion between yourself and the leadership of committees but a very serious consideration of whether we have simply produced another group of monsters who will function independently of each other and relatively inefficiently, as our first group of committees have.

The other major issue which has come up concerns site visits. There should appear a firm recommendation in the minutes for continuation of the Coordinating Center site visits of the small and informal nature, being carried out principally by Jim Neaton, Ann Marie Reynolds, and Trish Ashman as they have almost completed the rounds of all centers, and as it is primarily an information pursuit on their part. The larger issue of formalized and routinized site visits really requires our serious discussion with the Project Office and the Coordination Center. Otherwise we are likely to have various types of roving groups producing more or less useful information and more and less annoyance of principal investigators

in their function. The idea that we discussed briefly on the telephone of having representation of the project office, the principal investigators, the steering committee, the intervention task force, and the Coordinating Center was reasonably well accepted by the Steering Group. However, in informal discussions after the meeting, held between the Coordinating Center and the Project Office there was considerable concern about the nature of the site visits. The crux of the matter appears to be that it will require a tremendous amount of highly skilled function to routinize such visits with even as few as five people, visiting 20 centers annually, at great expense and at great loss of time in preparation of reports. On the other hand, the less formal information gathering site visits do not have sufficient authority or sanction of the Steering Committee to serve the purpose of reporting to the Steering Committee or to the contract office, the evaluation of clinic performance.

This important issue plus the very prompt beginning of regional training programs and the meetings of new committees leads me to suggest that you call a small meeting of the leadership, the Project Office and the Coordinating Center, and work out some of these matters prior to the April Bethesda Steering Committee Meeting. Obviously we will be happy to come to Chicago for that discussion which is sorely needed.

It should also appear in the minutes that the Publications and Presentations Committee approved submission of abstracts to both the American Heart Association and the American Public Health Association meeting for the fall. Maybe it would not be inappropriate to submit an abstract also to the Society for Epidemiologic Research.

In respect to other developments of the new committees the information exchange committee, and its assumption of important training functions, is critical. It is not at all clear to me who is taking the responsibility for the organization and standardization of this training. I would suggest that this be explored promptly between Dr. Kaelber and Dr. Kjelsberg to be sure that things are not left entirely in the hands of that committee or the host for the first training session but is well coordinated by experts in the needed fields.

The intervention committee is still the same old process as far as I can see because of the interim chairmanship of Mac Smith. I hope that things will change when Roger takes charge. As usual the hypertension situation is still not well in hand. As you know one of the primary reasons for early initiation of the training sessions is for introduction of correct procedures for utilizing new hypertension forms.

The quality control committee started out ambitiously embracing all functions of MRFIT but seemed finally to direct its energies to very worthwhile pursuits which do not conflict too seriously with the functions of the coordinating center or other committees.

The ECG center report was the shortest on record with the least negative

comment, and things seem to be moving there reasonably satisfactorily. I might remark confidentially that an expression of a personal interest would be worthwhile in the type of diagnostic statements and quantitative data in preparation, or now being forwarded from the ECG center in Halifax (and the ECG coding center in Minnesota) to the Coordinating Center; such an expression of interest on your part in this matter might be helpful at this time. I am not sure how rapidly those procedures are developing and if you express an interest in the nature of the electrocardiographic endpoints it might result in some action and clarification of purpose from the electrocardiographic centers. I think this could better be done in a casual query to Dr. Rautaharju and Dr. Prineas at the next meeting.

I still admire highly the flexibility of the Central Laboratory to do Steering Committees wishes even when they disagree in principle. But I am also concerned that our central laboratory lacks a certain epidemiological know-how and experience in standardized procedures for multiple centers studies. Here again a question on your part as to the function of the Central Laboratory to survey the individual centers on the degree of standardization of their baseline blood collection and preparation procedure should be very helpful and should assure that standardization will be much improved for the first annual blood specimens. Personally I feel this quality control has been entirely inadequately handled by the Central Laboratory. A rapidly changing protocol has contributed to insufficient standardization. The Central Lab should take direct responsibility for surveying the actual conditions under which baseline and follow-up blood samples for cholesterol, serum and plasma, were acquired, and that they enforce standardization of this procedure for the annual examination. If, as I expect, large differences will be found between centers in their practices of bloodletting at Visit II, etc. the practical and conceptual question will arise whether it is preferable for a center to continue its own standardized procedure based on its first year baseline performance, or conform to a general formalized protocol. This is a difficult question, but for my own center, if we should have departed from protocol in baseline bloodletting I would much prefer to have us continue to depart from protocol for the sake of internal integrity of our comparisons between baseline and first year and Usual and Special care. This of course must be traded off against a need to describe this study as a standard one using a standard protocol. But due to a lack of effective survey and enforcement, the lab protocol in this matter at the baselines as an important question has now arisen and more direct responsibility should be taken for this by the Central Laboratory and the Coordinating Center with immediate consultation with Design and Analysis and Quality Control so these matters can get informed consideration at the Steering Committee.

Tentative meeting dates were set up thought September and will be discussed with you by Dr. Kaelber.

Finally, following the Steering Committee meeting there was an informal meeting between the Project Office and the Coordinating Center staffs, at which I sat in for a couple of hours. Considering the relative understaffing and the many problems and the complexities of the study, I think things seem to be going very well. I saw distinct evidence of happenings I have previously experienced

with the Coronary Drug Project Coordinating Center personnel. This is in lack of professional satisfactions on their part, so terribly put upon as they are in their housekeeping responsibilities, with such little opportunity for professional betterment, thought,writing, and constructive advancement of methodology in this field. They tend to assume at times, unfair burdens. I have no real solution for this;most of it lies in the hands of Dr. Kjelsberg who must help his very effective collaborators establish areas of professional interest that they may pursue and develop in the course of this trial, so that they will emerge from it with sound accomplishments beyond the simple routine operation of a successful center. Klimt and Meinert helped this by rotating functions every year or two and providing 1 day "sabatticals" weekly, etc.

In closing, I feel a need for a continuing governing activity in the interim periods between Steering Committee meetings which we have tended to resist in the past and which would require a much closer working relatipnship between the Chairman and the Project Office and Coordinating Center. You will find in the minutes a unanimous statement from the Steering Committee of gratitude for your continuing to accept this large responsibility for MRFIT. This was an official proclamation of the Committee. It did take cognizance of the fact that you made clear to the group that your tenure was not to be considered a permanent one and that the committee might receive a request for your resignation at some future date, but hopefully not soon.

Cordially,

Henry Blackburn, M.D.
Vice Chairman