

Comments on Application #1353 (from Henry Rothschild, MD, PhD) entitled  
"Genetic aspects of lung cancer"

Overall impression: This is a moderately strong research proposal submitted by very well qualified investigators. The data they propose to gather will be extremely worthwhile for epidemiologic studies of lung cancer, although the stress in the proposal is on genetic aspects of this disease or class of diseases. The budget is, if anything, overly modest for the aims and procedures stated. The main weakness of the proposal is its emphasis on Mendelian transmission, which is quite unlikely to be the mechanism of genetic susceptibility outside of a few selected families.

Discussion of the specific aims: (1) The proposal for ascertainment of lung cancer cases on a current basis makes sense because of the short life expectancy and the importance of developing detailed information on the cases while alive. There was an expectation of 70% compliance stated in the proposal; one wonders what that figure was based on and whether it might be improved by assiduous persuasion or use of media campaigns.

(2) The emphasis on single-gene analyses reflects the "medical genetics" orientation of the investigators. This reviewer would be more attuned to the importance of measuring the levels of familial aggregation, the problems caused by delayed onset of the condition, and the relationship of environmental factors to expression. The possibilities for simulation of monogenic inheritance are very great in this situation.

(3) The separation of families into two classes, genetic and nongenetic, is fraught with methodologic hazards. Using the Fain statistic it would seem more reasonable to use a continuous scale

of classification.

Discussion of the methods of procedure: The reviewer was confused as to whether administration of the questionnaire should be done by the subject or the interviewer. It would appear that the questionnaire is difficult and complex, and that it would be hard to obtain valid information from a self-administered mode.

As far as the methods of analysis are concerned, given the basic orientation of the investigators these methods are quite appropriate. One would be happier if there were some cautionary remarks expressed concerning ~~the~~ possibly misleading results; since lung cancer is a fairly common disease, will not every such study yield some families in which clustering of cases is seen to occur? Does selecting only such families for genetic analysis constitute a valid application of the analytic technique, and if so, what generalizations can be made from the results? Have other applications of this method resulted in elucidating the existence of major genes which determine susceptibility to common chronic diseases?

The comparison of "genetic" and "nongenetic" families would seem to be a backwards approach to the problem; would it not be more enlightening to examine patterns of familial clustering in families not exposed to the environmental determinants of lung cancer?

Discussion of the qualifications of the applicants: Dr. Rothschild, the Principal Investigator, is Chief of the Section of Medical Genetics at LSU School of Medicine. His bibliography lists 26 publications in refereed journals, but few if any are in journals in the field of human genetics. Given his qualifications and training he would not be expected to grasp fully the epidemiologic complexities of this study.

He is supported by three colleagues: Robert Elston, Lester J. Vial, Jr., and Vivien Chen. Dr. Elston is an internationally known genetic analyst with energy and enthusiasm for genetic-epidemiologic work. Although his focus is rather narrow and, to this reviewer's judgment, overly clinical, he does bring unique ability and technical skill to the project. Drs. Vial and Chen are extremely junior investigators with marginal bibliographies. A senior epidemiologist on the project would have been more comforting, as the "consensus" likely to emerge on the findings will tend to be overly medical in emphasis. On occasion extravagant claims have been made for simple mechanisms to explain chronic diseases in families; the presence of a widely experienced epidemiologist is a valuable counterweight here. The project will suffer unless appropriate consultation or collaboration is arranged.

Discussion of the facilities and budget: The facilities appear to be adequate for the conduct of research. The budget seems too small because salary support for investigators is not included. A fifteen per cent indirect cost rate means that LSU will operate this project at a financial loss, unless grants and contracts are rare at that institution. It would appear that the investigators should derive salary support for such an undertaking.

Summary and recommendations: This is a typical "medical genetics" project with the usual strengths and weaknesses: strong analytic and laboratory techniques, but less than a fully thought out approach to the problem. The balancing factor weighing in favor of the project is the probable excellence of the data and its relatively low cost. In conclusion, the project should be approved with moderate enthusiasm and at an increased budget including investigator support.

November 6, 1957

Re: Application No. 1352  
Henry Rothschild, M.D., Ph.D.

Dr. Henry Rothschild  
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Department of Health Sciences  
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Dear Dr. Rothschild:

It is my pleasure to inform you that your proposal for a research grant has been accepted and a critical review.

Enclosed for you are two copies of the application, and two copies of the critical review. You have entire latitude on how you set down your comments. The Council provides a small honorarium for such evaluation.

As we are now preparing for our next critical review board meeting, we trust that we may hear from you within the next few days at the latest.

Please phone if there are any questions.

Sincerely,

Vincent F. Misanti, D.M.D.  
Associate Research Director

VFM/3p

Incls.