SCIENCE ADVISORY BOARD MEETING
APRIL 26-27, 1999

The meeting was called to order by the Chair of the Science Advisory Board (SAB), Dr. Marion Anders. He welcomed new Board member Dr. Catherine Donnelly, and requested attendees to introduce themselves. Board members present were Doctor's Anders, University of Rochester; Robert Bruce, University of Toronto; Catherine Donnelly, University of Vermont; Tomas Guilarte, Johns Hopkins University; Steven Hecht, University of Minnesota; Marcy Rosenkrantz, Cornell University and the Air Force Research Laboratory and Information Directory; Charles Wilkins, University of Arkansas. Liaisons to the SAB, Norris Alderson, CVM; Arnold Borsetti, CFSAN; Melvin Stratmeyer, CDRH; Meredith Grahn, ORA; and Dr. Richard Kennedy, UAMS. Dr, Richard Albertini, University of Vermont, and staff from the various divisions/offices at NCTR.

Dr. Anders requested approval of the May 6-7, 1998 Science Advisory Board Meeting minutes, with the exception of a few minor changes the minutes were approved as written.

Dr. Schwetz provided an update on the FDA and Center, he reported that Dr. Jane Henney had been appointed as the FDA Commissioner in November. He emphasized two of Dr. Henney's priorities were the development of the Agency science infrastructure and research within the FDA. He said science would be a prominent item in the 2001 budget, which was not the case in the 2000 budget. When the Commissioner talks about the science of the Agency, he said, she is not just talking about the research, it's the whole review function as well. It's estimated that 70% of the employees of the Agency could fall under this heading or be referred to as scientists, whether it has to do with bench research, review, surveillance, compliance. He also, announced that Dr. Henney had appointed him to the position of Senior Science Advisor to the FDA, and will continue to serve as the NCTR Director.

In discussing the budget, Dr. Schwetz said NCTR's appropriation is about $32,000,000 a year, with an additional eight to nine million dollars provided by NIEHS/NTP through an interagency agreement.

Addressing personnel changes, Dr. Schwetz announced that Arthur Norris, the Center's Deputy Director retired in January and this position was being combined with the functions of the Associate Director for Research, the new position title will be Deputy Director for Research.

Referencing a recommendation of the SAB's pertaining to cross-center research, he reported that the Office of Science had made available $300,000 to support, on a competitive basis, research that focused on cross center needs. NCTR received a portion of this money. Another activity that had a major emphasis on identifying cross agencies priorities was the Food Safety Initiative. He outlined that this involves the development of a three year research plan for the whole FDA, as well as integration with USDA, CDC and EPA research agendas. NCTR has a role in the food safety, the Divisions of Chemistry and Microbiology have

on going research as well as Division of Biometry and Risk Assessment has developed a new protocol on pathogen modeling and risk assessment. Another cross center priority activity is the development of a photo-tox science capability at NCTR within FDA with strong collaboration from CFSAN and CDRH. He reported that an FDA Neurotoxicology group, meets on a regular basis with NCTR providing the initiative.

Dr. Anders called upon Dr .Ralph Kodell to provide a response to the Biometry and Risk Assessment site visit. He summarized his written report with the help of slides (Tab 1-A). Following are some of the highlights of his presentation: the staff participated in a retreat to do long range planning, they agreed that they need to place an emphasis on working with FDA's product centers to address risk assessment needs, and need greater involvement in NCTR's studies of FDA nominated substances; greater attention needed to be paid to planning within the division, he plans to strengthen the program by establishing well defined research themes to which a number of staff members could contribute. Areas being looked at were dose response modeling for microbial risk assessment and linkage of physiologically backed pharmacokinetics and biologically based dose response models, as well as interspecies extrapolation and predictive toxicology.

Dr. Schwetz asked how FDA could organize those people within the Centers whose primary function it is to support risk assessment decisions and who do the modeling? Drs. Gaylor/NCTR, Borsetti/CFSAN and Alderson/CVM commented noting there was a lot of risk activity going on within the Agency particularly on Fumonisin. Dr. Alderson reported under the umbrella of the Joint Institute for Food Safety and Applied Nutrition (JIFSAN) a risk assessment clearing house was being set up for both FDA and USDA to address pathogen risk assessment.

Next, Dr. Slikker responding to the Neurotoxicology evaluation provided a written report and using slides (TAB 1-B) explained how the program, in some instances, had responded to the SVT recommendations, and it was work in progress on the others. He highlighted the Division's new approach of conducting fewer protocols and doing them well. He spoken of the initiative that had been put forwarded to organize Agency' neurobiology/neurotoxicology research resources. He then addressed the SVT's comments an recommendations of the Divisions eight focal areas(details can be found in TAB I-B).

Dr. Anders was next to report on the evaluation of the Division of Biochemical Toxicology(TAB 1-C). He reported they have done leadership work in the field. In looking to the future the SVT recommended the group would benefit from more cell biological approaches as the problems they face in the future will probably demand it. It is not to say that they are not doing things in this area already but the SVT was thinking about what lies down the road. The SVT recommending was not abandoning the chemistry but to add cell biology to it. They reported that this group has exploited the FDA/NIEHS interagency agreements and the Fumonisin is a good example and is a good paradigm for the future. Work on endocrine disruptors has begun and may need more cell biology. The division has a lot of talent in the characterization of DNA adducts and their quantification. They concluded, Dr. Beland provides strong and

effective leadership both scientifically and administratively and enjoys the respect of his colleagues.

Dr.Wilkins questioned the rationale of moving Mass Spectrometry from the Division of Chemistry to this group. Dr. Schwetz reported one person was moved from Chemistry into Fred Beland's division because the primary emphasis was research that was related to Fred's research as opposed to other work that was going on in Mass Spectrometry

The full Board approved the report.

.In Dr. Belands' absence Dr. Jill James Gaylor commented on the Division of Biochemical Toxicology draft site visit report (TAB 1-D). She stated that Dr. Beland had no specific comments on the draft SVT but wanted the Board to know that the following presentations were scheduled for the NTP, the Fumonisin two year bioassay and mechanistic studies, and the chloral hydrate and urethane/alcohol results. She reported that since the last SAB meeting the renovation of the phototox facility had been completed and they planed to start loading animals this summer.

She reported that the chronic bioassay and the mechanistic studies of two composite samples of coal tar disposal sites and benzo[a]pyrene were completed and the results have been published. She also said a manuscript was in preparation describing adduct levels, proliferation, oncogene activation and tumor suppressor gene inactivation as related to tumor incidence, which is in line with the SAB's recommendation that they pursue biologic end points. Also, the chronic bioassay and mechanistic studies of malachite green and leucomalachite green had been loaded and the N-demethylated derivatives of malachite green synthesis had been completed since the site visit.

She reported, the project on sexual dimorphism in the inflammatory response to biomaterials and the evaluation of host factors contributing to the differences in the response to biomaterials had been discontinued. The evaluation of the effect of genestein, methoxychlor, nonylphenol, vinclozolin and ethinyl estradiol in the feed to Sprague-Dawley rats and the evaluation of genestein on reproductive effects over multi-generations and chronic effects at various life stages was progressing. Loading of the genistein was being done and the multigene study is anticipated to be completed by the first of the year, and it's two year chronic bioassay for genistein was loading. The multi-gene aspect of the nonylphenol was also loading and they had completed the range finding studies on all five of the compounds. They're addressing the SAB's recommendation that they could use more expertise in the area of cellular and molecular endocrinology and plan, at the next Toxicology Study Selection and Review Committee (TSSRC) meeting, to specifically recruit experts in endocrinology so as the study progresses they can get help with the direction and advice for the mechanistic studies. They're also attempting to increase communication between NIEHS and other FDA centers to involve scientists with endocrinology expertise in mechanistic studies.

Dr. James-Gaylor reported they'd accepted the SAB recommendation pertaining to the project on the role of human metabolism and endocrine disruption, they will complete this project, but plan no further work unless mechanistic discoveries are made in the process that would warrant a follow-up protocol. A protocol on the project on the purification of ceramide synthase for fumonisin mechanistic studies has been submitted, and was about to be accepted.

She reported that progress in the project on the determination of anti-thyroid properties of dietary genestein in determining the mechanisms of isoflavone binding and inactivation of thyroid peroxidase had been hindered by a lack of availability of appropriate instrumentation, reporting they'd recently purchased a triple quadropole instrument, it's expected that there will be rapid progress on this project. The study on the development of analytical methods for the determination of malachite green and antithyroid effects has been completed, as has the project on the development of methods for analysis and confirmation of beta-agonists. The electrospray mass spectrometry for quantitative DNA adduct analysis project is progressing. The work on DNA adducts for 4-aminobiphenyl has been published and collaborations have started with molecular epidemiology. Methods have also been developed for the detection and quantification of etheno adducts and nucleoside analogues.

She reported on the their work on antigenic biomarkers of estrogen catechol metabolites for use in epidemiologic studies. They've been successful in obtaining support for a post doctoral fellow from the Arkansas Breast Cancer Research Program and additional support from the FDA Office of Women's Health. They've hired a post doctoral fellow with expertise in endocrinology and tamoxifen research to work in the area of gene-nutrient interactions involved in multistage carcinogenesis and in the maternal risk of Down Syndrome. She said they recently submitted a manuscript on the sight specific methylation within the rat p53 promoter and looked at human liver tumors and find hypermethylation 053 promoter in human tumor tissue as well. The project on modulation of apoptosis with dietary restriction and low dose chemotherapy, a novel anti-cancer strategy is AICR funded and these experiments are in progress. She reported that the data presented to the SAB on the 677-C→T mutation in the methylenetetrahydrofolate (MTHFR) reductase gene was accepted for publication. This work was extended in collaboration with the California birth defects registry and the Atlanta birth defects registry and they now have an end of 300, 150 Down Syndrome moms and 150 controls. She said there was an increase frequency of MTHER mutation in mother's of children with Down Syndrome, they've confirmed that DNA hypomethylation is associated with increase plasma homocysteine and SAH in these mothers, which is consistent with their hypothesis..

She reported the project on the effects of dietary restriction on the post initiation stage of alflatoxin-B1 carcinogenesis in F334 rats fed a methyl-deficient diet was essentially completed, the manuscript has been submitted and no additional studies were planned. She noted the SAB had reservations and concerns on the study of genotoxic and secondary mechanisms of riddilline carcinogenesis, because of the lack of human exposure data on riddilliine. But she reported an NTP/CFSAN site visit team strongly endorsed this project as an excellent model

system to further understand pyrrolizidine alkaloids-induced carcinogenesis. They will focus on the metabolic pathways leading to DNA adduct formation by pyrrolizidine alkaloids as a class of compounds then with an emphasis on riddilliine. Following Dr. James presentation there was interaction with the center representatives.

Next, Dr. Albertini presented the draft site visit report on the Genetic Toxicology Program (TAB1-E) to the Board. He said this was a highly productive group. The studies are basic but address fundamental questions relevant to the mission to the NTP and the FDA. The SVT reviewed six ongoing programs and three new initiatives. Of the ongoing programs there was one *in vitro* using transgenic cells studying apopotosies and mutation program cell death. The *in vivo* systems was using the rat lymphocyte HPRT assay. Proposed investigations of the *phi X* 174 transgenic mouse was reviewed. He noted that the work done on this model was superb, unfortunately the outstanding work made it appear obvious that this model could not go very far because it had a very narrow target. The new initiatives consisted of the development of two possible new transgenic mouse models, one using a fluorescent marker for direct ascertainment of mutations and the other using micro satellite instability. He noted the SVT was enthusiastic about the former, had some questions about some of the problems that might be encountered in the latter. Finally, one of the programs the SVT thought was high risk but with high pay off, was the gene expression as a result of toxin interaction using chip technology. He said the SVT thought that this was a program worthy of support, maybe even more support than it was getting.

There being no questions for Dr. Albertini, Dr. Anders entertained a motion to accept the draft report, it was seconded and unanimously approved

Next, Dr. Casciano provided the Board with an update since the SVT's review of the program. He reported that the coumesteral protocol had been reviewed and approved, and work initiated. The review of the ameloride protocol was positive, with a slight revision he said this protocol should be approved too. As a direct response to the work accomplished with genestein, a protocol is being developed on p53, this will a 26 week study and it's expected to be funded via the NTP.

Dr. Casciano reported they'd decided to generate a database developing the spontaneous mutant frequency and spectra database. He noted they'd been advised to continue development of the system in order to amplify the amount of clones, mutants that we identified, so they are continuing to develop the assay. A postdoctoral fellow was recruited and is on board and writing a protocol, because of the high priority given to this activity a technical support individual has been assigned to provide more support for this group. Using slides he went into more detail on there collaboration with the caloric restriction people and what the data has shown to date (TAB1-F).

Next he discussed a project that compares the transgene with the indigenous gene, saying that this was a relatively large project that has been ongoing for five years. Several papers have been published on the induction of mutations at the *Hprt* locust and the lac1 locust. He said data is being gathered and a paper written on the lac1 mutant frequency and mutational spectra in the mammary

gland which is the target organ of the particular study they've initiated. They are also analyzing a second reported gene that is in the transgenic animal for comparison of mutation at two different low sides in the transgene and they're preparing to study DNA repair in the Iac1 transgene.

He also discussed the *phi X* 174 transgenic mouse assay they are developing, a forward assay that would enlarge the target size and provide what they think is a higher sensitivity. He expects that the necessary data will be accumulated by the fall and at that time they will evaluate the system to determine if they will continue or not. Dr. Casciano said they were continuing to characterize the Tk+/- knock out animal.

He reported on the three new initiatives addressed in the draft report. The first one was on a new transgenic mouse that will directly evaluate mutations, the second one had to do with microsatellite instability. He said they were aware of potential pitfalls regarding the concept so it's been put on the back burner for rethinking. The third one was the use of three micro-rays to identify toxin induced gene expression and relating that activity to a control. Since the SV review the protocol was reviewed and accepted, and they are directing their efforts towards evaluating the effects of toxicants on human apatisites. The toxicant of choice chosen is aflatoxin B1. Initial efforts have been an attempt to compare the gene expression in cells that are attached to collagen matrix versus a matrigel matrix.

There being no questions for Dr. Casciano, Dr. Anders called on Dr. Hecht to present the draft report on the Molecular Epidemiology Program (TAB 1-G). Dr. Hecht commented there were three projects in the area of chemo prevention, three in area of epidemiology and post market surveillance, two in the area of exposure, biomonitoring and DNBA adducts, and one in DNA micro-ray technology. He said the SVT felt this was one of the few programs in the world that is actually carrying out meaningful studies where the biochemical aspects of carcinogenesis are actually being integrated into meaningful molecular epidemiology studies. The program focus is on colon, beast and prostate cancer.

He said the biochemical work on CEP 182 sulfa transferaces GSTs and aromatic amines and heterocylclic amines continues to be strong. He reported that the SVT felt if there were some way to do it, the group would benefit from more in house mass spectrometry. They also felt that the program while focused on carcinogenesis and highly relevant to the FDA's mission it needs to be integrated better into the whole FDA spectrum. He stated that the SVT weren't sure this was being done in a most effective way.

Dr. Anders entertained a motion to accept the draft report, it was seconded and unanimously approved. Dr. Kadlubar thanked the SVT for their review and provided a short update on the 14 projects that were reviewed during the visit. He went on to give a short update including a discussion of the future direction of each of the projects with special emphasis on the collaborations that he and his staff were perusing in the execution of the projects.

Next, Dr. Schwetz addressed the Board and FDA Liaisons with the question, given the unique resource represented by the three programs just reviewed, how can NCTR maximize and build upon this resource? How can we assure it moving in concert in a direction that assures the kind of leadership that these three groups represent? Dr. Schwetz encouraged the Center liaisons to think about whether the areas of research address the high priority carcinogenesis types of questions they have? How could NCTR adjust them better as we go forward? Is there something we should be doing that would make these groups even more productive by the interactions they could have as you look at the bigger picture of carcinogenesis research and the needs as it relates to consumer protection? What are the holes? There are a lot of other people that are also involved in some aspects of carcinogenesis research, what are the holes that we should be trying to fill through collaborations with our colleagues elsewhere in FDA. Dr. Schwetz asked that they identify what some of the holes are that we should be looking for. Whether it relates to nongenotoxic carcinogens, a specific skin concern. He also asked then to think about other groups we should connect with for leverage, as a leadership organization in carcinogenesis research.

Dr. Anders asked everyone to think about this and to come prepared to discuss in the morning. He adjourned this session of the meeting.

April 27, 1999

Dr. Anders called the meeting to order. He asked Dr. Schwetz to continue discussion on the Center's cancer research program.

Dr. Schwetz said he was hoping for several things from this discussion and would like to hear from the FDA colleagues, what they think needs to be done to help protect/support the decision making process for foods, drugs, devices, veterinary drugs. He wanted to know if they had observations about where the process could be improved to make it more efficient, more effective. The third thing, is the bigger picture, looking at what we know about the causes of carcinogenesis today, not just limited to chemical, but forms of energy and pathogens and non-pathogens, and other organisms that contribute to a cancer load that we have. Looking at this program over the next years should we continue with the present focus, or is there something that's of a higher priority looming on the horizon that reflects the direction we should be considering? Either on our own, or reaching out to make somebody else's program more complimentary to ours. For example, we can look at viral causes, viral predisposition, viral infection related predisposition's to cancer, or to things that we regulate that are viruses, drugs that might enhance.

Dr. Anders asked where biometry and risk assessment fit into the carcinogenesis program, saying they seem to be an intimate part of the program. Dr. Schwetz replied, that's part of the research tools whether it's doing a risk assessment of fumonisin that is mechanism based or whether it has to do with different approaches looking at multiplicity of tumors in a transgenic model. Dr. Anders said he thought the Center was struggling with "how do you get rid of the so-

called silos" that prevent the cross fertilization that's absolutely essential to the efficient conduct of science in these days. He said he didn't know if he was right in his perception, but if they are truly silos, how do you make them into non-silos, and get the free flow of information going? Dr. Borsetti asked what he meant by silos. He responded, individual components that don't communicate very much with the silo next door.

Dr. Casciano opined that he didn't think NCTR operated as silos and proceeded to give examples of communications currently going on. Dr. Guilarte said the problem is that as presented these things are not very apparent. Dr. Casciano agreed, saying it was very difficult at individual site visit reviews to talk about interaction between molecular epidemiology and biochemical toxicology when the genetic toxicology laboratory was being evaluated. Dr. Anders agreed, he said there were ways to allow to demonstrate the degree of collaboration, he said he suspected that there was a lot of stuff going on informally and formally, but it is not apparent to the SAB how much is going on. Their was further discussion between Board members and Drs. Casciano and Kadlubar, touching on resource barriers, communication, collaboration and peer review. A large part of the discussion focused on collaboration and the peer review system currently being used.

Dr. Anders asked the FDA liaisons what type of research they thought the Center should be doing to best foster the way their centers do their jobs? What type of information did they need to enhance their ability to manage FDA regulated products? Drs. Borsetti and Stratmeyer stated there was collaboration between NCTR and their centers. Dr. Borsetti suggested that under the auspices of the Senior Science Council maybe that collaboration could become much stronger, on NCTR's end with more complicated, intensive investigations into the mechanistic issues. Dr. Stratmeyer said CDRH seldom knows the chemicals they're working with so it's difficult to anticipate testing for a specific chemical, he said his group tends to rely more on the risk assessment end, relying more on the modeling. He said they were more interested in mechanistic data that helps them make species to species extrapolations.

A discussion ensued on budget issues, NIEHS/NTP funded projects and how/where this money is used, as well as the issues of geography, distance and communication, particularly linkages between centers. Dr. Anders asked if the new Deputy Director for Research could spend more time in the DC area to provide the link needed between NCTR and the other centers. Dr. Schwetz said he hoped the DDR would be opening doors, making it known exactly who the person was that a center needed to communicate with, arranging meetings, using the video conferencing between centers.

The next item on the agenda was the Research Plan for FY2001. Dr. Anders commented that Dr. Schwetz would be presenting this plan to the Commissioner and suggested that the Board could help by being very incisive in their questioning of this document.

Dr. Schwetz said he would be presenting to the Commissioner and other Center Directors at the NCTR Stakeholders Meeting on May 4, NCTR's Research Plans,

Toxicology Priorities of the FDA(TAB1-H). In addressing his presentation he would propose to credential the role and contribution of the NCTR as a critical resource for enhancing the science base of the FDA. The objectives are to foster discussion of the research needs of the product Centers and ORA, particularly as they relate to toxicology, and to present and have validated a research plan for NCTR for FY2001 and beyond that addresses priority scientific needs of the Agency.

He said results of toxicity studies conducted in laboratory animals have served a critical role in support of decisions related to product development and support of safety and risk assessment of products by regulatory agencies. Over the past 50 years of animal testing, protocols have been continually improved and variables that relate to animals, animal feed, husbandry conditions, data analysis, etc., have been controlled to minimize confounding effects. Despite this, animal studies are not fully predictive of toxicity in humans. Adverse effects from FDA-regulated products are sometimes discovered in consumers. Toxicology studies do not provide adequate information to guide the design of clinical trials, registries, epidemiology studies and other studies in humans to identify toxicities under use conditions. Understanding of mechanisms of actions has been slow to improve study designs. Toxicology studies required to address questions about product safety are still very expensive and time consuming despite considerable effort to develop *in-vitro*, short-term or alternative test methods.

Addressing, questions and issues of the next decade he opined that research testing and needs relate to, bringing products of new technology to the market rapidly while ensuring their safety and efficacy, and reduction of risks associated with products once on the market. At question or issue are: identification of hazard or risk from exposure to FDA-regulated products; methods to identify consumers at risk; better methods to predict toxicity and assure product quality; and scientific capability and capacity of the FDA. He identified NCTR's strategic goals, the development of new strategies to predict toxicity; the development of computer-based systems to predict human toxicity; and conduct method agent concept driven research.

Following Dr. Schwetz's presentation Dr. Anders said he had three questions/comments: First, was the inclusion of children, saying this was an important population, he thought the Agency had some things going on, some regulation changes; second was professional development, he asked what the reward was for an NCTR researcher to go learn how to be a regulator, or be more cognizant of the regulatory process and needs; and third was chronic toxicity, saying it still remains a serious problem. He asked if we could have developed an animal model that would have detected the Fen-Phen induced damage to heart valves? Dr. Schwetz responded that it wasn't just new product toxicity it's also delayed toxicity and the fact that the human population is an aging population. We expect to see more degenerative diseases than in a younger population. He said the process of evaluating the safety of products doesn't necessarily address the question to the extent that it probably should, about what the effect we expect to have on a less aging population, so, we're missing on both ends. He reported the Center is participating and has received Office of Women's Health resources to focus women issues. Dr. Schwetz said

the children's area is an important one, and it isn't very clear what the Agency does in this area. He said EPA has moved forward with this as a major issue for them. One way of interacting with them is in the guidelines they are developing and the proposals they are making for what kind of research to be done to protect children. He said the endocrine disrupter work currently being conducted at the Center does get to some of these issues. We're looking at manifestations on sperm count, the function of the nervous system, the function of the immune system, their vulnerability to cancer. In a way we're not advertising that well either, but clearly that addresses children's health issues.

In addressing professional development, Dr. Schwetz said at one time NCTR people spent a lot of time at the product center making connections, a lot of work resulted from that and we're now benefiting from those interactions. The NeuroTox group meets on a regular basis to talk about the research problems and priorities, this gets our people up in front of their product center counterparts to better understand what we can do for and with them. He said, in terms of our people taking a sabbatical, some have done that for from three to six months, but it's tricky to work this out. At this stage of their career, many people do not want this to be a time of decreased productivity, because of peer review. He said they could look at this on a selective bases for those particular people for whom this is an opportunity, but said the Center would have a hard time having a large presence at headquarters with scientist taking sabbaticals

In discussing Dr. Schwetz's presentation there was active interaction between the Board, Center liaisons and NCTR staff as they expressed what they thought should be addressed/covered in this presentation. Much of the discussion centered on how to improve interactions between centers, the issues of professional development, sabbatical programs, peer review, the possibility of more incentives from Congress for researchers to get out of the lab and work more with academia and industry. ,Also discussed was the need to change some of the rules we're now working with, as well as increasing FTE's while undergoing a budget cuts. They briefly touched on the issues of computational sciences, modeling, bioterrorism and interactions the Center has had with representatives from CFSAN, Army and CDC. They also provided possible questions that might come up during the presentation. Dr. Anders commented that this presentation was well focused and hit a lot of issues that were important to the Agency. Dr. Schwetz thanked everyone for their input saying it was very helpful.

Dr. Schwetz noted that the second round of review of the Endocrine Disrupter Knowledge Base was scheduled for June 9-10. He said this review would help NCTR decide where we've come with this technology and were we were going to go with it. He also noted there were two more divisions that have not yet been reviewed this cycle, Microbiology and Chemistry, dates for these reviews would be forthcoming.

This concluded the open meeting.

Approved as amended by the full SAB on 6/4/00