INTRODUCTION

One of the primary goals in sending activists to attend the ACTGs is to gather information about the development of treatments for HIV. An equally high priority is disseminating this information to an as wide an audience as possible.

This size and complexity of this report shows just how hard it is to accomplish both these tasks. The topic is so large and so arcane that it is difficult to grasp and just as difficult to explain.

All of the entries in this report are distillations from memory and/or huge stacks of notes. If you are particularly interested in a given section or topic, we invite you to contact the individual authors via ACT-UP/Golden Gate. They may well be able to give you far greater details.

The entries are listed in alphabetical order by the author's last name. All page numbers consist of an abbreviation of the author's name plus a number specific to that particular entry. (Thus: "MCB-3,4" means the topic is covered on the third and fourth pages of my entry; "JCD-1" refers to the first page of Jesse C. Dobson's entry).

In addition to the Table of Contents there is a Subject Index. Specific ACTG protocols and committees, as well as other assorted topics, issues, and meetings, are listed.

There are four brief appendices following the main body of the report. A Protocol Index, copied from the conference book, briefly lists all ACTG trials. Next is a copy of the meeting Agenda. Last is some stuff on the Community Constituency Group (CCG).

We welcome any and all feedback that you may have about the ACTG and/or this report. Direct comments to the Treatment Issues Committee of ACT-UP/Golden Gate.

Michael C. Botkin,
ACT-UP/Golden Gate, Treatment Issues
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WHAT I DID AT THE THIRTEENTH ACTG
by Michael C. Botkin, ACT-UP/Golden Gate

OVERVIEW

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ACT-UP/DC
AMSTERDAM CONFERENCE
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OVERVIEW

I was one of the ten (or so) ACT-UP/Golden-Gaters to attend the 13th meeting of the AIDS Clinical Trials Group. The activist presence at this conference was neither big nor loud; aside from ACT-UP were about a half-dozen activists each from chapters in L.A., San Francisco, Boston, and New York, plus a couple from the newly formed ACT-Windy City (i.e. Chicago). That list is essentially a roster of the ACT-UP chapters with a sustained and/or major interest in Treatment Issues, and it is significant that Boston and SF were both attending -- like myself -- for the first time.

Most of the 1200+ people at the conference were scientists, bureaucrats, or scientist/bureaucrats. Perhaps a hundred were not: in addition to the few dozen treatment activists were another few dozen members of the Community Constituency Group (and significant overlap between the two).

I found the meetings tiresomely bureaucratic for the most part. A typical committee meeting often began with a fight for the Chair, spent most of its time revising data forms, and maybe dished a little clinical data at the very end.

The fear of budget cuts and the pending elimination of many AIDS Clinical Trials Units (ACTUs) darkened the atmosphere of the meeting. The failure of an entire class of treatments -- the L-drugs -- deepened the gloom, threatening to send a half-dozen protocols down the tubes.

COMMUNITY CONSTITUENCY GROUP

The Conference proper began on Tuesday, but there was some pre-conference action. The Community Constituency Group (CCG) held extensive meetings, which are described in detail elsewhere. In general, many activists felt that there was considerable improvement in relations between the AIDS Activist wing (predominantly anglo and HVer) and the Community Activist wing (people of color, HIV negative) of the CCG. From what I saw, it appeared that the CCG was making faster and broader distribution of protocol information a major priority, and that they were having moderate success with this agenda.

SYMPOSIUM ON SURROGATE MARKERS

I went to part of a symposium on surrogate markers also held on Monday, as an informal part of the conference. It was one of the few times I saw fairly free-wheeling scientific debate going on at any length, and appeared to have been organized in an ad-hoc fashion at the last minute. The famous Dr. Fishl presented huge swaths of data on her numerous AZT studies, which almost incidently are a vast storehouse of virology info. British researcher Tom Peto really livened things up when he posed some tough questions about what makes for good surrogate
markers. Suppose, he said, you had a marker that was a good predictor of "soft" end points (eg T-cells, OIs) but a lousy predictor of death (a rather "hard" end point)? When and how would the slow, follow-up studies that might detect this be done; and how many EVAs might die in the meantime? This was NOT a popular line of questioning among his audience; many researchers decried being tied to the search for a single "holy grail", and didn't want to have mortality established as the "gold standard" of end points.

**Virology**

I went to lots of virology stuff on all days, as it was turf that seemed otherwise uncovered. It was very technical and wildly boring for the most part, but I think it is a "growth" field in AIDS research. The Virology committee is a "support" rather than a primary part of the ACTG. It runs no trials on its own (or doesn't yet; its first ones have been proposed), and instead provides technical support (read: bloodwork) for everyone else.

Virologists were generally pissed that they were so excluded from the trials design process (a complaint they hold in common with the other low-status committees, the CCG and the Activists). What and how you measure the effects of treatments is mostly Virology; but by the time their input was solicited all the key design elements had already been set. They felt they needed and deserved more clout at the ACTUs, too. Many dished stories of stupid Principle Investigators ignoring vital demands from the studies' Virologists, resulting in ruined or uninterpretable data.

(A miscellaneous note on the Virology committee of the ACTG: most of the hot-shot researchers pioneering new technology are men; most of the data-collectors and glorified lab-techs are women).

But the clout of Virology is indeed on the rise. The detection of viral resistance to treatments -- the current cutting edge of the anti-viral industry -- is Virology's bag, and their proposed trials are all of this sort. These include CONCEPT SHEET 340 and CONCEPT SHEET 023. CS 240, presented by Bob Coombs, would be a short (16 week) comparison of HIVers (t-cells 150 to 250) randomly assigned to AZT or AZT/ddI combo. The goal would be not to compare the efficacy of the two different treatments (solo vs combo), but to do complex and extensive bloodwork to investigate differences in the development of resistance.

(I think, by the way, that this a large part of the motivation behind the controversial ACTG 175; to compare vulnerability to resistance, rather than competitively test the clinical efficacy of various nucleoside analog combos.)

CS 023, proposed by Hank Balfour, would be a retrospective, case control study of ACTG 016 and 019 studies (the big early-intervention AZT protocols). This is a clever way to re-analyze and get more mileage out of clinical studies already done. Patients from the old study will be paired with a carefully selected matched case, and differences in the development of resistance charted.

It should be noted that this was the first ACTG where "concept sheets" were allowed to be presented and discussed publically. In the past, the Executive Committee banned any dishing of protocols in the planning stages, and only allowed examination and discussion of approved protocols. This was part of why ACTG 175 was such a mess, and that mess, together with CCG and scientist pressure, motivated the relaxation of the censorship ban. There was a lot of pressure to find ways to speed up the conveyor belt, and it seemed to have some effect. Too bad that most of this accelerated research is going along very narrow lines, encouraging the growth of the already massive nucleoside analog industry.

Virology, as a committee of the ACTG, is finally getting a few
hoc-holds in the structure and gaining some prominence; but since the entire structure is in a state of retreat and shrinkage, the net effect may be somewhat muted. The scientific technology of virology is making huge advances, and if they only had something good to study with it we might get somewhere.

ASSORTED PROTOCOLS

The first ACTG team meeting I went to, at 7:15 am (!) on Tuesday was prophetic. It was a very short meeting, as the honcho quickly explained that the protocol was suspended. ACTG 180 was a pediatrics trial of B1RG 587, an "L-drug" recently showed inactive against HIV, which develops effective resistance to the drug in a matter of weeks (as predicted months ago by the triumphant Dr. Richmond on the basis of test-tube studies). The corresponding trial with adults, ACTG 168, was continuing, but only in the high-dose combo w/ AZT arms. The fate of the peds trial was uncertain. They hoped that the L-drugs might have some value as an additive, to delay the development of resistance to AZT. But other data presented at the conference seemed to make this a forlorn hope. It looked like they just wanted to deny, at least for a little while, that -- just as the cuts loom -- this whole raft of studies is doomed.

I heard more about new and/or promising protocols at the PRIMARY INFECTION COMMITTEE's full meeting on Wednesday. They post-mortem the L-drugs (and ACTGs 164, 168 and 180). There was some optimism from the scientist (Dr. Batts?) working on ACTG 187 with the drug U87201E. This is a non-nucleoside analog reverse transcriptase inhibitor with little record of toxicity. Many expect it to flunk like the L-drugs, and for many of the same reasons.

Dr. Davey had high hopes for SCD4-PE40 (Concept Sheet 361). This is a protein-synthesis inhibitor that selectively attacks cells presenting gpl20, thus selectively destroying HIV infected cells (they hope). However, it doesn't cross the blood-brain barrier and it sounds like it has the potential to be horrendously toxic; I wouldn't want to go into any phase I/II studies on that stuff.

A phase I/II on COMPOUND Q is underway, but no one had any efficacy data or even dish; they're still looking -- upward -- for a therapeutic dose. NAC is also being considered, but more as an immune modulator than as an anti-viral.

WOMEN'S ISSUES

I went to a number of events concerning WOMAN'S ISSUES: some meetings of the ACT-UP Women's Network, the team meeting for ACTG 076, and a workshop on perinatal transmission. The Network meeting, and their behavior at this ACTG in general, confirmed all of the worst rumors I'd heard about them. In addition to generic and low-toned mutterings about "those New York women" (a somewhat unfair limitation; they included Bostonians), there was a story circulating in activist and CCG circles that the AU/WW had loudly and proudly interrupted the plenary session at a recent ACTG -- alas, just before the Women of Color caucus of the CCG were scheduled to have the podium for the first time. These two groups, who logically should be close allies, repeatedly still distrust and avoid each other as a result.

In general the Network took an adversarial stance, and if they were honest I think they would acknowledge that their goal at the ACTG was to expose a fraud rather than to collaborate in improving AIDS research. There was little cooperation between them and the treatment activists at the conference; they seemed more a part of the social activist wing of AU/NN that rode down for just the final day of the conference (of which more below). They would interrupt meetings to loudly and rhetorically ask what they considered damning questions; but
since they had their facts so hopelessly wrong they usually made fools of themselves instead.

For example, a Networker interrupted a plenary address to ask why a certain study completely excluded IV drug users. Instead of shriveling up in guilt, the researchers looked puzzled. But this study is being done at John Hopkins, they said: at least half of the subjects are drug users. Undaunted, she demanded to know why this study only had 13 women. Again, polite confusion among the researchers, who insist it has far more. The Networker waves a sheaf of paper, an ACTU site report that backs her up. Ah, they answer: this study includes a non-ACTU site, which happens to be where most of the women are.

The Network seemed to favor a hit-and-run approach, a quick delivery of a verdict of Political Incorrectness, rather than any attempt at dialogue. One rushed into the PERINATAL TRANSMISSION WORKSHOP and informed the assembled researchers that they didn't care about women, only babies. The startled gynecologists tried to explain that their entire professional specialty concerned women, not babies, but their challenger didn't stay to listen.

I did, but I wasn't impressed. The Pediatrics Committee got a huge windfall of money due to fancy lobbying on Capitol Hill -- those kids with AIDS are so photogenic, so difficult to vote against. The AIDS research funds are being cut across the board, pediatrics research is blessed with an embarrassment of riches (admittedly, only after years of neglect and underfunding based on the assumption that kids with HIV were just so much dead meat). So they had to come up with a bunch of protocols to use it or lose it. A study on perinatal transmission was a clever way to spread the funds around, and covertly subsidize a trial for (pregnant) women with Pediatrics money. Ideologically this is a repugnant subsumation of "Women" as a sub-group of Pediatrics; pragmatically it constitutes the ONLY trial in the ACTG specifically for females.

Alas, they hardly seem to know anything about perinatal transmission, except to guess that actually happens as part of the birth process, rather than before or after. Well, the only theory on how to prevent HIV infection is to give massive doses of AZT, so that's what they plan to do to the moms during delivery. As far as I know, the massive AZT dose approach has NEVER succeeded, to date, in heading off HIV infection, and it sounds like a long shot to me. But no one had any other ideas, so this one flew.

There was some interesting maneuvering in the ACTG 076 TEAM MEETING, of the perinatal transmission study mentioned above. Two women from the CCG showed up and quietly but firmly demanded that early info from the Data Safety and Monitoring Board of this ACTG had to be shared with representatives of the CCG's women's group. There were murmurs of support from most of the site staff, and several spoke to endorse this demand, stating that running the trials on the local level would be impossible without the input and trust of the CCG. The study Chair, taking carefull stock of the concensus, leaned on the DSMB rep to agree to release data. He balked and squawked, and said it could taint the "blindness" of the study; he offered to provide some very vague summaries. This was sharply rejected, and the exact nature of who would release what to whom was referred to committee, but it was clear which way the wind was blowing.

ACT-UP/DC

I hung out with ACT-UP/DC for an afternoon, attending a meeting and doing lunch with a couple of them (and John James, who also attended their meeting). AU/DC is planning to produce a legislative newsletter, giving their take on Congressional maneuvering on AIDS. No one is doing this yet, and I heartily endorse their notion of
"specializing" in legislative watchdogging, the way AU/GG and a few others focus on Treatment Issues. No one else is in a position to do it as well as they do, and they sounded pretty savvy to me.

For example, we discussed the current confusion over the Quayle Commission's move into regulating drug approval, and the liberal Democrat's knee-jerk resistance to this. They were planning to talk to all of the Democrats in question, but first they were going to chat with Orin Hatch's staff, who would give them a critical over-view of the Demo's positions and a stock of tough questions to ask. (AU/DC claims that Hatch, despite his generally reactionary politics, is pretty good on AIDS issues).

We might want to consider subsidizing their work, in particular the newsletter. Perhaps the ACT-UP Network can coordinate this.

AMSTERDAM CONFERENCE

There was a meeting of activists about the AMSTERDAM CONFERENCE, mostly attended by people from the Boston and SF chapters. This was entirely concerned with promoting the "FIFTH TRACK" of alternate treatments. In the early stages of Conference planning there were excellent arrangements for activist input on alternate treatments. But when it was moved from Boston to Amsterdam that whole structure was thrown out and never really replaced. Now alternate treatment activists have to be content with promises from the new honcho, Jonathan Mann, who some trusted and others did not.

Instead of a fifth track, which seems never to have been seriously considered, there will be alternate treatment "sub-tracks" in the B (Clinical) and D (psycho-social) tracks. It's not clear how receptive the established hierarchies in these tracks will be to "alternate" anything, or how seriously they will take this proposed sub-track structure. There is also supposed to be some official encouragement of "soft" studies using less rigorous scientific technology, but again it's not clear how much this is mere placatory rhetoric as opposed to genuine openness.

Conference officials have agreed to send out letters encouraging submissions from "alternate" treatment researchers and clinicians. Certainly the official "call for abstracts" makes absolutely no mention of alternate treatments, of sub-tracks, or of "soft" studies.

The extreme reluctance of the AIDS research establishment to look beyond its current, narrow, high-tech approaches is likely to be the major focus of activism at the Amsterdam conference.

TREATMENT ACTIVIST/SOCIAL ACTIVIST SPLIT

On the last day of the conference a train load of Social Activists (SAs) came down from New York to see if they could make some waves. I attended a planning meeting for a protest of a cocktail party planned for that afternoon. I was the only Treatment Activist (TA) in the room, something the New Yorkers kept forgetting as they went rambling off on long digressions about what sell-out pigs all TAs are and how we should be punished and driven out of the movement. Some members of AU/SF, perhaps out of regional loyalty, occasionally attempted to remind the Easterners that one of that despised breed was right there in the room, but they appeared too carried away by their own eloquence to notice.

Like the Women's Network, the SAs consider the ACTG hopelessly corrupt and beyond any reasonable chance of salvage (not a difficult point to make, but somewhat overstated in this case); thus, from their perspective, the role of activists is to expose the scam. TAs who collaborate with the devious Fed and its minions are therefore at best unwitting dupes, at worst nothing less than traitors. At the time of
this ACTG, TAG had already split from the main body of AU/NY and FAS was about to. It looks to me like this separation was long overdue. The Boston and LA chapters of ACT-UP appear to integrate their TA and SA wings with less hassle than most others. ACT-UP/Golden Gate, of course, split from the SF chapter a year ago, but the two groups now seem relatively comfortable working together. It will probably be a while before the New Yorkers attain this.

The TA/SA split isn't exactly news to me, but I wasn't prepared for how bitter the rivalry can get. The two groups literally ignored each other in public, and this was no where clearer than at that cocktail party/protest. Mark Harrington and other TAs chatted over drinks with Daniel Hoth and other ACTG bigwigs and pretended that the loud protest in the lounge wasn't happening. The SA's yelled and made loud stupid toasts, and pretended they wanted to "dialogue", despite all appearances to the contrary. A few people like myself wavered in the middle, feeling uncomfortable with either joining or ignoring the protest. "I feel like a reactionary." muttered one TA (from Boston?); but he couldn't bring himself to join the radicals, either.

The New Yorkers left just before hotel security, summoned by Hoth, arrived, so there was no direct confrontation. Some say that the TA/SA split allows us endless "good cop/bad cop" combinations. I hope so; it sure wasn't an inspiring picture of solidarity.

CONCLUSION

I left that dismal cocktail party early, to catch my plane home. Despite traveling on America's "most on-time" airline, my flight left an hour late and I would have missed my connecting plane if Minneapolis weren't gummed up by a massive blizzard. In fact, my plane was already sealed for take-off, and only the heroic efforts of the hunky gate attendant got me on it. He took one look at my "ACT-UP type" jacket, said "Don't worry, we'll get you aboard, hon." and proceeded to ram the plane a few times with the boarding ramp "to get their attention." It worked; I offer it as a metaphor for activism in general.

Activists looking for a fun junket would do well to ignore ACTG meetings. They are hard paced, technical and bureaucratic events. Often the incidental schmoozing is more important than the official content, and AU/GGers meetings with federal officials, drug corporations, and other activists was just as important as the workshops and committee meetings.

In closing, I'd like to advise future ACTG attenders to bring large dop kits. When you put a half-dozen AIDS activists in a suite you end up with a truly massive arnament of pills and whatnot in the bathrooms. We could have stocked a good-sized Walgreen's between us, and I think we had more nucleoside analogs around than most ACTUs.

Overall, the ACTG seems to be evolving for the better. But this could be happening too little and too late, and the improvements might be stillborne if the system suffers too much from budget cuts. AIDS research funding, allowing for inflation, is DOWN this year, as HHS honcho Louis Sullivan actually cut back the requests made by his constituent departments! The economy is tight, it's election year, and President Bush feels that he's already given too much money to AIDS. The failure of the second generation of anti-virals, the L-drugs, doesn't alarm him at all; his administration wrote us off as dead meat a long time ago.

In the short term, activists should work to continue to improve the ACTG's processes, on choosing, designing, and carrying out studies. In the middle term we should look toward re-orienting government research towards basic science, and away from subsidizing the anti-viral industry. And we should press hard for increased research and treatment dollars all the time.
AIDS Clinical Trial Group
Sunday 12/1/91
Community Constituency Group (CCG)
11:00 A.M.-5:00 P.M.

This was the only meeting scheduled for the entire day. Meetings for researchers were not set to begin until the following day, with registration taking place on Monday at 5:00 P.M. The meeting got off to a very slow start with only 9 CCG representatives present. The first hour was basically spent just killing time, waiting for more reps to trickle in. By noontime a handful of additional reps had arrived and a sort of free for all discussion ensued. It seemed unlikely that the existing agenda, which consisted of Committee Reports, Priority Setting, and New Membership, would be addressed. Certain reps were not yet present, making it difficult for reports to be given. Consequently the discussion focused around issues of attendance and the groups tribulations over communication and fulfillment of assigned tasks. Much frustration was expressed and few conclusions were reached.

Finally at 1:00 P.M. Jesse Dobson recommended that reports from the July ACTG meeting be reviewed. A printout had been sent to all CABs (Community Advisory Boards) late in October. Each CCG rep covered her/his assigned committee (with Jesse reviewing reports written by reps who were not yet present) and made recommendations for the entire CCG to consider. The following is a highlight of some of the reports which were reviewed, anyone interested in receiving the entire report may contact Treatment Issues.

Patient Advisory Committee
The role of this committee within the ACTG is to provide input into new Data gathering Systems (Data Control). Nurses, on the front lines, involved with enrollment are the key to proper data gathering.

Immunology Committee
1) There is a critical need to increase the number of immunologists in the ACTG.
2) We need to advocate for small subset studies of Immune Based Markers within existing protocols, such as T cell response to certain antigens and neoptorin and Beta 2 Microglobulin.
3) A prioritization of who has how much access to sera is necessary. Presently virology labs usually store samples, so that the Immunology Committee doesn't have direct access to sera. Sera from ACTG 016 and 019 are not available for marker analysis.
4) More Immune Based Therapy (IBT) research needs to be done on patients in advanced stage of disease. Both improving immune status and function need be addressed.

5) Concept sheets originating out of the Immunology Committee must be regarded as a priority by the Executive Committee of the ACTG.

Pharmacology Committee
1) A Protocol Pharmacologist should be assigned to each protocol.
2) Dosing within Phase I trials should be more commonly seen in protocol design.
3) A concept sheet has been written to examine the Valproic Acid’s ability to increase the bioavailability of AZT.

Protocol Evaluation Subcommittee
This committee was originally formed by the Executive Committee. Its members were handpicked. It was expressed by various members of the CCG that the Patient Care Committee should be making the decisions which are now being generated out of the PES. It appears that timetables and rules made by the PES are in need of a mechanism which will assure that they will be enforced. Although the CCG did not seem critical of the work done by the PES, it did seem skeptical of its ability, in its present form, to impact the ACTG.

Site and Data Management
1) The Executive Committee has established a Forms Committee which will be responsible for setting up entry forms for trials.
2) At present FSTR (Frontier Science) which is the Boston based computer data base for all ACTG trial data, has only two field reps to handle all the ACTUs. This is a major problem. Data analysis is lagging unnecessarily.
3) A recommendation was made that ACTUs, through the recompetition process, be required to upgrade their computer systems to meet ACTG data needs.

As previously stated, additional reports from the Oncology, Women’s Health, Pediatrics, Virology, etc... Committees were orally presented. That information is available upon request.

At 4:00 P.M. the CCG decided to split into the various existing subcommittees: Protocol Development, Patient Education Technology Transfer, New Members, and Accrual. It was decided that Priority Setting and New Membership would be discussed
at the next day's meeting. I attended the Protocol Development Subcommittee meeting. It is the objective of this subcommittee to identify priorities for each of the existing committees, which can be translated into the creation of concept sheets and protocols. Recommendations from this committee would then be brought back to the CCG for what would then amount to a pairing down process and reprioritization. This subcommittee spent the better part of 5 hours hashing out areas of research that have been left unattended by the ACTG. CCG rep Saundra Johnson (312-271-2070) can be contacted for the list of recommended priorities arrived at by this group. This was perhaps one of the most constructive meetings I have ever attended as an AIDS Treatment Activist.

INTERNATIONAL MEETING ON SERUM MARKERS
Monday 12/2/91
Unbeknown to Brenda and I, this meeting, which was not on the agenda we received, was scheduled for 8:00 A.M. to 4:00 P.M. As we made our way to the only other scheduled meeting of the morning, the CCG at 11:00 A.M., we noticed a room filled to the brim with researchers. Although no other activists were in that meeting, we decided to ignore what appeared to be a closed meeting and join in on the fun. Since we arrived on the scene late, it is unclear just how much and what we missed.

SI vs. NSI(Non-SI) Virus
How does virus phenotype determine outcome? In a study of 52 patients, 29 men receiving AZT and 23 on placebo the following was found:
Six individuals in each group progressed to CDC defined AIDS.
In the placebo group, 4 patients with NSI strain progressed to AIDS.
In the AZT group no patients with NSI strain progressed to AIDS.

Two questions are raised from this study. Does AZT inhibit NSI conversion to an SI strain of virus?
What are the differences in genome of NSI and SI?

Dr. Charles Boucher conducted a study of 24 asymptomatic patients who did not have AZT resistance, and determined that progression can be predicted for patients on AZT dependent on phenotype of virus. 21 of the patients had a baseline CD4< 500, with a mean of 383. The study took three years, during which time 9 patients developed AIDS. The 15 nonprogressors had a mean CD4 of 329 at the conclusion of the study.
In analyzing phenotypes two different assays were employed, PBMC and MT2 cell lines. The advantage to using MT2 is that less of a variance occurs.

In the group of 24 studied there were 12 NSI patients at the outset, of which only 1 patient progressed to AIDS. All of the 4 patients who started the study with SI strain progressed to AIDS. Of the remaining 8 patients who switched from NSI to SI phenotype it was determined that 4 patients progressed to AIDS and that a median time of 72 weeks to progression was seen after the switch.

Researchers than asked what is the relationship between virulence and AZT resistance? In a two year followup looking at 18 men they determined that all patients developed a partial resistance to AZT, as evidenced by a lack of certain codons. While 6 patients progressed to AIDS and 12 remained stable, it was observed that 5 mutant strains had developed which differed from asymptomatics to PWAs. During the stage of disease at which patients showed positive for NSI, all strains were wildtype before treatment. After treatment, mutations as evidenced by codons 70, 215, and 41 appeared. When patients switched to SI it was observed that codons 215 and 41 joined to develop codons 67 and 219 which are AZT resistant. The following conclusions were drawn. Patients demonstrating NSI with an MT2 negative (for syncitium?) assay who showed medium AZT resistance did not progress to disease over the course of the study. Patients demonstrating SI with an MT2 positive assay and medium AZT resistance did progress to AIDS.

SERUM MARKERS OF IMMUNE ACTIVATION (John Fahey: Immunology Committee ACTG)

In evaluating serum markers of immune activation we are observing the following phenomenon:
1) How serum markers used in conjunction with CD4 relate to prognosis and course of disease.
2) How immune activation impairs lymphocyte function: response to antigens.
3) The role of immune activation in contributing to neoplasias: B cell lymphoma and KS.
4) How immune activation may increase HIV produciton.

At present it is known that higher rates of both neoptorin and Beta 2 are considered to be abnormal and indicative of higher risk of disease progression. It is felt that CD4 with one or the other of these markers would serve as a better marker than just CD4 alone. In a study of 540 patients it was observed that CD4<250 coorelated to a 73% probability of
achieving AIDS, CD4 250-400 was coorelated with a 31% probablity, and CD4>400 was coorelated with an 11% probablity. When each category of CD4 was coupled with neoptorin levels more stratified probablity was determinable.(???)
Mark Jacobson is examining ACTG 019 data, while Mike Greco is reviewing ACTG 016, to determine clinical outcome based on Neoptorin and Beta 2. It is known that when examining these markers in patients taking AZT, that AZT was able to reduce the increases normally seen in both markers for up to 4 months (at which time a return to baseline was observed). No reduction was observed after one year. It is suspected that these two markers do not measure the same processes, despite the fact that both are stimulated by IgG. Up until now the ACTG has been utilizing 2 labs to assess these markers.

PREDICTIVE VALUE OF 90K ANTIGEN IN HIV INFECTION
90K was formerly used as a Tumor Marker, particularly for Breast Cancer. Elevated 90K has been associated with autoimmune disease as well as both B and C Hepatitis. Its cut-off value for normal range is 11u/ml.
In a study of 329 HIV positive IVDUs, from January 1990 to October 1991, it was determined that in a population of asymptomatics with CD4>500, 60% were found to be 90K antigen positive. The marker is best coorelated with endogenous Ifn, but does show coorelation with CD4, CD4/CD8% and Beta 2. 90K can be used as a sensitive and early marker of HIV infection, and may help in the identification of people with HIV who are at high risk of disease progression.

CD4 ANALYSIS 002 DATABASE (Patients with PCP on AZT)
Margaret Fischl
In an effort to determine whether CD4<50 is predictive of survival and can be used as an endpoint in future clinical trials, Dr. Fischl reviewed data from ACTG 002. Looking at CD4>50 vs. CD4<50, CD8>250 vs. <250, Total Lymphocyte Count >400 vs <400 and Observed Lymphocyte Count >600 vs. <600: all compared at baseline, 6 months, and 12 months. It was determined that a separation could be seen in survival in all groups with exception of CD4 at baseline. In other words, there is no difference in survival between patients receiving AZT between baseline and 6 months when comparing CD4< or >50. The implications of these findings are simply that if you have patients on a minimum of 3 to 6 months of treatment than you can use CD4<50 as an endpoint. This rationale will be used for ACTG 175.
Analysis of ACTG 019 (AZT in PWA's) determined a savings in time from using 50% CD4 decline over clinical endpoint. Simply put, the former can be reached sooner than the latter and will provide earlier information on drug activity. Clearly Dr. Fischl's hope is that both CD4<50 and a 50% decline in CD4 from baseline, as seen in consecutive measurable values, will be useful in providing information on drug activity and clinical outcomes. Additionally, a percent decline may allow for crossovers which will guarantee followup information.

In general research is seeking out markers to provide data on disease activity or disease progression. Markers must be reliable in the laboratory and demonstrate as little biological variation as possible. One would hope to find markers that can be useful in evaluating the greatest variety of drugs for activity. This creates a paradoxical condition when one considers markers such as plasma viral load, cellular viral load, fixed tissue viral load, or immune response during progression of disease. Certain drugs may result in a reduction in plasma viremia as well as a reduction in CD4. It is not always clear as to which direction markers need to move in, this may be dependent on the drug as well as the stage of disease. It is not always clear as to whether various markers are necessary for varying end organs (ie.. machrophages, CD4, CNS).

VIROLOGY TECHNICAL SUBCOMMITTEE
The committee discussed the need to establish a few Referee Labs to use as examples. The intention is not to establish a standard reference lab, but rather to ensure that labs which have repeatedly come up with false negatives can be crosschecked. Relative sensitivities of PVLs are based on a 2 log difference. Limiting Dilution Titers are employed: where the last dilution that gives you a titer is the endpoint. ACTG 175 will account for one million dollars in cell dilution cultures. The committee felt that more discussion should be had around cheaper and easier ways of achieving virological endpoints. There was some concern over the ability of smaller labs to be sustained on budgets of $100,000.00 per year, having 50 patients each with 6 bloodworks per year. An overall concern was raised over the recompetition and what and whom the ACTG is willing to fund for PCR. The issue of establishing PCR QA (Quality Assurance) was also raised. The PCR Subcommittee compared and contrasted the Roche and the Gen Probe Assays (both nonicytopics): I was not able to assess whether a determination was reached in selecting one over the other. It was suggested that the Gen Probe Assay showed a higher risk of false positives due to its having no UNG.(?) Anyway, the PCR Subcommittee hailed the benefits of HIV1 Detection PCR for quantitating viral load pre and post therapy, as well as in Pediatric Research in Neonatal diagnosis.
The entire committee expressed concern over the fact that the Virology database at FSTRF is incomplete as of December 1991. Apparently there are labs that have never transmitted results since they were first tested for QA. That means no cultures since day one! The committee decided that a mandate for compliance by January 1, 1992 was to be set. January would also see lab evaluations being reviewed through the Virology Core Committee.

Finally the committee addressed the concern of specimen collection. The collection and method of storage of samples necessitates projecting what kind of tests are going to be developed and used in the future. Anyone's guess is as good as the next virologists. The following was discussed: 1) ACD and not Heparin should be used as an anticoagulant, 2) Permutations would be 2-3 or 3-5 mls., 3) Expansion based on 30 mls. of blood would be between 5x10 to the 6th to 10x10 to the 6th, 4) Volumes of Sera(???)

IMMUNOLOGY -T CELL PROLIFERATION WORKING GROUP
December 3, 1991  7:00 A.M.
Dr. Laurel Beckett, Immunologist SDAC
Preliminary Report of the Natural History of Skin test Reactivities in Symptomatic HIV-1 Patients

"Is skin test the poor man's proliferation assay?" What is the rationale for using skin tests? Well, skin tests are certainly cheaper than assays, and although they are not always accurate, skin tests are faster. Merieux's skin test, using one control and 7 antigens, to assure a 95% pick up, can be read 48 hours after administration. A positive response is based on induration exceeding 2 mmltrs. larger than the control.
Both ACTG 002 and 016 were supposed to have skin tests at baseline, 8, 24, 48, 118 weeks and 3 follow ups. In 002 10% of the patients were positive for one or more antigen, but no statistical significance was observed between responders and nonresponders. In order to determine whether the ability to develop a positive antigen response is predictive of survivability we will have to look at 016. That will involve the following:
1) Characterizing natural history by specific antigen, using baseline and followup.
2) Examining the relationship between ST (Skin Tests) and both clinical endpoints as well as other measures of immune function such as CD8, Neoptorin, etc...
3) Assessing the effects of AZT therapy on ST.
4) Assessing potential as a marker for therapeutetic efficacy.
5) See if responses of particular antigen or group of antigens have greater predictive power. The type of antigen and type of response is critical in determining whether a positive ST is based on response to therapy or not.

Dr. John Johnson (Chief of Pediatrics, Univ. of Maryland)
Technical Report of CD3 Driven Blastogenesis

Dr Johnson is attempting to develop a consensus protocol for Pediatrics. The issue being what is the mechanism by which CD3 is driving cells and how do you drive assays? Should a soluble or bound antibody be used to drive the response and which antibody should be used? Apparently the antibody traditionally used was Orthoclone, which has been discontinued. The antibodies considered as options were Olympus or Ortho OK13, a diagnostic antibody. Dr. Johnson reviewed methodology of assay preparation. According to what I was able to comprehend it appears that the simplest method would be to take a well, add antibody, let it bind and then add cells the next day. The alternative approaches involve adding other steps such as merely washing after binding, or both washing and then adding soluble antibody as well before adding cells. The other option would be to start with soluble antibody from the outset. Apparently soluble antibodies may allow one to assess both lymphocyte and monocyte responses. (A four day assay will produce 100,000 cells per well.)

Discussion of Alternative Methods for Measuring Mitogen/Antigen Responsiveness

Adhesion molecules such as CD18, CD44, and LFA could be good easy markers on cell surface. While cell surface markers can be readily used, which internal markers are functional? The nuclear proliferation antigens, P105, PCNA, K67, and P120 which are traditionally used as prognostic markers in oncology may be useful.

Overview of Proliferation Responses in Infected Patients
Dr. Fred Valentine
Since we know that a loss of cell function and proliferation occurs early on in disease, the question was raised as to whether or not AZT is beneficial in generating a proliferative response beyond just CD4. According to data from ACTG 001 (AZT in patients with KS) in which antigens for CMV, TX, PPD, SK, and Candida were introduced, a 20 to 50 fold proliferative response was seen as coorelated to a one and one half time proliferation
of CD4. Those patients who continued to show proliferative response after 6 months also seemed to fare better than those who did not.

Immunology ACTG 175 Serum Markers
December 3, 1991 Tuesday 10:15 A.M.
John Fahey, Dept. of Microbiology and Immunology UCLA
This meeting was convened to determine which immunological markers would be studied in a subset of the 2100 patients targetted for enrollment in ACTG 175. Naturally quantities of additional sera had to be identified beyond the 50-100cc drawn from the 400 patient subset already earmarked for Virology. The CBC baseline will require 15ml. plasma for virology will require 10ml., cells for virology will require 20ml., and flow cytometry of cells will require an additional 5-7ml. Sera will be collected at 2 baselines and then weeks 4, 8, 20, and then every 12 weeks.

The committee first discussed serum activation as observed through various phenotypes. It was felt that given present PCR techniques, phenotypic activation related better to clinical outcome than viral load. The following phenotypes were initially considered for observation.

CD25- function is to IL2 receptor alpha chain(which has been studied by UCLA’s Dr, Hofmann)
CD71, CD38, and HLA-DR, all of which are elevated by HIV infection and reduced by AZT
CD57- which is found to be elevated in gay men, and further elevated by HIV, but not reduced by AZT. It was felt that phenotype would not be used in the ACTG but should nevertheless be examined with respect to CD8 and CD56.
C45RO and C45RA-which show up differently in children. (both of these phenotypes were specified as being in need of having a normal adult baseline determined. Apparently the same holds true for some other phenotypes as well).

Conclusion:
HLA-DR in both CD4’s and CD8’s will be used.
CD38 in both CD4’s and CD8’s will be used.
CD25 in both CD4’s and CD8’s will be used.
B cells’ CD19 will be used.
As for serum markers to be examined within ACTG 175 the committee made the following conclusions:
1) Both Neoptorin and Beta 2 Microglobulin would be used. The former has been shown to give a better prolonged response with respect to AZT.
2) Secondary recommendation would be soluble IL2 Receptor and alfa Interferon.
3) A secondary recommendation of cytokines would be IL6 and IfnG.

For Immune Function/Proliferative Response the following was determined:
Mitogens--Both anti-CD3 and Pokeweed were chosen, while PHA and Allogeneic were rejected.
Microbial Antigens-- Streptokinase, Tetanus, and Candida were chosen, with PPD being an optional add-on and CMV being rejected because of its high variability.
Sera Required-- 15ml. fresh and 15ml. frozen.

The question arose as to whether whole blood or flowcytometry would be used. Use of whole blood with soluble antigens raises the issue of whether one will need fresh or frozen samples. With regards to frozen samples there was equal concern over the process of shipping (with care needed to be taken in assuring liquid nitrogen transports to reduce risk of temperature change) and thawing.
Two approaches to CD3 were discussed. The first FH (Fipohypase Separation) means not using the whole blood, while the second Anti-B relies upon IgE bind.

Specific Immunity
Humoral ??? To be Developed
Cellular
The committee felt that HIV cell mediated cytotoxicity (CTL-Cytotoxic Lymphocytes) should be looked at as a priority. Because of the great expense associated with this work it was suggested that this be a site specific recommendation with only 2 to 6 sites participating. What will be examined here is CD8 suppression of viral replication. 20-30ml. of blood will be necessary. Autologus B cells will be used, possibly necessitating one baseline prior to therapy: aside from establishing the B cell lines which will take one month.
IMMUNED BASED THERAPY WORKING GROUP FULL SESSION
12:00 P.M. TUESDAY DECEMBER 3, 1991

ACTG 137 is a study of active immunization of asymptomatic persons with HIV with recombinant HIV gp160 antigen. This Phase I/II study of immunogenicity and toxicity is taking place at both Stanford and NYU. The target for enrollment was 52 patients. The study is overenrolled at 65 patients and is now closed. The study examines patients with CD4>400 who are all Hepatitis B positive. Of the total enrolled, 12 patients are in a control arm receiving a Hepatitis B Vaccine. The remaining participants are receiving vaccine at doses starting at 20mg. with randomization up to 1280mg. All patients have shown lymphocyte proliferation in 5 fold microbial antigen response prior to therapy. The study purpose is to determine which dose is immunogenic.

Interim results:
46 patients have had a 3 fold proliferative response to gp120. The aggregate group data shows a slight CD4 decline; but one need bare in mind that the study is small and was not designed to look at CD4. It has been observed that patients receiving the vaccine acquire the ability to produce or stimulate response of IL2. CTL activity has been documented, after one month, in 3/4 of the 19 patients at Stanford: the enhanced cytotoxicity has been seen through both a specific production of lymphokines as well as HLA restricted cytotoxicity specific to gag gene proliferation. Merrigan stated that his group is working on RNA and DNA PCR to determine if provirals have changed.

ACTG 141-A study of Peg IL2 to determine whether immunity can be enhanced through nonspecific means and what impact on virology can be had. The study calls for continuous dosing of Peg IL2 to show a CD4 lymphocyte elevation. One million units every two week was administered to 10 patients: 5 having CD4>200 and the remaining 5 having CD4<200. with one patient starting at CD4<50. Starting in December of 1991 the group with higher CD4 has had its dosage tripled in hopes of seeing greater CD4 rises. So far one patient has developed CNS (Multifocal) disorder which was reversible.

CD8 EX-VIVO EXPANSION
This study is taking place at both Pittsburgh (ACTG 080) and Miami. The Pittsburgh site has recruited 11 patients and performed 53 infusions to date. Patients are Leukophorised at three week intervals, using bolus method in Pittsburgh, as opposed to continuous infusion in Miami. CD8 alone, without rIL2 showed a half life of 48 hours.
With rIL2 the half life was shown to be 20 hours, demonstrating that the IL2 is a major determinant in clearing peripheral blood. Preliminary results Pittsburgh: Myalgia occurred in one patient, 2 patients experienced an abatement in weight loss and diarrhea, no changes in P24 status, modest increases in CD4, and improvement in subjective quality of life.

Miami Group
Six patients received treatment, all of whom were on AZT for greater than 6 months. Resolution of Hairy Leukoplakia, swollen lymphnodes and candidiasis was observed, as well as improvement in patients with KS as determined by reduction in size and quantity of lesions. One patient, who is presently on Compassionate Use of CD8 (for KS) received a 7th infusion which was purely IL2, due to a contamination of CD8. His KS recurred until he received an 8th infusion, at which time a re-resolution of KS was observed.

Mechanisms of Action
It appears that HIV repression activity is not due to cytotoxicity of CD8 cells, but by some unidentified secretion from the cells. Activity can pass through semipermeable membrane. It remains to be determined as to whether CD8 expanded cells recognize CD4 autologous cells which have just bound to gp120. Watching for CD8’s effect on other viruses (CMV, EBV, etc..) will be of additional interest.

Applied Immunesciences Inc, the manufacturer of the process used in CD8 expansion, estimates the cost of each full run to be between $2,000.00 and $3,000.00. The company is negotiating the set-up of cell production centers, in a number of major cities, that would be able to accomodate between 100 and 500 patients a month.

IMMUNOLOGY COMMITTEE; IMMUNE BASED THERAPY CORE COMMITTEE
December 3, 1991 2:00 P.M.
At present it is felt that one of the best approaches to a Vaccine study on seropositives is rgp120.
Recombinant gp120 is the major surface protein which mediates HIV1 to CD4 receptors. It is also a major viral protein which elicits neutralizing antibodies, and has shown success in immunizing chimpanzees from infection with a homologous HIV1 challenge. After two years 2 chimps still show no evidence of infection. Large amounts of 3B antibody titers were detected after the second booster.
Outline of 3B rgp120 Vaccine Trial (sponsor- Genetech Inc.)
This is an open label, double blinded, placebo controlled study. Dosing starts at 100mg. and escalated to 300 and 600mg. The immunization schedule is weeks 0, 1, 4, 8 and 16. Patients must be HIV1 seropositive with CD4>500.

Results from the low dose showed an ability to immunize and elicit response. 3 of 3 patients showed lymphocyte proliferation, and 5 of 5 patients showed a two-fold increase in antibodies to peptides. It is yet to be determined whether a correlation will be seen with viral burden assays or CD4 counts.

Genentech Inc. is working on developing a Phase I/II protocol which they are envisioning as being randomized and double blinded, looking at patients with CD4>500, no active OIs and no prior antiretroviral therapy. The company suggested using a 50% improvement in CD4 rate of decline vs. placebo as an endpoint. (The FDA was not responsive to this idea.) At this time, it appears that the company is willing to work with community activists in designing a protocol that all involved would consider worthwhile.

Meanwhile the following information was presented to us as part of the initial concept. The study would examine patients in 3 groups. The first group would receive a monovalent vaccine, the second a bivalent vaccine, and the third a placebo. Duration of study would be one year for accrual and two years for follow-up. If an endpoint of CD4 is used (as determined by rate of decline in the slope of CD4 counts) than the study would require 900 patients to achieve a 90% power to detect a 50% reduction in the annual rate of decline. However, if the study were designed to use clinical endpoints, as determined by time to clinical events, than 2775 patients would have to be enrolled to achieve 90% power to detect a 50% reduction in the clinical event rate for one year from 3% to 1.5%. A 2% to 1% reduction would require 4200 patients.

The efficacy parameters for the study were as follows:
1) CD4 rate of decline as an endpoint (recognizably not singularly sufficient)
2) Viral burden assays.
3) Trends in clinical events.
4) Relevant quantitative and qualitative immune response.
5) Beta 2 Microglobulin and Neopterin.
6) Antibody to HIV core proteins.
7) Follow patients past completion of the study to confirm rate of decline of CD4 counts and clinical endpoints.

The following were pivotal secondary endpoints:
1) Clinical AIDS defining- CD4 decline to <200.
2) Non AIDS defining-weight loss, thrush, sinusitis, hairy leuk., fevers (ie.,soft endpoints).

Representatives from Genetech, researchers and activists began a discussion around the potential design and objective of a large PhaseI/II protocol. Though nothing was resolved, the following issues were raised:

1) Designing the protocol to compare vaccine with Neucleoside analogues to neucleoside analogs alone, as opposed to vaccine vs. placebo. It was commented that 3 studies have already shown that immunogenicity is not impaired by concommitant use of AZT. A study which might demonstrate that vaccines with AZT showed survival benefit would get the vaccines approved for that purpose.

2) The need to conduct vaccine studies in patients with CD4 between 200-500 was raised. Studying this population should allow for a smaller sample size, as more clinical endpoints could be anticipated. On the other hand we can assume that the company will be somewhat resistant to this idea because of the complexity of treatment and prophylaxis regimens that subjects would potentially be on. It was suggested that a small Phase I Immunogenicity study be done in patients with CD4 of 50-500, from which a determination could be made about which population is best suited for a Phase II study.

3) Will the community be willing to participate in a study that has a no treatment arm. The feeling was that this would very much depend on the population being studied and the sites selected. For instance, the East Coast HIV community was perceived as being far less amenable to early intervention with neucleoside analogs and would consequently be more likely to provide individuals with CD4>500 who were neucleoside analog naive and willing to risk randomization into a no treatment arm. Finding "naive" participants on the west coast would be more difficult.

It should be clarified here that Genetech made no clear commitment to conducting this larger trial through the ACTG. Design issues, site selection, and how and where a future study will take place is yet to be negotiated.

FLOW CYTOMETRY WORKING GROUP
December 3, 1991  5:30 P.M.

The working group focused its discussion on the need to establish labs for normative (normal range) data of phenotypic markers. What is sought is a national cooperative of at least 10 labs with a total of 1000 samples that would be able to enroll normal healthy individuals to perform 3 color immunoflorescence of reagents (markers). Until now only
two color immunofluorescence was used. The new process will be helpful in identifying and differentiating between antigens that overlap in subsets.

The following markers were proposed to be combined in the 3 color process:

- CD3 with CD4 and CD8
- CD3 with CD56 and CD19 (NK relation)
- 45RA with 45RO and CD4
- 38DR with CD8 and CD28 or CD11B

The objectives for establishing normal ranges and changing from 2 to 3 color immunofluorescence are:

1) To set up studies to improve precision of phenotypic markers.
2) To establish optimal CD4 monitoring schedules to assess changes in CD4 in populations on antiretrovirals in the first 16 weeks.

The concerns raised were:

1) Will the labs be able to provide ethnic and age balancing in terms of samples? (This writer is uncertain as to whether this question insinuates that various phenotypes are more prevalent amongst persons of certain races over others, and that therefore normal ranges need to be established in different populations of adults.)
2) Will the normal group which is being used as sample be high risk HIV-negative individuals?
3) Is this the sort of study that should be done through the ACTG, whether tied to a clinical trial or done as an independent project, given the recompetition process and funding limitations, and the inability of many labs to perform this process?
4) Does the 2 color process serve us sufficiently well, at this point, to warrant not considering changing to 3 color?
5) What should be done about establishing normal ranges for Pediatrics?

Conclusions:

This proposal was removed and the decision was reached that a concept sheet would not be presented to the Executive committee. Individuals were encouraged to work on this as a non ACTG project.

HUMORAL IMMUNITY WORKING GROUP
Wednesday December 4, 1991 7:00 A.M.

The working group was examining IVAP (In vitro Antibody Production)

There are some technical problems with IVAP’s specificity, including:

1) Serum antibody carryover results in false positives.
2) Physiological immaturity of B cells in newborns results in false negatives.
3) B cells' possible impairment by HIV results in false negatives.
It was felt that a number of different processes which were used for developing this assay resulted in varying degrees of sacrificing sensitivity, by initially washing cells out for 12 to 24 hours, in order to achieve specificity (i.e., reduce likelihood of false positives). Dr. Savita Pahwa felt that this was resolved by the final assay which was used: culture the cells washed out for one hour, remove supernatent, wash cells again, add fresh medium, then at both 24 hour and 7 days you collect supernatent and measure antibody responses.

HIV SPECIFIC IgA ANTIBODY PRODUCTION IN INFANTS
Dr. William Borkowsky
Study 1
Looking at infants born to positive mothers the following was determined. At 2, 4 and 6 months the infants who were infected with HIV showed a mean IgA antibody production of 2.7, 20.0 and 34.0.
(It is important to note that it has been observed that at terminal stages of disease children who were IgA antibody positive became negative; i.e., no longer produced IgA antibodies) At 2, 4 and 6 months infants who were uninfected showed a mean IgA antibody production of 2.4, 1.9 and 1.2.

ONTOGENY OF IVAP AND INFLUENCE OF ANTIRETROVIRAL THERAPY
Study 2
Looking at HIV positive infants' IgA antibody production when patients are started on AZT therapy after six months of age, the following was observed. At baseline a mean antibody titer of of 31.2 was recorded. All titers at months 0-2, 2-6, 6-12, 12-18, and 18-24, showed a marked decrease in mean (3.9, 11.5, 13.2, 7.4, and 18.9). The obvious conclusion is that AZT when introduced to infants after the age of six months results in a reduction of IgA antibody production.
Looking at both CD4 and P24 one will see similar trends, as seen in antibody production, in this population.
Study 3
Looking at HIV positive infants' IgA antibody production when started on AZT at less than 6 months of age, the opposite conclusion of that reached above can be found. At baseline a mean antibody titer of 3.8 was recorded. All titers at months 0-2, 2-6, 6-12, 12-18, and 18-24, showed a marked increase in mean (10.4, 20.9, 25.7, 38.1, and 46.4). Obviously, introducing AZT when the immune system is less competent produces a difference in antibody production, or at very least does not result in a decrease of antibody production.

-16-
HIV SPECIFIC B CELL RESPONSES IN INFANTS OF HIV INFECTED MOTHERS

Using baseline blood from umbilical cords it was determined that circulating B cells from 85-90% of all infants born to a population of IDU HIV positive women exhibit IVAP showing specificity for gp160. This raises the question of how infected vs. uninfected children will compare as to the duration of IVAP? It has been observed that 100% of infected children over six months of age will show positive for IVAP. It has also been noted that there is no difference, when using PBL 10 to the 6th, in absolute number of B cells between 3 week olds who are HIV+ or HIV-.

PLENARY SESSION
Wednesday December 4, 1991 8:30 A.M.
Dr. Ron Desrosiers (New England Regional Primate Res. Center)
Use of SIV/Monkey Model to study AIDS Pathogenesis

Based on genetic sequence analysis 4 groups of primate lentiviruses are known that share biologic and genetic properties including a tropism for CD4 baring lymphocytes and macrophages, longterm persistent infection of the host and a similar genomic organization. These lentiviruses share auxiliary genes not found in other retroviruses. TAT, REV, NEF, VIF, VPX, VPR, and VPU. These genes are well conserved within a group and in some cases among all 4 lentivirus groups. The conservation argues for an important role of the genes in the virus life-cycle. Four of the 7 are uniformly present in all 4 primate lentivirus groups: TAT, NEF, REV, and VIF. (VPX is conjectured to possibly be a duplicated VPR) These auxiliary genes are classified as either essential or nonessentials. TAT and REV are essential genes because their deletion results in little or no viral replication. NEF, VPR, VPX, and VPU are considered nonessential genes because their deletion does not abrogate the ability of the virus to replicate. VIF falls somewhere in the middle, though generally considered nonessential. At this point it is felt that the understanding of all of these genes is yet rudimentary.

Studies conducted in DR. D's lab used an infectious pathogenic molecular clone of SIV MAC 239. Virus derived from this clone result in death in 40% of infected monkeys. The remaining 60% develop a protracted illness very much like that of HIV. The complete nucleotide sequence of this pathogenic clone is known, making it a system ideal for manipulation and making it easier to assess the functional role and importance of the nonessential genes. The genome organization within this clone's 10,279 base pair is like...
other members of the SIV MAC HIV2 class of virus. Genetic backgorund is VPX, VPR, and VIF and it has an in-frame stop code on it.

NEF Gene (Negative Factor)
NEF is found in all 4 groups of lentiviruses. Animal experiments were conducted using recovered virus. The importance of this research lies in the the ability to determine whether or not nonessential genes should be more closely examined for their role in pathogenesis. The conclusions seemed quite clear. The NEF gene appears to upregulate viral expression in the weeks directly after infection. 18 monkeys were examined after exposure to three virus types: NEF-Stop, NEF-Open, and NEF-Deletion. All animals became infected, but while 7 deaths occurred in the 12 animals in the Stop and Open groups, after two years none of the 6 monkeys exposed to NEF-Deletion have died. Furthermore, they have all maintained normal CD4 lymphocytes, and demonstrate no lymphadenopathy, or weight loss. After one year all 6 showed a continued strong antibody response. It was also necessary to use up to one million PBMC to recover virus in this group, whereas 20,000-100,000 sufficed for the other 12 monkeys. It is hoped that these results will encourage research into NEF as an area for antiviral drug development as well as a strategy for making live attenuated vaccine for experimental testing. It is hypothesized that a given gene may be responsible for the ability to spread the virus within the population or determine sites which conduct the virus from one individual to another. That can not be determined given the assay presently being used. Research into the other nonessential genes is ongoing, using other lentiviruses as well.

HIV SPECIFIC CYTOTOXIC T-CELLS AS HOST DEFENSE IN IMMUNE RESPONSE TO VIRAL INFECTION
Dr. Bruce Walker (Assistant Prof. of Medicine, Harvard)
In examining viremia we see high levels shortly after sero-conversion, with a tapering off during the asymptomatic stages of disease and than sharp increases during later stages of symptomatic disease. This tends to indicate that at an intital, acute, stage of disease a host immunity functions in a critical method. Cytotoxic T Lymphocytes' (CTL) activity have been observed in subjects infected with influenza and CMV. Prospective studies have shown that CTL is present and critical to recovery. There are two types of CTL and they are characterized by their specific restrictive patterns. CTLs of the CD8 phenotype are generally restricted by Class I MHC molecules recognizing processed viral proteins synthesized within a cell and presented to cell surface as a binary complex with a Class I molecule. Class II restricted CTL recognizes exogenously processed proteins in conjunction with a Class II molecule.
Components of CTL
1) Need Target Cells expressing HLA Antigens
2) Need Method of viral antigen expression on target cells
3) Need effector cells-killer cells

In this case Dr. Walker's group used B-cells which they infected with recombinant vaccinia HIV1.

CTL was subsequently identified in fresh lymphocytes, as well as in vitro stimulation.

CTL was also achieved in HIV negatives by repeated stimulation in vitro of HIV antigen. (To date only Class I mediated CTL response has been generated) In animal models it is suggested that CTL recognition expresses genetic cell mutation to escape CTL. Minor changes in amino acids may lead to a loss of or complete nonrecognition.

A review of ACTG 080, autologous reinfusion of NEF 10x11th specific CTL clone, came earlier in this report.

CTL can produce protective immunity or immunopathology. The latter has been observed in a mouse model examining CTL and encephalitis. Outcome seems to be effected by a variety of variables including virus strain, virus, and where CTL is placed (peripheral blood or central nervous system). Two references may be of interest in researching this subject: C. Waller et al. (HIV1 specific CTL, are they protective) Science 86, 234:1563, and Sethi et al., Nature 335:178 (CTL and AIDS Dementia Complex).

IMMUNOLOGY SYMPOSIUM
WEDNESDAY DECEMBER 4, 1991- 11:00 A.M.

This symposium covered Host Response in HIV Infection. Data was presented by Beckton Dickinson Pharmaceuticals on phenotypic markers and activation. I will provide only bullet points from this presentation, since this should be covered in more depth by other individuals attending the symposium.

1) Natural Killer (NK) CD8 is believed to be more closely associated with CD8 population seen in normals.
2) CD8 is a dynamic compartment which can lose or gain activation markers during the course of disease progression (T8 often upregulates).
3) CD57 is a carbohydrate antigen expressed on both NK and T-cells. It is a marker antigen in early HIV infection and in seronegatives that are in a high risk group but have not yet expressed HIV1.
4) Early marker of CD38 on CD8 may be a marker of rapid progression of disease. Looking at absolute CD4 one is not able to draw that same conclusion.

Additional data was presented on a Phase I study at University of Miami on CD8 expansion in recombinant IL2 as well as data from Dr. Alan Landay (Chicago) on CD8 phenotype function in HIV1 Infection. I will rely on others to report on this segment.

NK & T-CELL CYTOTOXICITY WORKING GROUP
Wednesday December 4, 1991, 1:00 P.M.
Dr. Celsa Spina (UC San Diego)
In an effort to Develop cytotoxicity assays and pave the way for consensus in methodology, a questionnaire was sent out to 17 sites, of which 6 responded. These six are the leaders in establishing methodology and applying it to research questions. What is going on now within the development of cytotoxic T cell function within HIV? Where can it be appropriately applied in the context of the ACTG, which has the directive of looking for the most efficient modes of therapy for HIV? It is important to note that little or no funding is coming directly through the ACTG to do this kind of research. Fortunately there are people who are involved in the ACTG who are willing to do this work outside the ACTG. Money is coming out of Vaccine Development programs, where one can assume that the development of CTL function will be important in learning about the pathogenesis of the disease. The most common responses amongst the six sites were the following:
1) The autologous B lymphoblastoid cell lines were the target cell system most often used.
2) gag, pol, and env were the most common HIV target antigens used. Within env, the 3B strain was most commonly used, with RF and MN being of consequence as well.
3) Vaccinia vector expression was used to express the antigen. More will be reported on this later in this section. Vaccinia Vector expression is lytic (kills the cells) which means that there is a fairly narrow window in which you can use the cells as the target. With other vectors (murine or pox viruses) although they get in the cell and can produce the antigen they do not lyse the cell or reinfect other cells. There are differences and times when one would be used over another.
4) Fresh PBL is most commonly used for effector cells. PHA activated or anti CD3 activated PBLs expanded without precursor cells were also noted by the sites that responded to the questionnaire. Other preferred effectors were: depleting for NK cell
phenotypes or enriching for CD8 cell phenotypes by depleting CD4 cells. Clones (CD4 or CD8) are mostly used to define epitopes of recognition.

5) Assay conditions most commonly seen are: 10X4th cells/well, 3 to 4 replicate wells, U bottom microplate, length of incubation being 6 hours for bulk cultures and 4 hours for clones, E:T ratios for adults being 50:1 down to 10:1, and for Peds 100:1. To determine whether or not the activity is specific for MHC recognition that is restricted to the CD3 positive CD8 receptor cells, some people are comparing with anti-CD3 or Anti-T-cell receptor, to avoid picking up non CTL effector cells.

6) Assay variability for quality control is an area that will need to be improved upon, particularly if more sites are going to be included in CTL function analysis.

What are the major questions in this area?
1) Does the subject have cytotoxicity to antigens before and after therapy, and what are the changes from before to after therapy?
2) What does it mean if the subject has CTL activity, and what does it mean at varying stages of disease? How will CTL activity at various stages of disease effect the kind of recommendations one would make to a patient about being on various therapies?

Where do you want to be doing CTL function analysis?
1) Vaccine Therapy 2) Immune Based Therapy (IBT) 3) Antiviral Therapy, where viral load is being suppressed (do CTL baselines and followup to determine at which point in disease progression antiviral therapy is no longer sufficient or IBT is needed to restore immune function).

Aside: Much discussion ensued over the possibility of getting B cell baselines on patients that are backlogged and awaiting enrollment in clinical trials. It was felt that this would be invaluable data for CTL research.***

VECTOR EXPRESSION SYSTEMS
Kent Weinhold PhD. (Duke)
Vaccinia (POX) Vectors and Retroviral Vectors
The AIDS Vaccine Evaluation Group approached Weinhold's group about developing a strategy to measure CTL activity which might be elicited in HIV negatives receiving these vaccines. Given an uncertainty over whether or not the strategy would elicit CTL, it became necessary to develop a strategy that would amplify (in vitro stimulation). In restimulation setting (which does not assure great applicability for direct measure) the following was found. Research focused on a population of seropositives in early disease who had very little detectable CTL activity and asked what can be done in vitro to amplify their CTL. Take PBMC from patient. and prep with Fipohypase, take a portion of these cells and acutely infect with POX virus vectors (VP16 and VSC8) for one and a half hours, wash them, recombine with remaining PBMC at a 10 to 1 ratio, then incubate for 7 to 10 days without IL2 (to avoid LAK activity). The vector used here was AVIVAC Vaccine which is in Phase I testing in France at this time. The results showed that this vector was of great utility as a CTL stimulator/activator, even without the virus or viral replication; but had very little value as a CTL target.

Aside: I have repeatedly reviewed my notes from this section and can not conclude much more than the above. This material was very difficult for me to comprehend. I will do my best to attempt to uncover the mysteries of merely speaking the language necessary for understanding this material.

Retroviral Vectors
Their promise is in the ultimate goal of the companies of fibroblasting and than transducing and giving back to the patient. (At the FDA now) When I can figure out what this means I'll let you know.

PROTOCOL IMMUNOLOGISTS WORKING GROUP
Wednesday, December 4, 1991; 2:30P.M.
ACTG 175. Chip Schooley is the Protocol Immunologist for this trial. It is anticipated that at very least, John Fahey, Carole Beck, Celsa Spina, and Kent Weinhold will have immunology protocols to nest into the study.

ACTG 182. This is a Pediatrics Trial which one of the immunologists was made aware of during the course of this conference. When asked to participate in this trial (merely by chance through a friend) it became evident to her that she had been brought into the process far too late and that it was impossible at this point for additional blood draws to be taken for immunologic study. Nevertheless the study will have an immunologist, and plasma from a subset determination will be examined.
The above experience once again highlighted, to all the immunologists, the need to be more involved in the overall process at the ACTGs. In terms of advocacy it was felt that immunologists should let SDAC know of all studies, and from amongst all nested studies, which are to be considered a priority for data analysis. Additionally it was felt the Immunology Committee should create Protocol Working Groups to generate new concept sheets. This was agreed upon. With regards to protocols generated outside the Immunology Committee it was pointed out that one should not be naive in thinking that early involvement in a concept sheet means that the principal investigator has not already written a protocol. Input does not assure that change will occur. In some cases a protocol may already be up and running and the PI is simply trying to turn her/his trial into an ACTG trial.

ACTG 181. There is a need to to some extended phenotyping.

The group discussed the need for every site to specify someone to handle shipping and storage for immunologists' specimens. Each site will have to develop its own plan for getting the specimens to a local repository (a central repository is planned for 1994). This will not be necessary for sites that do have a virologist, but many obviously don't.

In terms of improving communication within protocol teams, it was stressed that each Protocol Chair must include protocol immunologists in E-mail and on conference calls. As usual, most of the immunologists stated that they knew little or nothing of the protocols to which they had been assigned both before and after they were in the working. Though clearly not all protocols will be of use or interest to the Immunology Committee, a mechanism has to be established and implemented to assure that protocols that are of importance are not skipped over. This is very much dependent upon the Protocol Chair's ability to involve all parties concerned.

Aside: Quote of the day: Fred Valentine.
"We all like to gather nice new data, without a sample for power, but nailing it down is where it's at."

HYPERICIN STUDY; ACTG 150
6:30 P.M. December 4, 1991
This study is taking place in NYC, Boston, and Minnesota, and has a total patient target of 32. It is a Phase I dose escalating study of synthetic Hypericin in patients with less than 300 CD4.

The first, of 4 dosages each doubling the last, dosage is .25mg/kg. (administered IV in a benzol alcohol solution). At week 1 in the first five patients at NYU the pharmacokinetic results were: distribution half life of 2 hours, elimination half life of 24 hours, peak concentration of 4.3mg at one hour, no detectable levels in CSF. Volume distribution was found to be 4 hours, AUC 27mg, and clearance was 6ml. At week 5, with three patients, similar data to that of week one was determined.

Additional Information
1) Troph level is 180 grams, which is 1/10 the expected antiviral level.
2) No changes were seen in liver chemistry, CBC, and Hematologic.
3) The following uniform symptoms were noted: warmth, tingling in the face and hands (perhaps related to exposure to light).
4) One patient left the trial because of preexisting skin rash which became more severe.
5) One male patient experienced a resolution of anal warts.

This last observation is of importance, since there is at present no simple, painless, cost effective treatment for HPV; which untreated in the presence of HIV is likely to progress to neoplasia. A second patient in the study has cervical displasia which should be carefully watched. This writer has contacted Treatment activists from Boston, as well as researchers involved at that site, and asked that the patients HPV be cultured to determine which strains were present. The literature has previously documented the association between HPV16 and 18 and progression to neoplasia. At this time I have been told that it appears that more strains than not are linked to progression and that therefore culturing may not be of utility in this case. Nevertheless, the appropriate individuals have been contacted to at least assure that additional patients accrued into the trial be screened for HPV, so that Hypericin can be examined for efficacy against that particular virus.

Dr. Berger, announced his resignation citing reasons previously stated in the prior meeting of the Neuro. Comm Core meeting. Dr. David Clifford will be new chair. The vice chair will be from the existing committee. There was a recapitulation of the core comm. discussions. The concept sheet for CMV polyradiculopathy (polyradiculomyelopathy) was described with announcement of its passage through committee. Trail # 140 (AZT v/s DDI for AIDS Dementia Complex) stoppage due to a lack of accrual followed in discussion. This lead to discussion of trial # 162. #162 tests AZT and Nimodipine concurrently for ADC. FDA has in vitro data which suggests cross reaction between the two drugs.

The Pediatric Neurology Subcomm., Dr. Mark Mintz presented. First, Neurological complications differ in a developing person from adults. Dr. Mintz seemed confident that there would be good communication between the ped committees. Dr. Mintz discussed neuropsychological endpoints, the relevancy of assessment tools, a problem with poorly reproducible data, and mention of drug approval dispute these problems. A Neuropsychological battery is being developed to test neuropsychological endpoints in populations that do not speak English. There is question of the existing test being too complicated. Dr. Mintz made mention of the neuropsych endpoints but did not further discussion in that area. # 188 (Neurodevelopmental and Neurological study in HIV-1 infants and children) was stated as an example of a need for revised assessment tools the psychoneurological exam came without instructions. #043 was briefly mentioned because it used the terms normal and abnormal without any degree of gradient (personally, as mental health care provider this bothers me)

Another area of discussion revolved around a mention of behavior changes w/ AZT, but the discussion did not lead to anything conclusive to note.

12-3-91- The Peripheral Neuropathy symposium was delayed due to a late flight of the researcher from NYC. The Symposium occurred later in the evening however, I missed the announcement and attended the CAB networking meeting. Shortly, the symposium reviewed the most promising treatment to research for a variety of neuropathies that exist due to HIV infection, drug related side affects, and nutritional related HIV neuropathy. Nerve Growth Factor (NGF).

###162 Investigators meeting canceled: trial on hold.
###142 Investigators meeting canceled: trial stopped due to lack of accrual.

CAB Networking Meeting 7:00 12-3-91

Lynda Dee and Kevin Fong facilitated the meeting. Lynda and Kevin are the contacts for CAB members to the CCG respective to a CAB members chosen area of interest. This evolved from the idea from CABS to keep in close contact to CCG members that represent the committees of ACTG.
A sign up sheet was passed around and individuals chose an area of the ACTG to follow with CCG reps. This is also done at each CAB site.

Concept Sheets (CS): CSs are to be obtained from local ACTGs. Access to Concept Sheets is difficult for CAB members as well as between committees of the ACTGs. Access to concept sheets before the sheets go through the executive committee is even more difficult (eg #175).

The remainder of this meeting was spent venting frustrations of some CABs.

Kevin and Lynda went over the lemons of the CCG reps to the CABs:

The CCG reps are responsible to be available to CAB members for updating and input into the committees.

CAB members should be able to obtain protocols and concept sheets at the ACTUs. This would eliminate complications of the administrations office workers. If there is a problem from that point or a problem accessing a CCG rep, then Lynda or Kevin should be contacted.

Application to the CCG was discussed and disseminated. Contact Victor Rivera.

The rain stopped. Its cold. 12-4-91

8:30-10:00, Plenary Session. This is covered in several others reports.

10:15-12:15, #175 Investigators. This trial of large resource is an opportunity for many nested studies. For Neurology studies are in the concept draft phase to nest studies for peripheral neuropathies asso.w/ drug toxicity, HIV related cognitive impairment/ADC, HIV myopathy (myopathies are muscular conditions), and psychological changes. Everyone in the world wants to nest studies into this giant. Studies of interest involve serum markers, virology. On 1-5-92, an investigators conference call is scheduled to review concepts. This trial will begin enrolling in 1-92 at most UCTUs.

4:00-5:00- Other Viruses Working Group. I was hoping that this would be an appropriate place to hear of PML studies. Currently, there is no cure for PML, no animal model to use to test therapies, and no therapies to test. Human Papa. Viruses and there incidence outside of HIV were of lengthy discussion, many, there are very many, most treatable. Women have a higher incidence in general. There was no data relating directly to HIV.
Meeting with Larry Corey (M.D. Exec. Comm. Chair), Dan Hoth M.D. (Dir. Div. AIDS, NIAID), David Clifford (Neuro. Comm. Exec Chair), Derek Link (TAG), Matt Chappell (ACTUP, GG, NWG)

Meeting occurred following a demonstration in the beautiful Ashby Lounge during the cocktail party celebrating ACTG success. Noise made listening a chore. The purpose of this meeting was to facilitate discussion to stimulate better involvement of the Neuro Comm. in the ACTG process and suggest a means to increase visibility the importance. The Neuro comm. has yet to run a successful trial for treatments of Neurological Disorders associated with HIV.

I feel this meeting successfully facilitated a necessary discussion to begin to move the NC effort in an effective direction to develop treatments for Neurological Disorders asso. w/ HIV disease.

1) Trials: The need exists for further evaluation of scientific challenges proposed by trial effort. A short term trial design needs development because, many of the complications occur in multiply challenged populations. Strategies for reliable data collection for the incidence of ADC also need prompt development.

Trials do not seem to be interesting to subjects nor to other areas of research though there is significant overlapping. A vehicle to effectively nest trials into Primary infection as n opportunistic infection studies. The most effective solution coming from discussion is to have o a member of the neuro comm. on the primary infection comm and opp. infect. comm. and visa versa. Input into PI/OI protocol development is vital. Involvement in protocol development would give a possibility to assess drug interaction for possible side affects as well as give a vehicle to nest neuro study arms.

Long term use of antiviral therapies that cause peripheral neuropathies will be one area of increasing importance.

Structurally, the neuro comm meeting are usually consecutive making involvement in other committees difficult. Spacing the NC meetings to occur over the span of a few days may increase interest in this area.

Funding: The former chair Dr. Joseph Berger resigned partially because his site did not fund a neurologist. Dr. Hoth stated that with recompetition there would be better ability to maneuver "critical mass" around which may help with communication b/w ACTG comm.s to increase support for neuro trials. Hoth also recognized the size of the NCs frustrations. Hoth highly recommends a meeting with
Dr. Lou Barker, Dir. Treatment Research Div. of AIDS, NIAID. Derek will draft a letter requesting the meeting to further discussion with Dr. Hoths recommendation. This meeting could have a very strong impact on the ability to 'fix' the NC. The ACTG is not the only situation with the capacity to do this form of research, the NINDS & NIMH are also doing research under grant. Currently we are attempting to facilitate a better outreach capacity from these institutions to the ACTG efforts.

12-5-91......CCG........

This was the final meeting of the ACTG. Committee reps gave there reportbacks. Reports are published shortly after the ACTG. A CAB member is able to obtain them at their ACTU. I understand that this CCG meeting was very productive and that the CCG has worked its way through tedious discussion of process. Each member gave a 15 minute evaluation of its comm. including discussion. over.................................................................
ACTG REPORTBACK

Saturday, 11-30-91. Matt Sharp and I flew into Dulles Airport and road w/ Pierre Ludington to the remodeling Washington Hilton. The rain began. After a short rest, I checked out Dupont Circle and searched for possible cuisine.

Sunday, 12-1-91. CCG meeting. I feel that most reports of this meeting are accurate. I also feel that this group managed to get a necessary process/focus discussion which turned from a bitching session into a productive meeting. A few members were not present. The group proceeded in giving committee reports. The other members did a good job covering this therefor, I won't be redundant. It's still raining.

Monday, 12-2-91. CCG meeting continued. I found this to be tedious. Tedious is good. There was discussion of the process of accessing concept sheets and protocols throughout the development. It was decided that the proper place to obtain concept sheets and protocols is through local C.A.B.s. The executive committee will be distributing a letter to all ACTUs concerning the process. Kevin Fong and Lynda Dee are liaisons for CABs to the CCG. Kevin is the west coast liaison and is also a member of the UCSF CAB. Membership issues were also discussed. What are the responsibilities of CCG reps to the respective committees of the ACTGs, CABs and to the CCG? Terms of membership were reviewed. Many members are coming off committee therefor, applications were circulated to submit for membership. The term is currently 2 years. Currently, a member needs to be present at all CCG meetings & conference calls, and a member needs to submit written reportbacks to the CCG from the respective committees. Oh, a letter concerning membership was first circulated to the group for discussion. Discussion of responsibility to the CCG lead to a discussion of the tactical focus of each representative to its committee. In discussion, the structural/communicative problems of the ACTG became a consistent complication for most committee reps. As stated by most people; the ACTG is dominated by THE GANG OF 5 (members of the Primary Infection committee) This may change possibly with the election of the new chair of ACTGs. (HOPE SO) There is a great effort put forth by most members of the CCG and most members seemed pleased with the direction and function of the CCG, which apparently has begun to function at the capacity which was intended. Again, I won't be redundant in covering each committee because other attendees of this meeting did so already.

12-3-91 Neurology Day Rain
7:00 a.m. ACTG 184 A pharmacokinetic study of L-697,661 Alone and in combination w/ AZT. This drug is a non-nucleoside pyridinone compound
which inhibits the HIV-1 reverse transcriptase through direct binding with the essential enzyme. It was not found to be effective in vitro against HIV-2. The trial was designed to show effectiveness in combination w/ AZT. There was no cross reaction found however the trial was stopped due to raising p24 levels as well as other side affects; headaches, fever diarrhea, sepsis skin rash, all subjects (10) fell from baseline (CD4).

8:30 - 10:00 Plenary Session: reported on by other members

12:00 Neurology Core Committee
First there was no problem in attending. I understand that some committees do not allow others to attend unless there is an invitation.
The Neuro comm. is failing in its ACTG effort. There has never been a single successful trial by this comm. There are very few sites which fund a Neurologist, including the site for the resigning chair Dr. Joseph Berger. This was one of the reasons for his resignation. The neuro committee lacks leadership as well as attention by the other committees, especially the PIC. Dr. David Clifford, Washington Univ., St Louis, Mo., will be new chair. The vice chair will be nominated from within the committee only.

C.S.346 passed through committee constructive criticism. This is an open label trial of Gancyclovir w/ High dose Intravenous Immunoglobulin for treatment of CMV polyradiculopathy.

The number of neuro complication incidence linked too CMV is growing (no figure given). These include encephalitis, myelitis, and neuropathies. CMV polyradiculopathy (polyradiculomylopathy) presents acute/subacute lower extremely paresis accompanied by sphincter dysfunction. This onsets in advanced HIV and has been on the increase. Life expectancy is typically 8 weeks post diagnosis.
The treatment regimen proposed Gancyclovir 5mg/kg intravenous q12 hours for 14 days. Then 6 mg/kg/q maintenance therapy (5 days per week) for 24 weeks. Intravenous IgG 500mg/kg every other day for 10 doses. then 500 mg/kg biweekly for 8 doses. Antiviral therapy managed as in other Gancyclovir trials (copies of the c.s. are available)

175: Neurological nested studies concepts discussed but, not in great detail. Prior to the next 175 conference call (1/5/91) there will concepts for peripheral neuropathies, HIV- related Dementia and cognitive impairments, HIV related myopathies, and psychological changes. I have not seen any of the written concepts.

140. AZT (1000 mg) v/s DDI (250 or 375mg qd) for ADC. Study closed due to a lack of accrual, 3/80. Salvage of this trial involved a combo arm idea but in general, the consensus of the group was that it did not answer the question that are you better off on the DDI arm if you fail on AZT? Design of neuro trials is often complicated and may involve procedures which are not too pleasant e.g. a lumbar puncture to obtain Cerebral spinal
fluid samples. Generating interest is one area of accrual complication (it may be difficult to get to a trial or to adhere to a treatment regimen)
ADC used to be a common presenting illness, the current status of its occurrence is with other OIs in late stages of illness. The neuro comm.
needs to develop trials which answer significant treatment information in a short period of time.
162 ... Randomized Double-blinded Placebo controlled trial of Nimodipine for ADC as concurrent therapy w/ AZT. This trial is on hold due to FDA data indicating a cross reaction b/w the 2 drugs. Nimodipine is a drug which has great ability to cross the blood brain barrier, and is currently used in hemmoraging within the brain. It protects nerve cells from demyeliation. Please contact me if you have information @ the interaction b/w AZT and Nimodipine......
This lead into a discussion about the problems of the NC.Again the idea of short range studies in late stages of infection appeared. (short range= less that one year). The committee feels frustrated and recognizes that input into the protocol development process to indicate possible cross reaction, CNS/PNS complications(e.g.neuropathies), and to nest studies into PI/OI trials is essential. Long term use of antiviral therapy w/ neuropathies as a side affect will become increasingly more important in the near future.
11/7/91  Meeting Reports

1. Nat. Institute Of Neurological Disease & Stroke. (NIH)

2. Nat. Institute of Mental Health. (ADAMHA)

I arrived to a chilly NYC and caught a Carry bus to Madison Square Garden. Derek and I met on St. Marks for lame vegetarian Cuisine and tried to sleep.

We departed around 4:00 a.m. (1:00 West Coast time) and drove through pre-dawn Manhattan isl. with Anna Blume in a 4-wheel drive Jeep Cherokee (?) to the Jersey Turn-Pike. We stopped at every other Roy Rodgers for carnage based breakfast food and Maxwell House coffee in Styrofoam cups.

We arrived in Bethesda, Maryland, shortly before the scheduled meeting time and parked in a police parking zone because there were on available spots in the visitor lot, a fact which, consequently, promoted the use of 4-wheel drive to cross a small patch of government lawn.

( Background )

1 think some background information would be good before reporting in the NINDS / NIMH meetings.

in Oct. 91, AUNY T&D's Derek Link wrote to the ACTG Neurological Chair, Dr. Joseph Berger, raising the issues of the failing Neuro. Comm. efforts in the ACTG. Mainly, there has never been a successful Neuro. treatment trial to date. Factors for this may vary from a lack of interest/attractiveness of (or as the gov. often states "sexy") trials, to a lack of committee leadership which would be able to bargain for appropriate funds to be allocated with in the ACTG system. HIV/Neuro. complications will be/ are an important area for attention respective to "plague" increase.

Long term use of antiviral therapies which commonly cause peripheral neuropathies may further this importance not to mention immunologic disregulation which effects neurological function related to cytokine and macrophage involvement (and needs much research). Gee, not to mention CNS and PNS complications, AIDS Dementia Complex/ cognitive impairment, varied encephalitic complications, neurosyphilis, Progressive Multifocal Leukoencephalopathy (PML), other Primary infection/ Opportunistic infection related complications.

Dereks' well written letter offered several suggestions to the Neuro. comm. chair.

1) The executive comm. needs to require that the Primary Infection Committee nest neurological studies into Primary Infection trials. HIV/ AIDS neurological disease is generally part of HIV Primary Infection. The Primary Infection protocol development process should be able to include members of other committees, including the Neurological Committee.

2) a simplified Neuro-assessment which may be performed by study site clinicians needs development. Current assessments are said to be extremely
complicated. Neuro and Psychological assessments should be developed for non-educated and non-English speaking populations.

3) Guidelines for a standard of neurological care for HIV infected individuals needs prompt development and dissemination. Clinical research is important insofar as it impacts clinical care, HIV infected people and Physicians treating HIV infected people NEED neurological TREATMENT & monitoring. (The CPCRA's observational data base may be another useful tool).

4) The Neurological Committee mission statement needs to reflect the above stated points. Currently, the mission is to run trials for HIV related disease of the CNS and PNS (Central Nervous System/ Peripheral Nervous System) and Opportunistic Infection's The importance in the change including the above stated suggestions would be to place responsibility on the Primary Infection Committee & Opportunistic Infection Committee in conducting trials which gather necessary neurological data useful for successful trials.

Since the Neurological Committee appears to fall, other means to conduct HIV-Neurological research need to be sought. The NINDS and NIMH are likely to be such a vehicle to absorb these responsibilities of research and treatment oriented trials.

On 10-10-91, Derek sent a letter to Dr. Murray Goldstein, Director NINDS requesting a meeting to discuss the NINDS's clinical research programs for HIV. We also requested information of extramural/intramural grants. The NINDS responded positively to both requests. Anna Blume, AUNY, sent a similar request to Dr. Ellen Stover, AIDS Coordinator NIMH. The meeting was granted but the grant information was not sent. (If you are interested in peptide-T, Anna did much of the preliminary work with the NIMH to get peptide-T trials started)

so........11-6-91...............
Meetin w/ NINDS
attended by: Dr. Murray Goldstein, D.O., M.P.H. Director NINDS, Dr. Rodger Porter, Dep. Director NINDS, Dr. Carl Leventhal Extramural Director NINDS, Dr. Eugene Major, Intramural Director NINDS, Derek Link and Anna Blume, AUNY ,John Perry Ryan, AU Province Town, Matthew Chappell, AUGG

Overall, this was a productive meeting with willing and active participation in discussion of research of the NINDS related to HIV and AIDS. Information disseminated by the NINDS included an itemized list of both intra and extramural studies w/ bibliography, Neuro-AIDS budget(including a HIV budget relative to the Total NINDS budget), New and total # of extramural neuro-AIDS grants w/ cost per fiscal year, Neuro-AIDS grant applications received and funded yearly since 1985, AIDS grants paid 1991(a descriptive document) (copies available by request)
THE NINDS budget is 16 mil. for 1991. 7 new grants where added at 757k. 36 total current grants at @ 12,000 k. In 1991 25 grant applications received, 8 funded at 32% total budget for AIDS.

One of the most important outcomes of this meeting was agreement by Dr. Goldstein to attend, if invited, the ACTG exec comm. meeting to be held in 2-92 (I think) to discuss the ACTG Neurological Committee. Dr. Leventhal also expressed interest in attending. This may help the NINDS with its own problems as well. The NINDS has no funds allocated for an outreach capacity to have significant input into areas of the NIH necessary to improve neurological treatment and basic science research efforts at an expedited rate.

Another confusing funding issue is a "grey area" of research overlapping b/w the NINDS and the NIMH. This issue remained very grey. Its probably good to note a budget difference b/w the NINDS and NIMH of large degree; the NIMH HIV budget is @ 80 mil/per year, opposed to the NINDS @16 mil 1991 (a figure which has slightly increased each year since 1985).

A productive discussion of the means in which HIV damages neuro cells, cytokine involvement, direct infection of neuro cells of CNS/PNS (but not neurons)< products of HIV reactions and/or direct viral interaction killing neurons, and the involvement of the gp120 toxicity. ADC was very lightly brushed in discussion with no significant differing information to report.

PML research is a large area for Gene Major, Intramural Director. Gene discussed the problems of research; one, a lack of agents to test that show any affect, two, an animal model to test any potential agents. Gene states the animal model is in development and that the development is going well. IF you know someone who has PML, would be interested in trial participation, or is interested in PML current research, Gene Major can be reached and is open to discussion at NIH, NINDS, Div. of Molecular Virology& Genetics BLDG 36 rm 6213, Bethesda, Maryland 20892. ph# 301 496-2043 or 496-1635, fax, 301 402-0828.

Copies of the NINDS intra/extramural studies and budget are available upon request.

After the NINDS meeting we ate basic American food in a restaurant with lots of green and white tile and gobs of ceiling fans with chalkboard written specials w/ a serious lack of vegetarian interest. Fatigue set in, Maxwell house coffee didn't help too much.

NIMH meeting.................................................................       ......       ......                       

After careful negotiation around the area we found a parking space in front of the ADAMHA Bldg.
Attendance: Dr. Ellen Stover,AIDS Coor. NIMH, Dr. Peter Bridge Dir. extramural AIDS NIMH, various people in and out form the office,
the same AU individuals.

The NIMH did not give the information requested prior to this meeting making a productive meeting of substance difficult. Picture this, you ask for a budgetary breakdown, lists of discretions of grants accepted, funded and not funded, and they tell you its in the office. Now, aren't you at the office. "We'll mail it out out to you soon." "Don't worry, its all taken care of." (I start to worry)

The NIMH has an 80 mil budget, 1/2 goes to "changing behavior." The NIMH focuses primarily on psychosocial, behavioral, and educational aspects of AIDS. The NIMH is also the largest grantor of funds for clinical trials for treatments of neurologic and psychological manifestations of HIV. The NIMH effort critical, currently there are two trials funded for ADC, and 6 trials for neurological and psychological aspects of AIDS, and the Peptide -T trial for cognitive impairment. Unfortunately I have not reviewed any of the trials at this time and will relay the information when it is received. As a person who works in the Mental Health profession, I felt the discussion to go in circles. But, I feel this is the vehicle for treatment and the intention of the NIMH is good, the work important (generally). Enclosed is a follow up letter for further discussion with the NIMH which raises the issues.

For copies of the NINDS info or if you would like to discuss further HIV Neurology contact Matthew Chappell, 2536 Folsom St. S.F., Ca. 94102 415 821 1722 or better yet 510 251 5450 (voice mail)

We stopped at Roy Rodgers @ 4 times in our return to NYC.
COMMUNITY CONSTITUENCY GROUP
AIDS CLINICAL TRIAL GROUP

To: CCG Members, DAIDS, Immunology Core Committee Members
From: Jesse C. Dobson
Date: December 27, 1991
Re: Immunology Committee Report. 12/91 ACTG Meeting

From my perspective, this was a very frustrating and disappointing meeting for the Immunology Committee. The Core Committee left another meeting without a clear plan for progress, infighting between the chair and the DAIDS medical officer was arguably embarrassing and certainly unproductive. No new protocols or concept sheets were discussed in the Immune Based Therapy Working Group (IBTWG) and several key protocols in development reached the point of no return without immunology input to plan for data that could be crucial in asking surrogate marker questions. It was another meeting where the committee spent more time talking about how they will do something in the future, but very little was done. There were minor exceptions, however, particularly the description of a concept sheet for collecting immunology data in ACTG 175.

First, was the second meeting of the Surrogate Marker Working Group Core Committee, which had been expanded since the July meeting to include Margaret Fischl from Primary Infection and Bob Combs from Virology and Steve Lagakos representing the statisticians. The committee is a fairly balanced group from throughout the ACTG. The committee was formed to promote interaction between the various committees to accelerate the study of promising surrogate markers (SM's) within ACTG trials. The Primary Infection members were clearly annoyed by the process, as the PI committee had set up its own group (without telling anyone of course) to deal with this issue. The new committee was set up by Dr. Fahey (who chairs it) at the July meeting. The first half of the meeting was devoted to the sharing of preliminary data. Dr. Lagakos wanted to know if the open forum organized by the committee would be appropriate for very early data analyses as it may "end up in tomorrow's Washington Post". This discussion (which ended with a resounding consensus of probably not, but maybe), left very little time for the business of the committee, which was the next agenda item. In general, it was agreed that the core committee should focus on what are the key upcoming trials and what kinds of SM's would be best studied in each particular trial. The committee also allows for a place to work out details of sample collection, storage and ownership, which have plagued past efforts at SM studies.

Next came the Immunology Core Committee meeting, better known at this meeting as the Oxbow Incident. The first item on the agenda was Dr. Fahey's proposed restructuring of the committee. In the past, the committee had been divided into subcommittees that shared a common technology for detection of various immune system parameters (e.g., flow cytometry for phenotyping various kinds of cells, NK and Cytotoxic T-cells, etc.). Dr. Fahey felt that if the committee had committees structured around goals, perhaps the interaction of various technologists in the context of a specific plan would prompt more action and less talk, which is badly needed. Dr. Kagan of the program office made the obvious point, however, that since the Immunology Committee had not yet developed a set of goals, it would be difficult to structure committees around them. Most Core committee members (including myself) agreed and felt a discussion of priorities would be more appropriate before considering the proposed plan. Dr. Fahey, however, insisted that the proposal for the plan was the first order of business, and we must vote on it before moving on.
While this felt pretty unreasonable of him, to his defense, considerable work had been conducted prior to the meeting to assure at least there would be no dissent toward the restructuring plan. Dr. Fahey was plainly unhappy that Dr. Kagan had brought this up and reacted by being stubborn. What followed was a rather unpleasant and unprofessional exchange by both parties that no amount of discussion seemed to fix. The committee therefore agreed to vote on the proposal, which passed, so the committee is restructured. In order to cool things off, Dr. Fahey had me chair the rest of the meeting. All in all an unfortunate set of affairs for a committee in bad need of cooperation.

The new committee structure consists of nine groups which will meet each ACTG meeting:

1: Surrogate Marker Working Group - Described above
2: Humoral Immunity Working Group - Not much change here. The subcommittee is responsible for the generation of protocols for measuring B-cell phenotyping and function and antibody levels and function. Soluble factors such as cytokines would also be discussed here.
3: Cellular Immunity Working Group - Studies the immune function of various cell types. Examples would be CD8 cell cytotoxicity, proliferative responses to antigens, etc. I would assume any studies of macrophage function would also be done by this group.
4: Quality Assurance Working Group - The ACTG probably has the best (and certainly the largest) program for interlab QA. This critical function of the immunology committee would be preserved intact and is mostly administered by the program office.
5: Core Committee - Ostensibly provides direction and priorities to the subcommittees.
6: Protocol Immunologists (PI'ms) - This consists of immunologists assigned to protocol development teams for immunological input. Often in the past, they have not even seen the protocol until it was complete (e.g., ACTG 182 as explained below). The goal of this group meeting is to brainstorm about what immunological studies would be best conducted in which protocols.
7: Immune-Based Therapy Working Group (IBTWG) - Designs protocols for the study of therapies that fight HIV by boosting the immune system instead of directly attacking the virus.
8: Pediatric Immunology - While pediatric studies fall primarily under the Pediatric Committee, immunologists interested in pediatric studies felt a separate meeting would be useful. Several of these are members of the Immunology Committee and so it is listed here, although the Immunology Core will not have direct influence over this group.
9: Full Committee - Reviews and provides input into the plans of the subcommittees.

You may notice that the recently-formed Immunohematology Working Group (IHWG), which deals mainly Idiopathic Thrombocytopenia (ITP) (i.e., HIV-related low platelets), is not included. Dr. Fahey felt that this group should best be in another committee, since immunologists are not often concerned with platelets. On the other hand, ITP is generally considered an autoimmune phenomenon. Several community people at the meeting were not happy at the idea of studies of this life-threatening condition being dropped by the ACTG. The IHWG had its second meeting this time and had a fair attendance and expression of interest by researchers. I need more input from the community on how this should be resolved. It may be solved by default, however, since rumor has it that the ACTU of the chair of this committee will likely not be refunded under recompetition (more on this later). The IHGP, if it continues to exist, plans to work with the MACS study to look at ITP in gay men. Immune complexes have been implicated as the cause of ITP in this cohort.
Getting back to the Core Committee meeting, a tentative discussion of goals of the committee was held. The most useful and developed immune parameters were enumerated. Unfortunately, there was no time to prioritize them at this meeting. It is planned to have a prioritized list developed by the April meeting. Discussion of this list and how to implement it will be a major topic of discussion for the Core committee and all subcommittees. Some interesting markers were identified, however, and will be included in the plan to be discussed at the April meeting.

I missed the T-cell Proliferative Working Group, although Dr. Valentine reported no dramatic progress in this area in private discussions. I also had a conflict for the Pediatric Immunology meeting. Dr. Fahey held a special meeting with Dr. Katzenstein, the PI on ACTG 175, and other immunologists to discuss the collection and storage of samples for immunological monitoring of these patients for real time and possible future studies. Several activation markers, such as CD71/CD25, CD38, HLA-DR, neopterin, etc. were proposed in addition to cytokine levels (e.g., Interferon gamma. IL-6). These could be performed on stored samples and require little or no extra blood as long as they are set aside for these studies. Functional studies such as proliferative responses and HIV-specific cytotoxicity will best be done in real time and may be only practical at sites with past capability to do these studies.

This last point brings up one of the main concerns about site selection in recompetition. One of the largest criteria for refunding a site is its score as an ACTU which draws heavily on its ability to recruit and keep numbers of representative patient populations, but very little on the scientific abilities of the sites. We therefore may lose several of our ACTU's with the strongest immunology capabilities and the immunologists associated with them. For example, NYU (Dr. Fred Valentine) and Duke (Dr. Kent Weinhold) are rumored to have scored badly. Loss of these personnel would be a severe blow to the Immunology Committee. The program office needs to emphasize the overall scientific capabilities of the program at least equal to if not significantly greater emphasis than recruitment. Otherwise, we just end up with another CPCRA with even less hope of learning about HIV pathogenesis in the context of clinical trials than we have now. This is plainly unacceptable and must be fought at all costs.

The IBTWG open meeting had to change its agenda completely due to last minute cancellations by speakers. Discussions of ACTG 137 (gp160 vaccine in HIV positive people) and ACTG 141 (peg-IL2) revealed encouraging interim data. The vaccine definitely promotes increases in HIV-specific cytotoxic response. In patients with >50 CD4 cells/mm³, peg-IL2 gives a sustained increase in these cells of 10-15%. Reports on two studies of ex-vivo expansion of CD8 cells (ACTG 080 at the University of Pittsburgh and a company funded study at the Miami VA) showed no severe toxicity for the procedure, and the Miami study reported two significant remissions of KS lesions after treatment with >10¹⁰ CD8 cells and IL-2. Further studies are planned by the company, Applied Immune Sciences.

The IBTWG Core committee meeting began with a presentation by Genentech on some of their therapeutic vaccine work. They produce a gp120 based vaccine. Little data were presented, although there was some encouraging results in chimps. They were mostly after advice on how to design efficacy trials for therapeutic vaccines. Because this approach is expected to work better in those with higher CD4 counts, they prefer to test the vaccine in people with >300 CD4 cells/mm³. Unfortunately, the FDA has strongly indicated that a rise in CD4 counts will be insufficient for licensing a vaccine as a therapy. So, if it is necessary to take these patients to clinical endpoint (after offering them the option of AZT once they fail below 500 CD4 cells), this study will either have to be very large (over 3000 people) or last a long time (5+ years) to achieve enough endpoints to be significant. If a new therapy becomes approved in the meantime, it,
to be offered to the participants. Further confounding statistics, probably rendering the study meaningless. This free consulting session for Genentech lasted most of the meeting and produced few results, only identifying problems. The upcoming joint protocol with the AIDS Vaccine Evaluation Units (AVEU's) was discussed next. This placebo-controlled protocol was discussed in a recent conference call, and exclusion criteria were greatly reduced. An update on ACTG 160 (Pentoxifylline) was presented next. There seems to be little toxicity; numbers are too small to conclude anything about efficacy. Unfortunately, there was no discussion of future priorities for the IBTWG.

The Flow Cytometry Working Group discussed concept sheets for phenotype studies in ACTG 175. A minimum of CD8/CD38/HLA-DR receptors was proposed. Dr. Carol Bick suggested that sites who were capable measure these values during screening for 175 with the assumption that these would be adopted in the protocol, since the investment would be low if the assumption were wrong. There was also a discussion of how the ACTG can begin to take advantage of 3-color technology. The Flow Cytometry Advisory Committee reported that the standard deviations on CD4 counts have improved by a factor of three since the beginning of the QA program. They also plan to issue flow guidelines within two months and develop a method of determining the optimum schedule for CD4 monitoring on antiretroviral therapy.

The Humoral Immunity Working Group focused on pediatric studies, mostly involving measurements of in vitro antibody (Ab) production (IVAP) which measures the ability of B-cells to produce Ab's to HIV. Again, the numbers studied were too small and the technique too variable to reach definitive conclusions, although positive responses to AZT therapy were noted in infants over 6 months old.

A special immunology symposium on "Advances in Immunological Monitoring of HIV Infection followed. In addition to a repeat of the CD8 expansion data, several studies of phenotypic markers at various stages of disease were presented. Consistently it was found that those with high CD8/CD38 percentages progressed to AIDS faster. Other data presented were less conclusive. The NK and Cytotoxic T-cell Working Group spent most of their meeting discussing a survey of ACTU labs to determine their capabilities in these areas. The survey found only six labs fully ready to do these studies. The Plm's met only to spend another meeting talking about what will be done in the future. There is still no systematic way to assure that each protocol is assigned a Plm early in development. This was made evident by the fact that ACTG 182, a 400 patient study of AZT in infants made it all the way through the development process without the involvement (or even the assignment) of a Plm! Some input is now being provided as an afterthought to a complete protocol.

A long Surrogate Marker symposium followed where a truly wide variety of markers were discussed. Unfortunately, the analyses presented often raised more questions than they answered. One study showed that if missing data for 019 were left out instead of extrapolated, p24 antigen levels would be a good progression predictor. This comes after these data were used as a major factor in discounting this marker. Another study showed that if labs with poor standard deviations were left out of the 019 analysis, the predictive value of CD4 decline is greatly improved. But if only labs with poorer standard deviations were used, CD4 decline was predictive of slower progression! Clearly, there is a problem here, but what is very uncertain. Data on a new marker, DHEA levels, were presented with some interesting results. DHEA levels are low in HIV positive and seem to drop with disease progression. These results are particularly interesting since DHEA is a hormone that can be supplemented in therapy. It will be important to see if taking DHEA will increase these levels and slow disease progression.
Finally, the Full Committee meeting was wasted on reviewing the results of the subcommittee meetings, leaving very little time for discussion and comments, let alone planning or prioritizing. I complained strongly about this and made the following recommendations, which I feel are still appropriate.

1. The core committee must develop a specific plan for designing and implementing immunology protocols within the ACTG. The plan needs specific goals with priorities and a timeline.

2. The same sort of plan is needed for the IBTWG with the following considerations:
   
a. The IBTWG, like the people with HIV disease, does not have the luxury of waiting for potential treatments to come to them. Potential treatments must be sought out proactively.

b. Just because the ideal treatments (e.g., HIV specific monoclonal Ab's, better vaccines, etc.) are not yet available, does not mean that there are no compounds worthy of testing. Rationale for concept sheets for NAC, DHEA, IVIG, CD8 expansion in KS, etc. exists, where are they?

 c. Studies that help elucidate pathogenesis are desperately needed. Compounds that regulate various cytokines need to be tested. What is the effect of reducing circulating immune complexes (CIC's), particularly free gp120 on progression? Is there validity to the autoimmune theories of HIV pathogenesis?

d. Pilot studies of vaccines plus antiretrovirals are needed so that efficacy studies can begin ASAP. These studies need to be performed in people with <100 CD4 cells as well as those above to determine if a positive immune response, however small, is seen in this patient population.

e. Compounds which may hold promise for sustaining or improving immune function in those with <100 CD4 cells need to be identified and given equal priority with those for higher CD4 counts.

4. The Immunology committee must lobby the program office for increased funding for studies of cellular immune function, specifically CD8 cytotoxicity and natural killer activity.

5. An organized, systematic method of involving PIm's in the design of protocols needs to be devised and implemented.

6. Immunology Core, the IBTWG Core, PIm meeting and the Immunology Full Committee should be reserved exclusively for discussion of future plans for these committees instead of reviewing data and rediscussing these data in full committee. These plans should be developed in a protocol specific manner with priorities, timelines and key personnel assigned.

7. Other subcommittees should reserve enough of their meetings to discuss plans and assign generation of protocol-specific concept sheets to appropriate personnel.
ACTG
Dec. 2 thru 5, 1991

PCR Working Group

The priority of the group has been to develop an assay for nonisotopic HIV
I. View of current quantitative approach:

1. Cells — DNA PCR  
   — Culture
2. Plasma — p24 Antigen  
   — Culture  
   — RNA PCR

Abbott labs presented their HIV I RNA PCR assay method using fresh
samples and freeze/thawed. Both methods proving equally reliable, however
occasionally getting false positives on repeated sampling.

RESISTANCE WORKING GROUP

Working on a consensus protocol in order to develop a common language for
looking at and discussing drug resistance. They have been using p24 as an
endpoint and it was indicated that it costs about $500 per assay. They are
attempting to correlate resistance with clinical endpoints.
Interim results of a study which has been running 50 weeks indicates that
the development of ZDV resistant strains was not associated with clinical
deterioration.

CD4-PE TEAM MEETING

Interim evaluation of trial with Upjohn's soluble CD4 with Pseudomonas-E
Toxin. Grade 4 toxicities being reported. Elevated transaminase levels (SGOT and
SGPT), grade 4 liver toxicities at 15 micrograms per kilogram of body weight. In
the more severe cases of toxicity it took weeks for the patients to resolve. Peak
toxicity noted at day 2. The toxicities were dose related and therefore the Phase
I/II protocol is being modified to call for a more conservative dosing regimen.

CAB NETWORKING MEETING

1. New members sought for the Community Constituency Group,
   see attached handout.
2. National Networks initiated, sign up sheet passed around. See
   Protocol Development Subcommittee notes for explanation of
   National Networks.
ACTG Protocol Development Subcommittee
December 1, 1991

1. National Networks (Working Groups)
   Structure to be developed within the context of the ACTG, that is largely based upon the ACTG committee structure. It would function as a network of people to suggest and review protocols, as well as concept sheets.
   The Protocol Development Subcommittee would maintain the list of contacts that would comprise the network structure. The following organizations would be notified for names to be submitted.
   - Community Advisory Boards
   - ACT UP Network -- Bill Hunt
   - CPCRA

   The Protocol Development Subcommittee will recommend that the responsibility for maintaining these contacts be that of the CCG Rep. to each scientific committee.

2. CCG Priorities
   Oncology: Tabled for input from Michelle Roland, not present.

   Immunology:
   A. Advocate small nested studies of immune based markers within existing protocols
      a. T-Cell response to certain antigens
      b. Neopterin & Beta-2
      c. Tissue studies if appropriate
   B. Advanced stage patient immune based therapy research
      a. To improve immune function
      b. To improve immune status
   C. Protocol immunologists should be involved earlier so that samples can be identified & secured ASAP.

   Pharmacology:
   Needs to be a pharmacologist on each protocol

   Pediatrics:
   A. Develop O.I. and immune restoration studies.
   B. Purview of Pediatrics should be conception to 18 years of age, given that these trials will include pregnant women it is imperative that representatives from the Women's Health Committee be included.

   Opportunistic Infections:
   A. Conduct trials for all OI's including uninvestigated OI's (e.g. PML, Cryptosporidium, etc.) and design trials using agents for multiple prophylaxis.
   B. Compare various treatments & prophylaxis and where resistance seems likely, testing combinations from the start.
Neurology:
A. Nesting neurological studies in OI and primary infection studies (e.g. ACTG 175)
B. Develop studies for treatments of neurological conditions (e.g. neuropathy, AIDS dementia complex)

Virology:
A. Develop virological studies that best elucidate disease pathogenesis
B. Develop studies of markers of virological load in tissue not just blood (e.g. lymphoid system)
C. Develop a functional system sharing samples & storage with other scientific committees.

Women’s Committee:
A. Develop contacts with all other scientific committees
B. Development of scientific barriers that keep women out of trials
C. Determine criteria for establishing when women specific trials need to be done (e.g. exclusion of pregnant women, natural histories, separate pharmacologic studies, etc.)
Meeting with members of the staff of
Senator Edward Kennedy
Wednesday, December 4, 1991
Representative Henry Waxman
Tuesday, December 10, 1991

Subject: Reform of the U. S. Drug Approval System as it Regards Life-threatening Illness

Attendees:

Aides to Senator Kennedy:
Mark Childress, Counsel
Debra VonZinkernagel
Shawn Tunis

Aides to Rep. Waxman:
Bill Schultz, Counsel
Tim Westmoreland, Counsel

Patient Advocates:
Jim Driscoll, D.A.T.A.
John Dolan, ACT UP / Golden Gate
Beverly Zakarian, Cancer Patients Action Alliance (CanAct)
George Rehnquist, Families for Alzheimer's Rights Association
Charles Green, Families for Alzheimer's Rights Association
Mary Jo Kahn, Virginia Breast Cancer Foundation, Amer. Cancer Society
Kim Calder, Cancer Care, New York City

Notes:
There were introductory remarks by Jim Driscoll discussing the coalition of groups represented and the reason for our being there. Each patient advocate then made remarks concerning the problems faced by their constituency under the existing drug approval and regulatory system.

Significant issues discussed:

1. How the current system of drug approval is heavily weighted towards the broader concerns of consumer protection and does not adequately take into consideration the risks to patients of withholding approval while drug sponsors are required to conduct extensive efficacy testing.

2. The negative implications of the FDA's increased enforcement activity relative to the off-label use of approved cancer and AIDS drugs and the need for broader first label approval.

3. The reasons why Congress needs to address the statutory efficacy standard for life-threatening illness with legislation — the Campbell bill.

4. The Competitiveness Council 11 point reform plan. We asked that the debate not be politicized along party or traditional ideological lines, but that the focus be on the possibility of constructive change in America's drug approval system.
Specific examples of the problems at the FDA:

1. The FDA's foot dragging on the approval of ddC.

2. The FDA's mishandling of Tachrine as a treatment for Alzheimers

3. The FDA's mishandling of the blood test for early detection of recurrent breast cancer, made by Centicor.
International Symposium on Serum Markers
8 a.m. - 4 p.m.

Phenotypes of HIV which may be correlative to disease progression. These phenotypes are NSI and SI. These phenotypes are relatively easy to detect. The findings of the study suggest that those persons infected with the phenotype NSI had better prognosis than those persons infected with the phenotype SI. Some patients with phenotype NSI developed or "switched" to have both NSI and SI present. These patients had better prognosis than those with SI alone and worse than those with NSI alone.

Serum markers in immune activation, specifically Beta-2 microglobulin (B2M) and neoperin, 2 markers which may prove to be useful indicators of disease progression. Immune activation occurs early (not late) in infection and as disease progresses we see increases in B2M levels and to a lesser degree a rise in neoperin levels.

A newly isolated antigen called 90K may be an indicator of disease progression.

In examining 90K in HIV infection, there was a cross section analysis of subjects across the disease spectrum. The study which was examined was a population of 329 HIV+ injection drug users (IDUs).

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<tr>
<th></th>
<th>n</th>
<th># with 90K</th>
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</thead>
<tbody>
<tr>
<td>Control</td>
<td>150</td>
<td>7</td>
</tr>
<tr>
<td>HIV+ Asymptomatic</td>
<td>232</td>
<td>135</td>
</tr>
<tr>
<td>ARC/AIDS</td>
<td>97</td>
<td>80</td>
</tr>
</tbody>
</table>

In further studies, 90K was shown to correlate with CD4, CD4/CD8 ratio and B2M. It best correlates with IFN, however.

What we know about immune markers...

<table>
<thead>
<tr>
<th>Marker</th>
<th>Level which may be indicative of increased survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD8</td>
<td>Above 250</td>
</tr>
<tr>
<td>T Lymphocyte</td>
<td>Above 400</td>
</tr>
<tr>
<td>CD4</td>
<td>Above 50</td>
</tr>
<tr>
<td>Observed Lymphocyte</td>
<td>Above 600</td>
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We should be looking at other parameters other than CD4. The absolute count seems to always fair better than the percentages, and perhaps the percentages are more accurate. If you maintain CD4 counts and remain p24-, prognosis seems to be better.

In designing master protocols, in patients with "advanced" HIV-disease, CD4 drops to below 50 may be considered an adequate surrogate or intermediate marker of disease progression and may be equated to a clinical endpoint. If a patient's CD4 drops below 50 and is sustained or recurring after 3-6 months, this is considered predictive of death. In looking at the spectrum of CD4 ranges, rather than looking at CD4 falling below 50, other types of changes in CD4 must be considered when approaching the issue of using CD4 as an endpoint.
In master protocols for persons with 200-500 CD4, a 50% drop in CD4 may be considered a clinical endpoint as there is a relative risk of 7.8 of disease progression when this condition occurs. This is extremely important as it allows trials to meet endpoints and decrease the follow-up time, potentially decreasing the costs of trials significantly.

When using a change in CD4 as a clinical endpoint in trials for patients with 200-500 CD4, statisticians are able to decrease the number of patients necessary for a trial significantly, as was the case in ACTG 175 where the number of patients necessary to answer the scientific question was decreased from 3200 to 2100 and the follow-up period was shortened from 4-5 years to 1 year.

Benefits of using serum markers in clinical trials is that they present a possibly quick and cheap assessment of new treatments. A marker is chosen based on two major criteria, biological plausibility and epidemiological correlation with clinical progression of disease. There are two main types of markers, markers which measure disease activity and markers which measure disease progression.

- If we use serum markers what is the false positive rate?
- The "gold standard" is clinical expression of disease.
- To expedite the quick testing of new classes of drugs, we need to be able to use serum markers for endpoints.

If serum levels rise post treatment back to original levels, or perhaps surpass original levels it could be indicating that the drug was working and that the suppression of serum levels for a given period may not be harmful if the end result is an ultimate increase.

The statistical working group held this forum as a "special" forum to describe and explain the various Observational dBases being set up across the country, through AmFar, the CPCRA and others. The purpose of ODBs a varied. If they are designed well they are able to capture important epidemiological data. In the case of the CPCRA, where some sites have the facilities to operate their ODBs locally, they will provide demographically specific epidemiological data to facilitate designing trials that may adequately serve the needs of the affected communities in that area. The ODBs should be able to provide valuable information in CD4 trends, detect gender difference in the epidemiology of HIV and characterize populations enrolled on the ODB.
AIDS Clinical Trials Group Conference Notes -Summary
December 2-5, 1991
By: Brenda Lein
Page 3

AIDS Clinical Trials Group Conference
Tuesday, 3 December, 1991

Topic: Preliminary Report on the Natural History of Skin Test Reactivity in Symptomatic HIV-1 Infected Patients.

The premise behind looking at reactivity to an antigen skin test as a measure of immune function is to see if reactivity or the lack of reactivity to given antigens are correlative to clinical disease progression and to determine if using this type of test may prove to be useful as a measure of efficacy of therapies. The Merieux skin test was put forward as perhaps the "poor mans" proliferation assay.

When responders of the Marieux skin test in ACTG 002 were compared with non-responders, there was a slight increase in survival time. The increase in survival time was not statistically significant, however. This is what prompted them to look at ACTG 016 as well. Neither of these studies were designed to examine the efficacy of the Merieux skin test, however they helped to beg a scientific question as to whether or not the ability to respond to given antigens was correlative to disease progression.

The objectives for the data analysis concept sheet are:

- Characterize the natural history of the Merieux skin reaction.
- Examine the relationship between skin tests and clinical endpoints.
- Assess the effects of AZT on the skin test.
- Assess as a potential marker for therapeutic efficacy (this is important especially for the study of immune based therapy where you need to assess immune function).
- See if responses to particular antigens or groups of antigens have greater predictive power.

Topic: Overview of Proliferative Responses in Infected patients

Loss of proliferative response occurs early in the course of disease. When you introduce AZT do you see a restoration of function that tells you anything more than CD4?

- Proliferative response can be measured as part of clinical trials.
- Sustained or increases in the ability to produce a proliferative response to microbial antigens is an indicator or better prognosis.
- Increases in proliferative response is parallel to CD4 increases (comparative) but the magnitude is much greater.

Topic: ACTG 137

ACTG 137 is a trial of intramuscular gp160 vaccine to determine the dose which will be immunogenic in patients who are HIV+ (random doses with 4 fold escalation). The goal of ACTG 137 is to induce proliferative response in HIV+ persons, despite the condition of having no recall microbial antigens and to evaluate immunogenicity and discover what dose is immunogenic. The control for this trial is the hepatitis B vaccine. All patients are Hepatitis B positive. The studies are still blinded.

Looking at the overall CD4 data there looks to be a slight decline in CD4 -but this is aggregate data. Immune response matures with repeated exposure to the vaccines and there is a proliferative response. Those patients who were considered Non-responders had lower CD4 counts upon entry into the study. Patients did acquire the ability to produce IL-2 when stimulated with the antigen.
The difficulty in designing vaccine studies and other studies looking at immune restoration is determining efficacy. In a recent FDA meeting, using CD4 as a marker in these types of trials was unanimously defeated. What this means is that CD4 would not, in itself, be an adequate for licensure of these types of drugs, but it does not necessarily mean that information in regards to CD4 will not influence or help shape how we determine if these drugs and therapies are effective.

**Topic:** ACTG 148

ACTG 148 is an Intradermal study of gp120.

In the month after patients acquire proliferative responses they develop develop cytotoxic responses as well. Timing is fairly consistent. After a period of immunization their patients are developing responses to IL-2, which is one of the "hallmarks" of cellular immunity.

**Topic:** ACTG 141

ACTG 141 is a study of AZT/Peg IL-2. The question Merigan hopes to answer is can we enhance the immune system by a non-specific response? A Million units of peg IL-2 every two weeks seems to give sustained CD4 elevation. Thus far in Merigan's study he is seeing that 1 patient, with CD4 count below 50, is not responding to therapy. In other groups of CD4 at 100, 250 and 500, Merigan has noted sustained and prolonged elevation of CD4. In 5 patients with less than 500 CD4, they are going to triple the dose because they feel it is worth the risk. They expect to see a 10-15% sustained increase in CD4. The side effects of AZT/Peg IL-2 therapy are thus far 1 patient receiving 6 times the optimum dose acquired a CNS problem (multifocal optical problem). The condition was reversible.

**Topic:** Ex-Vivo CD8 Expansion

The (Pittsburgh) study looked at 11 subjects receiving a total of 53 infusions. The study involved the capture, expansion and activation of T-cells. Studies of CD8 expansion were done in two sites. In Pittsburgh the study was a cell trafficking study with and with out IL-2. In Miami the study was done solely on out patients and did not include IL-2 therapy. These studies showed a progressive increase in circulating CD8. There were absolutely no adverse reactions due to CD8 expansion.

Toxicity information (Miami) presented included:

- No adverse effects from cell reinfusion.
- Mild IL-2 adverse side effects in 4 subjects.
- Moderate IL-2 effects in 1 patient.

Although this study was designed to be a toxicity trial, the following efficacy information was presented (Pittsburgh study):

- All subjects experienced a (modest) increase in CD4 from the beginning to the end of the study. (It is important to remember that CD4 measures may not be either accurate or meaningful in this type of study). There was a decrease in CD4 decrease in CD4 correlative with in increased ability to repress viral replication.
- Two patients with chronic diarrhea had their condition clear upon first infusion of CD8.
- 1 patient with diarrhea experienced weight gain.
- Patients with candidiasis resolved.
- Patients with leukoplakia resolved.
- Patients with KS unchanged.
• Cells + IL-2 sustained improvement of KS.

The presentation of the CD8 expansion data was in attempt of the pharmaceutical sponsor (Applied Immune Sciences) to gain support for a multicenter phase II/III study. This study would be designed for HIV+ patients with KS. It would aim to achieve a greater than or equal to 10 to the 10th expansion of CD8 cells with IL-2 therapy. Outcome parameters would include KS progression, frequency and duration of OIs, quality of life and survival of 6 months. This therapy is not just putting back CD8 with HIV repressive capability but clearly these CD8 also have CMV (etc.) repressive capability as well. Currently they cannot isolate and determine specific repressive capabilities (eg. CMV).

**Immune-Based Therapy Working Group Core**

Genentech has determined that their best approach to seropositive vaccine studies is rgp120 because:

- **gp120** is the major surface protein which mediates HIV to the CD4 receptor.
- **gp120** is the major viral protein to elicit neutralizing antibodies.
- **rgp 120 vaccine** effectively protected chimps from infection with a homologous HIV-1 challenge.

Genentech proposed a randomized, double-blind placebo controlled trial of rgp120 is HIV+ persons with greater than 500 CD4.

Patients with previous history of OIs or prior antiviral therapy will be excluded from this trial. Patients with significant weight loss will be excluded from these trials. Efficacy endpoints of the trial will include:

- Decreased rate of decline of CD4 cells (50% reduction versus placebo).

**Joint ACTG AVEU Trial Venture**

A proposal to run a joint phase I/II trial with the National Institutes of Allergy and Infectious Diseases' (NIAID) AIDS Vaccine Evaluation Unit (AVEU) was proposed.

The results of the AVEU trials thus far show:

- No toxicities
- No hematologic toxicities
- No hepaticor renal toxicities
- No alternation of immune function
- Some fever and malaise (typically caused by the adjuvant)

The adjuvant itself hurts. Most side effects were related to the adjuvants.

**Topic: Pentoxifyline**

Pentoxifyline decreases HIV replication activity in infected human mononuclear cells. Reverse transcriptase activity is decreased and cell concentration remains relatively uneffected. Pentoxifyline prevents toxicity post bone marrow transplantation. Pentoxifyline reduces viral RNA in acutely affected cells.

Trial design: 27 patients (currently 13 enrolled). 400 mg pentoxifyline 3 times per day. At the eighth week the patient decides with the care provider if they will continue therapy. Evidence of TNF, triglyceride reduction and weight stabilization.
AIDS Clinical Trials Group Conference Notes - Summary
December 2-5, 1991
By: Brenda Lein
Page 6

AIDS Clinical Trials Group Conference
Wednesday, 4 December, 1991

The Use of SIV Monkey Model to Study AIDS Pathogenesis

This section of the plenary examined the benefits of looking at Simian Immunodeficiency as a model for examining the pathogenesis of AIDS. It used, as an example of these benefits, work researchers have done in determining the importance of the nef gene in the pathogenesis of HIV.

### Auxiliary Genes

<table>
<thead>
<tr>
<th>&quot;Essential&quot;</th>
<th>&quot;Non-essential&quot;</th>
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<tr>
<td>TAT</td>
<td>vif</td>
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<tr>
<td>REV</td>
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The absence of "non-essential" genes does not effect the ability of the virus to replicate in viral culture.

Examining nef in SIV

In SIV models, researchers have studied the "non-essential" nef gene and have determined that nef is doing something very important in the life cycle of the virus, especially at a point 2 weeks after infection.

Reversion of nef
- nef stop does not revert in-vitro.
- With nef deletion, after 20 weeks, the virus became more and more difficult to detect and negative responses were more frequent.
- nef stop reverts to nef open in-vivo.

Researchers say a decline in CD4 lymphocytes in animals infected with nef stop and nef open. nef deletion animals maintain stable CD4. Moreover, viral load was significantly lower in nef deletion animals. Though still present, it took large numbers of cells to detect viral load.

nef open - all 7 animals plasma antigenemic.
nef stop - all 5 animals plasma antigenemic.
nef deletion - never detected plasma antigenemia.

The animals which receive nef deletions have high antibody response, which is as high at twelve months as at the time of first infection.

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<tr>
<th>Type</th>
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<th>Progression to AIDS</th>
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<tbody>
<tr>
<td>nef open</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>nef stop</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>nef deletion</td>
<td>6</td>
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In the six animals which received nef deletion there has been no clinical signs of AIDS whatsoever. This suggests that nef is playing an important role for the virus in-vivo in infected monkeys. We cannot conclude that nef deletion SIVmac239 is not pathogenic -but there is suggestion. We still
have no clue as to what nef is doing. We can conclude that nef should become a target for antiviral drug development. Properties of virus with nef deletion suggests a strategy for making a live attenuated vaccine for experimental testing. The results of this study suggests that nef is a strong positive factor toward upregulating viral expression.

**HIV-specific CTL: An Antiviral Host Defence**

Summary:
- There is a vigorous CTL response in HIV infection.
- The response is mediated by CD8+ MHC Class I restricted CTL.
- Numerous epitopes have been recorded.
- Single amino acid changes may abrogate recognition.
- CTL inhibit HIV replication in-vitro and in an in-vivo animal model.

**Advances in Immunologic Monitoring of HIV infection**

CD38 is elevated in HIV infection. The CD8 compartment is adaptive, it loses markers throughout the course of infection. In high risk seronegatives, CD38 and CD57 is elevated. CD57 is linked to CMV infection. In HIV progression to AIDS there is an upregulation of the following markers; CD8, CD38, CD8DR and CD57. By profiling the expression within the CD8 compartment, we may be able to make correlates to disease progression.

**Topic: CD8 phenotype and function in HIV infection (collaborators - Levy, UCSF)**

- People with less than 10% CD8+CD11b have lesser antiviral activity.
- People with less than 45% CD8+HLADR have lesser antiviral activity.
- CD11b- supposedly correlates with anti-HIV activity.
- Long term survivors have good CD8 antiviral activity.
- CD8 anti-HIV activity resides in CD11b and HLA-DR+ subsets.
- The degree of CD8 antiviral activity correlates with a patients clinical status and number of CD4 in circulating peripheral blood.

**Topic: CD26**

- CD26 is decreased in HIV infection, but it is not specific to HIV-1 infection.
- CD2+CD26+ rises slightly with age.
- CD2+2D26 count decreases as CD4 declines.
- HIV infection results in a decrease of CD2 cells expressing CD26.
- CD4+CD26+ steadily decreases as overall CD4 declines.
- The number of CD4 cells expressing CD26 declines and then begins rising.
- CD8+CD26 remain unchanged throughout HIV infection.
- The number of CD8 cells expressing CD26 is decreasing (suggesting the expression of CD8 in early infection does not express CD26).
- It may be that CD26 suggests limited proliferative value.
CCG 1st Session

It was reported that several ACTG committees, such as Patient Advisory Immunology, Pharmacology, Site & Data Management, and Patient Care don't think they have enough power. Apparently, at least part of the fault is with the Executive Committee, which sometimes appoints its own subcommittees to do the work of existing committees.

Concerning the possible reduction of 12-20 ACTUs, someone reported that Hoth doesn't think this will disrupt the system. It was pointed out that if Cornell University is cut, then the cryptosporidium researcher will also be cut. Will she be replaced? The Executive Committee doesn't know.

Some pharmaceutical companies don't have any confidence in the ACTG, and so don't want to trust their drugs to it.

CCG 2nd Session

There was a discussion of distribution of protocols, and who should be responsible. David Barr suggested doing it through the CABs. Marty said he didn't think it would make any difference if more protocols were available; i.e., no difference in the bigger picture. ACTG 175 was cited by a few people as an example of the consequences of inadequate information-sharing. Marty again said it would not have mattered. Andy said that the CAB system is the way to go, and if people have problems with that, they should bring them to the next CCG meeting. This will be discussed further Thursday, at the third CCG meeting.

Membership-discussion of what should be expected of members. Membership on a CAB was mentioned as a possible requirement. Jesse said that since the CCG, as a part of the ACTG, is responsible for clinical trials, knowledge of, and experience with, clinical trials should be a mandatory requirement. Some thought it should be desirable, but not mandatory.

After some discussion about what to do next, it was decided to go through various ACTG committees, and bring up issues and concerns relevant to each committee.

Patient Care: What is the role of the committee?

Immunology: Controlled by the Primary Infection Committee.

Pharmacology: They need to be on protocol teams. They have no clear
sense of their role.

Pediatrics: Interaction of research with other agencies. There was concern about how pediatric trials are viewed it terms of women. The pediatrics rep, Carol DiPaolo, did not attend this ACTG because her son, who has HIV, is sick.

Site and Data Management: Problems with data collection. Another problem is the makeup of the Forms Committee.

Neurology: Communication with the ACTG operations office; also the role and agenda of the Neurology Committee.

Virology: Problems with sample storage, and decision-making and leadership on sample storage technology.

Women's Health: Role.

Executive Committee: Coordination, and communication between investigators. Investigator-initiated research, and communication between the Committee and the community. Pediatrics has 2 reps on the Executive Committee, Opportunistic Infections has none.

Oncology: Angiogenesis compounds, and relationship with appropriate women's health sub-committees.

Opportunistic Infection: No plan for follow-up if a new generation of drugs fails. Committee is shrinking its leadership. Simultaneous comparisons of all new treatments should be done. MAI-situation changing every week. Wasting syndrome-nothing being done in ACTG National Inst. of Digestive Diseases is doing research. Cryptogen concept sheets done. Ask community MDs for their input.

Primary Infection: Arrogant and condescending. Relations with rest of ACTG. Takes on too much work; resistance to nested studies; narrow-minded. Mark Harrington said that anger about ACTG 175 reflects anger that there is no new generation of anti-retrovirals.

Someone said that these committees do not have a life of their own. Jesse amended that to "All they have is a life of their own."

Some suggestions were: try to influence Executive Committee membership, figure out if within the N.I.H. we can take every single promising substance and figure out how it can be evaluated, and Michelle said the ACTG is too
slow and conservative. She called for a meeting with Fauci.

Jack Killian (NIAID) felt a conflict between creativity and dictating an agenda to researchers. Telling scientists what to do bothers him.

Marty said we should focus on issues, not ACTG politics. This was during a discussion of the election of a new chair of the Executive Committee. He said that what they are substantively doing is more important than who is on various committees. Jack made the same point—for us to identify what we want done, not who we want on committees. Michelle wants pro-active trial design. David Barr said that rather than prioritizing issues, it's more important to decide what we will do about each one.

Jesse said that the (inherent) value of an issue is not the point, but what needs to be pushed is. For example, women's issues are important, but those brought up in the Protocol Development Working Group are already being worked on.

**CCG 3rd Session**

Technical Resources Institute will inform us concerning the next ACTG (Apr. 12-15, Omni Shoreham Hotel in D.C.). We should not make any arrangements until then.

A new ACTG Co-Enrollment Working Group has been formed. It includes 2 reps from OI and PI committees, and one from each other committee. Michelle is the contact for anyone (CCG members) who wants to be on this working group.

A vote was taken on who is the CCG's choice to be chair of the Executive Committee. After much discussion, and several abstentions, John Fahr was chosen over Paul Volberding, the only other candidate.

In the pediatric reportback, the core protocol was mentioned. Pediatrics is working on a core protocol, that will be used to expedite trials. ACTG 152 (AZT v. DDI v.AZT + DDI in symptomatic children) is being used as a model for this.

In the Q&A, Mark Harrington said that vertically-infected children progress faster than laterally-infected adolescents.

Jesse brought up ACTG 182 (Early v. Late AZT in asymptomatic infants) He is not certain that this is scientifically justified.

Saundra Johnson wants to be contacted with any information on perinatal transmission.
Pediatric Virology Working Group

Proposal that a pediatric virologist become part of the Virology Committee, and also they formed the Pediatric Immunology Working Group.

One issue was the volumes of blood called for in protocols, and the equipment needed for drawing blood and other samples. Someone suggested having a standardized protocol for volume.

No pediatricians are on the Specimen Collection Working Group-yet. A sign-up sheet was passed around for this, as well as for the PCR Working Group.

More info is needed on quantitative analysis from a pediatric perspective.

AZT: Pediatric population is AZT_naive, providing study opportunities not available with adults. Some protocols call for AZT as soon as a baby is born. There was doubt expressed as to whether this is effective, or "just toxic".

WITS (Women's and Infants Transmission Study) will have more peds representation. It was decided that WITS, Pediatrics, and Perinatal Trans. have to communicate and coordinate, because there are mothers on adult studies, their children on peds studies, with no coordination.

Plenary 12/3/91

ACTG 021 (Aero-Pent v. TMP/SMX to treat PCP):

- TMP/SMX arm had more OIs than AP arm.
- No data on how many people should have primary proph for PCP to prevent a given percentage of cases.

Everyone should get secondary proph. For primary proph, criteria include:

- fever, thrush, any AIDS disease, any AIDS OI.

Recommended agents, in order of choice are TMP/SMX, then AP.

Possible protection against other OIs? Probably npt Aero-Pent, TMP/SMX "perhaps" useful against toxo.

IV Aero - Pent being used on children in New Jersey. Anecdotal info

IV pent being used on children in New Jersey. Anecdotal info shows it to be more expensive and toxic than AP.

CMV trial at Johns Hopkins Eye Inst.:

DHPG v. Foscarnet
sample size: 240
107 foscarnet  33% death rate
127 DHPG  51% death rate

when trial was stopped
Median survival: 8.5 mos on DHPG, 12.6 mos on foscarnet

In the panel discussion, it was stated that the survival advantage was probably explained by an anti-retroviral effect of foscarnet; however, no retroviral data has been presented to date.

No difference in retinitis analysis or visual acuity in the better eye.

Twice as many foscarnet patients switched to DHPG than the other way around, due to the toxicity of foscarnet. Foscarnet patients could tolerate more AZT than DHPG patients.

Activist slide:

THIS DRUG IS NOT FOR WOMEN, IVDUs, PEOPLE OF COLOR OR POOR PEOPLE. COST OF FOSCARNET: $30,000/YR.
NIAID: TEST DRUGS FOR ALL PEOPLE WITH AIDS!

Mark Jacobson said that the infusion equipment that is required for foscarnet is not reimbursed by Medicaid in N. California.

Since this trial included non-ACTG sites, the ACTG does not have complete enrollment info.

Pediatric OIs

MAI: Clari, azithro, and a sulfa drug might be useful for MAI proph. Small number of cases make treatment studies difficult.
Bacterial infections: How would IVIG and anti-microbial proph in children compare? Catheter infections are higher in children, and most oncology literature doesn't address this.
Clinically-diagnosed bacterial infections are as important as microbiologically-diagnosed infections to be included in protocols.
Measles: Vitamin A treatment or proph suggested. Some literature says that Vit A goes down during measles. Other treatments mentioned were interferon, ribovirin, and ribovirin + IVIG. The current measles
vaccine does not protect HIV-infected children. Chicken pox and Zoster: BVRU (Bristol-Myers) should be compared with acyclovir. Merck will not allow chicken pox vaccine for HIV-infected kids until it is licensed for healthy kids. Pancyclovir (Smith-Kline) is possibly more effective than acyclovir. Mucocutaneous candidiasis is 2d to PCP as a peds OI.

Pediatric Symposium: Pharmacokinetics and Pharmacodynamics of Antiretroviral Drugs

Goal of drug evaluation shifting from "Does drug work?" to "Instructions for Use" i.e., what does a physician need to know to use a drug intelligently? Analysis of drugs focuses on what we hope isn't happening, rather than what actually is happening. E.G., a patient getting sick, rather than the actual course of a drug's pharmacokinetic effect.

*** Trials can look like treatment.***

Epistemological Issues

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<tr>
<th>Empirical Method</th>
<th>Model Method</th>
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<tr>
<td>Freedom from assumptions</td>
<td>x</td>
</tr>
<tr>
<td>Certainty</td>
<td>x</td>
</tr>
<tr>
<td>Efficiency</td>
<td>x</td>
</tr>
<tr>
<td>Actual design=nominal design</td>
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Conclusion: non-stringent trials are attractive and can be informative. Age (of patient) most important factor affecting volume and distribution of drugs.

ACTG Team Meeting (AZT v DDI v AZT + DDI)  Peds. Study

A neurological study, jointly sponsored by NIMH and NICHD, is nested in 152- someone complained that the neuropsychologist that this study requires would be a drain on resources. Several complaints about redundant paperwork requirements. Sites are in the N.Y. Standard Consolidated Statistical Area-of 21 eligible sites, 10 have officially responded, and most of the others
FDA is allowing study (ACTG 152) to proceed with minimum pharmacokinetic data, but that will be required in the study itself. Some researchers were surprised by this.

ACTG 182 Team Meeting (Early v. Late AZT in asymptomatic children)

- Keeping the study randomized at time of crossover.
- Is loss of brain growth sufficient to change therapy? No.
- Should CAT scans be done on a routine basis? No. After some discussion, however, it was decided that they should be standard for future trials, at least at entry. CAT scans are expensive.

This meeting continued the next day, but I could not attend because of a scheduling conflict.

Pediatric Committee: Phase II/III Working Group

- Purpose: to write a core (standard) protocol for Phase II & III studies, so trials can start faster and enroll more patients.
- After dose reduction, everyone should be rechallenged at full dose.
- A single toxicity table, with grading, that can be used for all protocols.
- Age ranges for tox table:
  - Birth-6 wks
  - 6wk-3mos
  - 3mos-3yrs
  - 3yrs-13yrs

Immunology Comm wants CD19s on all peds studies.
- Discussion about defining positive concepts such as intellectual development, physical growth, etc. in protocols. It's mainly failure that has been defined in protocols.

Pediatric Full Committee

- About 1300 patients in protocols. 4000 in the pipeline.
- Vaccine studies are at Rochester, St. Louis, Seattle, Vanderbilt, and Johns Hopkins.
- Recombinant vaccine combined with envelope (Bristol-Myers' Omcogen) "Within 6mos we'll know a lot." - Pat Fast, who gave the presentation on vaccines.
- All vaccines safe in healthy subjects.
Needed-immunologic intervention for pregnant women who come in too late to qualify under existing standards.-Pat Fast

Oncology: More OI cancers, esp lymphomas, are expected in children with HIV. Estimate of peds AIDS lymphomas-5% of AIDS cases.

Lymphoma statistics-
350-1100 pediatric AIDS lymphomas projected in the next 5 years, excluding adolescents with high-risk behavior.

Urgent need for research.
Ped AIDS Lymphoma Network has been established to handle expected number of cases. They pay $1200 for each lymphoma specimen submitted to the Network.

Primary Therapy Working Group: Will develop 4 master protocols before March ACTG.

Opportunistic Infections: Core protocols will not work well for OIs. They hope to use the (adult) OI Committee's protocols, changing tolerance and safety for peds.

ACTG 152: Opened Aug. 19 when 1st patient was randomized.
Karen O'Donnell at Duke heads the Neuropsychological Working Group.

NCI Studies: Steady-state v intermittent dosage of AZT in children with encephalopathy. Continuous infusion seems to work better.
GCSF and/or erythropotien in children intolerant of AZT
Phase II/III study of clari in combo with anti-retro therapy
Phase II study of 3TC (Linda Lewis is protocol chair)

and others

ACTG 152 Investigator's Meeting

Administration of DDI- only 2 antacids, Maalox being one, can be used.

Issue of temperature stability of DDI brought up. Someone suggested that a cooler might be used, but a person from Bristol-Myers was there, and said wrapping it in newspaper is sufficient.
Sunday, Dec. 1:

First several hours of meeting spent in introductions and arguing over agenda and process.

Finally decided to give Committee reports, discuss new membership, and prioritize issues.

Committee Reports are as follows: Patient Advisory Cmte.;
not doing a lot, no resources.; Immunology; the cmte. got a bad start, studies have not been done, important researchers aren't attracted cmte. is not big enough, what the cmte. needs (4 out of five) 1) an increase in researchers, 2) cmte. doesn't have access to lab samples, 3) must have a greater emphasis on immune based therapies, 4) how exec. cmte. makes decisions. (report given by Jesse Dobson); Pharmacology; pharmacologists don't have a role, they aren't involved from the beginning, must bring in protocol pharmacologist; Protocol Evaluation Subcmte.; still trying to define it's role in ACTG, is it just another cmte. that could be another cmte.; Pediatric; Ped. trials may be over funded in relation to # of children w/ AIDS; ACTG 185 (HiVig) protocol has been written; Site and Data Mgmt.; not working very well because it was set up by exec. cmte., should be combined w/ patient care, there is no funding and computers are not adequate.; PCP Pathogen Study Grp.; again, virology has blood samples, BW566C80 needs trial.; Oncology; only doing chemo. trials, work is duplicated at NCI, what their role should be, lack of communication w/ CCG; Neurology; the alternate system is not working, getting a lot of attention because it's not doing anything, many trial sites don't have neurologists; Virology; the cmte. is a mess, a lot of the same problems as the CCG, different technologies are competing; OI Cmte.; a problem in accruing people because after a compound looks good in vitro they want access. Women's; a struggle between maternal/fetal and pediatrics, made up of recycled scientists; Exec. Cmte.; serum specimen bank, new chair election, who will vote?, PI's will have votes, ACTG structure, what are the roles of people in protocol development, why trials take so long, publications, 175, not a lot of new drugs available.

Cont'd CCG Mtg. Mon., Dec 2.

Who is responsible in distribution of protocols? Concept Sheets?

New membership discontinuance document was passed out and discussed.

Budget was discussed.

Some of the priorities in accordance w/ CCG for the ACTG:
Role of patient care cmte., immunology studies are controlled by primary infection cmte.; pharmacologists need to be in on trials from the beginning, what is their role?; role definition of PES; pediatrics interaction with other cmte.'s; women's issues; site and data need technical support, data collection; improved diagnostic method in PCP; neurology has communication problems w/ ACTG, what is the agenda?; virology needs organization and communication, sample storage problem, decision making; what is the role of the women's cmte.;
exec. cmte. must coordinate efforts w/in ACTG and other researchers, communication of investigators, the concept of investigator initiated research, communication btwn exec. cmte. and community, leadership role in epidemic, resources; oncology cmte. must study angiogenesis compounds, role of NCI w/ lymphoma, relation w/ women's health; ACTG is out of balance in terms of OI trials and anti-HIV prophlaxis trials; in CMV the issue w/ Syntex, MAI and Crypto need new trials, study of wasting syndrome, new compounds for PCP, 175, relation between primary infection cmte. and exec., workload problem, a resistance to nested studies.

Over all issues:
The ACTG (gang of five, powers that be, etc.) don't think pro-actively, there is NO SENSE OF URGENCY, leadership, ea. sub-cmte. should have a rep. on exec. cmte., better coordinating effort, access to lab samples.

A pediatric trial of BI-RG-587 alone and in combo w/ AZT in mild to moderate symptomatic children where resistance was observed in adults so the trial has been suspended. Data still not all collected, so they don't exactly know where to go from here. The combo. trial will continue in adults.

Tues. Plenary Session:
ACTG 021 secondary prophlaxis comparing aerosol pent. w/ septrax. One of the first trials to include people of color, trial opened in July 88 and closed in Nov of 90; shows efficacy of septrax, not a lot of data on septrax prophlaxis for toxo; consideration of combining septrax and AP for more aggressive therapy; basically not a lot of new news...
ACTG 129 comparison of DHPG/Foscarnet and management of small peripheral retinal lesions; both drugs behave similarly; need new drugs for CMV; some possible immune benefit of Fosc.; DHPG is bone marrow suppressing and anti-retroviral can be w/ Fosc. the protocol was suspended; Fosc. is hard to admin¬ister (infusions must be timed accurately) and it is highly toxic and incredibly expensive; clearly not a drug for the poor; ,speaker announced ACT UP "LOWER FOSCARNET'S PRICE" buttons and the drug rep made a fool of herself by explaining that the drug is available free on compassionate use and expanded access; she was hissed off the microphone...

12/3, Immunology Subcmte. Immunohematology Working Group:
John Fahey, chair of the Immunology Cmte. is trying to dissolve this sub cmte. and Roy Steigbigel was trying to find ways to save it. He even called on ACT UP to help. Apparently the cmte. is too small and there is not enough interestin the issue. Ways to keep the cmte. alive were discussed; using existing trials for collecting data on thrombocytopenia and neutropenia, and add on to a large existing study or nest on to 175, it seems that 175 shows early disease data for symptomatic thromb. even though 175 is an early stage disease trial. It was suggested that the cmte. propose to utilize existing data within the clinical trials system to save the cmte. and study this important AIDS associated blood disorder.
12/3, Oportunistic Infection Cmte., CMV/Viral Diseases Pathogen Study Group:
Reports given in three trials; 1)ACTG 183 Oral Gancyclovir vs. placebo for maintenance after treatment of CMV colitis, description of endpoints have changed and the size of the trial is 170 patients.; 2)ACTG 151 Combination trial of Foscarnet and Gancyclovir in maintenance therapy for patients w/ Retinitis after induction therapy, to early to report significant data, too early; 3)ACTG 172, Trifluorothymide for Acyclovir resistant Herpes, a pilot study w/ only three patients enrolled, again, no significant data. There seems to be a problem w/ a CMV prophlaxis trial for oral gancyclovir and an acyclovir pro-drug BW256U87, Syntex is reluctant to supply the drug because of data management and low supply of the drug

12/3, Executive Cmte. Mtg. w/ PI's, Cmte. chairs and vice chairs:
The main news of this cmte. mtg. involve the election of the new chair of the ACTG. Nominations include John Phair and Paul Volberding. The hemophilia group or NICHD will not have votes. June 22-24 will be the next mtg. and it will be a retreat because of conflict w/ the Int. AIDS Conference. Three basic problems were discussed; must do more immune based therapy research, re-evaluation of the PES, what is the form and function, a malaise in concept sheets.

New staff: Lew Barker from FDA Virology, Red Cross will be in charge of clinical research program, scientific content of all programs, and treatment research operations.
Bill Duncan used to be at the NIH, an immunologist will be in charge of operations and budget.

ACTG Recompetition: Priority scores will be released wk. of 12/9; summary statements will be released early 92, final composition of new ACTG will be available after the NIAID funding applications early 92.

12/3, ACTG 186 Team Mtg.:
John Zurlo, chair, a prophlaxis trial for sinusitis, four arm study, placebo in 2 arms, all patients will receive decongestant, 132 patient accrual, possibly 240, protocol was passed out at the mtg., some basic modifications, all the drugs used are safe and known, some discussion regarding radiographic criteria and that patients may drop out of the trial because of endoscopy.

12/4, ACTG 175, Investigators Mtg.:
Obvious that this trial is well under way from this mtg. It's apparent that the researchers involved have heard our complaints and certain revisions have been made, however several activists raised questions at this mtg. that did not go unheeded. The related demo at the cocktail party was held this evening in conjunction to alternative therapy activists. The demonstrators passed out flyers and wore lab coats and placards.

12/4, OI Cmte., Mycobacterial/Bacterial Pathogen Study Group:
ACTG 157 Clarithromycin for MAC in AIDS; this study to study safety and efficacy in clar., a 12 week study enrolling 56 patients, 12 weeks being the endpoint. Some resistance problems found in vitro, however there were no resistance prior
to 8 weeks into the study. The trial has shown some clinical improvement; no real evidence. New combination trials are being conceived.

ACTG 177; Comparison trial of INH to Pyrazinamide/Rifampin for TB prophylaxis. Very large trial of 2,000 patients but accrual will be split between ACTG an CPCRA. Questions were what effects MDR TB will have in this trial. MDR TB develops quickly, the patients wouldn't qualify. Also if a patient has had MDR TB they wouldn't qualify because they have had treatment. The MDR outbreak in NY is not totally drug resistant, two drugs are effective for a longer treatment period and are more expensive. Current MDR strains seem to be related, mostly identical.

ACTG 196, (not sure of protocol #) prophylaxis, 500mg clarithromycin vs. placebo for MAC in patients less than 100 cd4. phase III, double blind, randomized, comparative study. Endpoint being MAC or disseminated. Second endpoint being death or drug toxicity. Over twelve years old inclusion. A 24 month study. Issues w/ this trial are: In order for a placebo to not be used, the rifabutin study must be competed quickly so a comparative drug will be available. Co-enrollment of women, a 3 arm dose ranging trial, and there are time constraints by the drug manufacturer wants to be ready by Feb.
ACTG NOTES & REPORT  DECEMBER 1991  Andy Zysman

Plenary Tues Dec 3

ACTG 021 secondary prophylaxis presented by Dr. David Hardy
Comparison of Aerosol Pentamadine (300mg q 4 wks.) versus
TMP 160 / SMZ 800 daily ( 1 Septra DoubleStrength)
All subjects took azt 600 mg./day. Treatment started 10 weeks
post 1st episode of PCP. People with prior drug reaction were al¬
lowed if rxns. not treatment limiting. 59 % had a hx of prior
septra rxn. Mean CD4 = 56

At 18 months, rate of PCP recurrence: 11.4% of septra v.
27.6% of AP. (less than half as much!) Because of crossover
design, all 36 cases in AP group were still on ap when they
developed pcp, but only half of septra group (7/14) were on ap at
time of pcp

There were 90 deaths total: 43 in septra, 47 in ap. There
was no difference in survival between the 2 groups, but only 5
deaths were due to PCP.

There were a total of 48 crossovers, 42 of these were on
septra and crossed to ap; but there was no significant difference
in serious hematological or hepatic toxicities between the two
groups

Analyzing the pcp cases, 7 of 14 of the septras had only
been on septra a short while; all ap’s had been on a long time

If septra proved so much better in preventing pcp, why was
there no survival difference? Because pcp and toxo were rare
causes of death (3% each). Insufficient power in this short trial
where people die of other things. They are adding a QOL assay in
a different study.

MASUR - New USPHS Guidelines will be released soon. They include:
monitoring: at least every 6 months. Decision should be based on
absolute CD4 count of 200 (but some suggested 250 or 300)
(recomendation will not include %’s but some wanted CD4:<20 %)
clinical: unexplained fever or thrush irrespective of CD4 count.

Recomendation: TMP/Sx 1 DS/day is first choice
Aerosol pentamidine is second choice.
(There is not yet enough data to recommend dapsone or BW566.)

Before starting AP, must rule out active TB! Volberding
asked, are there any circumstances to use both? Panel: NO, very
low breakthrough. A pedi from NJ said they have good results
with iv pentamidine. Masur says it is too expensive, perhaps ok
if pt lacks alternatives. ACTG 081 will continue for more
answers.
SOCA- Study of Ocular Complications in AIDS Dr. Jabs

This trial was designed to address gancyclovir (GCV) vs. foscarnet (Fos) and how to handle small peripheral ocular lesions in CMV retinitis. People with big lesions were randomized immediately. People with non sight-threatening could elect to defer treatment or randomize and treat immediately.

AZT was prohibited for GCV pts. during the induction period, but then ok. With Fos, all antivirals ok.

Relative Risk mortality = 1.77 (excess in GCV) survival median 8.5 months vs 12.6 months. Subgroup analysis: people with creatinine clearance <1.2 have a Relative Risk of .56, while those with poor kidney function (>1.2) had a RR of 4.6. So in the small subgroup with good kidneys, survival favored GCV.

Study stopped due to increased mortality with GCV. Incidentally, no difference found in drugs’ effect on retinitis.

Review of morbidity: neutropenia 1.88 (excess GCV) kidney failure .35 (excess FOS)

Twice as many foscarnet pts switched; this was because of toxicity not disease progression. Switching drugs did not affect mortality data. The baseline cd4 count was 29. GCV lost 6 cells while fos gained 4 cells at 4 wks.

Foscarnet pts got more anti-viral drug use, particularly azt. But irrespective of concomitant use, foscarnet seemed to have its own effect in preventing mortality.

Panel discussion: There is little agreement on what this study means, and what treatment recommenations should be made.

Hirsch: differences probably due to foscarnet’s antiviral effect.

cost: lyr foscarnet $27,000 gcv $9,000 wholesale drug only.

Cytotoxic T cell response to infection

Incomplete notes: I didn’t follow this well.

CTL (Cytotoxic T Lymphocytes)

Class I restriction pattern CD8: recognize endogenous processed proteins

Class II CD4: recognize exogenous(Phagocytized)

Experiment done with SCID Mouse with reconstituted human T and B cells, using Adoptive CTL Transfer protocol. They reconstituted mice from with immune system a seronegative donor. HLA matched CTL cells prevented ability to culture (though still PCR POS); no effect if not HLA matched.

Current studies: ACTG 080: Ex vivo expansion of CD8 by IL-2; autologous reinfusion

Cliff Lane at NIH doing same next week in 1 pt.

ACTG notes December 1991 Andy Zysman page 2 of 4
People with Different HLA types recognize HIV sites differently. Transfusion of activated cells may need to be HLA specific (or individual specific). That is, can rarely give 1 persons CD8’s to another; but expansion of own cells and re-infusion might work.

A minor changes (single AA mutation) may lead to complete virus immune escape. Like the L-drug problem.

WARNING: These CTL clones may cause pathology. (in mice, CNS injection can lead to death)

This may be related to ADC (AIDS dementia Complex) They found it easy to isolate CTL cells in CSF from ADC pt. Excess concentration of these cells in CNS of ADC patient. Perhaps it is caused by the release of cytokines by CTLs like ifn-gamma causing an inflammatory response.

PHARMACOLOGY COMMITTEE  Dec 4
NAC- Robert Walker
  Antioxidant, blocks effects of PMA, TNF, IL-6 in cell cultures, nac inhibits p24 production (Herzenberg and others). Tox: IV anaphylactoid rxn (0.2-3%) GI toxicity ?ulcers
  Half life 5-6 hrs oral bioavailability = 9%

Study: Open Label dose escalation
Group  IV dose 2/wk oral qid x 6 wks
I  3.7mg/kg ?
II  ? 300
III  ? ?
IV  100mg/kg 1200

(I missed the ? doses; all levels get both IV and oral)
So far 10 enrolled, data on 6 reviewed. Thiol assays at Stanford by Howard Sussman.
so far just dose 1 and 2 given. Oral - no free NAC levels at 300 mg qid (but this may be the wrong measure to use)
oral dose will go up to 1200
IV dose #2 has a Cmax of 55uM.
Clinical: so far not much side effects, not any real efficacy data.

Schoenfeld COMBINATION THERAPY: Assessing Synergy

Sounded good, but I got little out of this session. SYNERGY: 2 drugs have greater effect than "expected". This may lead to smaller doses needed, this may lead to less toxicity. But toxicity also may be synergistic.

ACTG 175 Meeting: Interaction with other committees

OI committee: nested study possible for people who drop below 200 CD4’s. ? prophylactic protocol. Maybe TB PX or Zoster tx protocol. ? after they get sick, treat on acute care protocols. possibly nest a primary PCP PX, but unclear if they will have a dose or plan in time.

ACTG notes  December 1991  Andy Zysman  page 3 of 4
(Plans for an advanced treatment protocol may do coenrollment with cmv and mai prophylaxis protocols)

**Women's Committee:** Wofsy wants to ensure sufficient female enrollment (20%) to allow data to evaluate female specific endpoints (low Hgb, Cx. abnormalities).

- Wants to include GYN assessment plan
- AIDS related OI's or Cancers; including pneumonia, sepsis, vag dysplasia, pid
- Could assess relation between the endpoints and at which level it occurs.
- Contraception, methods used, compliance

**Neurology:** Concept sheets will be coming. Collect neuropsychiatric data, as disease progresses. Looking at peripheral neurotoxicity: can antivirals be started in people who already have some degree of neuropathy.

**Myopathy:** Is it AIDS or is it drug therapy?

**Pharmacology:** medication compliance: They have a dispenser which records the time they open the bottle. They have determined that doing a pill counts is worthless in assessing compliance. They suggest a short study: 2 months in a subset of virology subjects. Dispense RX with cap on one that records when the cap was opened. If opened every 8 hrs, then compliant. 8 acyivists in roo, including me, argued this was a ridiculous and ineffective way to determine compliance.

**Immunology**
(I missed most of this) 4 vials of cells and 4 vials of serum frozen. (Virology is 11 subsets). Immunology would like some of these to be same as virology subset group.

**Oncology Committee**

I attended a few Oncology session. Most work was done trying to create a study of prophylaxis vs. anal cancers in men and cervical cancers in women, which are both caused by the HPV (Human Papilloma Virus). Two different concept sheets were presented, and in meetings I was not at, with the Women's Committee, an attempt is being made to integrate these into one working protocol.

New chair is Alexandra Levene at U.S.C..

Lymphoma studies are not enrolling well, probably because drugs are all on market and physicians prefer using their own clinical judgement to being randomized. Attempts to enroll pts from referral physicians discussed. No prelim data reviewed.

K.S.: only study discussed was VP-16; dose ranging study almost complete. They are happy with efficacy data so far, and have selected a dose for larger studies now planned.

ACTG notes December 1991 Andy Zysman page 4 of 4
Draft of minutes, AZ Meeting with FDA December 4, 1991

Participants:

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Project Inform

John James
AIDS Treatment News

John Dolan
ACT UP Golden Gate

Andrew Zysman
ACT UP Golden Gate
Question: Is it a Drug or a Biologic? Dr. Burke: Recent advising published in Federal Register. If natural source: Biologic. Probably AGM-1470 is a drug, SP-PG is a biologic. (rPF4 likely also a biologic.) Note if you change manufacturing procedure, what was once a biologic may become a drug.

To obtain an IND, for a cancer drug of such priority as these, less animal testing is needed to have it approved. Essentially all they want is acute toxicity data, in one or two animal species.

Acute toxicity is just one or two doses, watched a short time. If the Phase I plan is for a long term treatment, all they would need is a months toxicity data in one species.

They need less data than in the standard NCI mini cytotoxic panel.

What is needed for IND application? It is largely flexible, hence great desirability of pre-IND meeting.
1. substance and manufacturing must be well characterized.
2. Some quality assurance manufacturing standards, but there is no set level of purity required.
3. protocol for clinical trial: To whom given, how administered, how stopped.
4. acute toxicity data in two species.

Carcinogenicity is not an issue in this class of drugs! Don’t need to do for it for IND (May want to do later, or simultaneous with Phase I to extend indications, etc.)

CBER said they do take a pro-active role. They encourage meeting with sponsors before the IND is submitted. They have a brochure called "Things to Consider" that they will send to us. CDER likewise.

If a sponsor came with minimal animal data and you really needed to send them back, how long would it take to come back with all required data? CDER estimated 3 months. CBER estimated 4-5 months. Once the IND is submitted, FDA has 30 days to do a Safety Review. If OK, trial can start.

Burke says that Takeda may already have enough toxicity data based on his knowledge of animal studies already performed to file the IND now.

It is up to company if they wish to bring others to the IND and pre-IND meetings. In past, this has usually happened only with institutions. FDA has no objection, would not look unfavorably upon community or activist participation.

What would be required in subcutaneous (intra-lesional) data, if that is planned administration method for Phase I? a few rabbits, test some sub-Q doses; it should not make an ulcer. Not a big obstacle, could take 2 weeks to perform.
## Appendix I

### PROTOCOL INDEX

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<td>Dextran sulfate PK (oral, IV)</td>
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<td>AP deposition in 021 and 081 pts.</td>
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<td>ACTG 080</td>
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<td>CD8 w/ or w/out IL-2</td>
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<td>*ACTG 082</td>
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<td>*ACTG 093</td>
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<td>Pediatrics</td>
<td>rCD4 in infants &amp; children</td>
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<td>*ACTG 102</td>
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<td>Pyrimethamine PK in AIDS/ARC</td>
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<td>*ACTG 103</td>
<td>Pediatrics</td>
<td>AZT conc. vs int. AZT vs int ddI in sympto kids</td>
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<td>ACTG 106</td>
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<td>AZT/ddC combination</td>
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<td>ACTG 107</td>
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<td>Oral VP16 in KS: dose-escalating Phase I</td>
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<td>*ACTG 112</td>
<td>Primary Infection</td>
<td>AZT vs ddC (002 f/u)</td>
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<td>*ACTG 118</td>
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<td>ddI in ZDV intolerant</td>
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<td>AZT + ABV in KS (Phase I)</td>
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<td>*ACTG 076</td>
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<td>AZT vs. placebo in pregnant women &amp; their newborns</td>
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<td>*ACTG 077P</td>
<td>Opportunistic Infections</td>
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<td>AZT vs ddC in long-term AZT ARC/AIDS pts.</td>
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<td>Itraconazole for acute treatment of dissem. histo.</td>
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<td>FIAC dose-ranging (in pts. shedding CMV)</td>
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<td>5 Drug Combo vs. 4 Drug for MAI</td>
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<td>ACTG 136</td>
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<td>Phase II ddC - kids</td>
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<td>*ACTG 151</td>
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<td>*ACTG 152</td>
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<td>BV-ARA-U vs Acyclovir in Localized Zoster</td>
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<td>ddI/AZT vs ddC/AZT vs AZT vs ddI w/CD4 200-500</td>
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<td>Dapsone as PCP Proph in kids intolerant to TMP/SMX</td>
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<td>*ACTG 180</td>
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<td>BI-RG-587 Alone &amp; in Combo w/AZT in Mild-Mod. Sympto Kids</td>
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<td>Pk Study of the effects of L-697,661 on AZT</td>
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<td>Pediatrics</td>
<td>HIVIG for Prevention of Maternal-Fetal HIV Transmission in Mothers on ZDV</td>
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<td>Neurodevelopmental and Neurological Study of HIV-1 in Infants and Children</td>
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<td>Fluconazole vs. clotrimazole for sys fungal disease</td>
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THIRTEENTH AIDS CLINICAL TRIALS GROUP MEETING

Washington Hilton
December 2-5, 1991

AGENDA

Monday, December 2, 1991

11:00 a.m. - 4:00 p.m. Community Constituency Group
Conservatory

3:00 p.m. - 5:00 p.m. NHF Regional Coordinators
Chevy Chase

4:00 p.m. - 6:00 p.m. Virology Committee: Virology Technical Subcommittee
Dupont

4:00 p.m. - 7:00 p.m. Statistical Working Group
Thorougbred

4:00 p.m. - 7:30 p.m. PPD and NICHD Site Monitors
Edison

5:00 p.m. - 8:00 p.m. Registration
Concourse Level

6:00 p.m. - 7:00 p.m. Virology Committee: Pediatric Virology Working Group
Dupont

ACTG Surrogate Marker Working Group Core (members only)
Farragut

6:30 p.m. - 7:30 p.m. Patient Care Core Committee (members only)
Military

7:00 p.m. - 8:00 p.m. Site and Data Management Core Committee (members only)
Map

7:00 p.m. - 9:00 p.m. Executive Committee (members only)
Hemisphere

Virology Core Committee (members only)
Dupont

Immunology Core Committee (members only)
Chevy Chase
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<tr>
<td>7:00 a.m. - 5:30 p.m.</td>
<td>Registration</td>
<td>Concourse Level</td>
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<tr>
<td>7:00 a.m. - 8:20 a.m.</td>
<td>Executive Committee (members only)</td>
<td>Hemisphere Caucus</td>
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<tr>
<td>7:15 a.m. - 8:15 a.m.</td>
<td>Immunology Committee: T-Cell Proliferation Working Group</td>
<td>Chevy Chase Military</td>
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<td>7:20 a.m. - 8:20 a.m.</td>
<td>ACTG 153 Investigators Meeting</td>
<td>Dupont Map</td>
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<td>8:30 a.m. - 10:00 a.m.</td>
<td>Virology Committee: PCR Working Group</td>
<td>IBR Center Map</td>
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<td>8:30 a.m. - 10:00 a.m.</td>
<td>Plenary Session</td>
<td>IBR Center Map</td>
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<td>10:15 a.m. - 11:00 a.m.</td>
<td>Immunology Committee: Immunohematology Working Group</td>
<td>Hemisphere Edison</td>
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<td>10:15 a.m. - 12:00 noon</td>
<td>Pediatric Committee: Primary Therapy Working Group</td>
<td>Farragut Conservatory</td>
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<td>10:15 a.m. - 12:15 p.m.</td>
<td>Pediatric Committee/Women’s Health Committee: Perinatal Transmission/OB/PED Working Group</td>
<td>Military IBR East</td>
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<td>10:15 a.m. - 12:15 p.m.</td>
<td>Pediatric Committee: Opportunistic Infections Working Group</td>
<td>Military IBR East</td>
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<tr>
<td>10:15 a.m. - 12:15 p.m.</td>
<td>Pharmacology Core Committee (members only)</td>
<td>Conservatory Military IBR East</td>
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<td>10:15 a.m. - 12:15 p.m.</td>
<td>Oncology Full Committee</td>
<td>Conservatory Military IBR East</td>
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<tr>
<td>10:15 a.m. - 12:15 p.m.</td>
<td>Opportunistic Infections Full Committee</td>
<td>Conservatory Military IBR East</td>
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<td>Primary Infection Committee: Phase II/III Working Group (members only)</td>
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<td>Protocol Development Process Review Committee</td>
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<td>11:00 a.m. - 12:00 noon</td>
<td>Immunology Committee: Pediatric Immunology</td>
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<td>Patient Care Full Committee</td>
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<td>11:00 a.m. - 1:30 p.m.</td>
<td>Virology Full Committee</td>
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<td>12:00 noon - 1:00 p.m.</td>
<td>Protocol Evaluation Subcommittee Full Committee</td>
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<tr>
<td>12:00 noon - 1:30 p.m.</td>
<td>Immunology Committee: Immune-Based Therapy Working Group Full Session</td>
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<tr>
<td>12:00 noon - 3:00 p.m.</td>
<td>Pediatric Core Committee (members only)</td>
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<td>12:00 noon - 10:00 p.m.</td>
<td>Poster Display</td>
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<td>12:15 p.m. - 2:00 p.m.</td>
<td>Neurology Core Committee (members only)</td>
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<td>12:30 p.m. - 2:00 p.m.</td>
<td>Opportunistic Infections Core Committee (members only)</td>
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<td>12:30 p.m. - 2:30 p.m.</td>
<td>Oncology Core Committee (members only)</td>
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<td>1:00 p.m. - 2:30 p.m.</td>
<td>NIDA/NIAID Session</td>
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<td>1:00 p.m. - 5:00 p.m.</td>
<td>Primary Infection Core/PI Working Groups Joint Meeting (members only)</td>
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<td>1:30 p.m. - 2:30 p.m.</td>
<td>Site and Data Management Full Committee</td>
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<td>2:00 p.m. - 3:00 p.m.</td>
<td>Virology Committee: Protocol Virologists Subcommittee</td>
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<td>Site Pharmacists Meeting</td>
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<td>2:00 p.m. - 4:00 p.m.</td>
<td>Immunology Committee: Immune-Based Therapy Working Group Core (members only)</td>
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<td>2:15 p.m. - 3:15 p.m.</td>
<td>Opportunistic Infections Committee: <em>Pneumocystis carinii</em> Pathogen Study Group</td>
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<td>2:30 p.m. - 3:30 p.m.</td>
<td>ACTG 142 Investigators Meeting</td>
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<td>Site and Data Management: Data Managers Workshop</td>
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<td></td>
<td>Site and Data Management: Field Representatives Workshop</td>
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<td>2:30 p.m. - 4:00 p.m.</td>
<td>Clinical Site Monitors Working Group</td>
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<td>3:00 p.m. - 4:00 p.m.</td>
<td>Women’s Health Committee: Gynecology/Oncology/Endocrine Working Group</td>
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<td>Neurology Symposium: Toxic and HIV Related Peripheral Neuropathies</td>
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<td>3:00 p.m. - 5:00 p.m.</td>
<td>Pediatric Symposium: Pharmacokinetics and Pharmacodynamics of Antiretroviral Drugs</td>
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<td>3:15 p.m. - 4:00 p.m.</td>
<td>Quality of Life Working Group: Business Meeting</td>
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<tr>
<td>3:15 p.m. - 4:15 p.m.</td>
<td>Virology Committee: VRL Advisory Committee (members only)</td>
</tr>
</tbody>
</table>
**Tuesday, December 3, 1991 (Cont.)**

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>3:30 p.m. - 5:00 p.m.</td>
<td>Opportunistic Infections Committee: Cytomegalovirus/Viral Diseases Pathogen Study Group</td>
<td>IBR East</td>
</tr>
<tr>
<td>4:00 p.m. - 5:00 p.m.</td>
<td>ACTG 162 Investigators Meeting</td>
<td>Chevy Chase</td>
</tr>
<tr>
<td></td>
<td>ACTG 081/981/181 Investigators Meeting</td>
<td>Conservatory</td>
</tr>
<tr>
<td></td>
<td>ACTG 143 Investigators Meeting</td>
<td>Military</td>
</tr>
<tr>
<td></td>
<td>Quality of Life Seminar Session: Special Issues on Quality of Life and Cost Effectiveness in HIV Clinical Trials</td>
<td>Cabinet</td>
</tr>
<tr>
<td>4:00 p.m. - 5:30 p.m.</td>
<td>Immunology Committee: Flow Cytometry Advisory Committee (members only)</td>
<td>Caucus</td>
</tr>
<tr>
<td>4:30 p.m. - 5:30 p.m.</td>
<td>Virology Committee: Resistance Working Group</td>
<td>Georgetown West</td>
</tr>
<tr>
<td>5:00 p.m. - 6:30 p.m.</td>
<td>Executive Committee with Principal Investigators, Committee Chairs, Vice Chairs and PSG Heads</td>
<td>Thoroughbred</td>
</tr>
<tr>
<td></td>
<td>Patient Care Working Group: IVDU</td>
<td>State</td>
</tr>
<tr>
<td></td>
<td>Patient Care Working Group: Gay/Bisexual Men</td>
<td>Conservatory</td>
</tr>
<tr>
<td></td>
<td>Patient Care Working Group: Pediatrics</td>
<td>Hemisphere</td>
</tr>
<tr>
<td>5:30 p.m. - 6:30 p.m.</td>
<td>Virology Committee: Quantitative Working Group</td>
<td>Georgetown East</td>
</tr>
<tr>
<td>5:30 p.m. - 7:30 p.m.</td>
<td>Immunology Committee: Flow Cytometry Working Group</td>
<td>Caucus</td>
</tr>
<tr>
<td>6:00 p.m. - 8:00 p.m.</td>
<td>Hemophilia Investigators Meeting</td>
<td>Independence</td>
</tr>
</tbody>
</table>
**Tuesday, December 3, 1991 (Cont.)**

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>7:00 p.m. - 8:00 p.m.</td>
<td>ACTG 152 Team Meeting</td>
<td>Jackson</td>
</tr>
<tr>
<td></td>
<td>CD4-PE Team Meeting</td>
<td>Chevy Chase</td>
</tr>
<tr>
<td></td>
<td>ACTG 081/981/181 Team Meeting</td>
<td>Conservatory</td>
</tr>
<tr>
<td></td>
<td>Advanced Disease Team Meeting</td>
<td>Hamilton</td>
</tr>
<tr>
<td></td>
<td>ACTG 140 Team Meeting</td>
<td>Edison</td>
</tr>
<tr>
<td></td>
<td>ACTG 150 Team Meeting</td>
<td>Farragut</td>
</tr>
<tr>
<td></td>
<td>ACTG 076 Team Meeting</td>
<td>Grant</td>
</tr>
<tr>
<td></td>
<td>ACTG 186 Team Meeting</td>
<td>State</td>
</tr>
<tr>
<td>7:00 p.m. - 9:00 p.m.</td>
<td>Virology Committee: Dataworks Training Session</td>
<td>Military</td>
</tr>
<tr>
<td></td>
<td>Community Constituency Group</td>
<td>Map</td>
</tr>
<tr>
<td></td>
<td>CAB Networking Meeting</td>
<td>Cabinet</td>
</tr>
<tr>
<td>8:00 p.m. - 9:00 p.m.</td>
<td>ACTG 173 Team Meeting</td>
<td>Edison</td>
</tr>
<tr>
<td></td>
<td>ACTG 180 Team Meeting</td>
<td>Farragut</td>
</tr>
<tr>
<td></td>
<td>ACTG 182 Team Meeting</td>
<td>Grant</td>
</tr>
<tr>
<td>8:00 p.m. - 10:00 p.m.</td>
<td>Women’s Health Core Committee (members only)</td>
<td>Caucus</td>
</tr>
</tbody>
</table>

**Wednesday, December 4, 1991**

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>7:00 a.m. - 5:30 p.m.</td>
<td>Registration</td>
<td>Concourse Level</td>
</tr>
<tr>
<td>7:00 a.m. - 8:20 a.m.</td>
<td>Executive Committee (members only)</td>
<td>Hemisphere</td>
</tr>
<tr>
<td></td>
<td>Immunology Committee: Humoral Immunity Working Group</td>
<td>Caucus</td>
</tr>
<tr>
<td></td>
<td>Perinatal Investigators Meeting (ACTG 076, 082, 185)</td>
<td>Edison</td>
</tr>
<tr>
<td>7:15 a.m. - 8:15 a.m.</td>
<td>ACTG 187 Start-Up Meeting</td>
<td>Dupont</td>
</tr>
</tbody>
</table>
**Wednesday, December 4, 1991 (Cont.)**

7:20 a.m. - 8:20 a.m.  
Women’s Health Committee:  
Protocol Design/Polysubstance Working Group  
Farragut

8:30 a.m. - 10:00 a.m.  
Plenary Session  
IBR Center

8:30 a.m. - 10:00 p.m.  
Poster Display  
Concourse Level

10:00 a.m. - 11:00 a.m.  
Women’s Health Committee:  
Epidemiology Working Group  
Grant

10:15 a.m. - 11:15 a.m.  
Pediatric Committee: Phase II/III Working Group  
Edison

10:15 a.m. - 12:15 p.m.  
Primary Infection Committee:  
Phase I/II Working Group  
(members only)  
Farragut

10:30 a.m. - 12:00 noon  
ACTG 175 Investigators Meeting  
Georgetown West

10:30 a.m. - 12:30 p.m.  
Opportunistic Infections Core Committee (members only)  
Caucus

10:30 a.m. - 12:30 p.m.  
Pharmacology Full Committee  
Georgetown East

11:00 a.m. - 12:00 noon  
Infrastructure Grantees Meeting  
Grant

11:00 a.m. - 12:15 p.m.  
Site and Data Management Full Committee  
Monroe West

11:00 a.m. - 12:30 p.m.  
Immunology Symposium: Advances in Immunologic Monitoring of HIV-Infection  
IBR East

11:00 a.m. - 1:00 p.m.  
Virology Committee: Virology Laboratory Subcommittee  
Monroe East

12:00 noon - 1:00 p.m.  
ACTG 068 Investigators Meeting  
Dupont

12:30 p.m. - 2:00 p.m.  
Opportunistic Infections Committee:  
Mycobacterial/Bacterial Pathogen Study Group  
Jefferson West
### Wednesday, December 4, 1991 (Cont.)

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:00 p.m. - 2:30 p.m.</td>
<td>Patient Care Working Group: Women</td>
<td>Hemisphere</td>
</tr>
<tr>
<td></td>
<td>Patient Care Working Group: Hemophiliacs</td>
<td>Map</td>
</tr>
<tr>
<td></td>
<td>Immunology Committee: NK &amp; T-Cell Cytotoxicity Working Group</td>
<td>Conservatory</td>
</tr>
<tr>
<td>1:00 p.m. - 3:00 p.m.</td>
<td>Primary Infection Full Committee</td>
<td>Caucus</td>
</tr>
<tr>
<td>1:00 p.m. - 4:00 p.m.</td>
<td>Pediatric Full Committee</td>
<td>IBR West</td>
</tr>
<tr>
<td>2:00 p.m. - 3:00 p.m.</td>
<td>ACTG 135 Investigators Meeting</td>
<td>Thoroughbred</td>
</tr>
<tr>
<td></td>
<td>Clinical Site Monitors</td>
<td>Georgetown West</td>
</tr>
<tr>
<td></td>
<td>PRAB: Questions and Answers</td>
<td>State</td>
</tr>
<tr>
<td></td>
<td>Virology Committee: Dataworks Users Meeting</td>
<td>Georgetown East</td>
</tr>
<tr>
<td>2:00 p.m. - 4:00 p.m.</td>
<td>Women's Health Full Committee</td>
<td>Monroe</td>
</tr>
<tr>
<td>2:30 p.m. - 3:30 p.m.</td>
<td>Combined Session: Other Viruses Working Group of the Virology Committee and CMV/Viral Diseases Pathogen Study Group of the OI Committee</td>
<td>Jefferson West</td>
</tr>
<tr>
<td></td>
<td>Immunology Committee: Protocol Immunologists Working Group</td>
<td>Farragut</td>
</tr>
<tr>
<td>3:00 p.m. - 4:00 p.m.</td>
<td>MAI Protocol Start-Up Meeting</td>
<td>Thoroughbred</td>
</tr>
<tr>
<td>3:00 p.m. - 5:00 p.m.</td>
<td>Patient Care Full Committee</td>
<td>Georgetown West</td>
</tr>
<tr>
<td></td>
<td>Primary Infection: Combination Therapies Working Group (members only)</td>
<td>Edison</td>
</tr>
<tr>
<td>3:30 p.m. - 5:00 p.m.</td>
<td>ACTG Surrogate Marker Working Group</td>
<td>IBR Center</td>
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</table>
**Wednesday, December 4, 1991 (Cont.)**

<table>
<thead>
<tr>
<th>Time</th>
<th>Event Description</th>
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<tbody>
<tr>
<td>3:45 p.m. - 5:15 p.m.</td>
<td>ACTG 154/156 Investigators Meeting</td>
</tr>
<tr>
<td>4:00 p.m. - 5:00 p.m.</td>
<td>Virology Committee: Other Viruses Working Group</td>
</tr>
<tr>
<td>4:30 p.m. - 6:30 p.m.</td>
<td>Social Hour to Acknowledge the Accomplishment of the ACTG</td>
</tr>
<tr>
<td>5:00 p.m. - 6:00 p.m.</td>
<td>Opportunistic Infections Committee: Systemic Mycoses Pathogen Study Group</td>
</tr>
<tr>
<td></td>
<td>Virology Committee: Virology Transition Working Group</td>
</tr>
<tr>
<td>5:00 p.m. - 6:30 p.m.</td>
<td>Immunology Full Committee</td>
</tr>
<tr>
<td>5:15 p.m. - 6:30 p.m.</td>
<td>Patient Care Core Committee (members only)</td>
</tr>
<tr>
<td>5:30 p.m. - 6:30 p.m.</td>
<td>ACTG 155 Investigators Meeting</td>
</tr>
<tr>
<td>6:00 p.m. - 7:00 p.m.</td>
<td>ACTG 159 Investigators Meeting</td>
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<tr>
<td></td>
<td>ACTG 152 Investigators Meeting</td>
</tr>
<tr>
<td>7:00 p.m. - 8:00 p.m.</td>
<td>ACTG 190 Team Meeting</td>
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<td></td>
<td>ACTG 157 Team Meeting</td>
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<tr>
<td></td>
<td>ACTG 183 Team Meeting</td>
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<tr>
<td>7:00 p.m. - 9:00 p.m.</td>
<td>ACTG 175 Team Meeting</td>
</tr>
<tr>
<td>8:00 p.m. - 9:00 p.m.</td>
<td>ACTG 189 Team Meeting</td>
</tr>
<tr>
<td>Time</td>
<td>Event</td>
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<tr>
<td>-------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>7:00 a.m. - 12:00 noon</td>
<td>Registration</td>
</tr>
<tr>
<td>7:00 a.m. - 8:20 a.m.</td>
<td>Executive Committee (members only)</td>
</tr>
<tr>
<td>7:15 a.m. - 8:15 a.m.</td>
<td>ACTG 179 Investigators Meeting</td>
</tr>
<tr>
<td>8:30 a.m. - 10:00 a.m.</td>
<td>Plenary Session</td>
</tr>
<tr>
<td>10:15 a.m. - 11:15 a.m.</td>
<td>ddI Investigators Meeting</td>
</tr>
<tr>
<td>10:15 a.m. - 11:45 a.m.</td>
<td>Opportunistic Infections Committee: Protozoan Pathogen Study Group</td>
</tr>
<tr>
<td>10:30 a.m. - 11:30 a.m.</td>
<td>ACTG 170 Investigators Meeting</td>
</tr>
<tr>
<td></td>
<td>Pediatric Committee: IBT/Immunology Working Group</td>
</tr>
<tr>
<td></td>
<td>Virology Full Committee Summation</td>
</tr>
<tr>
<td>11:00 a.m. - 1:00 p.m.</td>
<td>Adverse Experience Reporting Working Group</td>
</tr>
<tr>
<td>12:00 noon - 5:00 p.m.</td>
<td>Community Constituency Group</td>
</tr>
</tbody>
</table>
Appendix III

CCG: PCP PATHOGEN STUDY GROUP (PSG)

Interim Report for the
JULY 1991 ACTG MEETING

Michelle Roland

1) ACTG 021, a prophylaxis trial in people who had already had one bout of PCP, was stopped by the data safety monitoring board (DSMB) because people on the Bactrim (Septra) arm had fewer episodes of secondary PCP than those on the aerosolized pentamidine arm. I have more written information for people who are interested. Please contact me at the meeting.

This data will be presented at one of the Plenary sessions.

2) There was only one conference call between the July and December meetings. A concept sheet was discussed on this call (CS 355 "A Randomized Trial of Three Oral Anti-Pneumocystis Agents for the Primary Prevention of Serious Infections..."). There were many problems with this concept sheet, including that the investigators proposed using clindamycin, a drug which caused so many side-effects in the CPCRA trial that it had to be dropped. In addition, 566C80 is still not absorbed well, and a new formulation will not be ready for some time.

My concern with this group is that a series of concept sheets have been submitted since I've been (somewhat) involved which have receive valid criticism, but noone seems to be taking a proactive role and writing what seems to me to be the next obvious protocol: septra (standard prophylaxis) vs 566C80 vs WR6026. Although the Walter Reed drug hasn't even entered Phase I, and the Burrough's Wellcome drug is awaiting better formulation, we know that writing a protocol takes A LONG TIME in the ACTG process. I believe we/they should start work on this idea now. Any thoughts on this? If I can muster the energy, I will approach individuals on the PSG with this idea, see if anyone's already doing it, and if not, try to initiate it.

3) The PSG session will include discussion of ACTG 167 data (566C80) and updates on other on-going trials.

4) Accrual to ACTG 108 continues to be dismal. Unless a couple more large sites start accruing to this protocol, it will fail. There have been some changes to the protocol, which are unclear to me at the present.

5) ACTG 173 (WR6026) protocol is apparently in it's final draft. The chair of the PSG has seen it. I requested it from the Operations Office and was told that it was still in draft form and I would get it when it was final. I have not had the energy to pursue the PI or the Chair of the PSG for a copy.

6) Dr. Bozzette has not resubmitted CS 331, the one I discussed last time combining aerosolized pentamidine and systemic prophylaxis. I will talk to him again to find out when he plans to re-submit this CS.

Unfortunately, because of the lack of conference calls and my inability in the last couple of months to be terribly aggressive, that's about all I know about the status of PCP work at the ACTG. I would appreciate if anyone has any additional information if they would let me know about it. I also think I could use some help on this committee...
December 23, 1991

From
Alison Wojciak, ACTG Operations Office

Subject
Community Constituency Group new membership solicitation

To
CCG Members and CAB Contacts

Enclosed please find a request for new applicants to the Community Constituency Group. Please send letters of interest and resumes by February 7, 1992 to Victor Rivera at the enclosed address. Inquiries on the east coast should be directed to Jonathan Wadleigh at (617) 432-3243. Thank you.

Enc.
COMMUNITY CONSTITUENCY GROUP
REQUEST FOR NEW APPLICANTS

The Community Constituency Group (CCG) is currently comprised of twenty four (24) individuals representing diverse communities affected by HIV. The CCG began in November 1989 in response to criticism by several organizations, most notably ACT UP, that people with HIV and their advocates were not being included in the formulation of the HIV research agenda. The CCG was created to allow for input, and more importantly, to integrate people with HIV and their advocates into the HIV research agenda as it relates to the AIDS Clinical Trials Group (ACTG).

We are currently seeking new persons for membership and encourage all who are interested to apply. We especially seek applications from persons representing the following communities:

-Persons with HIV/AIDS
-Clinical trial participants
-Activists, and community physicians with knowledge of HIV disease
-Incarcerated populations
-Adolescents
-People from the Haitian community
-African Americans
-Latino/a, Chicano/a
-Native Americans/Alaska Natives
-Asian/Pacific Islander
-Injection drug users, former IDU's, or people with drug treatment experience
-Persons with hemophilia or other clotting disorders
-Persons infected through blood or blood products
-Parents of children with HIV
-Gay men
-Gay men of color
-Women, women with HIV infection
-Lesbians, lesbians with HIV infection
-People from rural communities, Hawaii, the South, and Puerto Rico
-Members of local ACTG Community Advisory Boards
-Immigrants, non-documented persons, their advocates
-Physicians with knowledge and experience of community based clinical trials system
-Virologists, oncologists, pharmacologists, neurologists, immunologists, gynecologists, pediatricians (ideally who have worked with HIV in the past) and others with knowledge of these sciences.
Cover letters and resumes are due by February 7, 1992. Decisions will be made by February 28, 1992. If you have submitted an application previously, please resubmit if you still wish to be considered.

Please send letters of interest and resumes to:

Victor Rivera  
Community Constituency Group  
1200 South Jackson, Ste. 25  
Seattle, WA. 98102  
(206) 322-7061

Inquiries on the east coast should be directed to Jonathan Wadleigh at (617) 432-3243.
AIDS CLINICAL TRIALS GROUP
COMMUNITY CONSTITUENCY GROUP (CCG)

Membership Commitments

In order to avoid misunderstanding and to maintain a standard of participation that enables broad constituencies to be represented as best as possible at the ACTG meetings, the CCG has instituted basic membership commitments. These basic membership commitments are to be maintained by all CCG members in order to best serve people with AIDS and HIV disease. In the event that a member cannot keep these commitments their membership may be discontinued. The basic commitments are as follows:

1) CCG members are required to attend all ACTG meetings. CCG members are also required to participate in their respective core committee meetings as well as a majority of conference calls (both CCG and core committee calls).

This is the primary responsibility of CCG membership. If a CCG member is unable to attend due to poor health or the death of a loved one they can retain their membership if they notify the CCG point person, CCG membership committee point person or ACTG Operations Office in writing prior to the first CCG meeting of the ACTG meeting of their absence. It is preferred that this notification be in the form of a personally signed original. However it is recognized that this is not always possible. In instances where written notice is not possible telephone notification either to the CCG point person the operations office will suffice. This notification can be presented by any member of the CCG or a representative of the operations office, to the CCG at the beginning of their first meeting at the ACTG meeting in question.

2) CCG members are required to submit a report on their core committee within two weeks of the ACTG meeting. CCG members are also required to file interim reports of their core committee activities.

If the report will be late the CCG member must advise the point person of this within the two week period in order to retain their membership. The notice of the delayed report will include a commitment on when the report will be delivered to the point person.
MEMBERSHIP DISCONTINUANCE

A CCG member may be discontinued if either of the above two requirements are not fulfilled. This can be done only through a majority vote of the membership committee at a meeting when no less than 3/4 of the members of that committee are present. All committee members are full CCG members and have notified the point person in writing of their interest in serving on the membership committee at the ACTG meeting prior to the commencement of their service. Any person who disputes their discontinuance may appeal the decision to the full CCG.

In addition to the above commitments to the CCG, members are also required to participate in their local ACTG Community Advisory Board. If participation is not possible (transportation, no ACTU site) the CCG member may request a waiver.
<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>December 1987</td>
<td>First ACTG meeting</td>
</tr>
<tr>
<td>November 1989</td>
<td>ACTUP/New York attends 7th ACTG meeting uninvited.</td>
</tr>
<tr>
<td>January 1990</td>
<td>NIAID sponsors meeting of 10 community representatives and ACTG members in San Francisco.</td>
</tr>
<tr>
<td>March 1990</td>
<td>Community representatives plus two from San Francisco meeting attend 8th ACTG meeting as invited observers.</td>
</tr>
<tr>
<td>May 1990</td>
<td>Community representatives meet in Dallas, expand group to 22 members striving to become more representative. CCG is born.</td>
</tr>
<tr>
<td>July 1990</td>
<td>CCG attends 9th ACTG meeting. Representatives are allowed to sit on Executive Committee and core committees as observers. CCG expands to 23.</td>
</tr>
<tr>
<td>September 1990</td>
<td>CCG meets in Chicago to choose representatives to Executive Committee and core committees.</td>
</tr>
<tr>
<td>November 1990</td>
<td>CCG attends 10th meeting as full ACTG members. CCG addresses plenary session of meeting.</td>
</tr>
<tr>
<td>Winter 1990-91</td>
<td>CCG seeks new, committed members to expand its effectiveness.</td>
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</tbody>
</table>
THE HISTORY OF THE COMMUNITY CONSTITUENCY GROUP
OF THE AIDS CLINICAL TRIAL GROUP

In 1989, ACT UP/New York initiated a series of meetings with Dr. Anthony Fauci of the National Institute of Allergy and Infectious Diseases (NIAID) and the staff of the Division of AIDS at NIAID. The purpose of these meetings was to discuss the lack of community involvement in the AIDS Clinical Trials Group (ACTG). The ACTG at that point was closed to formal community input, consisting only of the investigators and staff of the AIDS Clinical Trials Units (ACTUs) and NIAID staff. The activists held that the lack of community involvement led to research priorities that were not consistent with the real needs of people living with HIV disease and to difficulty in recruiting patients to studies, particularly women and people of color.

While these negotiations were ongoing, members of ACTUP/New York attended, without an invitation, what become a stormy and confrontational ACTG meeting in November 1989. In January 1990, NIAID called for and facilitated a meeting of community representatives and members of the Executive Committee of the ACTG, which took place in San Francisco that month. Ten community representatives and three members of the ACTG Executive Committee were present.

This initial small group of activists was given the charge to design a mechanism for community involvement in the ACTG and formed a new group, called the Community Constituency Group (CCG). This led to a series of meetings (detailed in the timeline below) and much vigorous debate among all parties involved. Issues about the role and empowerment of the group and debate (both within and outside the group) about the representativeness of its membership followed. The CCG questioned the best way to set its own agenda, realizing that a truly representative group would have to tackle many big issues, including racism, sexism, and homophobia, as well as set research priorities. The CCG then expanded itself to make it more representative of the diverse communities impacted by HIV disease.

During this time, the ongoing dialogue between the CCG and the ACTG has led to the belief by both groups that community involvement is crucial to the effective operation of the ACTG. Through this mutual respect, the CCG has secured two positions on the ACTG Executive Committee and one position and one alternate position on all core committees.

The CCG after only one year is ready to fully participate in the setting of research priorities and in making AIDS clinical trials more accessible to all people impacted by this virus.