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VIII. Summary

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Summary of the Conference
G.W. WRIGHT ✓

This has been, as far as I am concerned, one of the finest conferences that I have attended. Very stimulating to me, not only in terms of the presented papers, but also because of the opportunity to discuss the problem as a whole with others working with related matters. To arrange a conference of this sort takes a tremendous amount of effort on the part of one or more individuals. I would simply like to say to Dr. Mitchell and his entire committee that I believe all those who have attended this meeting are extremely grateful.

A little over a year ago, Dr. Mitchell asked me to be the final summarizer of this Seventh Annual Conference on Research in Emphysema, and he stated that the session was to be comprised of topics related to the pathogenesis of chronic obstructive bronchial pulmonary disease. I was aware in a somewhat intuitive way, that I should plead a prior commitment, but the date hadn't been set and the responsibility seemed quite distant; after all, everyone hopes to be less pressed for time a year hence. I neglected entirely to ask myself just what it was I was expected to do. I accepted the task, further seduced by the misconception that I would have sufficient material to scan prior to the meeting. At this very moment, I wish I had been more intuitive. Since receiving the same abstracts, no more and no less, that all of you have, I've queried myself as to the responsibilities of a summarizer. I noted in the program that each of the half-day's program was to have a summarizer. Not one of those listed actually have done a summarization, so, my original intent, which was to summarize the summarizers, simply vanished. It was obvious that I would have to decide upon one or another of several alternatives. I propose, in this statement, to refrain, as much as possible, from attempting to give the gist or essence of the papers and discussions. I certainly cannot present a critique of data, most of which is unfamiliar to me and almost none of which I have had an opportunity to digest. Moreover, in this particular meeting, the variety of papers is so great that the program does not lend itself well to a structured summary. I propose, instead, to do something a little different.

As some of you know, I have been interested and to some degree active in this general subject for twenty years, and I propose, at the risk of future embarrassment, to state some of my impressions of the manner in which the discussions of these past three and one-half days appear to me to bear upon the general problem of chronic obstructive lung disease. I would also like to say that my comments may, in part, arise from erroneous impressions, as well as inadequate considerations and, hence, I want to apologize to those of you who have gone to such great pains to make things clear, if, in some way, I have misunderstood you. Also, if some interesting information appears not to have representation in that which follows, I hope no one will be offended. I can say without any hesitancy whatsoever, that everything that was presented and discussed was of great interest. Some of it, however, I don't know where to place in the problem as a whole. I would like to commend each presenter for the general high quality of material and presentation.

While the motivation underlying research in the subject of this conference, in part, may be the pursuit of new knowledge for the considerable satisfaction of that activity alone, I believe the major drive on the part of all of you is the desire to contribute to the relief of suffering and the prevention of disease. Hence, if the information that has been presented these past few days and the molding of thought that stems from this conference has value, it is apt, in a large part, to be relative to this latter motivation.

This conference is concerned with the study of the pathogenesis of chronic obstructive bronchopulmonary disease. Such a study should assist us, to some degree, in learning about two major features, namely etiology and treatment. An understanding of the etiology is requisite if we are going to have an intelligent approach to prevention. Studies of pathogenesis will not only bear upon etiology, but also, gives us an understanding of the mechanisms of alteration of function and these, in turn, provide the basis for intelligent treatment. This isn't to say that, lacking complete understanding, there should not be empirical approaches, or that we need wait until all the knowledge is in before we set in motion any sort of thing that might be useful in controlling the disease.

Throughout this conference, there were frequent allusions to this, that, or the other thing as "causing" the disease. It seems to me rather important to restate a view that I have in regard to the use of the words "cause of disease". I think one needs to separate what

might be called the necessary cause of disease from all the other sorts of things that we think of as being a condition, or secondary, causes of disease. By "necessary cause of disease" I mean the one or more causative feature that has to be present in every instance of subsequent development of disease. Needless to say, I don't think any of us believe that such a feature has been discovered for bronchitis, no matter how you define it, nor for emphysema, no matter how you define it. There is, however, another way of thinking of "cause" and I believe this is the way in which the term is so commonly used. I like to recall a word picture of this that was related to me by Dr. J. S. L. Brown of McGill University. He used the example of an iceberg. In his conception, disease, as we recognize it clinically, comprises that portion of the iceberg above the water, both as to the numbers of cases and various features of the disease. In fact, however, there is a great submerged body of the same sort of abnormality that we are not cognizant of. If you approach either bronchitis or emphysema with this model in mind, then it is not difficult for me to understand that a factor which I would consider an *aggravant* simply brings a larger number of cases into clinical recognition, so that when epidemiologic studies are done, one is apt to think that such an *aggravant* is a cause. Well, it is a cause of increased numbers of "clinical" cases and, in that sense, a very important feature, but it doesn't constitute the necessary cause. I make this point because I have been disturbed during this conference by the assumption that certain features that I would consider *aggravants*, as for example cigarette smoke, have been used as though they were the necessary cause. Cigarette smoking cannot be thought of as the necessary cause because of the considerable number of individuals who have full-blown chronic bronchitis, no matter how you wish to define it, either clinically or anatomically, but have never smoked a cigarette in their life. The only smoke they have inhaled is by sitting in a room where someone else smoked. The same can be said in regard to emphysema.

Another disturbing feature has occurred frequently throughout this conference. I had hoped that after this long period of time, we could arrive at a generally agreed upon use of the words bronchitis and emphysema. I have no strong feeling that either must be defined one way or another. Just a few moments ago, the plea was made, rather wistfully I think, as to what simple dilatation was to be called if it couldn't be called emphysema. I have no objection to calling this emphysema, provided you put some sort of a modifier on it, so

that I know what form of emphysema is indicated. The simple, unadorned word "emphysema" can mean so many things to the listener that he may be misled completely as to what the speaker intends. It seems to me that, in a group as experienced as we supposedly are, we should no longer be committing this sort of lapse. It leads to confusion. Perhaps, if we have another meeting of this kind, it would be well to have the first thirty minutes devoted to defining the terms that we are going to use during the conference. It doesn't mean that everyone else must use such definitions later on. This same confusion exists not only in regard to "emphysema" which has numerous interpretations, but was beautifully displayed in regard to bronchitis. I find it very difficult to believe that the chronic inflammatory change that was demonstrated histologically in one of the papers, is exactly the same disease as that characterized by mucus gland hypertrophy. They may co-exist, but to me they look so different, that I would think they are different diseases. Yet, both are called chronic bronchitis and when you use only this term, the listener has slight chance of knowing which of these anatomically quite different appearing things is being referred to. So we still have this problem even after all these years.

I have some comments in regard to the methods that are to be used for epidemiologic studies. I believe that studies using the discipline of epidemiology are absolutely essential for increasing our knowledge, both in regard to bronchitis and in regard to emphysema. I am disturbed by the fact that, at the present time, there still is a desire and an activity on the part of some individuals to make use of vital statistics that were obtained years ago, and still are being obtained, in a manner that cannot possibly lead to accurate or useful information relative to the problems in hand. Death certificates, as they were originally developed, have very little relevance for our problem. They were designed primarily as records to indicate, for legal purposes, that the designated person had died. There was some interest, doubtless, as to the medicolegal aspects, hence, the requirement that a cause of death be assigned. I doubt if more is intended for these certificates at the present time. This is certainly the attitude that seems to be taken by those who require that such documents be made out. I don't know whether the individuals who use vital statistics have ever gone to a general hospital and watched the procedure of the signing of a death certificate. It is sometimes done by the man who has been in charge of the patient and who knew the patient well.

Sometimes the certificate is not made out until the autopsy is finished. More often, however, it is done without an autopsy and is based on what the physician thinks is the most likely cause of death. It is sometimes influenced by the knowledge that what he puts down may have some bearing on the individual's insurance, or what the physician believes is his duty to the living. There are many pressures of this kind. Quite often it is made out by the intern or resident, who may actually never have seen the patient. Because death occurs at night and the undertaker is waiting at the door and wants his death certificate, the resident or intern *on call* is brought up to sign this most important document. It seems to me that this kind of a certificate is a tool that is entirely unreliable. There are a number of studies in the literature comparing the disease listed on the death certificate to the conditions found at autopsy. It is astonishing how poorly these two correlate, particularly in regard to respiratory disease in the United States. What it's like in other countries, I do not know. I said at the outset that I think epidemiology is essential. If we are going to make use of knowledge concerning conditions present at the time of death, then we need to do two things. We should put less emphasis on the cause of death and instead, record *all* of the abnormalities present at the time of death. Secondly, we must set about improving the methods for producing vital statistics. When I had the good fortune of spending some years with Professor *Carl Wiggers*, one of his continuous admonitions was that if you must make a division of your time, spend it preferably in the development and mastering of the method. Unless you do so, all the subsequent work is apt to be somewhat cloudy and difficult to interpret. I would question the wisdom of putting such tremendous efforts into glean- ing information from vital statistics that are of such questionable reliability. Isn't it possible to create in some geographical regions, a category of trained persons who would check every death as thoroughly as possible by going to family, to physician and to hospital, to make sure that everything known as to conditions exist- ing at death appear on this final document. I would think this would be an excellent expenditure of money and time. Ten years goes by rather quickly and the time to begin to get some reliable data of this sort is now, not wait another five years for someone else to make the same plea. The need for such information was well recognized by one of the reporters whose effort is mostly in the direction of getting prospective data.

Also bearing on the subject of methods is the matter of just how questionnaire data is to be used. I do not refer to the validity of the answers to the questions, but rather to the validity of how the answers are to be used. We have gone to great lengths to define "emphysema" and "bronchitis" in terms of anatomical appearance. While the questionnaire seems able to categorize populations as to prevalence of coughers, spitters and breathless persons, I am not aware of data demonstrating the validity of the questionnaire method for recognizing and quantitating the severity of anatomical emphysema, or bronchitis. Until such information is obtained, we must exercise great restraint when interpreting epidemiologic data obtained by questionnaire, as being applicable to the study of the cause of emphysema, or bronchitis. The considerable number of persons shown at autopsy to have more than a minor portion of the lung involved by emphysema, but who, according to themselves and close relatives, did not experience unusual cough, expectoration, or even breathlessness during life, speaks eloquently of the need for such restraint. These same comments apply also to the need for restraint in applying pulmonary function data in a similar manner. Those workers, some of whom presented data at this conference, who are trying in a systematic fashion to relate anatomical appearances to symptoms and measurements of function, deserve our appreciation and support.

Another point connected with questionnaires was emphasized by this conference. This is the absolute necessity, no matter to what length one must go, of learning the smoking history of the individuals who are involved in chronic respiratory disease surveys. Throughout this conference, the influence of cigarette smoking on pulmonary function measurements has been clearly demonstrated. I think there will be no question in anyone's mind but that this can be clearly demonstrated also in terms of the clinical history. What is not determined and what needs very serious consideration is something that was inappropriately laughed at in this conference, and that is, how are we going to measure smoking intensity? I don't believe we do this well and I don't know exactly how one can do it better, but somebody ought to put his mind to it. We are in the same position here, as we are with vital statistics. I don't believe that this task should be put off, with the result that we come back five years later and still have somebody say, "Well, how much of the cigarette was smoked?" and so on.

I was impressed by the studies on the bacteriology of chronic

bronchitis and the production of different kinds of mucus, the character of the mucus changing *in situ* in those individuals who have severe mucus gland hypertrophy. I don't know what the latter observation means. I had rather hoped that I was going to hear something about the physical characteristics of these two kinds of acid and neutral mucopolysaccharides. One thing occurred to me in regard to these studies including those on clearance. I would suspect that something we might call the transit time of mucus in the bronchus might be important in terms of whether or not organisms will become established there. It takes time for organisms to divide and multiply and it's my understanding that to make a culture positive requires at least a minimum number of living organisms. It seems reasonable to assume that the longer mucus would stay in the tracheo-bronchial tree the better will be the opportunity for organisms to grow and, therefore, the greater the probability that colonies be established. In this regard, I thought the clearance studies were exciting. They rather clearly indicate that the clearance time may be considerably delayed in these individuals that we say have chronic bronchitis. If this is true, then, of course, the chance for colonizing and having a good growth of organisms in mucus would occur. This may have some bearing on the etiology of chronic bronchitis. It would, of course, have a great deal to do with therapy, because if you can speed up the transit time, the chances of getting infected would be reduced. We know how to reduce the transit time, apparently, by stopping cigarette smoking and other things. Wouldn't it be possible in some way to develop a method of speeding up the transit time?

The problem of the study of viruses is just so staggering that most of us only speculate about it. I have the feeling that this is perhaps the area which might give us the greatest step forward in regard to the etiology of both chronic bronchitis and the crippling forms of emphysema. When I speak to my virologist friends and say that I think it's time we really get something going about this, they just throw up their hands because the technology for doing this is apparently so overwhelming. I was rather pleased to learn in a conversation with Prof. Stuart-Harris, that his group is on the verge of being able to initiate such studies, although of course, still on a limited scale. We are an influential group. You may not think so, but I believe we are. In terms of dollars that are being spent for other things, it would seem to me to be a rather minor expenditure if one or two competent laboratories could concentrate on this problem.

Why can't such studies be promoted now? Why don't we urge it strongly? Single studies in individuals, horizontal studies in the same individual, and so on. This general problem of the acute and chronic infection of the bronchial tree is one that deserves tremendous support. I believe this somewhat intuitively, but also because another conversation I had impressed me in this regard. Some of you know that Dr. Bates and his co-workers have a study going on in which the same individuals are under observation periodically. I asked whether or not in this study, there was evidence that would give me some idea of how rapidly measurable permanent obstructive disease could occur. I wanted to know that because, if it never occurs rapidly, your thinking goes in one direction. If it can occur quite rapidly as patients' histories do suggest, we must think of other things. I'm not certain that I heard correctly, but I got the impression that passage from known normal measurements to persistent, easily recognized abnormal measurements could occur in 7 to 10 days. This, I thought, was exciting. If it is true, it lends more and more support to the idea of a virus or some sort of bacterial etiology.

It is difficult to see where one might place the extraordinarily interesting discussions concerning surfactants in relation to the problem of emphysema, or chronic bronchitis. For the moment, I don't see a strong relationship between the two.

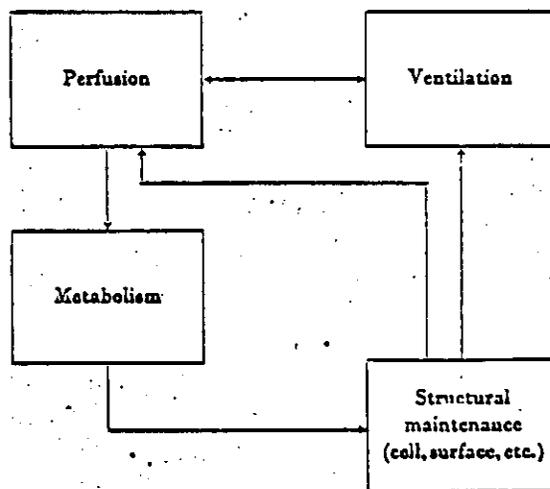


Diagram on blackboard used by Dr. Geo. Wright in summary. Dr. Wright credits Dr. John Clements for scheme.

A few minutes ago, Dr. *Clement* showed me a diagram included in his summary of the sion on surfactants. I think this is a rather neat way of saying schematically, something that I was planning to discuss. He depicts the enormous interdependence of the lung on its various components. In my own lifetime, we have gone from the idea that the lung is a system of tubes suspended in a passive sac that is moved by the thoracic cage, to a realization that it is one of the most active organs, not only mechanically, but biochemically and probably immunologically and enzymatically, that we have in the entire body. Dr. *Clements'* diagram (see page 427) indicates that in order to have a proper Ventilation/Perfusion relationship, we must have a good structural organ, and there are activities that go on, having to do with the maintenance of the structural integrity of the organ. Alteration of perfusion influences ventilation. A reduction of ventilation reduces perfusion. Perfusion can clearly influence metabolism, as was beautifully shown at this conference. This, in turn, greatly influences structure, which can, in turn, influence both ventilation and perfusion. The thing intrigued me about this diagram is that it's a nice way to say that no matter what happens to any one of the functions each of us might be interested in, there is almost always a reaction elsewhere in other parts of the lung. In this connection, Dr. *Cournand* used the word "adaptation". I'm not sure whether he meant it in the strict sense of the word, or whether he meant "adjustments". It is apparent that when persistent alterations of perfusion or ventilation occur, there are adjustments that are made. When there is poor ventilation in some one area because of structural abnormalities, there are concomitant perfusion alterations which attempt to maintain a normal VQ relationship. A great deal was talked about in the conference about mechanisms controlling this adjustment.

A number of cases were shown that raised a question as to why there was such an abnormality of the arterial blood gases in some cases that seemed to show a rather minor amount of anatomical alteration. It seems to me that the over-all effect depends on the strategic location of the lesions. If all of the abnormality is essentially confined to, or the equivalent of, one lobe with a large volume of normal lung present, very little blood gas abnormality develops. This can go on so long as you have good healthy lung tissue through which blood is preferentially directed by regional differences of vascular resistance.

On the other hand, when you run out of good lung to push the blood through, marked alterations of blood gases develop. This was nicely demonstrated in some of the studies where, instead of having involvement of perhaps one entire segment, or one entire lobe, the abnormality was distributed rather evenly in all parts of the lung, so whatever mechanical effects this had would be influencing all segments of the lung and, therefore, no good lung tissue existed through which one could direct the blood flow. That's one way of explaining it. The second way of explaining these unusual cases that seem to be so impaired functionally with relatively little anatomical alteration is that, if we agree that there are these adjustments, so that a poorly ventilated area becomes poorly perfused, there is no reason in the world to think that this adjustment might not fail. Simply because in most instances the capillary flow is diminished in areas of hypoventilation, there is no reason to assume this always happens. In fact, this would be most unlikely because in all biological systems, there are failures. I would think that, quite possibly, we have not studied carefully enough, the mechanism of failure of adjustment to occur. I say that because, if we could learn why the failure occurred, we might be able to alter this from a therapeutic point of view. If we had in our armamentarium, a device whereby we could close off the circulation where it persists in badly ventilated areas, we might do this patient a good service and prevent, or minimize the secondary effects which are really the fatal effects of what is going on in the lung, namely, the chronic hypoxia, the pulmonary artery hypertension, the cerebral changes, cor pulmonale and eventual heart failure. I would like to suggest that we become interested in whether adjustments fail, as well as why they occur.

I would agree fully with the idea that there are two kinds of cases of respiratory failure. I don't like the terms "blue bloater" and "pink puffer". This is an oversimplification which tends to obscure the real problem. Someone leaned over to me when these terms were used and asked, "Well, don't the blue bloaters puff?" Well, they do; the problem is they don't puff enough and they don't puff in the right places. There is no question but that there are these two categories; the ones in which there are extensive anatomical changes with relatively little blood gas abnormality, and the reverse, marked blood gas abnormalities with all of its sequelae and relatively little total anatomical change. More studies correlating anatomical and function change are needed in this regard.

I only have one other comment in the brief time remaining. I have the impression that some of the differences of opinion regarding the total picture of emphysema and chronic bronchitis arise from a different kind of case material. This was not talked about. The place where most of the studies are apt to be made is obviously where there are large laboratories with adequate personnel devoted to this. As a result, hospitalized cases are apt to constitute the bulk of reported studies. This means, in general, people who have broken down, whose adjustments are not as good and who have very severe abnormalities. There are some exceptions to this, and the ongoing study in Canada is one. There may be similar ones in this country also. I have the impression that the cases that I see are a little different from those of others in terms of frequency with which the types of abnormality occurs. Those of us who do some private practice are apt to see much earlier abnormalities, or lesser degrees of impairment. Experience with these cases makes me reluctant to accept the concept that the ventilation-perfusion relationship is the key to everything. It is the key at one phase. But at an earlier phase while adjustment is still going on, people are first impaired because of exertional dyspnea about which almost nothing was said at this meeting. In my experience, dyspnea with little or no blood gas alteration is the common limiting phenomenon in people who are still active in the pursuit of their business. This brings to mind one other thing which I believe is rather important and that is the question of the development of cor pulmonale. Nice data were shown to demonstrate the variation between one group and the other, in the frequency of cor pulmonale and, hence, I would say pulmonary hypertension. In general, the group who had cor pulmonale were the ones who have the better maximum breathing capacities or its equivalent and to some, this seemed a little bit strange. To turn it around, the people who had the most severe impairment of ability to respire were the ones who had the least cor pulmonale. I think there is an additional factor in cor pulmonale that was not discussed here. This is that cardiac output must play a role. Those individuals who still have sufficient breathing abilities to permit some increase of exercise, experience greater augmentation of cardiac output and, hence, reach higher levels of pulmonary artery pressure. I wonder if there isn't a built-in sort of protection which may account, in part only, for the difference in the frequency of cor pulmonale between these two groups. The man who has chronic bronchitis is the fellow who has

severe hypoxia and hypercapnia and possesses in general, a somewhat better maximum breathing capacity; he is also apt to be a bit younger and under greater economic pressure to continue to work. It has been my experience that such persons are more active, physically, than is the severe case of emphysema whose maximum breathing capacity is about 20. I would be inclined to throw into consideration the question of physical activity contributing to cor pulmonale. I believe this is somewhat important because it is one of the features that is amenable to treatment, in the way of advising people suffering from respiratory insufficiency as to what to do with their life.

I have taken all the time that I should. I hope I will not be too embarrassed later on by what I have said.