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Original given to  
Dr. Heffron  
1/5/78

June 4, 1952

Dr. Roderick Heffron  
The Commonwealth Fund  
1 East 75th Street  
New York, New York

Dear Dr. Heffron:

At this moment as I am writing what is possibly my last report to you, my thoughts return to the time some  $11\frac{1}{2}$  years ago when our first application for financial support was submitted to the Commonwealth Fund. That was one of the most critical periods in my scientific career as it was then that I found myself totally deprived of funds for the continuation of my research.

Having decided to withdraw from the field of sex endocrinology, I had tried to obtain support for a study of one of two major problems, the first being the exfoliative cytology of uterine cancer and the other, the incidence of spontaneous tumors in the senile guinea pig and its relation to the functional state of the endocrine glands. Both projects were rejected by every one of the societies supporting cancer research to which I turned for help. In order to keep my laboratory going, I had to share my salary with my two assistants for a period of six months.

originally underestimated. I am sure that you must have been disappointed with the delay in its completion, however we hope that now it will be only a matter of a few weeks until the manuscript is in your hands.

4 | I still feel that the Atlas will be of great value as a practical guide for the study of exfoliative cytology and its application in the diagnosis of cancer. Moreover the selection and the arrangement of the material has been conducted with the idea of forming a basis for a comparative evaluation and classification of the normal and abnormal cells found in body secretions. Such a study is a necessary step in the further development of exfoliative cytology as a branch of the morphologic sciences.

XI | Our special course in Exfoliative Cytology has been continued during the past three years. In addition to those regularly enrolled in our course, other doctors and technicians, coming from this country as well as from other parts of the world, have spent various lengths of time in the study of our large collection of representative slides. Since the initiation of our course in 1947, a total of over 500 doctors and technologists have received instruction in cytologic diagnosis in our laboratory. This continued demand for instruction is a measure

of the increasing interest of the medical profession in this new field.

The method of cytologic diagnosis of cancer may now be considered well established, a fact which is attested by its widespread introduction as a routine procedure in a large number of hospitals and clinics. Future progress of Exfoliative Cytology should be further promoted through the recently established Inter-Society Cytologic Council. This body will greatly assist by affording guidance for the adequate training of personnel and the proper practice of the cytologic method of diagnosis.

The cytologic method of cancer diagnosis has been extended to all accessible fluids and secretions of the body. In the past three years much progress has been made in its application to the gastrointestinal tract, chiefly the stomach, sigmoid, colon, and rectum. The fundamental work in these applications has been conducted in our laboratory in cooperation with the New York and Memorial hospitals.

During the past few years, the examination of smears prepared from breast secretion has convinced us of the possibility of detecting, by this method, the presence of carcinoma, at least the intraductal variety, at a very early stage of the disease even before a local growth is discernible. This contention is based on three cases in which a diagnosis of a very early carcinoma was made by

breast smears and later confirmed by operation performed solely on the basis of the positive cytologic findings. Spontaneous secretion was the only clinical evidence.

We are now more actively engaged in the study of the normal and malignant cytology of the breast. This project, which was part of the research program submitted to you in 1948, is supported by the American Cancer Society. The results to date are very encouraging.

The problem of dyskaryosis, i.e. the specific cytology of the early carcinoma of the cervix, is still of major importance. There are four distinct dyskaryotic patterns corresponding to what is termed by pathologists as carcinoma in situ or intraepithelial carcinoma. Each has a different prognostic value. In the superficial and intermediate squamous cell types, for instance, regression may often occur, whereas in the parabasal and endocervical types, a progressive course is the rule.

The fact that some of these early lesions undergo spontaneous regression is of particular interest and opens a new and very important investigative field. We have accumulated considerable data on such cases. Following the completion of the Atlas, it is our plan to make a thorough analysis and tabulation of this material. Of course, any reports on this work will carry an acknowledgement of the support which this investigation has received from the Commonwealth Fund.

A nother study, conducted by Mrs. Doris G. Holmquist, is that of the detailed structure of nuclei of normal and malignant cells under magnifications greater than those used in routine diagnostic work. During the course of these observations, attention has been drawn to the mitotic figures present among the exfoliated cells in various body secretions. An evaluation of the normal and abnormal mitoses and a correlation of their incidence with clinical and pathological findings are being made in an effort to ascertain the possible diagnostic significance of mitotic figures found in cytologic smears.

A brief report of this work was presented at the Symposium of Exfoliative Cytology, Scientific Session, Annual Meeting of the American Cancer Society in October, 1952. Also, two plates of the Atlas have been devoted to the illustration of the most characteristic mitotic aberrations.

This investigation as well as Mrs. Holmquist's assistance toward the completion of the Atlas have been supported by the Commonwealth Fund. Since December 31, 1951 this program has been continued through your generosity in allowing us to use part of the unexpended balance of \$2292.01 in payment of one-half of her salary.

It is felt that this investigative work is of primary importance and we are anxious to have it continued, but no

other funds are available for it at present. Mrs. Holmquist will be forced to interrupt this work if her full salary has to be carried by the only other fund at our disposal, the grant from the American Cancer Society for the Breast Project.

We are facing the same problem with regard to Mr. Constantine Railey who has been helping us with the photomicrography as well as other aspects of the work on the Atlas. As in the case of Mrs. Holmquist, one-half of Mr. Railey's salary since December 31, 1951 has been paid from the unexpended balance of your grant to us.

Since plans have been made for the publication of additions to the Atlas for the next three years, it would be very desirable to continue, if possible, to pay one-half of the salaries of Mrs. Holmquist and Mr. Railey from a special fund for this work. Such a fund would provide for their continued work on the Atlas and the above mentioned investigation and afford freedom from other specific obligations which would be entailed if their total salary were transferred to another project grant.

In reviewing our past accounts, you may note that on two occasions unexpended money has been returned to you in the amounts of \$5989.68 on June 30, 1950 and \$2615.30 on April 18, 1951. If this money has not been diverted

to other uses, I wonder if it would be possible for you to make this available to cover our present needs.

The total of the yearly salaries of Mrs. Holmquist and Mr. Railey is \$7900. A continuation of our present arrangement of carrying half their salaries on the grant from the Commonwealth Fund would require approximately \$3950 per annum. Thus the sum of \$8604.98 would be sufficient for about two years.

If it is possible to make this sum available to us, it will certainly be deeply appreciated and will greatly facilitate the continuation of our work without alteration of our present plans.

A more detailed budget is as follows:

12-31-51	Unexpended balance	\$2292.01
5-31-52	Deficit	319.38
6-30-52	Needed ( if payment of one-half of the salaries of Mrs. Holmquist and Mr. Railey and final payment of \$100 to Mr. Murayama plus 1% for social security are from this fund)	382.50
6-30-52	Total deficit	701.88

Amounts refunded to the Commonwealth Fund

4-18-51	\$2615.30
6-30-50	5989.68
Total	\$8604.98

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Proposed requirements for continuation of payment of one-half the salaries of Mrs. Doris Holmquist (\$4500 per annum) and Mr. Constatine Railey (\$3400 per annum) plus social security charges.

Mrs. Holmquist (one-half salary)		\$2250.00
Mr. Railey	" "	1700.00
	Social Security	59.25
	Total per annum	\$4009.25

In closing, I wish to express once more to the Commonwealth Fund and to you personally my gratitude for the wonderful cooperation and support extended to us over many years.

Sincerely yours,

*George N. Papanicolaou*  
George N. Papanicolaou, M.D.