discussed by Dr. Carlos. Performed well, these modern trials could reduce the number of large trials required for establishing validity.

I have a feeling that many of us are grappling with the same problem, and an appropriate testing process will evolve eventually. Unfortunately, evolution takes a very long time, at least without grant support.

REFERENCES

1. National Institute of Dental Research: The Prevalence of Dental Caries in the United States Children, 1979-80. Washington, DC: National Dental Caries Prevalence Survey, NIDR, 1981, pp. 1-12.
2. BOHANNAN, H.; KLEIN, S.; LEONE, F.; DISNEY, J.; and GRAVES, R.: Caries Prevalence in the National Preventive Dentistry Demonstration Program, IADR *Progr & Abst* 60:No. 199, 1981.
3. ZICKERT, I.; EMILSON, C.; and KRASSE, B.: *Streptococcus mutans, Lactobacilli* and Dental Health in 13-14-Year-Old Swedish Children, *Community Dent Oral Epidemiol* 10:77-81, 1982.
4. KOHLER, B. and BRATTHALL, D.: Practical Method to Facilitate Estimation of *Streptococcus mutans* Levels in Saliva, *J Clin Microbiol* 9:584-588, 1979.
5. BAKHOS, Y. and BRUDEVOLD, F.: Effect of Initial Demineralization on the Permeability of Human Tooth Enamel to Iodide, *Arch Oral Biol* 27:193-196, 1982.
6. KLEINBERG, I.: Prevention of Dental Caries, *J Prev Dent* 5: 9-17, 1978.
7. KLEINBERG, I.; CHATTERJEE, R.; DOMOKOS, A.; CASTALDI, C.R.; FAIR, M.; and CHEBIB, F.: An Ultraviolet Photographic Technique for the Early Detection of Carious Lesions. In: Methods of Caries Prediction, Bibby, B.G. and Shern, R.J., Eds., Washington and London: Information Retrieval, Inc., 1978, pp. 271-280.

General Discussion

BEISWANGER: I think this morning's presentations are going to cause a number of us who are active in caries studies to re-think those things which we are doing and consider whether there are better methods of diagnosis, better methods for pre-selection of subjects, and laboratory and other parameters that we can be checking along the way to make our trials more efficient.

DAVIES: One of the items discussed that has interested me is the place of radiographs in our clinical studies. We seem to have heard a variety of views here. We have heard Dr. Mainwaring pointing out that radiographic readings are an important component in clinical trials. I think I heard Dr. Fischman say to more or less dismiss them. We ourselves don't use them in the U.K., and we are losing a potential benefit, according to Dr. Mainwaring. I wonder what the FDA feeling on this might be.

HOERMAN: I think perhaps we are going to be forced by the low prevalence of dental caries, in children particularly, to develop some kind of an index to assess the dynamics of enamel. We need to be able to measure the advancing enamel lesion, the stabilized enamel lesion, the remineralizing enamel lesion, and, of course, handle errors in that realm. The disturbing thing is that there is constant change in all four of those factors, and how do we clinically measure that, and is it necessary to measure that, and can it be incorporated into the standard DMFT/S scoring? I think Dr. Marthaler and Professor Scheinen have used systems of that nature. Perhaps some discussion on that might be appropriate. I would concur with Dr. Mandel, that we shouldn't be too complacent about this lower prevalence of dental caries. The challenge is still there. It really might be treacherous to predict that that same effect would hold true in an aging population, and certainly I was very interested to hear that point of view brought out. Also, I would be interested to hear Dr. Marthaler discuss the observation that he made – that in 1965-66, the detection of pit and fissure caries was very low in the population, and ten years subsequently, he found that caries had developed and the tooth had then been filled. There was a significant rise in caries scoring for 20- 25-year-olds at that point, with pit and fissure caries prevalence one of the main increases. I would like to ask the question of what a school-based sealant application program would do to the prevalence scores in addition to what we now see in the smooth surface area. I think Dr. Bohannan may have some information on that, too, in the experience of delivery of sealants in some kind of a public health school-age program.

Dr. Mandel, do you consider either the ICT test or the butazolidin permeability test as a frank, straightforward experimental clinical trial rather than a laboratory experiment?

SCHEINEN: I know that Tommy Marthaler published papers years ago discussing such things as pit and smooth surface caries on the same surface, for example, buccally on molars. Are there methods to distinguish these using present-day techniques?

The other thing to consider would be a kind of older lesion, such as buccal lesions, which are border area lesions in the sense that the examiner can't really distinguish whether these are located buccally or mesially. A lot of variation – so-called "examiner error" – is due to this fact.

MARTHALER: What I said essentially was that the diagonal element is always stronger in a transition matrix; it is always stronger when a correction has been applied. That means that when the size or width of incipient lesions not in effect already, these sites tend to remain in that state rather than to progress. For future clinical trials, I think that's an important item, especially when we look at the modern techniques of remineralization which are being developed. When we talk of arrest of a lesion, we need to talk of incipient lesions. Otherwise we can't study arrest. I can't say anything about sealants as an epidemiologist. I am pleased to see that very few fissures are sealed in Switzerland.

GRAVES: I would like to comment on Dr. Marthaler's paper relating to the surface-specific methods of detection of caries. Yesterday we spent a good bit of time talking about mis-classification issues and the reversal problems, particularly when we go from carious back to sound enamel. A good deal was said about the declining incidence of caries and how caries tends to be confined to the fissures with reduction in attack rate on proximal surfaces. I am referring specifically to these new methods of caries detection which were mentioned. I thought his paper was somewhat glowing in the usefulness of the electrical resistance apparatus, which White has reported. In Dr. Fischman's response, he said this procedure had not been clinically evaluated. Maybe some of the rest of you have had much more experience than have any of my friends in using these gadgets. If they are effective and you have given it a two-plus here, and the explorers are given a one-plus, it has a degree of usefulness.

I would like to hear some comments about that.

MARTHALER: Well, I readily admit that the two-plus judgment was made somewhat early. I think that White's paper, in 1981, was one of the very few instances where a study has been made on technique material. Except for radiographs, very few longitudinal studies have been reported on diagnostic methods.

HOROWITZ: I think everyone in this room knows that fluoride has a differential effectiveness according to the type of tooth surface – much more profound on smooth, proximal surfaces than in pits and fissures. I personally feel, and I think that data will provide support, that sealants do have a very strong role to play in total caries prevention, considering this known differential fluoride effect. As an example, I'd like to cite the data that Dr. Heifetz used in his paper yesterday. In Nelson County, where we have had a combined fluoride program going now for eleven years, we found, after our most recent examinations done after eight years, that we had reduced decay by 49%. But there was as much as 86% lower prevalence of decay on proximals. As a matter of fact, 94% of all remaining decay in Nelson County among children six to fourteen years of age in 1980 was in pits and fissures. Therefore, we are planning to initiate an efficient sealant program there beginning next year or the following year, to try to mop up the remaining decay that exists in Nelson County, because we think we have gone about as far as we can go with fluoride. It has been mentioned by a few speakers during this meeting that there is evidence that dentists who are "hungry" are intervening earlier in placing restorations on teeth than was done formerly. I would like to know what data exist to support that allegation or conclusion.

FISCHMAN: I don't think there are any hard data to support that allegation, but in Lou Ripa's data, 80% of the increment is due to filled teeth, and this was true in past years. That shouldn't be. The less caries we see, the fewer fillings we should see. People are suggesting that might happen. Also, when we work in different sites around the country, the dentists in the community who may also be the examiners there told us they have the same feeling. It is all very subjective. I don't have any hard data that would support the statement that others and I have made.

HOLLOWAY: I have actually examined this phenomenon in some detail in Britain. I can find no evidence at all to suggest that dentists in Britain are restoring teeth at an earlier stage as the caries prevalence drops. I have examined the national data on this phenomenon, and if we look at the drop in caries prevalence in Britain, for example, it is 40%, whether you look at children receiving regular care from dentists or children who only go to the dentist when they are at home. So it seems to me that if the dentists were filling teeth unnecessarily, we would see a considerable difference between the two groups. Alternatively, if you compare the caries prevalence in children treated by salaried dentists (where there is no incentive to fill) and those treated by private dentists (who are paid on a fee-for-service basis), there is no difference between the caries drops in those two groups. Finally, if you look at the number of fillings *per* course of treatment in Britain (and this is very well-documented in our own national health service), the change in number of fillings *per* course of treatment in children has gone down 40% – a drop which mirrors the reduction in dental caries in the last ten years. I have also looked at it in Denmark, where the data yield the same results. So I can find no evidence at all, in Europe, to suggest that dentists are unnecessarily restoring teeth which are either very early carious or not carious at all.

Dr. Marthaler has been a little unkind in Table 3, when he looks at fiber-optic transillumination. I don't know if people in the United States are using this, but we in Britain and in our group in Manchester are using fiber-optic transillumination for our epidemiological work. To begin with, the intensity or quality of light is far better. If you wish to detect very early lesions, then I think we can now show that the transillumination technique actually detects as many lesions as we would expect to find on radiographs. We have actually taken this out into the field now.

RIPA: In regard to the dentists being overexuberant in filling lesions or potential lesions, the report that was referred to by my group did not, in fact, show or even indicate that dentists were being overexuberant in filling lesions. What we reported was that, when a fluoride intervention was in place for several years, there was an absolute reduction in the number of decayed surfaces. There was also an absolute reduction in the number of fillings. Conversely, when that happens, if it doesn't happen equally, there was a percentage reduction in the number of decayed surfaces, but an actual increase in the percentage of filled surfaces. We said that this percentage increase can occur if the dentists do absolutely nothing differently than they were doing before. It is simply something that has to happen in an area where decay is there but where the level of restored care has remained the same. So I can find no evidence either.

CARLOS: With respect to these proposed new methods of detection of caries, as enumerated by Dr. Marthaler, there are some problems that I think we have to recognize. What these methods are intending to do, I assume, is to measure the same process that we traditionally measured, but measure at a much earlier stage in the development of a lesion. That suggests the need for validation of the results obtained with any new methods. Unfortunately, the only satisfactory way to validate an early detection method is to observe the diagnosed lesion for a sufficient length of time until it becomes a clinical cavity. Then we will know we were measuring dental caries and not something else. Obviously, there is an ethical problem in doing so, because if we believe that we are, indeed, detecting dental caries at a very early stage, then we are obligated to do something about it, to try and arrest it or remineralize it. So, I think if we are going to begin to use some of these methods without the ideal way of validating them, it is going to become even more imperative that such studies include confirmatory evidence of the kind that Bill Bowen was talking about. Otherwise, we should have relatively little faith that we are actually detecting dental caries.

MARTHALER: The usefulness of fiber-optic transillumination . . . I will be glad to do that. As to the placement of fillings, I have given some figures in my paper. We found that from 1963 to 1967 we had a very marked decrease, from 6.4 down to 2.9, in decayed surfaces. In the remaining 12 years, however, when caries declined but about 50%, the number of unfilled decayed sites remained almost constant. In the remaining period of 12 years, it fell from 2.9 to 2.0. So this longitudinal epidemiological finding incorporates very well what has been said by Lou Ripa and Phil Holloway. There may be cases when one or another dentist may be too quick on filling cavities, but, on the average, I don't think that the decline of caries is related to the filling activities of the dentist.

HOROWITZ: We have had a lot of discussion about explanatory as opposed to pragmatic studies, or the studies in which efficacy is determined, as opposed to community effectiveness. I fully appreciate and understand why an in-

dustrial company or a research agency may want to know the full potential clinical efficacy of an agent, but I have some trouble in determining the applicability of that information. Let's take a case in point of a dentifrice. There has been a lot of discussion about how we can reduce the numbers of subjects by pre-selecting on baseline parameters of previous caries experience, age, etc. Yet, the product is ultimately going to be sold to the general public and certainly the general public of children. In any review paper, the results of studies tend to be cumulative. A mean reduction appears in a table that compiles the results of all these studies. No distinction of the rigorousness is made among the tests which were performed. I'm sure that a commercial company that runs an efficacy study in which, let's say, a 50% reduction in decay is achieved is not going to advertise that this product is shown to produce 50% reduction in decay when used among girls who have more than three DMFS surfaces, including occlusals of molars. The company will advertise its product to the public, claiming that this product reduces decay by half. I'd like to hear a response from people to say how the findings of clinical efficacy will be put in perspective in terms of application to products, particularly ones that are sold over the counter.

GREENBERG: I am concerned about the emphasis on selecting high-risk groups for efficacy trials using the age, sex, perhaps race or socio-economic status, and plaque and saliva tests in order to reduce the number of subjects, the time required, and the costs. This can be a dangerous trend. There is too much artificial distinction being made between efficacy testing *vis-à-vis* the community pragmatic trial. Every time one adds another pre-selection factor for susceptibility, the representativeness of the subjects is automatically reduced. Although the clinical test results in efficacy trials when randomization is practiced, eventually the hypothesis being tested is a meaningless one for any real community. The history of the design of experiments started in agriculture, and we should learn by way of experience. The mecca of such research was Rothamsted in England, but there were dozens of experimental farms elsewhere in England, Wales, and Scotland, because the soil, rainfall, temperature, and sunshine differed from those in Rothamsted. The ability to study the importance of all the interactions and synergisms will be lost if the trial continues to seek the fast responder without worrying about real life in the target population.

DOWNER: I think one has to take the point that perhaps the results of the trial of the type we are talking about cannot be extrapolated to any great extent to a wide range. One has to accept that. Nonetheless, there are now in existence many standard forms of dentifrice which are used as active controls. The properties and effects of these dentifrices are widely known on a wide age range of subjects and on tooth surfaces. I wonder now whether the dentifrice manufacturers don't want some quicker, more efficient trial of these new formulations compared with existing well-known products, and whether this generality which is being asked for can perhaps be sacrificed. I think if you do have a larger, wider, less homogeneous population testing the dentifrice, at the end of the day it is still a highly artificial population which bears little resemblance to the true public health benefit of the agent.

GLASS: Some of the points that Dr. Downer brought up in his paper are quite real and illustrate some of the problems we are going to face in the future in caries research in general and in clinical trials in particular. In our last clinical trial, we accepted everybody who volunteered and excluded nobody. 41% of the children age seven through eleven were free of dental caries or free of prior dental treatment at the outset. They contributed nothing to the trial and experienced a low caries rate during the course of the study. We are unable to demonstrate a statistically significant treatment effect in this particular subset, although there was a highly significant treatment effect in the entire group of 853 participants. This reminds one of the situation of trying to test the efficacy of aspirin in a group of people who don't have headaches, assuming the aspirin was used only for headaches (Jellinek). There are some more practical problems here, and we can't take them out of context with groups such as regulatory agencies. One is reminded of the package label insert that says, "This product has been found to be effective in eleven- to twelve-year-old females living in such an area where 2.5 to 4.6 DFS are selected teeth surfaces". As Martin Downer pointed out, there are key surfaces at risk, but these are highly dependent on age and different data sets, and in all likelihood this is of academic but not practical interest in developing more effective ways of trials.

SCHEININ: Because studies on fluorides were done traditionally in children, there grew up this view that fluoride was only good for children, and, therefore, adults would not profit by it, and it was a waste of time to use fluoride in adults. Let me say that the most dramatic example of the benefit of fluoride is in older patients whose glands have been irradiated because they have cancer of the head and neck, who have no saliva, who without fluoride would have decay down to the gum line in 12 to 18 months. You put them on daily fluoride, and they have zero caries. If that does not tell me that this is an efficient technique for preventing caries when you get somebody who is at extreme risk, and I would ask the statisticians, would not one extrapolate from such a situation and say, therefore, younger people at much less risk would profit as well? In other words, maybe we have been turning the whole thing over and not examining it in the most appropriate way.

LU: It is my understanding that Downer's is a technical approach to get to the problem quickly and do some preliminary screening. This reminds me of how the networks used selective precincts to predict a national election. They were very successful. They ignored the popular return but only looked at selected precincts which they have been looking at for 30 years, which always come out on the winning side. My question, therefore, is this: Have you really selected a twelve-year-old kid, a girl with certain qualifications, and repeated the study with the same child and obtained the same results? If you have, then we need you to go and establish this kind of credibility. Otherwise everybody will be questioning, what is the error and how can I feel comfortable about someone who is 22?

FLEISS: I have two comments. One is to second Downer's defense of strategies for studying high-risk groups. The purpose of a controlled trial is to ascertain, under control experimental conditions, what it is that a treatment does, and if the treatment is effective, we have to give it a chance to prove itself. I think his work is just on the mark.

Second, I'd like to rise to the defense of the two-tailed tests. Dr. Mainwaring hadn't much good to say about it. I think his major reason for moving toward or suggesting a one-tailed test was that we know the experimental treatment can't do harm. I think it was Ambrose Bierce who said, "It is not what we don't know that hurts us, it is what we know that ain't so".

O'NEILL: I am from the FDA, but I am not talking

from a policy perspective. I would like to say that this high-risk issue is not specific to the anti-caries trial. I think there is a place for considering doing clinical trials on high-risk groups, at least at the Phase Two stage. Legally you need two studies to demonstrate an effect. The second Phase Three trial may be an assorted group, but there is some sense in looking at high-risk groups. It has been looked at in the cardiovascular area and in the areas where you pick people with high levels of cholesterol, give them a cholesterol-lowering agent, and see if they will have a five-year reduction in mortality. The idea is that it is a rare end point, and you want to pick the high-risk groups. In angina, you pick people who have a certain number of attacks during the week, and you are getting a high-risk group. So I think there is a place to consider it.

A second issue gets into labeling claims and how one should label the drug. That's a tricky issue and is actually a legal document. It specifies what you are allowed to state in your advertising. I do believe in the previous comment, that you should not abuse a study which is allowing you to show the general use of an agent in a population for which that may not be the claim that you are really going for. I guess what it speaks to is, you have to have a pretty good plan up front in terms of how you are going to use these studies and what you are going to expect to claim from them. It starts to bear on the comparative claim issue. I think that's a touchy issue right now. There is really not too much ground that's been broken on comparative issues. It is very difficult for any drug to go up against an active control and get a comparative claim that is better because that relates to the population which you have tested with it. You get into many issues, such as whether you have chosen the right dose, the right sample selection. So issues of comparability – "I am as good as somebody else" – might fly with these kinds of studies, but not "I am better than" because you could use a truer population to try it in or use an overall product that would be superior in any context. Again, the ultimate decision on where a study like this fits in, I think, calls in some ethical issues where if you have a product that could be withheld from somebody, it ought to be tested in its most efficient manner. I don't know whether that's true in the caries area, because there are alternatives out there which are doing the job. You are not talking about something like Timerol, a beta blocker which was approved on the basis of one large study in which coronary mortality in men was demonstrated by a reduction in coronary death due to myocardial infarction. It was considered unethical to repeat that study because there was no alternative treatment. I am not so sure that is the case in the caries studies. I am trying to give a flavor for the considerations that come into play where high-risk groups should be considered. I think it is something that deserves further study.

MANDEL: One comment is in regard to the use of the lactobacillus count as part of the profile for a susceptibility test. Dr. Bowen recommended the combination of the mutans as well. You are quite correct. The use of the lactobacillus counts probably indicates exposure to carbohydrate. That's its best association. What we are dealing with is a complex of diseases, and it is getting more complex all the time because of the tremendously ambient level of fluoride. When selecting populations, for instance, to do studies on a bacterial-related disease from a patient with carbohydrate, one of the things that you want is people who need carbohydrates and have a substrate available. The lactobacillus count is an indication of this. The population at risk is one in which a carbohydrate diet produces an environment conducive to caries. That's why I appreciate Dr. O'Neill's remarks so much, because they support this concept. I did want to respond to the question that Dr. Hoerman raised earlier, relating to testing foods. I think the techniques, for instance, of Brudevold with the iodine permeability and the technique that von der Fehr suggested will lend themselves very nicely to a whole lot of other concerns in caries, and that is testing cariogenicity of foods or food supplements, in that manner. That's very important.

That's also part of the same thing. The laboratory procedures that one uses depend upon how they interfere with the caries process. If I were in Scandinavia and I were doing a study with a chlorhexidine gel, I would not look at factors that are necessarily affecting remineralization initially, but would look for the impact on *Strep. mutans* and lactobacillus counts. We always look at the punishment fitting the crime, but the device we use to test has to fit the agent on trial.

BURCHELL: It is my feeling that caries rates should be quoted as surfaces at risk. We need to take those surfaces which are genuinely at risk and not apply them to whole mouth indices. We need to talk about fissure caries regarding the fissures at risk and proximal caries and proximal surfaces which are at risk – in other words, where there are contact points.

STAMM: I think it would be well-advised, as one speaker indicated this morning, that the Schwartz evolution concept be examined as it was originally formulated. One of the ideas that has come out of the Schwartz group is that we should really think in terms of the process of developing an agent right from its beginning to its application by the practicing dentist or, in his case, the practicing physician. Four steps were envisioned: One was the initial laboratory research; the second was the animal testing; the third was the explanatory trial; and the fourth, which was tied into the third, the pragmatic trial. On that topic, I think it is worthwhile to point out that the pragmatic trial, as described by Schwartz, does not resemble the community trial described by Dennis O'Mullane. O'Mullane described non-random application, and he also suggested no control group. Both of those things were not part of a situation that Schwartz initially authored. The reason I even bother to make the point is that while I think it is perhaps wise to judge the efficacy of fluorides based on an explanatory trial, I think the reason we wouldn't accept that judgment is that we have been talking about fluoride preventives. I feel, rather, that there should be other types of interventions that need to be evaluated relative to dental caries – other interventions which are not as easily judged by just the explanatory trial. So, for example, the fissure sealants as a caries preventive could be evaluated by the explanatory trial, but the explanatory trial without the pragmatic trial tied right to it as part of the research development program is almost useless because the real crucial issue in the fissure sealants debate comes down to: Is it useful for the larger population?

We should remember the real difference between many of the medical clinical trials and the trials in dental school. In the medical clinical trials, they are testing interventions aimed at combatting an existing disease, but we in dentistry when talking about our trials are talking about taking healthy subjects and keeping them healthy. We are applying intervention to a non-diseased group and trying to keep them non-diseased, or, if you will, to non-diseased teeth and keep them non-diseased. I think this is an important distinction. I would like it to appear that the pragmatic

trial has a considerable role to play in this particular area.

HEFFERREN: When you talk about plaque acidity in the mouth, first of all, if you consume an acidic fluid, the salivary pH will neutralize that acidity in a matter of minutes. On the other hand, if you take an acidic fluid that contains an equal amount of carbohydrate, while the salivary pH will return to neutrality within a few minutes, the plaque acidity will normally stay down for about half an hour. If you take a solid food, you are talking about plaque acidity for hours. I just wanted to differentiate between salivary and plaque pH. The neutralizing power is in the saliva.

HOROWITZ: I have a question and a comment. In terms of using any screening method for picking subjects who might be suitable for running an explanatory study, whether it would be laboratory-type data or baseline characteristics, the question I have is, how have people who have run those kinds of studies managed to handle that objective operationally? To explain, for many years I have been involved in clinical studies of children, and we usually open these studies to volunteers within a given school system or district, and I envision problems in screening children in a school system and saying, first of all, you must get permission from parents for children to be in the study, and then, after examination, saying, in effect, we will take you, you, and you, and thanks to the rest of you for answering this call, but don't call us, we will call you. In a private practice situation where patients are showing up in an office, I think you can handle this potential problem more reasonably. In public settings, however, I envision a problem in running explanatory studies through the school system. The comment I have to make is that I would like to emphasize John Stamm's comment that most dental studies are run on prevention, whereas most medical studies are run on treating the diseased state. For example, a thing that Bob O'Neill referred to, of diets with lower cholesterol or getting people to lower their intakes: There may be a subset of the population that will benefit from such maneuvers or interventions, and yet there has been the same criticism in the medical area of making recommendations to the general public that may only be applicable to a small subset of that public. I think the analogous situation exists in the medical field for preventive techniques.

DAVIES: Dennis O'Mullane's concepts of the clinical trial were based very closely on Schwartz' pragmatic clinical trial. Dennis and I have just completed our first attempt at a pragmatic clinical trial on fissure sealants. It played a very important part in the design of that study.

GREENBERG: I think we owe a debt to the dental profession for getting the statisticians to argue with one another. So I would like to respond to Joe Fleiss and Bob O'Neill. First of all, Bob, with reference to the beta blockers, I hope the FDA was not recommending that the entire population go on beta blockers. I think that's what John Stamm was referring to. Let me give you two examples from the medical literature of what the dangers are if you pick too high a responder. I was not proposing that it was desirable to pick some criteria which may help to limit the number of subjects needed. I was trying to stress that going overboard may be that you are testing a meaningless hypothesis. I listed age, race, sex, socio-economic status, saliva, and so on. We have a beautiful example where a very high respondent was picked in the case of estrogens. The original estrogen belief was that it was helpful in preventing heart attacks. Persons who had their first myocardial infarction were picked in the Chicago area and were given estrogens, and they had no effect in preventing the second myocardial infarct. As a result of this, for 15 years now it has been accepted that estrogens had no effect in preventing cardiovascular disease. It is only within the last year or two that some other studies have been performed showing that women taking estrogen contraceptives have had lower rates of cardiovascular disease. It has taken 15 years now to correct a misconception because they took so high a respondent group that they got a different kind of result. The other example I want to use is the "Mr. Fit" study – costing over $100,000,000 – which showed that exercise and dire reduction in smoking made no difference, since some of the original observations were made on a very highly responding group. So, there are dangers involved in being too selective in the group of subjects you are using in your clinical trial.

O'NEILL: Let me clarify what I was trying to say. Given that one has to replicate a finding, which is what the regulatory rule is, and given that you have two studies, both of which have to show an effect, I am saying that there is a place for one of those studies being in a high-risk group, maybe the first one that's done. The second one, the larger one, has to show the effect in the general population for which the agent is going to be labeled. I think that needs to be clear. I am not saying that the last thing you do is demonstrate something in a high-risk group where you then have a reasonable case for arguing that you cannot extrapolate. What I am saying is, given that you have two studies, there is a place for a high-risk group in the first one, and that rightfully falls into a Phase Two study. But that's not to be dismissed lightly. It is still going to take a reasonably large sample size but not on the order of what it might be on a Phase III study. That's what I was trying to get across.

BOWEN: I'd like to emphasize and support what Irv Mandel and Bob Glass pointed out. There is really very little point in studying preventive agents in groups of people who are not going to develop a disease. I think a lot of people here refuse to accept that we are dealing with a dietary and bacterial disease. The etiology of what's happening in Timbuktu or North America is essentially the same. Therefore, I find it difficult to understand the opposition to exploratory or explanatory clinical trials. If you do look at the caries people, why does it not prevent caries in a less-susceptible group or even have more effect on a *more* susceptible group? If we use the clinical observations together with laboratory tests, I see no reason why the rules shouldn't be changed.

CHILTON: I would like to point out that, in the past, the maximum use of an anti-caries agent has often been used to demonstrate its efficacy, such as supervised twice-a-day brushing with the agent – even though people do not brush twice a day under supervision. Thus, the general usage is often not the same as that which was used in the experimental study. Hersch Horowitz kept referring to the use of school populations. I think it is time that we started looking for other types of populations, because we are now starting to see caries manifested in populations besides young children – for example, the root caries studies. Because of the fact that we have limited so many of our activities to school populations, it is very difficult now to start to work out mechanisms for obtaining study populations in older age groups. I think the RFP's being put out for root caries or for other studies in young adults are going to have a rather limited response because of the lack of available populations. I think that investigators will have to look into the availability of these populations.