vessels during systemic hypoxemia* causing an increased pulse pressure to be transmitted downstream to the resistance vessels.

If local atelectasis or hypoxia causes the resistance vessels of the affected lung to operate as a vascular waterfall, then the increased systolic pressure may raise mean flow significantly. The increased flow through resistance vessels in systole thereby would reduce the blood volume available for retrograde flow during diastole. This effect may exaggerate or prolong the effect of a moderate or transient hypoxic episode in subjects with acute atelectasis, since increased flow through the alveolar region may increase pulmonary shunt, further lowering arterial \( P_O_2 \). Thus, there appears to be a chemoreceptor-mediated interaction between local and systemic effects of hypoxia on the pulmonary circulation, which has aspects of a positive feedback system.

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**Summary of the 19th Aspen Conference**

**Thomas C. Lloyd, Jr., M.D.***

To be invited to summarize an Aspen conference is a well-recognized honor, and before proceeding, I want to thank the organizers of the meeting, and my unknown sponsor, for giving me this distinction. Beyond the importance of the honor, I was pleased to have been provided this opportunity, for I wanted to attend on any terms, and to come as summarizer seemed easier, at the time, than to prepare an abstract. But it turns out that this is a very difficult job, and late at night while preparing for the final session it occurred to me that the “honor” may, in this case, have been bestowed as retribution for some past offense. This parenthetical has only partially dissipated upon exposure to sunlight.

My interests in the pulmonary circulation have been in the response to alveolar hypoxia, in neurogenic regulation of pulmonary vessels, and more recently, in regulation of systemic vessels secondary to reflexes initiated by pulmonary vascular congestion. Regulatory systems have been important to me, and I will freely incorporate that bias in this summary, in the belief that the summary should not be a synopsis, per se, but should be an opinionated, but (I hope) provocative overview. In doing so, I regretfully will fail to give adequate recognition to many of the presentations, and will probably misinterpret others.

We all know that the pulmonary circulation has at least three roles to play: 1) it provides blood for gas exchange and has the apparent ability to optimize that function by setting its tone in accord with gas tensions; 2) it intervenes as an active metabolic system between systemic veins and arteries which alters blood composition by scavenging some materials and producing others; and 3) it provides a sensory system for cardiopulmonary control by way of several lung reflexes influenced by the vascular status. This conference has particularly stressed the first two, but even so has revealed such a diversity of topics that it was difficult to organize discrete sessions under a single title. This diversity is a sign that we are more aware of the complexities of the lung vessels. Furthermore, it is an indication that we are welcoming the inquiries of different groups, such as cell biologists and biochemists, to what long has been a plumber’s trade. Indeed, the absence of hemodynamic review at this meeting would have been complete had it not been for a somewhat nostalgic argument that arose concerning the best way to represent vascular resistance. Diversity, however, makes my job harder, and I confess to feeling at times more like a spectator than a participant.

The effects of hypoxia have been summarized separately by Dr. Cournand, but because of personal interests, I will include some of the effects of hypoxia in my view. I will try, however, to convince you that much of the material reported under that topic is not germane to hypoxic vasoconstriction in whole lung, but is more a study of general properties of smooth muscle.

In that regard we have heard from Drs. Bohr, Claman and Souhrada how the pulmonary artery may behave if it is deprived of oxygen, and of its dependence upon oxygen or glucose for energy. Dr. Bohr reviewed the sequence of events leading to constriction, including the role of calcium, and Dr. Souhrada showed that calcium to be a determinant of the response of isolated vessel to severe oxygen depletion. Both groups showed that aerobically as well as anerobic pathways can generate ATP, and Bohr showed that anerobic capacity can be enhanced by storing vessels under hypoxic conditions. Such “adapted” vessels were able to contract in response to epinephrine where they otherwise would not. I infer that Dr. Bohr believes the pulmonary artery to be relatively hypoxic in vivo and to have developed anerobic...

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**REFERENCES**

sources to provide energy for contraction when alveolar hypoxia occurs. On the other hand, Dr. Souhrada found that contraction of isolated strips of pulmonary artery occurred only if they were depleated of both oxygen and glucose, i.e., if both aerobic and anaerobic metabolism are impaired. While it may be possible to cause contraction of isolated arterial strips by these techniques, I do not believe this relates to the response to alveolar hypoxia for several reasons, the most important of which are that pulmonary arterial wall is never particularly hypoxic compared with systemic vessels (it should have a PO2 somewhere between that of alveolar gas and of mixed venous blood), and it probably has adequate anaerobic substrate. Furthermore, the whole-lung response is exquisitely pH and temperature-sensitive, which are not noteworthy properties of isolated vessels. Dr. Clyman gave other information useful to refute a direct action of hypoxia as a cause of contraction when he showed that hypoxia had no effect on cAMP, but decreased cGMP or prevented its increase with pressor agents. Those effects are consistent with a decreased ability of hypoxic pulmonary vascular muscle to contract, which is what most of us find when using fresh vessel, modest hypoxia, and adequate anaerobic substrate. In his discussion of calcium, adenine nucleotides, and pH Dr. Clyman also brought out that acidosis enhances microsomal calcium sequestration leading to relaxation, whereas we again note that acidosis enhances the response to alveolar hypoxia. To add another dimension to the effect of hypoxia, Dr. Clyman reported that while hypoxia inhibits increase of cGMP, inhibition of oxidative phosphorylation does not; consequently, the effects of oxygen include more than oxidative phosphorylation.

I conclude that contraction of isolated strips as observed by Bohr and Souhrada, and myself for that matter, are things which a vessel can be taught to do, but we should not be hured into accepting them as models of hypoxic vasoconstriction. When I first saw Dr. Souhrada's results with substrate depletion I was convinced that he had provided good evidence that what I found when using isolated strips of naked artery in nonaqueous baths was probably not equivalent to contraction in situ, or of vessels exposed to hypoxic lung parenchyma. On the other hand, I believe these studies provide important information about fundamental properties of pulmonary arterial muscle.

In the session on vasoactive compounds Dr. Kadowitz introduced us to "dynamite"—the endoperoxide and thromboxane intermediates in prostaglandin synthesis which apparently are so much more active than the prostaglandins that the latter may better be thought of as degradation products. However, the intermediates are short-lived. From a control viewpoint, the lability of the most active compounds is intriguing. Lability puts limits on distances between sites of formation and of action and potentially allows for rapid variation of concentration. These characteristics open the possibility for rapid "turning" of the pulmonary circulation (and airways) in the microenvironment surrounding sites of prostaglandin synthesis.

Endothelium, long a neglected pulmonary vascular component, has received attention with exciting results, presented by Drs. Junod, Gallagher, Will, Block and Gillis. The range of compounds metabolized is impressively large, and includes amines, nucleotides, peptides and lipids, while peptides, amines and lipids are either generated or released. Discrete information regarding the process is becoming available. For example, serotonin and serotonin are removed by a process whose rate is limited by transeellular transport. That transport is saturable and dependent upon temperature and sodium. The transmembrane transport of prostaglandin F2 may be carrier mediated. We learned that these functions of endothelium are not unique to lung, but occur in the systemic vessels as well. The importance to lung seems to be that the compounds which are produced or degraded have numerous and prominent effects in lung.

In the course of discussion it was brought out that the effectiveness of removal of some compounds, for example serotonin, is so great that it is difficult to see how much could ever pass from lumen to vascular smooth muscle. Indeed, it has not been possible to show passage in histologic preparations, yet we know that serotonin quickly increases perfusion resistance of excited lobes. Vascular response seems to arise from a much smaller amount of agent than I thought. I infer that such a remarkably effective removal mechanism would allow small changes in effectiveness to have proportionally large effects on the amount of material which might reach muscle, i.e., the difference between 99% and 98% removal would be to double effective concentration, and one would probably not be able confidently to detect the difference in venous blood. It is little wonder that arteriovenous gradients sometimes seem to bear little relation to changes in vascular resistance.

Dr. Block showed that serotonin clearance is impaired in rats exposed to oxygen at high ambient pressure, and that this deficiency was exaggerated by vitamin E deficiency, but minimized by addition of suprasoxide dismutase. This was an interesting look at a specific effect of oxygen toxicity. It occurred to me that this would be a place to apply Dr. Junod's "Hautchen" technique and determine whether there was a preferential effect on venous endothelium, compared with arterial, as I would expect.

The studies reported by Gillis and by Block brought out the importance of defining endothelial surface area and blood contact times before concluding that arteriovenous chemical gradients are related to reaction kinetics, for those hemodynamic variables importantly determine the outcome. I was impressed that variations of venous concentration may be more controlled by hemodynamic events than by changes within individual endothelial cells. Shouldn't we add the transit time/surface area product as a variable to be considered when studying lung function in such things as shock?

Turning now to consider the phenomenon of hypoxic pulmonary vasoconstriction, Dr. Bergöisky reported studies which attempted to relate that response to alpha-adrenergic mechanisms, and he was partially successful.
Dr. McMurtry used perfused rat lungs and showed that hypoxic vasoconstriction was less with plasma than with blood, and nearly absent when using salt solution. Neither angiotensin nor platelet additions restored responsiveness (contrary to other reports), but addition of red cells to the perfusate enhanced responses beyond any expected effects of the viscosity change. Potential red cell effects include removal of a circulating vasodilator, addition of an activator, or depletion of glucose. Dr. Tucker reinvestigated the possibility that histamine is the hypoxia-induced mediator by using specific \( \text{H}_1 \) and \( \text{H}_2 \) antagonists. After demonstrating that both receptors were present in the dog he found evidence to support the hypothesis that although histamine is released by hypoxia, it primarily activates \( \text{H}_2 \) (dilator) but not \( \text{H}_1 \) (constrictor) receptors and should therefore detract from, not cause, hypoxic vasoconstriction.

If one concludes that the response to hypoxia should have a mediator, the disagreements about its nature are obvious. Histamine, serotonin, noradrenaline, angiotensin, hydrogen ion, adenosine nucleotides and others have been identified as responsible and just as confidently refuted. Because of this, some have concluded that there is no mediator. Still, it is obvious that there is sufficient evidence to indicate a direct effect. I interpret the search for potential mediators as indicating that there is no single mediator. At any one time the pulmonary vascular muscle is exposed to a multitude of potential mediators which, by their relative amounts, set quiescent tone. Cannot the effect of hypoxia be to upset the balance by influencing one or more of the component parts? What seems to be a single mediator in a specific experiment may be ordained by choice of initial conditions, (species, pH, degree of hypoxia, length of exposure, anesthia, etc.) which allow a dominant factor to develop. Given the plethora of vasoactive materials present, the lungs have maintained limits of lung, and the general tendency for all biologic control systems to be multivariate, I consider the search for a single mediator of hypoxic vasoconstriction to be ill-advised. The first task is to prove that the response is dependent upon something in the milieu. The next assignment would be to discern how or where the balance is upset, and why it appears to be upset of oxygen tensions that are rather high in relation to requirements for metabolic inhibition.

Or is there an \( \text{O}_2 \) receptor somewhere?

Dr. Biggs and Schoeneberger described movement of proteins across endothelium and alveolar epithelium and the associated microscopic anatomy. Apparently, transendothelial movement occurs both by pinocytotic vesicles (large molecules) and through intercellular spaces (smaller molecules). Transendothelial movement is limited to pinocytotic vesicles and epithelial permeability is much less than that of the endothelium. Zones of occludentes between capillary endothelial cells are made up of particles contributed by both cells. These junctional particles are less numerous near the venous end, in association with an increased permeability. The less permeable epithelial junctions are composed of single fibers shared by two cells. I wonder, perhaps naively, if some control of vascular smooth muscle is obtained by these properties of endothelium which may variably limit exposure of the muscle membrane to many things present in intraluminal blood. One man’s leak is another man’s communication system. Are events that disrupt endothelial integrity going to lead to altered vasomotion as well as pulmonary edema?

In reports related to pulmonary edema, Dr. Staub found that edema in sheep caused by increased capillary pressure is associated with protein-poor lymph and concluded that capillary pressure does not influence pore size. Dr. Strang confirmed in fetal and newborn lambs that endothelium was more permeable than epithelium and found pore size in the fetus to exceed that in the newborn. He concluded that pore radius was a function of capillary pressure. Dr. Efron followed sodium, water and albumin movement and found that electrolyte extraction was not affected by transit time. About 75% of water movement passes through junctions, while 25% goes through the cells. All electrolytes, however, must go through the cells. He concluded that this preferential loss of water would lead to plasma concentration and osmotic buffering of the capillary water movement, and that filtration rate would be set by solute permeability.

Electrolyte movement of another sort was presented by Dr. Gatzy, who studied bullfrog alveolar epithelium using classic short-circuit current methods. He found no active sodium transport, but instead found active transport of chloride and other halides. The short circuit current was essentially equal to net chloride flux. While three epithelial cell types are present in the bullfrog (squamous, cuboidal and ciliated) his studies probably exclude ciliated cells as responsible for the chloride transport. These are clearly different electrolyte transport properties than most of us are accustomed to seeing. To the surprise of some cell biologists, there is little known about these fundamental properties of lung epithelium. I am glad that the program committee recognized the uniqueness of Dr. Gatzy’s studies and included him in spite of his having failed to use the word ”vesel” anywhere in his abstract! Membrane transport is a phenomenon of obvious importance in all other organs and the lung could provide additional important examples.

Several aspects of the fetal circulation were considered, including its control, maturation, responsiveness to prostaglandins and filtration characteristics. I have included some of these in foregoing sections. It was at this session that discussion of definition of resistance surfaced. I believe that there are conditions under which calculated values of resistance can be misleading. What we want are pressure-flow graphs themselves, since derived expressions, especially if based upon a single point, are influenced by the non-linearity and non-zero intercepts of that relationship. (Dr. Gordon Cumming once said to me that before one is allowed to calculate the quotient of two variables, he should have met the requirements of a licensing board.)

Dr. Heymann demonstrated progressive development
of the fetalpressor response to hypoxia and of the dilator response to acetylcholine as term approached, but found this not to be associated with any change in the amount of smooth muscle. More investigation of this phenomenon is indicated. Can the immature muscle, unresponsive to hypoxia, be converted to a responsive form? Perhaps someone will be stimulated to evaluate immature and mature fetal vascular smooth muscle in vitro as Drs. Bohr, Sourbade, and others have done with adult vessels.

To one principally interested in neural control of the circulation, the elegant demonstration of rich innervation of pulmonary arteries and veins by Dr. Ellison was frustrating. Why is it that we have such difficulty finding hemodynamic evidence for neurogenic vasoconstriction? Lack of physiologically significant neurogenic vasoconstriction is not a universal finding, but it is by far the most common. Are we missing an effect because we have not sought changes in network resistance, when the effect may be to keep net resistance constant while varying resistances within the network? If the zones perfused by the variable resistances are small, and collateral ventilation minimizes regional ventilatory differences, how are we to find such an effect?

After commiserating over an absence of evidence for pulmonary neurogenic control we were presented with an unusual positive feedback reflex by Dr. Juratch. He found that distention of the main pulmonary artery resulted in pulmonary vasoconstriction. In the intact animal such a reflex would lead to the most intense contraction of the vessels, and it is hard to see how the initial perturbation that would induce the response could ever be avoided. To further confuse us, the response appears to use non-vagal afferent and non-norepinephrine efferent pathways. This response troubled me all week, and in turn I have pestered Dr. Juratch. But to no avail. He still believes it happened, and I still can’t find a reason why it shouldn’t. Similar reflexes have been described infrequently in the past and never were adequately explained or well accepted.

Several studies can be included in what I shall call clinical reports. Dr. Godfrey made interesting use of the famous Hammensmith cyclotron by generating isotopic nitrogen for study of ventilation and perfusion distribution in children with high pulmonary vascular resistance. A surprising finding was that an inspired bolus of nuclide was normally cleared by subsequent ventilation, but the ventilatory clearance of radionuclide given intravenously was delayed. No further definition of the two alveolar populations was provided by Dr. Godfrey. While this shows that ventilation of small units of perfused lung may be abnormal if the vessels are abnormal, it raises the serious question of the meaning of many studies in which regional ventilation/perfusion relationships are estimated by separate perfusion and ventilation techniques. For example, an apparently normal radioalbumin scan and equally normal distribution of an inhaled xenon bolus cannot be used as evidence for normal ventilation/perfusion ratios unless we know that each tracer has gone to the same terminal units.

Another use of radioscopy was to measure right ventricular ejection fraction in patients with decompenated cor pulmonale. Dr. Ellis reported that ejection fraction was commonly reduced, but that it did not correlate with pulmonary arterial pressure. The ejection fraction did not improve following ouabain therapy, but it did improve following long-term oxygen therapy. Evaluation of high left atrial pressure in the presence of chronic obstructive lung disease has always been a tricky business. Dr. Bone reported that one might be able to distinguish between normal and high atrial pressure by use of relative size of pulmonary arteries and veins in the upper peribronchial area of a routine chest radiograph.

Studies of pathologic changes in vessels in chronic obstructive pulmonary disease were presented by Dr. Shelton. In patients with right ventricular hypertrophy there was peripheral extension of muscle into smaller pulmonary arteries, but muscle hypertrophy or hyperplasia occurred in small veins as well. Patients disabled with obstructive disease, but without right ventricular hypertrophy, had similar but less extensive changes. This may be a generalized vascular response to hypoxia, and in support of that, similar changes were produced in rats by exposure to hypoxia. A second animal type, of a form intermediate between smooth muscle and pericyte, was found in partially muscular arteries, and the question arose as to whether this represented a transformation that resulted in new muscle. In another study of pathologic changes, Dr. Zapol reported findings from a group of patients with severe acute respiratory failure who had fixed and elevated pulmonary vascular resistance. He found major reductions in the numbers and sizes of capillaries, as well as altered morphology of larger vessels. The cause of the extensive reduction of capillaries remains to be discerned.

Dr. Huntley made an interesting comparison of protein synthesis and development of pulmonary hypertension in young rats fed monocrotaline. Although initially depressing net protein synthesis, monocrotaline apparently stimulated protein synthesis in lungs and right ventricle as the pulmonary vascular and cardiac hypertrophy developed. The ventricular hypertrophy could be prevented by concomitant administration of propranolol.

This, then, has been the 19th Aspen Conference from one person’s viewpoint. I apologize again to those I have failed to cite, and even more to those I have misrepresented. This has been a stimulating conference, representative of a number of interests which now properly belong within the province of those of us interested in the pulmonary circulation. The Program Committee is to be congratulated for their perception. We are discovering, although somewhat late, that the pulmonary circulation may do more than passively prepare a thin layer of blood for exposure to alveolar air; and there is a new generation of investigators to welcome.