Lung Physiology
Committee:
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TOBACCO INDUSTRY RESEARCH COMMITTEE

150 East Forty Second Street New York 17, N.Y.

#289

Application For Research Grant

Date: August 23, 1960

1. Name of Investigator: Enrique Valdivia, M.D.

2. Title: Assistant Professor of Pathology

3. Institution & Address: The University of Wisconsin Medical School
426 North Charter Street
Madison 6, Wisconsin

4. Project or Subject: Microscopic Observations of the Pulmonary Vessels "In Vivo."

Pulmonary vessels of dogs and guinea pigs will be observed microscopically in vivo. When the normal anatomic relations of the various vascular patterns are established they will be compared with those of animals subjected to hypoxia. Similar observations will be made to determine the effect of various vasomotor drugs upon the pulmonary vasculature.

5. Detailed Plan of Procedure:

The study of acclimatization to high altitude has been the primary interest of the applicant over a period of years. Most of the previous investigation has been done by exposing guinea pigs to experimental chronic hypoxia in low pressure chambers. Tissue alterations, rapid dilation and hypertrophy of the right heart have been observed in the experimental animals. Radiological and histological studies have demonstrated evidence of right heart failure and increase in size of the branches of the pulmonary artery. These findings, and the reported evidence of pulmonary artery hypertension in acute and chronic hypoxia, indicate that there must be alterations in the pulmonary vasculature. For this reason, it was decided to observe these vessels "in vivo", under controlled physiological conditions and under different experimental variables.

Our method of procedure has followed two lines of approach to the problem, the first is the observation of pulmonary vessels "in vivo" in dogs and guinea pigs; the second is to establish the anatomic relations of the structures being observed in the same animals. This anatomical study is being done with radiograms obtained after the injection of the bronchial tree, pulmonary artery and pulmonary veins with a radio-opaque medium. Additional information is also obtained from casts of the same structures made after the injection with vinylacetate. The extent of the injections and minute anatomical relations are also checked by histological examination.

The observations of the pulmonary vessels "in vivo" are made at magnifications of 50 X to 750 X, measurements and some enlargement is obtained from cinematographic records. The preparation requires general anesthesia, open thorax and immobilization of the lung. Determinations of pulmonary artery pressure, femoral artery pressure, breathing rhythm, electrocardiogram, oxygen and carbon dioxide content of the blood, hemoglobin and hematocrit are made during the course of each

experiment in dogs. The experiments with guinea pigs cannot be so well controlled because the size of the animal does not permit withdrawal of blood without interfering with the course of the experiment. The immobilization of the lung as reported by Irwing et al (Anatomical Record 119:391, 1954) and based on the Meltzer preparation (J. Exper. Med. 11:622, 1909) produces good oxygenation but significant carbon dioxide retention. Furthermore this method does not control the endotracheal pressure, our findings indicate increase in the pulmonary artery pressure and evidence of pulsatile flow when the oxygen endotracheal pressure is 12 cm. of water or more.

Our new method of immobilization of the lung permits controlled automatic respiration, because only one small area of the external surface of the lung is kept immovable. The illumination of the observed area is obtained with an incident light illuminator plus an additional reflection box such as commercially made for the metalurgic type of microscope. This method permits us to make observations anywhere on the surface of the lungs.

Our aim is to obtain basic line information under controlled conditions and then to compare these results with the ones obtained from animals submitted to chronic hypoxia.

Any vasomotor action on the pulmonary vessels can be directly observed after the injection of drugs such as adrenaline, acetylcholine, hexamethonium, serotonine and nicotine.

6. Budget Plan:

Salaries	4,800
Expendable Supplies	1,400
Permanent Equipment	2,400
Overhead (15%)	*1,290
Other	--
	*$9,890

*-Recalculating the overhead with exclusion of the $2,400 for permanent equipment gives:
$930.00 for overhead at 15%
$9,530 Total

7. Anticipated Duration of Work: 3 years

8. Facilities and Staff Available:

The facilities of the Department of Pathology, University of Wisconsin Medical School. The staff available is formed by the director of the project, one full-time technical assistant and part-time student help. The equipment: 3 low pressure chambers; one x-ray machine with a fluoroscope for cardiac catheterization in dogs; one microscope with built-in direct illumination, one 16 mm. movie camera; one Grass multi-channel Recording equipment partially equipped; tables and rotary stage for animal surgery; two Van Slyke apparatus; one Sanborn electrocardiograph; one automatic respirator.

9. Additional Requirements:

Completion of the equipment for the recording apparatus. Parts for the Van Slyke apparatus. Cardiac catheters. One oxymeter. Equipment to determine pulmonary artery flow (under study).

10. Additional Information:

A complete curriculum vitae of the director of the project is included. Histological studies of the total capillary bed in muscle, and myocardium and demonstration of succinicdehydrogenasa activity in different tissues from animals submitted to experimental hypoxia are currently investigated under financial support from the Wisconsin Heart Association.

Signature Enrique Valdivia, M.D.
Director of Project

A. W. Peterson
Vice President - Business and Finance