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Right Heart Catheterization

Its Contributions to Physiology and Medicine

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The study of the right heart in man has held a continuing place in the researches of Andre Cournand and myself over the past 25 years, both under physiological and pathological conditions. Measurements made in this exact location have provided a key to almost all the integrations that we have attempted in elucidating the nature of cardiopulmonary function.

In the realm of pathology, pulmonary heart disease also occupies a key position, affected as it is by all manner of pulmonary, as well as circulatory, dysfunctions. With many of these we are particularly concerned in our research studies of the present day.

Using these two subjects as a central theme, I should like to give a brief account of our research from its beginning.

Background in Physiology

The origins of any systematic research are many, extending widely, as well as far back in time. Many also are the supporting and sustaining research activities which are in progress simultaneously. We find ourselves deeply indebted to our colleagues throughout the world for such assistance over many years. We wish to acknowledge also the institutions which have given us financial support, especially the Commonwealth Fund, the Life Insurance Medical Research Fund, and the United States Public Health Service.

The foundation upon which the research of Cournand and myself chiefly rests is the work of Lawrence J. Henderson of Harvard University. Biochemist, physiologist, natural philosopher, student of Arrhenius, ardent disciple of Claude Bernard, Henderson achieved as his great single contribution the definitive integration of the respiratory function of the blood (*1*). But his horizon was far wider than this. He was a general physiologist in the broadest sense. For him the physical chemistry of the blood was but a single link in the whole circulorespiratory synthesis. Such breadth of view was inherent in everything he thought or did, and this could not help but be reflected, in some degree, in those whose good fortune it was to be associated with him. It was from Henderson that we derived the simple but essential concept that lungs, heart, and circulation should be thought of as one single apparatus for the transfer of respiratory gases between the outside atmosphere and the working tissues.

This concept was, of course, not new; it was in fact in the great tradition of Krogh, of Lindhard (*2*), of Liljestrand (*3, 4*) and their collaborators, who with the methods then available, worked out to a remarkable extent in man the performance of the normal cardiorespiratory apparatus, in rest and exercise. Liljestrand made also a number of studies in disease. In the late 1920's and early 1930's the active research team at the Harvard Fatigue Laboratory under Henderson continued this exploration of cardiocirculatory patterns (*1*), to which their complete studies of the respiratory function of the blood constituted an important contribution.

During all this time, however, and indeed for a total period of nearly 40 years, there was in the study of the heart and circulation in man one measurement or set of measurements which was conspicuously in default—namely, the state of the blood as it enters the right heart, its respiratory gas contents, its pressure relations, and its rate of flow.

Although the full potentialities of these measurements were not then appreciated, it was well known that an accurate figure for the respiratory gases in the mixed venous blood would, under conditions of a physiological steady state, permit a reliable measurement of total blood flow through the lungs. The principle was the simple one originally stated by Fick (*5*) of dividing the arteriovenous difference—the amount of oxygen taken up (or carbon dioxide given off) by a unit volume of flowing blood—into the total amount of this gas taken up (or given off) by the lungs per minute.

Only those who have worked through all or a part of those times can appreciate how ardently this information was sought after, and by how many devious approaches. The majority of these involved the use of the lungs as a tonometer, equilibrating the oxygen or the carbon dioxide of the lungs with that of the incoming pulmonary arterial blood. The early experiments of Loewy and von Schrötter (*6*), the rebreathing techniques of Plesch (*7*) later of Christiansen, Douglas, and Haldane (*8*), and of Yandell Henderson (*9*), were among the more important of these.

Early Investigations

I give special emphasis to this in the present account because it was to this long-standing problem that Cournand and I applied ourselves when we began

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our work in 1931, in the service of James Alexander Miller in Bellevue Hospital. There was nothing original in our approach. We simply tried, as others had done before, to establish gaseous equilibrium between lungs and blood by rebreathing procedures, and to do this especially in patients with chronic pulmonary disease. But as others had also found before us, diseased lungs would not mix air evenly, and after 3 years it became apparent that we had failed completely in these attempts (*10*).

And yet the failure was not quite complete. There proved to be some highly interesting things about uneven mixing in diseased lungs. Robert Darling, working with us, extended earlier work in the same field by developing a breath-by-breath analysis of intrapulmonary mixing of inspired air, using the simple method of washing out intrapulmonary nitrogen through inhalation of pure oxygen (*11*). This subject has since been further studied by many investigators, and it now constitutes an important branch of pulmonary physiology. In our early experiments with Darling, two immediately practical features were worked out: an open-circuit method of measuring residual lung volume, and in the same procedure, a rough but useful index of intrapulmonary mixing—namely, the nitrogen remaining in the lungs after oxygen breathing (*12*).

At this time also, with Eleanor Baldwin we were developing other practical methods of measuring pulmonary functions, greatly aided here by similar work in progress elsewhere, especially in the clinic of Knipping and Anthony in Hamburg (*13, 14*). By the late 1930's, we were able to describe the ventilatory functions of the lungs, and, with pulmonary measurements supplemented by arterial blood studies, in rest and exercise, to define to some extent the mixing and the diffusional aspects of pulmonary alveolar or alveolar-capillary functions (*15*). But we still could not measure blood flow through the lungs and could not, therefore, move into those broader concepts of cardiopulmonary function which now began to be our goal.

Catheterization of the Right Heart

We were aware of the earlier experiment of W. Forssmann (*16*) and had followed closely its isolated uses in Germany, Portugal, South America, and France. Dr. Forssmann has given an excellent review of this in his Nobel lecture. It suffices for me to say that, late in 1940, Cournand and Ranges (*17*) took up the catheterization technique, showing in their initial studies that consistent values for blood gases could be obtained from the right atrium and that, with this, cardiac output could be reliably and fairly accurately determined by the Fick principle, and, furthermore, that the catheter could be left in place for considerable periods without harm. Not long after, through the interest of Homer Smith and the assistance of Bradley, pressure recordings by a Hamilton manometer were added to the other techniques. Blood volumes by Gregersen's method were also included (*18*).

By this time, therefore, after 10 years of work, we had assembled a fairly comprehensive group of methods for the analysis of cardiopulmonary function, methods which could be applied not only to normal men but to patients even in the most severe and acute stages of decompensation.

Traumatic Shock

The stage was now set for study of cardiac and pulmonary functions in many forms of clinical disease. First to be undertaken was an investigation of traumatic shock in man (*18, 19*). The United States was by this time at war, and further information on the hemodynamics of shock and quantitative measurements of this and of the effects of treatment were urgently needed. These studies proceeded quite rapidly. It was demonstrated: (i) that, with a deficit of 40 to 50 percent in blood volume, there were critical depressions in cardiac output and in return of blood to the right heart, worsening as shock continued unrelieved: (ii) that peripheral resistance tended to be maintained in hemorrhage and skeletal trauma and greatly increased in severe burns; (iii) that an important corollary of this was reduced peripheral blood flow, demonstrated particularly in the case of the kidneys; and (iv) that whole blood offered great advantages over plasma as sustaining therapy. Other forms of treatment were evaluated. Vasomotor factors, problems of so-called "irreversible" shock, were approached but not solved. In certain cases of severe burn, the catheter was left in place for more than 24 hours to provide a means of intravenous treatment, with no harm resulting—a further indication of the safety of the procedure.

Even during these war years a number of basic contributions were made. Dr. Cournand (*20*) will discuss the advancing of the catheter, first into the right ventricle, and then into the pulmonary artery, permitting new measurements to be made, some of them as important physiologically as the original right atrial (*21*). In the field of clinical heart disease, cases of heart failure with high cardiac output were identified and differentiated from "low-output" failures (*22*). McMichael and Sharpey-Schafer (*23*) in London had made similar observations independently. Baldwin (*24*) studied a case of congenital heart disease with interventricular septal defect. There were numerous improvements in technique.

Congenital Heart Disease

With the cessation of hostilities in 1945, we were free to look more broadly at problems of disease. By this time, others were at work with the same procedures, in various parts of the world.

The application of cardiac catheterization to the diagnosis of congenital heart lesions was an obvious one, and a number of investigators became interested in, and pursued, this inquiry with great skill. The early studies of Cournand, Janet Baldwin, and Himmelstein (*25*) were extended by much additional work by Bing (*26*), Dexter (*27*) and others. It should be noted that the great advance represented by the surgery of congenital heart disease, under such men as Gross (*28*), Blalock (*29*), Crafoord (*30*), and Brock (*31*), was under way before cardiac catheterization, and that it has moved fundamentally on its own. The cardiac catheter has been, however, a primary aid. Sharing with angiocardiography the ability to define the anatomical lesions, the catheter also quantitates the volumes and pressures of abnormal flow, thus defining for the surgeon both the nature and extent of the disorder. By repeated catheterization, the degree to which a normal circulation has been restored can be determined postoperatively.

Congestive Heart Failure

The measurements now available were adequate for a more general study of the physiology of heart failure; particularly since these could be carried out under conditions of cardiac decompensation and again following recovery. Pressures and flow in the pulmonary circulation gave an index of performance of the left ventricle; the same measurements in the right heart and in the great veins, an index of performance of the right ventricle. Many forms and degrees of failure were defined, and their responses to treatment were measured: limited or fixed cardiac output, not responding to exercise; left ventricular failure with pulmonary hypertension; right ventricular failure with systemic venous hypertension; the congestive state with high blood flow, and with low; very low cardiac output without congestion; the

dynamic effects of cardiac arrhythmias; the circulation in constrictive pericarditis (*32, 33*). The congestive state as such was established as a dominant aspect of heart failure, regardless of the level of general or regional blood flow.

An important contribution, in its therapeutic, as well as its physiological, implications, was the analysis of the action of the digitalis glucosides, by Ferrer and Harvey in our laboratory (*34*), also by McMichael and Sharpey-Schafer (*23*), by Bloomfield (*35*), and others. It was established that digitalis acts favorably only on overdilated ventricles, with excessive filling pressures and inadequate emptying; that in such hearts it acts rapidly to increase the energy of contraction, increase stroke volume, and promote adequate emptying, thus relieving the congestive state; that it performs with regular, as well as irregular, cardiac rhythms.

This large body of new knowledge of the dynamics of the circulation inevitably brought again under critical review the original Starling principle (*36*)—namely, that the energy of ventricular contraction is proportional to fiber length, that is, to diastolic ventricular volume; and that this relation holds up to a certain optimal fiber length, beyond which myocardial contraction progessively fails. Alternatively, in clinical studies, the more readily measured diastolic filling pressure has been commonly used, instead of diastolic volume, a relationship developed before Starling, by Otto Frank. In this general inquiry, contrary to the usual sequence, it was the clinical physiologists who stimulated the general physiologists to further research (*37*), and additional work in animals, especially by Hamilton (*38*), by Rushmer (*39*), and others, has added much interesting material. Many questions are still in controversy, but there would appear to be fairly general agreement that, in the normal heart under stress, the basic Starling relation is overridden by other influences, such as sympathetic control of muscle tone, the heart in exercise increasing its emptying, rather than its filling, volume; but that in the failing heart the fundamental relation between fiber length and energy of contraction may again emerge.

Mitral Stenosis

One particular form of acquired heart disease that has come under intensive study in the last 6 years is, of course, mitral stenosis. The magnificent achievement of cardiac surgeons in the partial or complete relief of this mechanical block has permitted also the comparative study of the hemodynamics of the circulation before and after this surgical procedure. Many factors are involved in the selection of patients for surgery (*40*). By and large, clinical improvement postoperatively has coincided with fall in pulmonary arterial pressures, and frequently with increase in resting or in exercise cardiac output. The total physiological readjustment, however, is a complex one, and the interrelations between cardiac output, pulmonary and systemic pressures, and ventilatory and other pulmonary functions have not yet been fully worked out. Among many important contributors in this field may be mentioned Ellis (*41*), Werkö (*42*), Dexter, Soulié, Donald, and Lequime.

The further extensions of the catheterization technique that are now being made, exploring the left atrium, the left ventricle, and the systemic aorta, are beyond the scope of this discussion.

Pulmonary Physiology—Diffusion

These numerous excursions into cardiac physiology, which I have just reviewed, have indeed been a major feature of our work, and yet they somewhat obscure the fact that Cournand and I have from the beginning thought of ourselves as primarily pulmonary, rather than cardiac, physiologists. I should like to outline now, though in the briefest possible terms, some of the aspects of clinical pulmonary physiology that have also been under study in our laboratory during the past several years.

I return for a moment to the work of our former colleague, the late Eleanor Baldwin, and in doing so wish to pay tribute to her for the vital part that she played in our whole research achievement. With the group of standard methods to which I have referred, she studied over a 10-year period a large number and variety of cases of chronic pulmonary disease. Inclusion of circulatory data from cardiac catheterization in many of these patients completed the picture of cardiorespiratory failure. It was found that these cases on analysis fitted well into the broad categories of pulmonary insufficiency that we had earlier described: the gross ventilatory, with restrictive or obstructive aspects; and the alveolar-capillary, with primary disturbances in respiratory gas exchange. Some disorders, such as pulmonary emphysema, were complex with various combinations of these factors. One definitely new physiological group emerged, that of the diffusional insufficiency or alveolar-capillary block, with the major interference at the alveolar-capillary interface (*43*).

This type of broad physiological analysis, with subsequent therapy directed to precise and specific aspects of insufficiency, has proved to be of great value in the clinical management of this large category of chronic disease.

In the past decade there has developed a much more exact analysis of intrinsic pulmonary function, to which I can refer here only briefly and inadequately. It is a development, however, which constitutes one of the most significant advances in basic physiology that have been made in the various fields to which cardiac catheterization has contributed. The general subject is that of diffusion of gases across the alveolar-capillary membrane and of the ventilation-perfusion relationships in the lungs. Two independent groups of investigators have been largely responsible for this development. At the University of Rochester, Rahn and Fenn (*44*) approached the subject initially by way of a description of the various possible relationships between oxygen uptake and carbon dioxide elimination in the lungs—the respiratory exchange ratio. The other, consisting first of Riley and Lilienthal, and later of Riley, Cournand, Donald, and associates (*45*), developed first a simple formula for the determination of mean alveolar oxygen tension, then proceeded to study the special properties of the oxygen dissociation curves of blood. Using the principle that at high oxygenation, equilibrium of oxygen between air and blood is complete, whereas at low oxygenation there is a distinct alveolar-capillary oxygen gradient, they found it feasible to use high and low oxygenations in human subjects to measure the diffusion process. Extension of the work led to a general definition of ventilation-perfusion relationships, separating effective "alveolar" ventilation from ineffective "dead space" ventilation, on the one hand, and effective "alveolar" perfusion from ineffective "venous admixture," on the other. Developments in this field, under Riley, Comroe and Forster, Rossier, and others, cannot be further reviewed here.

Pulmonary Heart Disease

The discussion up to this point has indeed been an overlong introduction to the problem of pulmonary heart disease. Yet this information is not irrelevant. The heart in chronic pulmonary disease is at a crossroads, itself a consequence of both pulmonary and cardiocirculatory disturbances.

Pulmonary heart disease—cardiac hypertrophy and dilatation secondary to disease of the lungs, or cor pulmonale—was clearly delineated by Laennec nearly 150 years ago, but it has attracted considerable attention only within the past generation. Its importance and its incidence are increasing, in large part because patients with chronic pulmonary disease now live longer, being protected

somewhat from infection, and relieved and sustained, in some instances for considerable periods, by symptomatic therapy.

At the present time, a very considerable proportion of patients suffering from chronic pulmonary disease with progressing pulmonary insufficiency will eventually develop cor pulmonale. In some instances, the heart failure becomes chronic and continues for years; in others it appears only terminally; in still others there may be repeated episodes of right heart strain and failure, especially during recurring pulmonary infection. These clinical patterns are only now beginning to be defined, as the cases are followed over many years; as yet, a generally accepted classification of pulmonary heart disease has not been made. In the present brief sketch, I shall move rapidly through some of the more frequently encountered forms, their natural history and physiological components. This description is based chiefly on the work of Harvey and Ferrer (*46*) in our laboratory.

It will be convenient to use as a prototype chronic diffuse pulmonary emphysema, concentrating on the features concerned with the flow of blood through the lungs and the action of the right heart.

The principal factors inducing right ventricular strain, hypertrophy, and failure can be stated very simply: (i) pulmonary hypertension, from one cause or another; and (ii) secondary influences throwing a burden on the right heart, such as anoxia, increased blood volume, polycythemia, increased cardiac output, disordered breathing mechanics.

The division of pulmonary emphysema, as originally made by Baldwin *et al.* (*43*), into four physiological groups, is applicable also to a consideration of cor pulmonale. We assume here the most common pathogenic form of emphysema, that proceeding from chronic bronchitis and bronchial obstruction, moving on to the hyperinflated obstructive type of ventilatory insufficiency.

In the first and mildest of these groups, the disturbances of pulmonary mechanics are not associated with arterial hypoxia or difficulties with elimination of carbon dioxide. In these cases pulmonary vascular pressures are within normal limits and there is no significant right heart strain (*21*).

In the second group, ventilatory function is more severely curtailed, often to one-fourth or one-fifth of normal, and anoxia appears. Work or effort of breathing is much increased. Carbon dioxide elimination is still adequate. It is extraordinary in some cases how much destruction of pulmonary tissue can exist and how little the remaining effective diffusing area is with the lungs still able to carry on carbon dioxide exchange.

Similarly, pulmonary arterial pressures can remain normal, at least during rest, with a remarkably small proportion of available vascular channels. In general, pulmonary arterial pressures seem to rise roughly in proportion to the degree of arterial hypoxia (*32*). That this is due in large part to the constricting effect of anoxia on the pulmonary vascular apparatus is suggested by the fact that, physiologically, this hypertension is frequently reversible when the patient's compensation has been restored and the anoxic state relieved. On the negative side, we have found not too clear a correlation between the degree of pulmonary hypertension and the extent of anatomical pulmonary vascular change, either muscular hypertrophy or arteriosclerosis. Clinically, the right heart often begins to show objective evidence of hypertrophy and dilatation when pulmonary arterial pressures exceed twice normal values.

In the next or third group, anoxia is more profound and carbon dioxide retention with hypercapnea is added. The aeration of the alveolar spaces has entered its final stage of decompensation, and the full state of alveolar hypoventilation is established. Here the primary constricting effects of anoxia send the pulmonary arterial pressures to higher levels; and secondary effects of both anoxia and hypercapnea place their added burdens on the heart.

The extent of breakdown here, actually of reversal of supposedly homeostatic mechanisms, is remarkable. Profound arterial oxygen unsaturation leads to marked polycythemia, total blood volume increasing by the amount of the increased red cell mass. This overfills the blood bed, including the heart, and this drives the heart, so to speak, to increased output and eventual failure. The pulmonary vascular channels may also be congested, with further anoxia resulting. That this is not a favorable homeostasis, but an unfavorable excess response, can be shown directly by a phlebotomy, which often brings immediate and striking improvement in all functions.

Even more widespread are the systemic effects of elevated carbon dioxide. The rise in alveolar and blood carbon dioxide tensions produces at the kidneys, as is shown by the work of Pitts (*47*) and of Gilman (*48*), a retention of bicarbonate, thus further raising blood and tissue carbon dioxide levels, though, of course, relieving in part the uncompensated gaseous acidosis. Continued high carbon dioxide tension apparently depresses the sensitivity of the respiratory center to the carbon dioxide stimulus, although recently some question regarding this effect has arisen. What further effects the retained bicarbonate may have on electrolyte and water balances in the body is not known.

Most extreme of the forms of physiological dysfunction in emphysema are those rather uncommon cases of severe alveolar hypoventilation, sometimes called the Ayerza syndrome, in which all the afore-mentioned trends are manifested to maximum degree, and yet sometimes with only mild anatomical changes in the lungs (*43*). Functionally, however, there is always bronchial obstruction, marked alveolar hypoventilation (*49*), and the most severe disturbances of ventilation and perfusion. Even in these cases, the entire circulation can often be restored to normal, with normal pulmonary arterial pressures and cardiac output reduced to normal values, by vigorous symptomatic therapy, relieving bronchial obstruction, hypoxia, hypercapnea, polycythemia and hypervolemia, and by active treatment of congestive failure.

There are other forms of pulmonary disease in which cor pulmonale is a significant complication. There is a category, for example, in which there has been a progressive loss of function or a destruction of total pulmonary tissue, down to a critical level, to an irreducible minimum. Cor pulmonale with failure may develop in such cases, usually terminally or as a very late stage (*50*). Such cases include those of severe kyphoscoliosis, occasionally widespread and far advanced pulmonary tuberculosis, some cases of bullous emphysema with replacement or compression of active lung tissue. I mentioned in a preceding section another newly defined form of pulmonary dysfunction, that of diffusion insufficiency or alveolar-capillary block. Such cases, in the advanced stages with continuous hypoxia, commonly have right-sided heart failure as a late complication. Still another important type is that of primary pulmonary vascular narrowing, represented by multiple pulmonary embolization, pulmonary schistosomiasis, and the somewhat controversial entity called primary pulmonary hypertension. In these the right heart strain is directly proportional to pulmonary hypertension, and the patients go eventually into massive right heart failure with low and diminishing cardiac output (*49*).

Conclusions

I have dealt with this particular subject, pulmonary heart disease, in somewhat greater detail than the rest of my account, partly to show the type of functional analysis that can readily be made in clinical cases, but partly also to illus-

trate what is perhaps obvious, that such analysis is at best superficial, does no more at the present time than set forth what some of the more fundamental problems are.

It is no part of a survey such as this to predict the future, but I should like to mention a few of the areas in which we believe that further basic research might well be concentrated. Dr. Cournand will touch on an important field—namely, the pharmacodynamics of the lung, and especially of the pulmonary circulation (*20*). Another that interests me greatly would be an effort to bring together function and structure, a re-examination of pulmonary anatomy by pathologists who are aware of functions and dysfunctions. May it not be possible to obtain, by such collaborative effort, more fundamental evidence on pathogenesis in such presently obscure and yet devastating conditions as pulmonary fibrosis in its many forms, the emphysematous change, bulla formation, the many-sided problem of pulmonary vascular change, the disorders of the bronchial circulation? Fortunately, work is already under way on many of these problems, by a new and dynamically minded generation of pathologists. So also with many of the other problems that I have touched upon, in renal and electrolyte physiology, as related to pulmonary disease, in blood formation, the physiology of the respiratory center, and so on.

I have endeavored to present in this review a brief account of the development of cardiac catheterization in our hands and some of the adventures that we have had with it. These have carried the work into many aspects of cardiopulmonary physiology and pathology. Our findings have been for the most part preliminary, revealing new problems more often than solving old ones. Of great value has been the interest which has been aroused and the excellent new work that has been stimulated in many laboratories and clinics in many countries.

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Mechanisms of Oxygen Metabolism

H. S. Mason

Application of tracer techniques to biochemistry has often been followed by fresh insight, sometimes at a level of generalization. In the study of oxygen metabolism, which has been badly prejudiced by the influence of the expression "½ O_2," the use of oxygen-18 as a tracer has become broadly feasible only recently. Formerly, it was difficult to recover oxygen quantitatively from organic compounds in a form suitable for mass spectrometric analysis, but this problem was largely solved in 1953 by Doering and Dorfman (*1*).

Since then, the mechanisms of action of a number of enzymes that catalyze reactions of molecular oxygen ("oxidases") have been examined by means of tracer oxygen. The purpose of this article (*2*) is to summarize the results which have been obtained and to show that molecular oxygen is metabolized by three broad classes of enzymes, which I have named "oxygen transferases," "mixed-function oxidases," and "electron-transfer oxidases" (*3*, p. 55C; *4*).

Oxygen Transferases

By *oxygen transferase* (*5–8*) is meant an enzyme that catalyzes the consumption of one molecule of oxygen per molecule of substrate (*9*), both atoms of consumed oxygen appearing in the product (Eq. 1; the related system described by Eq. 1a is also possible, but it has not been observed).

$$S + O_2 \rightleftharpoons O_2S \qquad (1)$$

$$2S + O_2 \rightleftharpoons 2OS \qquad (1a)$$

To identify an enzyme as an oxygen transferase, it is therefore necessary to

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