Minutes of the Special Called Meeting of the Executive Committee of the Board of Trustees of the University of Kentucky, Thursday, March 10, 1983.

The Executive Committee of the Board of Trustees of the University of Kentucky met in a Special Called Meeting in the Board Room on the 18th floor of the Patterson Office Tower on the Lexington Campus at 11 a.m. (Eastern Standard Time) on Thursday, March 10, 1983.

A. Meeting Opened and Roll Called

Mr. William B. Sturgill, Chairman, called the meeting to order at 11:10 a.m. and the invocation was pronounced by Mr. William R. Black.

The following members of the Executive Committee of the Board of Trustees answered the call of the roll: Mr. William B. Sturgill (Chairman), Mr. William R. Black, Mr. Tracy Farmer, and Mr. John C. Darsie (Assistant Secretary, ex officio, of the Executive Committee). Absent from the meeting were Mr. Albert G. Clay and Mr. A. Stevens Miles. Members of the Board of Trustees attending the meeting were Mr. James W. Dinkle, Mrs. Edythe Jones Hayes, Mr. W. Terry McBrayer, and Professor William F. Wagner. The University administration was represented by President Otis A. Singletary; Dr. Donald B. Clapp, Vice President for Administration; Chancellors Peter P. Bosomworth, Art Gallaher, and Charles T. Wethington; Dr. Raymond R. Hornback, Vice President for University Relations; Mr. Henry Clay Owen, Controller and Treasurer; Mr. David I. Carter, Special Assistant for Business and Financial Affairs; Dr. Paul G. Sears, Special Assistant for Academic Affairs; and Dr. Wimberly C. Royster, Vice Chancellor for Research and Dean of the Graduate School. Members of the various news media were also in attendance. The Secretary reported a quorum present, and the Chairman declared the meeting officially open for the conduct of business at 11:13 a.m.

B. Adoption of Resolution Accepting the Successful Bid for the University of Kentucky Consolidated Educational Buildings Revenue Bonds, Series H (PR 3A)

Thereupon, a motion was made by Mr. Farmer and seconded by Mr. Black that the following titled Resolution, which was read in summary form to the Executive Committee, be adopted:

A RESOLUTION RELATING TO THE $8,500,000 UNIVERSITY OF KENTUCKY CONSOLIDATED EDUCATIONAL BUILDINGS REVENUE BONDS, SERIES H.

(The full Resolution being attached to these Minutes as Exhibit 1.)

Upon a vote being taken on the motion, the result was as follows:

Yeas	Nays
William B. Sturgill	None
William R. Black	
Tracy Farmer	

Thereupon, the Chairman declared that the motion had carried and that the Resolution had been passed and adopted and directed that the same be recorded in the Minutes of the Executive Committee of the Board of Trustees. (See PR 3A at the end of the Minutes.)

C. Scientific Advisory Committee Report, Tobacco and Health Research Institute

President Singletary reminded the Trustees of the appointment several months ago of a Scientific Advisory Committee, Tobacco and Health Research Institute. The Committee has submitted its first report and President Singletary said he wished to share it with members of the Board. He then called on Chancellor Gallaher who made introductory comments and introduced Dr. Layten Davis, Director of the Tobacco and Health Research Institute. Dr. Davis summarized the report, a copy of which is appended to the Minutes.

The Chairman indicated the Board's approval and support of the Institute and complimented President Singletary, Dr. Davis, and the administration on the progress being made at the Institute. Mr. Sturgill then accepted the report of the Scientific Advisory Committee, Tobacco and Health Research Institute.

D. Meeting Adjourned

There being no further business to come before the meeting, the Chairman declared the meeting officially adjourned at 11:35 a.m.

Respectfully submitted,

John C. Darsie

John C. Darsie
Assistant Secretary, Ex Officio
Executive Committee
Board of Trustees

(PR 3A (Exhibit 1) and the THRI Scientific Advisory Committee Report which follow are official parts of the Minutes of the meeting.)

(EXHIBIT 1)

Office of the President
March 10, 1983

PR 3A

Members, Executive Committee, Board of Trustees:

RESOLUTION ACCEPTING THE SUCCESSFUL BID
FOR THE
UNIVERSITY OF KENTUCKY CONSOLIDATED
EDUCATIONAL BUILDINGS REVENUE BONDS, SERIES H

Recommendation: That the Executive Committee approve a Resolution accepting the bid of Seasongood and Mayer with a net interest cost of 8.435319% for the purchase of $8,500,000 Consolidated Educational Buildings Revenue Bonds, Series H, dated March 1, 1983.

Action: Approved X Disapproved _____ Other _____

Date: March 10, 1983

EXHIBIT 1

RESOLUTION RELATING TO THE
$8,500,000 UNIVERSITY OF KENTUCKY
CONSOLIDATED EDUCATIONAL BUILDINGS
REVENUE BONDS, SERIES H

WHEREAS, the Executive Committee of the Board of Trustees of the University of Kentucky ("the Board") at its meeting on January 25, 1983, passed and adopted two Resolutions, entitled, respectively,

> A RESOLUTION AUTHORIZING THE ISSUANCE OF $8,500,000 UNIVERSITY OF KENTUCKY CONSOLIDATED EDUCATIONAL BUILDINGS REVENUE BONDS, SERIES H, OF THE BOARD OF TRUSTEES OF THE UNIVERSITY OF KENTUCKY
>
> - and -
>
> A RESOLUTION AUTHORIZING THE ISSUANCE OF $8,500,000 UNIVERSITY OF KENTUCKY CONSOLIDATED EDUCATIONAL BUILDINGS REVENUE BONDS, SERIES H, OF THE BOARD OF TRUSTEES OF THE UNIVERSITY OF KENTUCKY AND THE ISSUANCE OF $8,500,000 UNIVERSITY OF KENTUCKY CONSOLIDATED EDUCATIONAL BUILDINGS REVENUE BOND ANTICIPATION NOTES, SERIES H, OF THE BOARD OF TRUSTEES OF THE UNIVERSITY OF KENTUCKY IN ANTICIPATION OF THE ULTIMATE ISSUANCE OF SAID SERIES H BONDS,

said Resolutions being referred to herein, respectively, as "the Series H Resolution" and "the Alternate Series H Resolution;" and

WHEREAS, pursuant to Section 5.3 of the Alternate Series H Resolution, on or about February 15, 1983, the Treasurer of the Board duly polled each member of the Finance Committee of the Board, all of whom preferred the issuance of the Series H Bonds authorized by the Series H Resolution to the issuance of the Series H Notes authorized by the Alternate Series H Resolution; and

WHEREAS, pursuant to Section 2.10 of the Series H Resolution, the Treasurer has caused to be published a Notice of Bond Sale with respect to the Series H Bonds for the information of potential bidders and has furnished copies of an Official Statement and Official Terms and Conditions of Bond Sale to interested persons requesting the same; and

WHEREAS, under the terms of the Notice of Bond Sale and the Official Terms and Conditions of Bond Sale, it is provided that proposals for purchase of the Series H Bonds would be received by the Board until 10:30 a.m. on March 10, 1983; and

WHEREAS, the following proposals for purchase of the Series H Bonds have been received in due time and acceptable form:

A. Bidder: Seasongood & Mayer
Cincinnati, Ohio

Bonds Maturing May 1,	Aggregate Principal Amount Sought	Coupon Rate Offered	Net Interest Cost
1986-1990	$1,255,000	6.75%	8.435319%
1991	310,000	7.00%	
1992	340,000	7.20%	
1993	365,000	7.40%	
1994	400,000	7.60%	
1995	435,000	7.80%	
1996	475,000	8.00%	
1997	525,000	8.20%	
1998	575,000	8.40%	
1999	630,000	8.60%	
2000-2003	3,190,000	8.70%	

B. Bidder: Smith Barney, Harris Upham & Co., Incorporated
New York, New York

Bonds Maturing May 1,	Aggregate Principal Amount Sought	Coupon Rate Offered	Net Interest Cost
1986-1990	$1,255,000	7.00%	8.699996%
1991	310,000	7.20%	
1992	340,000	7.40%	
1993	365,000	7.70%	
1994	400,000	8.00%	
1995	435,000	8.20%	
1996	475,000	8.40%	
1997-1998	1,100,000	8.60%	
1999-2000	1,320,000	8.75%	
2001-2003	2,500,000	9.00%	

C. Bidder: Blyth Eastman Paine Webber, Inc.
New York, New York

Bonds Maturing May 1,	Aggregate Principal Amount Sought	Coupon Rate Offered	Net Interest Cost
1986-1988	$ 700,000	6.40%	8.7376%
1989	265,000	6.70%	
1990	290,000	6.90%	
1991	310,000	7.10%	
1992	340,000	7.40%	
1993	365,000	7.70%	
1994	400,000	7.90%	
1995	435,000	8.20%	
1996	475,000	8.40%	
1997	525,000	8.60%	
1998	575,000	8.80%	
1999-2003	3,820,000	9.00%	

D. Bidder: Johnston, Brown, Burnett & Knight, Inc., John Nuveen & Co., Inc., Prudential - Bache Securities, Inc. and Associates
Lexington, Kentucky

Bonds Maturing May 1,	Aggregate Principal Amount Sought	Coupon Rate Offered	Net Interest Cost
1986-1989	$ 965,000	6.65%	8.7934%
1990	290,000	6.90%	
1991	310,000	7.15%	
1992	340,000	7.40%	
1993	365,000	7.65%	
1994	400,000	8.00%	
1995	435,000	8.20%	
1996	475,000	8.40%	
1997	525,000	8.60%	
1998	575,000	8.75%	
1999	630,000	9.00%	
2000-2003	3,190,000	9.10%	

E. Bidder: Morgan Guaranty Trust Company of New York
New York, New York

Bonds Maturing May 1,	Aggregate Principal Amount Sought	Coupon Rate Offered	Net Interest Cost
1986-2003	$8,500,000	8.75%	8.88154%

WHEREAS, the Executive Committee has considered the matter of which bid is most advantageous to the Board;

NOW, THEREFORE, THE EXECUTIVE COMMITTEE HEREBY RESOLVES AS FOLLOWS:

1. that the proposal of Seasongood & Mayer, as follows, for the purchase of the $8,500,000 "University of Kentucky Consolidated Educational Buildings Revenue Bonds, Series H," dated March 1, 1983 ("the Series H Bonds") is hereby accepted as the highest and best bid:

Bonds Maturing May 1	Coupon Rate	Aggregate Principal Amount
1986	6.75%	$215,000
1987	6.75%	235,000
1988	6.75%	250,000
1989	6.75%	265,000
1990	6.75%	290,000
1991	7.00%	310,000
1992	7.20%	340,000
1993	7.40%	365,000
1994	7.60%	400,000
1995	7.80%	435,000
1996	8.00%	475,000
1997	8.20%	525,000
1998	8.40%	575,000
1999	8.60%	630,000
2000	8.70%	690,000
2001	8.70%	755,000
2002	8.70%	830,000
2003	8.70%	915,000

Net Interest Cost = 8.435319%

2. that the interest rates on the Series H Bonds are hereby fixed at the rates set out in the said accepted proposal;

3. that the Series H Bonds as identified in the Series H Resolution shall be delivered by the officers of the Board in accordance with the terms of the Series H Resolution as soon as ready;

4. that the confirmation of the said accepted proposal subjects the Board to no liability if it is unable to obtain the final approving legal opinion of Wyatt, Tarrant & Combs, Louisville, Kentucky, Bond Counsel, or if the interest on the Series H Bonds should become subject to federal or Kentucky income taxation, or if the Series H Bonds should become subject to Kentucky ad valorem taxation, prior to the delivery of the Series H Bonds; but also that the purchaser shall not be required to take up the Series H Bonds without the final approving legal opinion of Bond Counsel aforesaid or if the Series H Bonds or interest thereon should become so subject to taxation;

5. that this Resolution shall be in full force and effect from and after its adoption.

SCIENTIFIC ADVISORY COMMITTEE REPORT, TOBACCO AND HEALTH RESEARCH INSTITUTE

Submitted to: Dr. D. Layten Davis, Director, University of Kentucky Tobacco and Health Research Institute

Subject: Report of the Scientific Advisory Committee, Tobacco and Health Institute concerning site visit held December 15-16, 1982 at the University of Kentucky, Lexington, Kentucky

Scientific Advisory Committee:

Leo G. Abood, Professor, Center for Brain Research, University of Rochester Medical Center, Rochester, NY 14642

Donald Heistad, Professor of Medicine, University Hospital, Iowa City, IA 52242

Aaron Janoff, Professor of Pathology, State University of New York at Stony Brook, Stony Brook, NY 11794

Fred Bock, Senior Scientist, Papanicolaou Cancer Research Institute, Miami, FL 33101

Thurston J. Mann, Assistant Director, North Carolina Agricultural Research Service, North Carolina University, Raleigh, NC 27650

SUMMARY OF THE REVIEW

It was the Committee's view that the aims of the research program of the University of Kentucky Tobacco and Health Research Institute (THRI) address many timely and important issues relating to tobacco and the health consequences of smoking. The program is a broad-based one involving a number of capable investigators from numerous departments throughout the University of Kentucky whose interests range from the neurobehavioral and cardiovascular-pulmonary effects of smoking to matters dealing with product modification and passive exposure to the constituents of smoke. In addition to contributing to a better understanding of the basic mechanisms associated with the health consequences of smoking, the investigations were appropriately directed towards the missions of 1) identifying and reducing the health hazards in both the smoking and non-smoking population, 2) emphasizing numan studies, and 3) attempting to develop appropriate animal models for research on smoking. The research program is unique in its scope and the concentration of qualified investigators devoted to research on smoking.

In summary, the Committee concluded that the research program of the THRI is comprised of a number of projects of high scientific merit, is clearly relevant to the issues of tobacco health, and is being effectively administered.

COMMENTS ON THE INDIVIDUAL RESEARCH PROJECTS

The majority of the research projects were highly meritorious,

particularly 1) The involvement of elastase-antielastase in emphysema, 2) the chemistry and function of α_1-protease inhibitor;3)the neurobehavioral projects dealing with multiple nicotine receptors and their neuroanatomical loci of action; 4) the cardiovascular program, particularly the studies on ventilatory mechanisms, the studies on the use of non-invasive techniques to evaluate high-risk cardiovascular patients, the studies on drug disposition, and those on thromboxane-prostacyclin production; 5) a number of the projects dealing with passive smoking-smoke components, particularly those on nicotine-derived nitrosamines, the role of methylation in nicotine toxicity, and on the growth and coagulation of tobacco smoke aerosols; 6) the projects on product modification within the College of Agriculture, particularly those on nicotine metabolism on modification of the tobacco plant and on viral gene expression in tobacco cells. All of the principal investigators responsible for these projects were considered to be highly competent and productive, while the projects themselves were in the forefront of research on smoking and tobacco health.

There were some projects that were considered to be satisfactory but could be improved by a revision of experimental procedures. Included in this group were the projects 1) aimed at developing a model of lung injury induced by chronic exposure to cigarette smoke coupled with steroid treatment, 2) examining the relationship between the accumulation of tobacco smoke and pulmonary emphysema, 3) determining the effects of passive smoking on interferon production, and 4) determining the effect of cigarette smoking and age on drug disposition in man.

Other projects were somewhat less promising and/or productive. Included in this group were the projects on the early detection of and susceptibility to smoking-related emphysema, at the treatment of emphysema, the studies attempting to develop a smoking induced model of lung injury, the project on cutaneous blood flow in man, the project on the tissue distribution of smoke carcinogens, and the project concerned with the cholinergic system of brain synaptosomes. Some of the projects were often lacking in tenable hypotheses, originality, and potential for disclosing new, significant findings.

I. Pulmonary Program

1. The underlying hypothesis behind one study is that amines in cigarette smoke are avidly bound by lung cells or extracellular receptors, leading to phospholipid accumulation in pulmonary macrophages. Macrophage phospholipidosis, in turn, is thought to cause cell death with attendant release of elastase and destruction of adjacent pulmonary tissue. No mechanism is suggested for the accumulation of phospholipids in macrophages due to amine-binding in the lung, nor is it made clear why such accumulations should cause macrophage death. Some data were presented showing that labelled imipramine, preloaded into animal lungs, is partly displaced following subsequent *in vivo* exposure of these animals to cigarette smoke inhalation, thus supporting the suggestion that amines in smoke may bind to amine receptors in lung tissue.

(a) The bulk of the data are derived from an *in-vitro* isolated lung perfusion model, in which amine-containing fractions of smoke-condensate are

added to the perfusate and efflux of labelled imipramine is then measured. The physiological relevance of such experiments is questionable, since uptake of smoke amines by pulmonary endothelium in the investigator's model may be very different from uptake by pulmonary epithelium in smoking animals or man. Why not ventilate the isolated, perfused lung with cigarette smoke so as to bring the in vitro and in vivo experiments onto a common footing?

(b) If phospholipid accumulation in macrophages (or some other effect of amine-binding on these cells) causes macrophage death and dissolution, this is unlikely to lead to significant elastase release in the lung. Macrophages do not store elastase in their lysosomes, rather they continuously synthesize and secrete it into their medium. Therefore, macrophage death is associated with decreased, not increased, elastase production. It was shown that alveolar macrophages sequester neutorphil elastase and that this enzyme is released by injured macrophages (e.g., severely anoxic cells). Is this the mechanism of lung injury proposed by one of the investigators? A more detailed exposition of the working hypothesis is needed to help clarify these and other questions.

2. A second project proposes to synthesize ^{14}C-labelled carbamates to be used as elastase-specific substrates and to use such reagents in a screening program to detect smokers at risk of developing emphysema. The rationale is that high-risk smokers may have increased lung elastolytic activity. Aerosolizations of the labelled substrate into the lung, then, may permit detection of such individuals by measurement of exhaled $^{14}CO_2$. Alternatively, the assay may be used to measure elastase activity in plasma.

(a) Smokers with emphysema are likely to have derangements in ventilation, such that the inhaled substrate-aerosol may not be adequately exposed to lung regions where higher than normal elastase activity is present (diseased regions).

(b) Detection of increased plasma or serum elastase activity in high-risk smokers is very unlikely, because of the overwhelming concentration of α1-proteinase inhibitor in plasma. It is more feasible to measure neurtrophil elastase in plasma by immunological techniques, since neutrophil elastase retains its antigenicity in α1-proteinase inhibitor complex. Indeed, screening of smoking populations using such measurements (RIA, other) are already in progress in several laboratories.

(c) Other non-invasive chemical tests are currently being developed and have already been reported in the literature, which may be more promising for detection of high-risk smokers. These tests include ELISA for elastin-peptides in serum (Darnule et al., Anal. Biochem. 1982, 122:302) and RIA for desmosine in urine (Harel et al., Am. Rev. Respir. Dis. 1980, 122:769).

3. A third study seeks to develop desmosine analogues to inhibit monocyte chemotactic responses to desmosine-containing elastin-peptides. Such drugs would hopefully blunt the further recruitment of monocytes (macrophages?) to regions of smokers' lungs containing degraded elastin, thus reducing the risk of developing emphysema.

This work is largely based on earlier published work by Senior et al.

showing that elastin-peptides are chemotactic for monocytes and suggesting that the chemotactic fragments were enriched in desmosine cross-links (J. Clin. Invest., 1980, 66:859). Recently, however, Senior has observed that non-cross-linked tropoelastin and also desmosine-free synthetic peptides (with amino acid sequences characteristic of repeating peptides in elastin) are chemotactic for human monocytes. He mentions these observations in a second paper (Senior et al., J. Clin. Invest., 1982, 70:614) and concludes: "it appears that cross links are not necessary for chemotactic activity of elastin peptides."

4. A fourth study of the Pulmonary Program is conducting an extensive correlation designed to evaluate the protease-antiprotease imbalance hypothesis of pulmonary emphysema. Parameters being explored include: smoking history, individual smoking habits (puff-volume, puff-duration, etc.) plasma thiocyanate and carboxyhemoglobin levels, number of polymorphonucleocytes (PMN) in the circulation, elastase and myeloperoxidase contents of PMN, total plasma α 1-proteinase inihibitor (immunological assay), ratio of trypsin-inhibitory to elastase-inhibitory activities of plasma (functional assay of α1-proteinase inhibitor), complement levels in plasma, neutrophil chemotactic responses to zymosan-activated plasma and to n-formyl-methionyl-peptides, and pulmonary function tests including spirometry and single-breath nitrogen washout.

Preliminary results on 50 matched subject pairs (smokers vs. non-smokers) were presented at the visit. Statistically significant negative correlations were found between pulmonary function and levels of complement, neutrophil

myeloperoxidase and numbers of circulating neutrophils. These data suggest that increased inflammatory mediators and attendant increases in total neutrophil protease "burden" may be important pathogenetic determinants of lung injury in smokers. Of special interest is the observation of increased neutrophil myeloperoxidase in high-risk smokers, since this enzyme has been implicated by other workers in the oxidative inactivation of α l-proteinase inhibitor.

The group working on protease-antiprotease imbalance is a hard-working, impressive one, who is fully competitive with the best in its field at other lung research centers. Moreover, the group has made an exensive effort to characterize their smoking subjects in terms of mg tar per cigarette, depth of inhalation, puff retention time, puff volume and number of puffs per cigarette, in addition to the usual indices of packs per day x years of smoking. They should now take greater advantage of available statistical resources at THRI to examine possible correlations between parameters of inflammation, protease-antiprotease balance, and individual smoking habits.

5. Another study seeks to develop a model of lung-injury induced by chronic cigarette smoke exposure coupled with steroid treatment to suppress the pulmonary macrophage response to cigarette smoke. In the absence of the normal macrophage pool in the lung, cigarette smoke exposure is observed to cause severe accumulation of phospholipid-protein complexes (tubular myelin arrays) in the alveoli, resembling those seen in human alveolar proteinosis. It is clear that emphysematous (destructive) changes also take place in this model. It was hypothesized that, in the absence of normal numbers of

phagocytic macrophages, secretory products (perhaps augmented in smoking animals) cannot be properly removed from the alveoli.

(a) The dose of steroid employed to produce the above effect in animals is extraordinarily high and has no physiological relevance. The dose corresponds to 35,000 mg/day/70 kg man as opposed to the usual clinical dose of 100-200 mg/day. (The latter is, itself, a pharmacological dose as opposed to a physiological dose.) At the dose level used in the animal studies, there is a 30% mortality from the steroid alone. Under these conditions, little can be said regarding the mechanism of action of the steroid-smoke combination, since steroids have wide-ranging effects even at physiologic doses.

(b) In view of these potential problems in data interpretation, a recent study has initiated experiments using lower doses of the drug combined with smoking. However, even this current dose is about 10x higher (corresponding to 1,750 mg/day/70 kg man) than the usual clinical dosage. Data on lung effects of this modified regimen were not available at the time of the site-visit.

6. A study is being undertaken on the <u>in vitro</u> and <u>in vivo</u> studies of the chemical and biological changes in α_1Pi induced by oxidizing agents and by cigarette smoke. Data were summarized at the site-visit showing that 4 out of 6 tyrosine residues in the free inhibitor molecule are normally suscpetible to nitrosylation with resultant loss of pancreataic elastase-inhibitory activity. However, α_1Pi complexed to trypsin or to pancreataic elastase appears conformationally altered, so that these same 4 tyrosine residues are no longer

susceptible to nitrosylation. Furthermore, and perhaps of greater relevance to the smoking and health issue, mild oxidation of α 1Pi converts 2 of 8 methionine residues in the inhibitor to their sulfoxides with loss of elastase-inhibitory activity (as observed by others); whereas stronger oxidizing conditions lead to conversion of 4 methionine residues to methionine-sulfoxide. Under these conditions, reductants cannot reactivate α1Pi, but they can do so when only 2 methionine sulfoxides are present. This information is new and potentially of great importance, since chronic cigarette smoking has been reported to convert half of the α 1Pi in the lung to an oxidized form containing 4 methionine sulfoxide residues per molecule (Carp et al., PNAS, 1982, 79:2041).

Studies are now in progress dealing with chemical changes and activity measurements for α 1Pi treated with cigarette smoke fractions in vitro, as well as for inhibitor recovered from lung fluids and plasma of animals following acute cigarette smoke inhalation. Longer-range plans include structure-function studies of 1Pi obtained from chronic smoking animals and humans.

The studies of ventilatory mechanics in unanesthetized dogs is certainly an appropriate preparation. Preliminary observations that nicotine may stimulate airway receptors are provocative and potentially important. It will be important in those studies 1) to obtain simple hemodynamic measurements, such as arterial pressure, which may have important effects on ventilation, and 2) to perform systematic pharmacological evaluation to determine whether the airway receptors that are activated are indeed nicotinic receptors.

II. Neurobehavioral Program

The main objective of this program is to explore the mechanisms and the various sites of action of nicotine in rats and dogs with a view toward elucidating the role of nicotine in smoking health and behavior. The group is attempting to characterize the physiologic and pharmacologic nature of the various receptors for nicotine within the central and peripheral nervous system employing an extensive battery of pharmacodynamic, electrophysiologic, psychophysical, and biochemical techniques.

The overall objectives of the program were well-delineated and addressed important issues related to tobacco health, while the experimental design and protocol was well-conceived and appropriate. During a relatively short period, many experimental procedures were developed and refined, which were required to accomplish the objectives, and also significant data was generated concerning the nature and function of multiple nicotine binding sites within the brain. Among the significant findings were those demonstrating that low concentrations of nicotine may enhance nicotine binding and that the analgetic action of nicotine involved the medulla oblongata rather than the opioid system.

Convincing data was presented showing that nicotine is self-administered (i.e., reinforcing) when administered directly into rat lateral hypothalamus, while being adversive when administered into the pons-medulla. Although other studies have demonstrated that nicotine is reinforcing when given systemically, this study is the first to show that it is self-administered

into a brain area, specifically the lateral hypothalamus. Such studies contribute to our knowledge of why people smoke and help elucidate the brain sites and mechanisms involved in nicotine's action.

In summary, the projects have considerable relevance to the stated objectives of THRI and are in competent, experienced hands. The progress to date has been very good and is expected to continue to be so.

Neurochemical Studies:

This project dealt with the effects of chronic nicotine administration on the cholinergic system of synaptosomes isolated from rat and mouse brain and on the transport of ^{14}C-isoaminobutyric acid (AIB) transport across the mouse placenta. The likelihood that the synaptosomal studies will result in significant new findings concerning mechanism of the action of nicotine is not great, since this approach has been used by innumerable investigators in the past and to little avail. Although effects of chronic nicotine on placental transport are worth investigating, the rationale behind the studies on AIB transport are not clear. It was stated that acetylcholine mediates AIB transport across the placenta, but the implications or significance of this observation are obscure.

The studies dealing with the effect of nicotine on the catecholaminergic system of rat brain are not promising, since this approach has not proven fruitful in the hands of other investigators. Following the negative findings on the effect of chronic nicotine on the level of tyrosine hydroxylase in

neonatal brain, little information was provided concerning alternative approaches or future plans concerning this project.

III. Cardiovascular Program

The studies on the effects of smoking on cardiac patients are appropriate and worthwhile. The investigator is aware of strengths and limitations of the methods. Characterization of effects of smoking on ventricular performance and on the response to treadmill excerise are likely to provide valid data, although new concepts are not likely to be derived. Further studies using isotope ventrilculograms are to be encouraged. Preliminary findings that smoking leads to increased likelihood of repetitive ventricular responses are extremely important. The finding, if confirmed by continuing studies, may provide insight into the high incidence of death from coronary disease in smokers. The investigators should be encouraged to pursue mechanisms that contribute to the electrophysiologic effects that have been observed.

Studies of effects of smoking on thromboxane and prostacyclin production are important. The investigators are competent, they have obtained preliminary results, and their studies appear meritorious.

The rationale for the study of the effects of smoking on cutaneous blood flow is weak and the approach is unlikely to provide definitive new insight. Unless a more extensive review uncovers more scientific merit than was evident at the site visit, the proposal does not appear to be promising.

Another study was concerned with the effects of smoking on pharmacokinetics. The experiments are likely to generate valid, worthwhile information, although they are not likely to provide important new insight. The area of research and the specific studies that are proposed appear to be worthwhile.

IV. Passive Smoking--Smoke Components

General Impressions

At this time, the THRI and the academic groups associated with it are a unique resource. No other facility, in the United States or elsewhere, combines in one area such a broad spectrum of scientific expertise with a solid core of specific tobacco science and technology. The potential value of the Institute to the University and to the State of Kentucky is very great.

The overall quality of the work conducted under the auspices of THRI is good and shows substantial improvement in the recent past. The core facility is excellent; the core staff appear to be enthusiastic and competent.

With respect to the specific problems that arise in tobacco and health studies, the University of Louisville groups appear to be less sophisticated than their University of Kentucky counterparts. If real, this difference may reflect the ease of communication between core staff and grantee. The THRI staff should encourage improved contacts with the Louisville groups.

Overall, the grantees should be strongly encouraged to consult the core statistical group at the time their studies are planned. Such consulation is an expressed goal of the Research Support Service. The goal might be more efficiently realized if each application, prior to technical review, carried a one-sentence statement by the core statistician regarding the statistical efficiency of the research design.

A final general comment concerning the establishment of the program segment entitled "Passive Smoking". Use of this terminology tends to give a mystique to the composition of "passive" smoke that may distort the thinking of both lay advisors and the less sophisticated professionals. To the extent that "passive" or "sidestream" smoke components are studies in the program, they could just as well be called smoke components.

Studies of NNN Localization in Tissues

These studies as reported during the visit and in the September 1982 report to the Board are not encouraging. The original concept had sufficient merit to justify pilot investigations designed to determine the direction of more extensive work, if any. The reports suggest that, at this time, further work in this area is not likely to be effective.

Effects of Passive Smoking on Interferon Production

The biological system appears to be well controlled. However, the selection of compounds in this study is simplistic. It would have been

reassuring to have heard a plan to test non-carcinogenic analogs of compounds that were selected, in part, because they were reported carcinogens.

It is particularly distressing to read in the manuscript submitted to Oncology that comparisons of a handful of pure compounds are used to characterize the likely relative activity in man of sidestream or mainstream smoke. The proposed studies with in vivo exposure to whole smoke would be more acceptable. The investigators should be encouraged to consult with the core staff to see if in vitro exposure of cells to whole smoke would be feasible.

Metabolic Activation of Nicotine-Derived Nitrosamines

The work proposed and the summary of work to date are very encouraging. The plan is very good and should yield valuable information concerning an important class of smoke carcinogens that may be important in the area of tobacco and health.

The Role of Methylation in Nicotine Toxicity

At this time, the studies are preliminary. The plan and the approach suggest that the study will be well conducted and deserves support.

Coagulation of Tobacco Smoke Aerosol

This project is very impressive. It addresses a critical area in tobacco smoke technology: What are the physical changes in smoke between the time it leaves the cigarette and the time it impinges on human tissue or the tissue laboratory test systems? An understanding of these changes is critical for the design of experimental studies and for the interpretation of experimental results. The approach is good and brings a variety of measurement methodologies together in the studies of particle coagulation. The work should deserve high priority in the program of THRI.

V. Product Modification

A number of investigators have made very significant contributions to all projects relating to smoke generation and inhalation by experimental animals. The methodology and protocol they have developed should markedly reduce the variabililty in smoke exposure and, in so doing, will increase the statistical reliability of experimental data.

A vast majority of the funded projects are concerned with studies of cardiovascular, pulmonary, and neurobehavioral influence of tobacco smoke. This is surely in keeping with the mission of the Institute; at the same time it is well that consideration is being given to product modification. The College of Agriculture at the University of Kentucky is internationally recognized for its research in tobacco production, and faculty from that college should have strong ties with the Institute.

Research on nicotine metabolism in the tobacco plant represents the type of research that can yield valuable information on how the chemical components of tobacco and tobacco smoke are synthesized. An understanding of these processes may well make possible modifications in the chemical composition of tobacco and smoke through genetic, cultural, or curing techniques.

Basic information from the studies of "Viral Gene Expression in Tobacco Cells" may well contribute to control of diseases of tobacco, as well as how genes of host plants and virus particles interact in plant development and product production. Also impressive was the research on the influence of smoking on biochemical and defense mechanisms.

Basic studies, such as the three listed above, are indeed appropriate to the mission of the Institute and can serve as vital connecting links between the medical and agricultural research on tobacco.

Finally, the research on aerosols in tobacco smoke is at the cutting edge of smoke chemistry and physics and should be continued.