A NDRÉ F. C OURNAND

Control of the pulmonary circulation in man with some remarks on methodology

Nobel Lecture, December 11, 1956

At the outset it is my pleasant duty to express my profound gratitude to the Collegium of the Royal Karolinska Institute and to the members of its Nobel Committee for rewarding my studies with their most coveted prize. From the unique vantage point which they have so kindly allowed me to occupy for this one day, I wish to survey the development of our knowledge of the pulmonary circulation in normal man which has followed the introduction of the cardiac catheter.

For us in 1943, the cardiac catheter was only the key in the lock - although this is in no way to minimize Dr. Forssmann's brilliant and courageous experiment. To guide our hand in turning this key, we had all the knowledge accumulated through the years by physiologists in their studies of animals; and to one, Dr. William F. Hamilton, I owe a more personal debt of gratitude for his constant advice and kind criticism. Basically our difficulties were then, as they are still, of measuring flow and pressure and volume. And, since the reliability of experimental data is no better than the reliability of the measuring techniques employed, I should like, before discussing our present understanding of the pulmonary circulation, to consider for a short while the limitations of our methods.

As Dr. Richards remarked in the previous lecture, at first the measurement of pulmonary blood flow in man did not appear to pose an important problem, once catheterization of the pulmonary artery, cannulation of a peripheral artery and spirometry supplied the data necessary to apply the principle described by Fick in 1870. But the application of the Fick principle involves more than the simple substitution of analytical values into a readymade equation, and the problem which had to be solved is an illustration of the caution necessary when physical principles are applied to biologic measurements[1,2,3,4,5].

The Fick principle can be used to measure flow in a physical system in which a stream. of constant velocity enters a chamber of constant volume, the volume being sufficiently small so that an indicator substance continually

added to the chamber is instantaneously mixed with the volume therein. Then, if the rate at which the indicator enters the chamber is measured, and if the difference in concentration of the indicator in the fluid entering and leaving the chamber is determined, flow can be calculated by dividing the volume of indicator added per unit of time by the volume of indicator gained per unit of fluid flow. But these ideal conditions are not realized in the body, since pulmonary blood flow is pulsatile and since the rate of transfer of
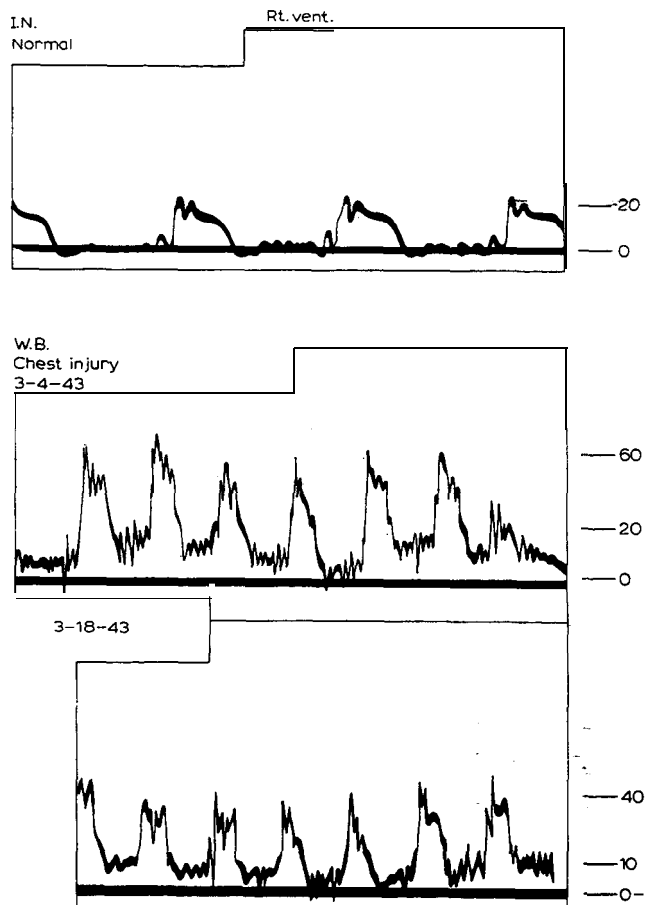

Fig. 1. Photographic reproduction of the first reported pressure pulses recorded in the right ventricle of a normal man and of a patient with severe traumatic chest injury. (Chart 13 in Ref. 9.)

These tracings were obtained through a catheter attached to a Hamilton manometer; they are. undamped; the coarse vibrations are due to impacts upon the catheter. (The scale is in mm Hg.)

oxygen, the indicator substance, into the pulmonary capillaries is influenced by the cyclic character of ventilation, and may only be measured at the mouth rather than at the alveolocapillary membrane. Furthermore, blood samples required for the determination of the oxygen content of the blood entering and leaving the lungs are integrated in respect to time rather than in respect to volume; in addition they must be collected for a finite period rather than being available from instant to instant, as would be necessary in order to make a continuous measurement of flow. However, as a result of extensive investigations in animal and in man, it would appear that these theoretical considerations do not introduce an error of large magnitude in the measurement of pulmonary blood flow, provided certain criteria regarding the maintenance of a steady state of ventilation, circulation and gas exchange are met. Thus the problem of periodic variations in flow velocity and of arterio-venous oxygen difference, and the matter of time-integrated rather than volume-integrated samples, do not affect the measurement of flow except under the most extreme circumstances. It was pertinent to the solution of this question to demonstrate that the volume of flow measured by the dye-dilution technique which involves a somewhat different principle, agrees rather closely, under a wide variety of conditions, with that obtained by application of the Fick principle[6,7,8].

In the early days, pressures in the right atrium and in the right ventricle were recorded[9,10,11] through a single-lumen catheter, connected to a Hamilton manometer, a coupling which raised important technical questions. Whereas in animals it had been possible to limit the distance between the heart and the manometer to the length of a short metal needle, the use of a catheter interposed a column of fluid at least 100 centimeters long between the pressure to be measured and the pressure-measuring device. Moreover, the fluid was contained inside a tube, the stiffness of which was considerably less than that of metal; an important consideration in view of the fact that the fidelity of a recording system is a function of the stiffness of its parts. It was necessary, therefore, to construct a catheter in which a compromise was made; it had to be sufficiently stiff to transmit pressures accurately, but not so stiff that its introduction into the heart would be dangerous. In addition, damping had to be considered because of the low natural frequency of the system, and in order to minimize the artifacts imposed by the mechanical impact of the beating heart. In general the proper degree of damping is best determined empirically, as it varies with heart rate, height of pressure and the location of the tip of the catheter. An important progress in technique
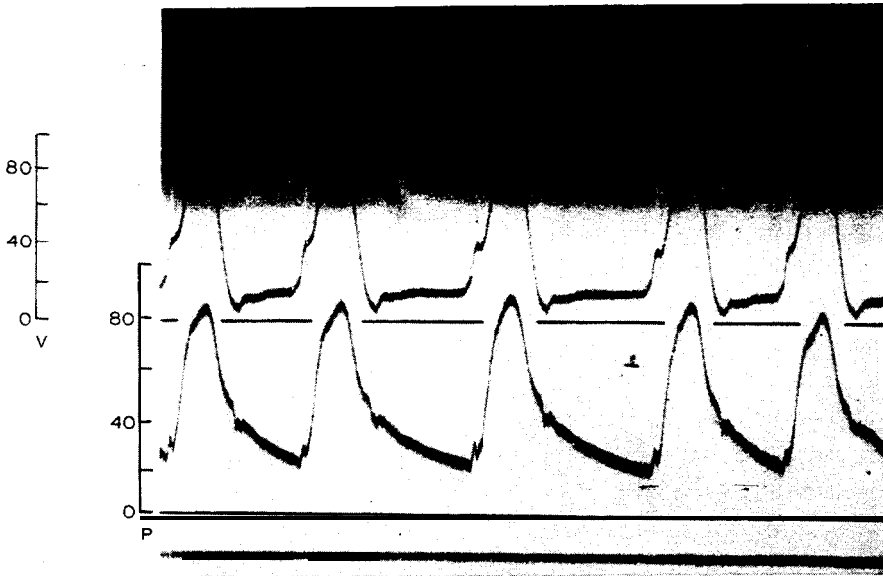
Fig. 2. Photographic reproduction of the first reported pressure pulses recorded in the
pulmonary artery of man. (Ref. 12.)
The simultaneous tracings in the pulmonary artery and the right ventricle were
obtained through a double-lumen catheter attached to the Hamilton manometer in a
patient with severe pulmonary hypertension. (The scale is in mm Hg.)

was the development of a double-lumen catheter through which simulta-
neous pressures in two contiguous heart chambers and large vessels could be
recorded. The first two tracings of blood pressure pulses recorded simulta-
neously within the right ventricle and the pulmonary artery are presented
here. They served to illustrate a paper published in 1945, in collaboration
with Henry Lauson and Richard Bloomfield[12], on the use and advantages of
this newly designed double-lumen catheter. For tie this tracing holds a
unique place, since it is the first demonstration that the tip of a catheter was
placed in the pulmonary artery of man in order to record pressure pulses.
Subsequent progress in our knowledge of the dynamics of the pulmonary
circulation in man[13] owes much to the technique of catheterization of the
pulmonary artery. The part played by Lewis Dexter and his associates in this
latter technical development deserves special mention[14].

Apart from our efforts to evolve a satisfactory catheter, considerable atten-
tion was also required for proper operation of the Hamilton manometer.
Stanley Bradley, assigned by Professor Homer Smith to the team studying

shock at Bellevue Hospital during the war years, was initially in charge of this delicate and essential function. Although the Hamilton manometer was subsequently replaced by a strain gauge in association with electronic re-corders, it is well to recall that most of our early knowledge of pressure pulses was obtained by using this device.

During the past few years recording machines have become increasingly complex and useful. But no matter how sensitive may be the manometer employed, the catheter system itself still remains the limiting factor in re-producing faithfully human pulse pressures, under all circumstances.

An estimation of the pressure drop across the entire pulmonary vascular system had been of particular concern to physiologists interested in the dy-namics of the pulmonary circulation. Catheterization of the pulmonary ar-tery supplied the necessary data, concerning pressure at the origin of the system; but the pressure at the end of the system, that is, in the left atrium, although predictable from the diastolic pressure in the pulmonary artery of the normal subject, could not be accurately determined. A first step in the proper direction was made when pressures were recorded from the left atrium and large pulmonary veins in human subjects under the abnormal conditions provided by interatrial septal defects's; however, it was not until very recently that by means of needles direct measurement of the left atrial pressure in intact man have been secured. Prior to the latest development, an ingenious indirect method for this measurement had been developed sep-arately in 1949 by Hellems and Dexter[16], and by Lagerlöf and Werkö[17]. It consists in advancing a cardiac catheter in a peripheral branch of the pul-monary artery until it is firmly wedged. At first it was assumed that the recorded pressure was that in the first freely anastomosing segment of the pulmonary vascular bed distal to the point of wedging, i.e. the capillary bed. Theoretical considerations suggest, and recent comparisons indicate, that the pulse contour and the mean pressures recorded after wedging correspond with those obtained from the left atrium, particularly in subjects with pul-monary venous congestion. This pressure, therefore, can be used with cau-tion to derive a fairly accurate figure for the pressure drop across the entire vascular bed, particularly in cases where vascular pressures throughout the pulmonary circuit are elevated.

Since the pulmonary circulation constitutes a distensible reservoir inter-posed between the right and the left ventricle, measurements of pulmonary blood volume and of its variations under various physiologic conditions has attracted the interest of clinical investigators. The use of the dye-dilution

technique referred to above, provides an indirect means of measuring this volume, according to a principle first correctly stated and then experimentally established by Hamilton and his school. However, the "central blood volume" thus measured has somewhat vague limits, and includes the volume in the left heart and a large part of the arterial tree. Furthermore, the error of the technique is of the order of 15% of the volume measured; hence, variations of volume amounting to 150-200 ml may not be significant.

Concluding this long preamble on methodology, I shall now turn to the main theme of my lecture - the control of the pulmonary circulation in normal man.

From the large body of previous work in animals, particularly in dogs, it was already evident at the inception of our investigation that the relationship between pressure and flow in the pulmonary circulation was quite different from that in the systemic circuit. Although the stroke output of each ventricle is approximately the same, except for temporary differences, the mean pressure in the aorta is six times that in the pulmonary artery. This is an expression of a much higher viscous resistance to flow in the systemic circulation - a resistance located mainly at the arterioles, the walls of which are endowed with a thick and circular layer of smooth muscles. By contrast the walls of the small branches of the pulmonary artery have only a very thin muscular media.

From these anatomic observations it might be expected that the influence of the activity of this thin muscular coat on the viscous resistance to flow in the small pulmonary arteries would be a relatively weak one. Moreover, if the vasomotor tone is weak, the part played by purely mechanical factors, such as variations in blood flow and blood volume in controlling the pressure in the pulmonary artery becomes proportionally more important.

The effects of such mechanical factors are however, not simple. For instance, if the resistance to flow in the pulmonary vessels remained constant, then the pulmonary arterial pressure should be directly influenced by variations in flow and by variations in left atrial pressure. Since, however, the whole vascular system is distensible, the resistance in the circuit is itself dependent on variations in distending pressure. Thus an increased flow, or an increased left atrial pressure, will by themselves increase the distending pressures in the various pulmonary vessels, change the geometry of the system by opening up new channels and thereby lower the pulmonary vascular resistance. From this it follows that the relationships between pressure and flow in the pulmonary circulation should not be expected to be rectilinear.

Indeed, it was soon apparent, from our studies, that there was not a linear relationship. For example, measurements before and after pneumonectomy showed that the pressure in the pulmonary artery rose very little when the entire output of the right ventricle flowed through one single normal lung[18]. Hence, the vascular resistance is strikingly dependent on the rate of flow, and the pulmonary vessels appears to be remarkably distensible within this range. Further support of this observation is provided by the relatively small rise in the pulmonary arterial pressure associated in normal subjects with a large increase in pulmonary blood flow during exercise and in patients with large left to right intracardiac shunts. Beyond a certain point, however, increases in pulmonary blood flow cause greater increments in pulmonary arterial pressure, and this is presumably an indication of the shape of the curves which relate distending pressure to cross-sectional areas the pulmonary vessels. In this respect it is interesting to recall that Lilienthal and Riley have recently called attention to the relationship existing between the critical level at which pressure in the pulmonary artery increases significantly and the maximum oxygen diffusing capacity, a function closely related to the size of the total alveolo-capillary interface[19].

Our experiments on the effects of the normal respiratory cycle, positive pressure breathing and the Valsalva maneuver[20,21,22] showed also the mechanical results of altering the effective, or net distending pressure in the pulmonary vessels. In addition they revealed that the hemodynamic situation was further complicated by differential changes in the filling pressure and thereby in the stroke output of each ventricle. They directed our attention to the important notion of heterodynamism of both ventricles, particularly fruitful in the understanding of isolated ventricular failure.

Since remarkably wide variations in vascular resistance can normally occur in a purely passive fashion, the task of demonstrating the active part that the smooth muscles in the wall of the small vessels may play in its alterations, becomes very difficult. Nevertheless, we have knowledge of two agents which appear to affect the resistance to flow in the pulmonary circulation by modifying the muscular tone of its vessels. These two agents are hypoxia and acetylcholine.

Our interest in hypoxia was stimulated by the observations of von Euler and Liljestrand, who in 1946 demonstrated a rise in the pulmonary arterial pressure of cats breathing low concentrations of oxygen[23]. In man, we were able to confirm this phenomenon in collaboration first with Motley, Werko and Himmelstein[24]. More recently, we established with Fishman, McClem-

ent and Himmelstein that the rise of pressure in the pulmonary artery is associated with some increase in the pulmonary blood flow and we suggested that this increase in flow is not by itself sufficient to account for the change in pressures.

Others have shown that the pulmonary wedge pressure in man, and the left atria1 pressure in animals and in man are not altered by hypoxia. There is, therefore, very strong evidence that hypoxia causes pulmonary vasoconstriction.

At what site has this vasoconstriction happened? We are not sure. How is it caused? We do not know. We assume that it arises directly or indirectly from the action of a low partial pressure of oxygen at some point in the body. Is it a local reflex activated at the level of the alveoli or of the pulmonary veins? - Does it involve the autonomic system as a result of the stimulation of chemoreceptors in the carotid body or the aorta? - Is it due to a direct action of excessively hypoxic mixed venous blood in the precapillary segment of the pulmonary vascular bed? Is there some other vasoconstricting substance liberated in the body under the influence of hypoxemia and carried by venous blood up to the lungs, or is such a substance activated in the pulmonary tissue itself under the influence of local hypoxia and of other factors! Does severe hypoxemia cause a shift of blood from the systemic to the pulmonary circulation as a result of systemic vasoconstriction?

Although we are in no way near to a final solution to this problem, there are observations which give a partial answer to some of these questions as far as man is concerned. In the first place, we have not been able to demonstrate a significant increase in central blood volume under the influence of severe arterial hypoxemia. In the second place, we have studied the effect of hypoxia in a patient before and after he underwent extensive bilateral sympathectomy for Raynaud's disease. The sympathectomy which included the stellate ganglion, the upper three thoracic ganglia on each side, and the mid-cervical ganglion on one side, had no influence on the rise in pulmonary arterial pressure caused by hypoxia. Thus we reached timidly the tentative conclusion that this effect is not mediated by the sympathetic system.

Liljestrand[25] and von Euler[26] pointed out that, if the pulmonary vascular resistance were regulated on a regional basis, by a purely local action of the alveolar and blood oxygen partial pressures, this action could provide an important mechanism for maintaining the most effective ventilation/perfusion ratio throughout the lungs. To examine this attractive hypothesis, several workers have studied the local effects upon blood flow of a hypoxic gas

mixture given to one lung in animals, and we have in association with Himmeistein, Fishman, and Fritts[27,28] made similar observations in man. The technique is difficult since it includes the simultaneous use of bronchospirometry, cardiac catheterization, and arterial cannulation. By means of this technique the flow of blood through each lung can be separately measured.

It was found that concentrations of 8 to 10% oxygen in the inspired gas given to *one* lung caused no modification in the partition of flow of blood between the two lungs and no change in the pulmonary arterial pressure. Yet, giving a somewhat higher concentration of oxygen (12%) to both sides causes a considerable rise in pressure in the pulmonary artery. The role of a local viscerovascular reflex arising from the low oxygen tension in the alveolar gases has therefore been questioned. The capillary and pulmonary venules, however, cannot be excluded as a site of origin for such a vasoconstricting reflex, since the calculated oxygen saturation of the pulmonary venous blood on the hypoxic side did not fall below the 80% level, which in bilateral experiments is the critical level for pulmonary hypertension. We have, however, four observations on the effect of giving concentrations of oxygen as low as 6% to one lung. Here the calculated pulmonary venous oxygen saturation fell below 80%. In three of these studies there was no change in the partition of flow, as compared to the control period. In one of them there was a diminution of flow to the hypoxic lung; suggestively enough this is the only instance where mixed venous blood and pulmonary venous blood had an identical oxygen saturation, and where, therefore, no oxygen uptake in the hypoxic lung could be measured. Further work with even lower O_2, concentration is in progress and may well resolve the discrepancy between some of our results in man and experiments on animals in which the giving of pure nitrogen to one lung caused undisputably a diminution in blood flow on this side.

Here, then, the problem of the effect of hypoxia upon the pulmonary vessels lies partly unsolved, and tantalizing. 1 turn now to the effects of acetylcholine on the pulmonary circulation. This drug has been known, since the early experiments of Sir Henry Dale, to have a strong vasodilating influence throughout the systemic arterial tree. As far as the pulmonary circulation is concerned, however, reports on the effects of this preparation in animals have been contradictory. In normal man we have found in collaboration with Harris, Fritts, Clauss, and Odell[29], that infusion of acetylcholine into the main pulmonary artery at a rate of 0.5 mg per minute caused a slight
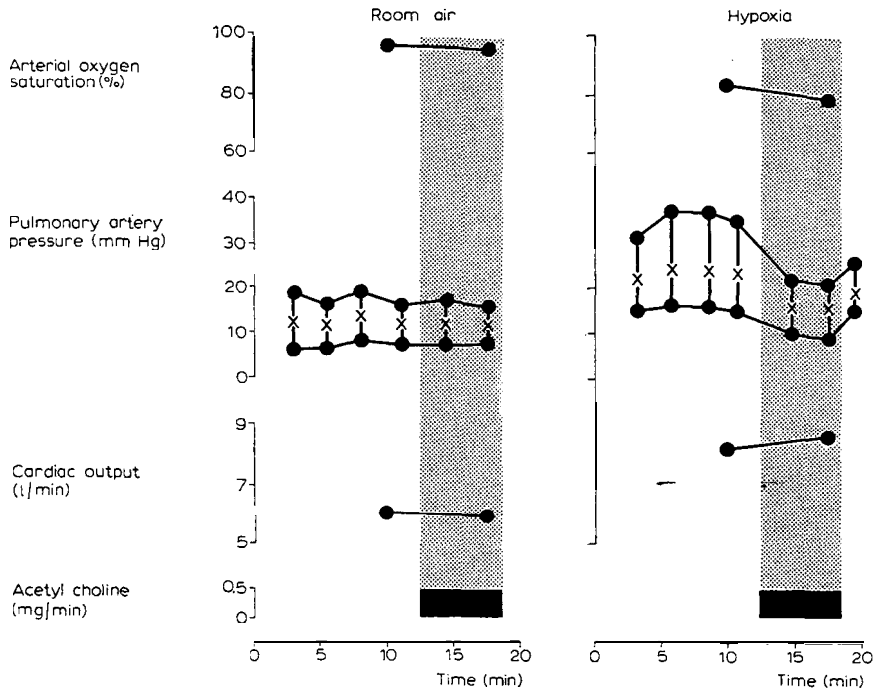
Fig. 3 . Schematic representation of the effects of acetylcholine upon the pulmonary arterial pressure in a normal man.

(Left): the subject is breathing 21% O₂ in nitrogen. *(Right)*: the subject is breathing 12% O₂ in nitrogen. Acetylcholine was given in a continuous infusion of the main pulmonary artery at the rate of 0.5 mg per minute *(shaded urea).*

questionable fall in the pulmonary arterial pressure. When the pulmonary arterial pressure had been previously increased by hypoxia, however, the fall in pressure due to acetylcholine was very significant, although the hypoxic stimulus was maintained. This fall in pressure in the pulmonary artery was associated with no change in pulmonary wedge pressure. The cardiac output, which had increased as the result of hypoxia, remained unchanged or rose slightly further. When given in these small amounts, acetylcholine had no effect on the systemic blood pressure or pulse rate, presumably because of its rapid rate of destruction in the blood stream.

It seems fairly certain, therefore, that the action of the drug had been limited to the pulmonary circulation, that this action is one of vasodilatation, and that the degree of vasodilatation is largely dependent, as one might expect, on the pre-existing tone of the smooth muscles of the pulmonic

vessels' wall. As in hypoxia, we do not know whether the site of action is in the pre-capillary or the capillary, or the post-capillary segments of the pulmonary vascular bed. Again, as in hypoxia, we do not know through what mechanisms the drug acts. Although they left these questions unsolved, the experiments nonetheless have to their credit three important results. They revealed that firstly, blood-borne substances can act directly on the wall of some segment of the pulmonary vascular bed, secondly that the effects of hypoxia in causing both an increase in blood flow and a vasoconstriction can be neatly separated, and thirdly that the vasoconstriction associated with hypoxia, whatever the site of its action, can be reversed.

Although I am here mainly concerned with the relative importance of mechanical and vasomotor factors in the pulmonary circulation of normal man, it might be of interest to dwell for a few moments on the question of how such factors are altered by disease. In certain diseases high pressure develops in the pulmonary artery and this is associated with a high vascular resistance, and thickening of the walls of the small branches of the pulmonary artery. The hemodynamics of such a natural experiment provide an interesting contrast to those which hold good under normal conditions. The Eulmonary artery pressure of these patients is found to be considerably more dependent on variation in flow and volume than it normally would be, and one may well ascribe this to a diminished distensibility of the thickened pulmonary arterial branches.

The results of experiments with sympathetic blocking agents in this group of diseases have led other workers to assign to the autonomic nervous system an important role in the control of the pulmonary circulation. I am inclined to believe that there are other alternative explanations for the striking drop of pressure in the pulmonary artery following the use of these agents than to claim that it is the result of blocking the nervous apply to the pulmonary vessels. For instance, translocation of even small amounts of pulmonary blood following systemic vasodilation, could have the same effect in a poorly distensible pulmonary vascular bed.

To summarize our present knowledge, it can be said that we have acquired some understanding of the relations between pressure and flow in the pulmonary vessels of normal man. We know also that these relations can be influenced by mechanical factors and by at least two chemical stimuli - hypoxia and acetylcholine. However, the mechanism of action of these stimuli is but poorly understood. And, when we come to fit them into an integrated concept of the control of the pulmonary circulation, we are troubled by sev-

era1 doubts. The first doubt is, how far such unphysiological concentrations of inspired oxygen and doses of acetylcholine throw any light on what happens under normal circumstances. The second is how to extrapolate into indefinite time the results from very short-term observations. The final doubt is whether these notions may be justifiably extended to the solution of physio-pathological problems, when the physical properties of pulmonary vessels and of the surrounding pulmonary tissue have been greatly altered.

Now, what of the future? Perhaps the only incontestable prophecy that can be made is that advances in methodology and advances in understanding will go hand in hand. Any attempt to define the limitations of our present methods of measuring pressure, flow, and volume in the pulmonary circulation points automatically to the directions in which improvements are at the moment being made. For pressure, our hope is for a reliable, pressure-sensitive head to the cardiac catheter. For flow, we look for a method of instantaneous measurement. For volume, we need some much more distinctive quantity than the central blood volume.

As progress is made, more results will pour in. Let us, then, beware of the danger of seeking security for our concepts in the accumulation of facts. As the poet has said:

> "Knowledge is proud that it has learned so much,
>   Wisdom is humble that it knows no more."

1. A. Cournand, Measurement of the cardiac output in man using the right heart catherization, *Federation Proc.,* 4 (1945) 207.
2. A. Cournand, J. Lequime, and P. Regniers, *L'Insuffisance Cardiaque Chronique. Études Physiopatkologiques,* Masson & Cie, Paris, 1952, pp. 28-29
3. A. P. Fishman, J. H. McClement, A. Himmelstein, and A. Coumand, Effects of acute anoxia on the circulation and respiration in patients with chronic pulmonary diseases studied during the "steady state", *J. Clin. Invest.,* 31 (1952) 77.
4. M. B. Visscher and J. A. Johnson, The Fick principle: Analysis of potential errors in its conventional application, *J. Appl. Physiol.,* 5 (1953) 635.
5. R. W. Stow, Systematic errors in flow determination by the Fick method, *Minnesota Med.,* 37 (1954) 30.
6. W. F. Hamilton, R. L. Riley, A. M. Attyah, A. Coumand, D. M. Powell, A. Himmelstein, R. P. Noble, J. W. Remington, D. W. Richards Jr., N. C. Wheeler, and A. C. Witham, Comparison of the Fick and dye injection methods of measuring the cardiac output in man, *Am. J. Physiol.,* 153 (1948) 309.

7. A. Cournand, A. M. Mitchell, and A. P. Fishman, Applicability of the direct Fick method to measurement of pulmonary blood flow during induced acute hypoxia, *Federation Proc.,* 13 (1954) 31.

8. H. W. Fritts Jr., E. Braunwald, A. P. Fishman, and A. Cournand, Influence of induced hypoxia on central blood volume of normal man, *Federation Proc.,* 15 (1956) 68.

9. *Semi-annual Report of Work under Contract with Office Emergency Management, Committee Medical Research (OEM cmr 107) for the period from September 1942 to March* 1943. Responsible investigator: D. W. Richards Jr., Research team: A. Cournand, R. L. Riley, E. S. Breed, H. D. Lauson, National Research Council, Washington, D.C., pp. 35, 58 and Chart 13.

10. A. Cournand, H. D. Lauson, R. A. Bloomfield, E. S. Breed, and E. de F. Baldwin, Recording of right heart pressures in man, *Proc. Soc. Exptl. Biol. Med., 55 (* 1944) 34.

11. R. A. Bloomfield, H. D. Lauson, A. Cournand, E. S. Breed, and D. W. Richards Jr., Recording of right heart pressures in normal subjects and in-patients with chronic pulmonary disease and various types of cardiocirculatory disease, *J. Clin. Invest.,* 25 (1946) 639.

12. A. Cournand, R. A. Bloomfield, and H. D. Lauson, Double lumen catheter for intravenous and intracardiac blood sampling and pressure recording, *Proc. Soc. Exptl. Biol. Med., 60* (1945) 73.

13. A. Cournand, Recent observations on the dynamics of the pulmonary circulation, *Bull. N.Y. Acad. Med., 23* (1947) 27.

14. L. Dexter, F. W. Haynes, C. S. Burwell, E. C. Eppinger, R. P. Sagerson, and J. M. Evans, Studies of congenital heart disease. II. The pressure and oxygen content of blood in the right auricle, right ventricle and pulmonary artery in control patients with observations on the oxygen saturation and source of pulmonary "capillary" blood, *J. Clin. Invest.,* 26 (1947) 554.

15. A. Cournand, H. L. Motley, A. Himmelstein, D. T. Dresdale, and J. Baldwin, Recording of blood pressure from the left auricle and the pulmonary veins in human subjects with interauricular septal defect, *Am. J. Physiol.,* 150 (1947) 267.

16. H. K. Hellems, F. W. Haynes, and L. Dexter, Pulmonary "capillary" pressure in man, *J. Appl. Physiol.,* 2 (1949) 24.

17. H. Lagerlöf and L. Werkö, Studies on circulation of blood in man; pulmonary capillary venous pressure in man, *Scand. J. Clin. Lab. Invest., 7* (1949) 147.

18. A. Cournand, R. L. Riley, A. Himmelstein, and R. Austrian, Pulmonary circulation and alveolar ventilation-perfusion relationships after pneumonectomy, *J. Thoracic Surg.,* 19 (1950) 80.

19. J. L. Lilienthal, Jr. and R. L. Riley, Circulation through the lung and diffusion of *gases, Ann. Rev. Med.,* 5 (1954) 237.

20. H. D. Lauson, R. A. Bloomfield, and A. Cournand, The influence of the respiration on the circulation in man, with special reference to pressures in the right auricle, right ventricle, femoral artery, and peripheral veins, *Am. J. Med.,* 1(1946) 315.

21. D. W. Richards Jr., A. Cournand, and H. L. Motley, Effects on circulatory and respiratory functions of various forms of respirator, *Trans. Assoc. Am. Physicians,* 59 (1946) 102.

2.2. A. Cournand, H. L. Motley, L. Werkö, and D. W. Richards Jr., Physiological studies of the effects of intermittent positive pressure breathing on cardiac output in man, *Am. J. Physiol.,* 152 (1948) 162.

23. U. S. von Euler and G. Liljestrand, Observations on the pulmonary arterial blood pressure in the cat, *Acta Physiol. Scand.,* 12 (1946) 301.

24. H. L. Motley, A. Cournand, L. Werkö, A. Himmelstein, and D. T. Dresdale, The influence of short periods of induced acute anoxia upon pulmonary artery pressure in man, *Am. J. Physiol.,* 130 (1947) 315.

25. G. Liljestrand, Regulation of pulmonary arterial pressure, *Arch. Internal Med., 81* (1948) 162.

26. U. S. von Euler, Physiologie des Lungenkreislaufs, *Verhandl. Deut. Ges. Kreislauf,* 17 (1951) 8.

27. A. P. Fishman, A. Himmelstein, H. W. Fritts Jr., and A. Cournand Blood flow through each lung in man during unilateral hypoxia, *J. Clin. Invest., 34* (1955) 637.

28. A. Himmelstein, H. W. Fritts Jr., A. P. Fishman, and A. Cournand. (Unpublished data.)

29. P. Harris, H. W. Fritts Jr., R. H. Clauss, J. E. Odell, and A. Cournand, Influence of acetylcholine on human pulmonary circulation under normal and hypoxic conditions, *Proc. Soc. Exptl. Biol. Med., 93* (1956) 77: