THE OXYGEN CONTENT OF THE BLOOD IN LOBAR PNEUMONIA.*

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For two reasons it seems possible that a study of the oxygen content of the blood in pneumonia might yield results of interest. In the first place, the disease affects primarily the lungs, so that a disturbance of the respiratory exchange of gases might take place. In the second place, the growth of the pneumococcus produces a marked change in the hemoglobin molecule. Butterfield and Peabody[1] have shown that, as a result of its growth on blood *in vitro,* the hemoglobin may be converted into methemoglobin. As yet, however, practically no direct determinations of the oxygen content of the blood in pneumonia have been made. The following study was therefore undertaken to obtain some evidence as to the extent and manner in which the disease affects the oxygen of the blood, and the relation of any changes in the oxygen to the symptoms and course of the disease. Analyses of arterial blood were, of course, greatly to be desired, but in a study on patients it seemed safer to use only venous blood. Since this work was finished, however, Hürter[2] has shown that it is both safe and comparatively easy to take blood from the radial artery. While analyses of peripheral venous blood are not wholly satisfactory, there are certain facts of interest which are brought out by them, and which may serve as a basis for further study.

The method used was that of Barcroft and Haldane,[3] as modified by Brodie.[4] This has been briefly described, together with the

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[1] Butterfield, E. E., and Peabody, F. W., *Jour. Exper. Med.,* 1913, xvii, 587.

[2] Hürter, *Deutsch. Arch. f. klin. Med.,* 1912, cviii, 1.

[3] Barcroft, J., and Haldane, J. S., *Jour. Physiol.,* 1902, xxviii, 232.

[4] Brodie, T. G., *Jour. Physiol.,* 1909–10, xxxix, 391.

technique of taking the samples of blood, in a previous paper[5] in which the results of the analyses of the same bloods for carbon dioxide were discussed. It is perhaps well to repeat here that the blood was taken without obstructing the flow in the veins. Nearly all observations were made in duplicate, and few analyses had to be discarded on account of the results failing to agree.

Control observations were made on normal individuals and on patients during convalescence from pneumonia. Twenty-one specimens of blood from seven convalescents and five normal adults showed an oxygen content varying from 9.23 to 15.02 per cent. Of these only three, all from convalescents, were below 10 per cent., and only one, from a normal individual, was above 14 per cent. It is thus important to realize that with subjects at rest and in what may be considered normal conditions, the oxygen content of the peripheral venous blood may vary within rather wide limits. Buckmaster and Gardner[6] report a series of eleven observations made by a different method on their own venous blood, and found the oxygen content to range between 2.63 and 10.8 cubic centimeters per 100 cubic centimeters of blood. In the present study figures as low as some reported by these authors were rarely met with, and then only under pathological conditions.

The material for study consisted of twenty-five cases of lobar pneumonia. In many cases repeated observations were made during the course of the disease and also in convalescence. The total number of determinations was eighty. The results obtained may be conveniently considered in three groups.

The first group of observations was made on cases in which the disease was running an uncomplicated course and in which no abnormality of the oxygen content of the blood was found. This series consists of forty analyses of blood from fifteen cases. In seven cases only a single specimen of blood was taken in the febrile period, but in others as many as six or eight observations were made during the disease and in convalescence. Twenty-seven of the samples were taken during fever and thirteen at a time when

[5] Peabody, F. W., *Jour. Exper. Med.*, 1912, xvi, 701.

[6] Buckmaster, G. A., and Gardner, J. A., *Proc. Roy. Soc.*, 1912, lxxxv, *Ser. B, Biological Sciences*, 56.

the temperature had become normal. The earliest were taken on the third, the latest on the eighteenth day of the disease. In all of the forty observations the oxygen content was between 9.03 and 14.52 per cent., while only four specimens gave more than 14 per cent., and only six gave below 10 per cent. Several cases had a rather higher oxygen content during the febrile period than during the subsequent afebrile period.

This group of cases, which constitutes by far the greater number of uncomplicated instances of pneumonia, shows, then, an oxygen content of the peripheral venous blood which is well within the normal limits. The differences found during the various stages of the disease and the differences between the febrile and convalescent periods do not exceed those found in health. The extent of lung involvement appears to have little influence on the oxygen. In one case the temperature was 103° F. and the rate of respiration thirty-two on the day before the crisis, and the oxygen content was 14.52 per cent. On the following morning the temperature had dropped to 98° F. and the respiration to twenty-four, but the oxygen was 13.55 per cent., in spite of there being no noticeable change in the physical signs in the chest. There is no definite relation between either temperature or respiration and oxygen content, except the rather obvious fact that during the acute stage of the disease the normal oxygen level is associated with a more or less increased respiratory rate. By this increase in the rate of respiration, and perhaps by a more rapid circulation, the organism is thus able to compensate fully for the decrease of respiratory surface caused by the pulmonary exudate. Such compensation is easy, for the lungs have a comparatively large factor of safety. Loewy and von Schrötter[7] state that if one lung were completely shut off by the occlusion of its main bronchus, the venous blood would contain 8 per cent. of oxygen instead of the normal 14 per cent., even if there were no compensation on the part of the respiratory or circulatory systems.

The second group of cases consists of only two patients. Like those in group I, both ran an uneventful course ending in recovery.

[7] Loewy, A., and von Schrötter, H., *Ztschr. f. exper. Path. u. Therap.*, 1905, i, 197.

Both, however, had a diminution in the oxygen content of the blood during the height of the disease. In the first case this diminution was only found once, on the fourth day of illness. The oxygen was then 5.67 per cent., but two days later it was normal and it remained so afterwards. In the second case the low oxygen was found at three separate times during two days. The lowest observation was 2.77 per cent. Before and after this period the oxygen was normal. Both cases were rather more cyanotic than was usual. Blood cultures were negative in both. In both cases the low oxygen figures were associated with values for carbon dioxide which were much higher than normally. The combination of low oxygen and high carbon dioxide suggests some pulmonary or circulatory interference with the normal gaseous exchange. In the second case, however, several observations showed that the blood lacked the power of taking up oxygen normally, even when shaken vigorously in the air. It is thus not improbable that there had been some change in the hemoglobin, and the case is somewhat similar to case 8 which will be discussed in more detail below.

The third group consists of those cases which terminated fatally. Death in pneumonia may result in a variety of ways. It often comes suddenly as the result of cardiac or of respiratory failure. It may be the result of a complication. Not infrequently, however, the clinical history is somewhat as follows: Towards the end of the first week of the disease the patient, who has been doing well, begins to show serious symptoms. The pulse becomes rapid, weak, and perhaps irregular. Respiration is shallow, labored, and rapid. Cyanosis becomes marked and toxemia deepens. After some hours coarse, moist rales begin to appear in the chest. A general pulmonary edema, associated with coarse tracheal rales, develops, the patient becomes increasingly weak and toxic, and dies in twelve to twenty-four hours. This more or less gradual type of death is the one which is most frequently met with, and was present in the majority of the fatal cases in this series. Dochez[8] has analyzed a number of these typical, slowly progressive cases, with a view to finding the actual cause of death. He concludes that in general the patient can withstand the original infection, and that

[8] Dochez, A. R., *Jour. Exper. Med.*, 1912, xvi, 680.

death is due to a spreading of the infection and to the failure of the patient to resist the secondary insult. The spread of the infection may be in either or both of two ways. There may be a further involvement of the lungs, or there may be a spread to the blood and the development of an intense bacteremia. The degree to which the infection may spread in the lungs or in the blood before death ensues depends, of course, on the resistance of the patient.

Eleven fatal cases are reported here. Ten of these were of the slowly progressive type just described. One case (No. 11) died very suddenly, apparently of respiratory failure. There was no pulmonary edema and the heart sounds were audible for three minutes after respiration stopped. Blood cultures were made in ten cases. In nine of these they were positive, and bacterial counts by Dochez (table I) show that there was often a bacteremia of progressively increasing intensity. The number of organisms was frequently over 1,000 per cubic centimeter of blood at the time of death. In one case (No. 8) blood cultures were negative, even on the day of death, but the physical signs and autopsy showed a rapidly spreading pulmonary lesion.

Observations on the oxygen content of the blood during life were made in ten of the eleven fatal cases. In the one case that died suddenly (No. 11), the oxygen content of the blood was normal two hours before death. In one case (No. 10) the last specimen of blood was taken twelve hours before death and showed a normal oxygen content. In the other eight cases observations were made one or more times during the final stage of the disease and in every case the oxygen content was below normal. Moreover, these cases show (table I) that during the terminal stage the fall of the oxygen content of the blood is, roughly, a progressive one. Thus samples of blood taken from different cases ten, five and one half, and three hours before death contained 6.89, 8.40, and 8.12 per cent. of oxygen, respectively. Others taken two hours, one hour, and thirty minutes before death contained 4.68, 2.30, and 2.07 per cent. of oxygen. A specimen taken five minutes after death contained no oxygen. In several cases (Nos. 3, 4, 5, and 8) the oxygen content of the blood had previously been found to be normal, and the fall in the oxygen content accompanied the develop-

TABLE I.

The Oxygen Content and the Oxygen-Combining Power of the Blood in the Fatal Cases of Pneumonia.

No. of case.	Date (1912).	Per cent. of oxygen content of blood.	Per cent. of oxygen-combining power of blood.	Blood culture.[9]	Remarks.
1	Mar. 29,	7.80		4,500 colonies per 1	Marked cyanosis. Many
T. W.	10 A.M.			c.c. of blood	coarse rales.
525	10 P.M.	8.40	16.35		
	Mar. 30		7.87		Blood taken 10 min. after death.
2	Jan. 31	2.30			Cyanosis. Edema of
H. L.					lungs. Blood taken 1
453					hr. before death.
3	Mar. 29	9.03	16.02	Positive on Mar. 28.	
M. M.	Apr. 2			15,000 colonies per 1	
533				c.c. of blood	
	Apr. 3	2.07	13.23		Cyanosis. Many coarse rales. Blood taken 30 min. before death. Hemoglobin, 96 per cent.
4	Jan. 15	10.97		Positive on Jan. 14	
T. C.	Jan. 16	4.68			Many coarse rales. Cyanosis not marked.
423					Blood taken 2 hrs. before death.
5	Jan. 25	10.41			
J. McL.	Jan. 26	6.89		100 colonies per 1	Marked cyanosis and
438				loop of blood	edema. Blood taken 10 hrs. before death.
6	Apr. 9	8.27		Negative	
J. R.	Apr. 11	6.86			Slightly cyanotic.
547	Apr. 13	3.94	16.29	4 colonies per 1 c.c. of blood	Hemoglobin, 88 per cent. Cyanosis marked.
	Apr. 15	8.47	16.71	21 colonies per 1 c.c. of blood	Hemoglobin, 88 per cent. Cyanosis less marked.
	Apr. 16		13.95		Died suddenly. Blood taken 10 min. after death. Serum reacts alkaline to litmus paper.
7	Apr. 6	3.61	18.59	Negative on Apr. 5	Cyanosis very marked.
N. A.	Apr. 8	4.44	17.50	Negative on Apr. 9	
544	Apr. 12		15.09	2,500 colonies per 1 c.c. of blood 1 hr. after death	Pulse weak. Many rales in chest. Blood taken 2 min. after death.

[9] The blood cultures were made by Dr. Dochez.

TABLE I.—*Continued.*

No. of case.	Date (1912).	Per cent. of oxygen content of blood.	Per cent. of oxygen-combining power of blood.	Blood culture.	Remarks.
8	Feb. 2	10.81		Negative	
J. D.	Feb. 3	11.98			
460	Feb. 4, 4.30 A.M.	6.84	15.07		Coarse bubbling rales throughout chest.
	9.30 A.M.	9.07			
	2.30 P.M.	9.71			
	9.45 P.M.	12.09			Chest much more clear. Few rales. Cyanosis much less.
	Feb. 5 10.00 A.M.	8.12		Negative	Many rales in chest.
	1.00 P.M.	0.00	15.05		Blood taken immediately after death. Autopsy showed almost complete solidification of right lung,—apparently a spreading lesion.
9	Mar. 4		16.38	125 colonies per 1 c.c. of blood	Blood taken 2 min. after death.
I. J. 535					
10	Feb. 12	7.78		Negative	Cyanotic and exhausted after a long walk to the hospital.
W. H. 472	Feb. 13	12.64			
	Feb. 14	11.93		Positive	
	Feb. 15	12.71		Positive	Blood taken 12 hrs. before death. Pulmonary edema.
			16.84	1,000 colonies per 1 c.c. of blood	Blood taken 8 min. after death.
11	Feb. 21	13.28	19.35	150 colonies per 1 loop of blood	Blood taken 2 hrs. before death. No pulmonary edema. Respirations very rapid, but became slow and stertorous before death. Heart sounds audible for 3 min. after respiration stopped.
W. H. 480					
					Average capacity of 6 normal individuals and 6 convalescents, 19.57 per cent.

ment of the severe terminal symptoms and of the bacteremia, or, as in case 8, the rapid spread of the process in the lung. Thus in almost all cases of pneumonia running an uneventful course, the oxygen content of the blood remains within normal limits, but in

the majority of fatal cases, the terminal stage is marked by a progressive decrease in the oxygen content of the blood.

Since the pneumococcus shows an intense avidity for oxygen, it was possible that the mere presence of the organism in the blood was sufficient to explain the decrease in the oxygen content of the blood. It was therefore important to determine whether there was any actual change in the hemoglobin molecule which interfered with its taking up oxygen normally. For this purpose samples of blood were shaken in air until saturated with oxygen, and then the total combined oxygen was determined. Six specimens of blood from five convalescent pneumonia cases and one normal individual gave an average oxygen capacity of 19.57 per cent. In eight of the fatal pneumonia cases, similar observations were made. Case 11, which, as has been said, died very suddenly, had a normal oxygen content of the blood two hours before death and showed at the same time a normal oxygen-combining power. On the other hand, all the cases which had a low oxygen content showed also a low oxygen-combining power in specimens of blood taken just before or, as nearly as possible, at the time of death. The progressive nature of this fall in the oxygen-combining power of the blood was shown in four out of five cases, in which more than one observation was made during the terminal stage. In the fifth case the blood had as low a capacity twenty-four hours before death as it did at death. The amount of oxygen given off by fully saturated samples of blood taken at death varied considerably from case to case. The highest was 16.84 per cent., the lowest was 7.87 per cent. Four were between 13.23 and 15.09 per cent. In general, then, although the fall in the oxygen-combining power of the blood is slightly less marked than is the fall in the actual oxygen content of the venous blood, the two run parallel to one another.

The blood after death was very dark and often of a brownish tint. It coagulated much more slowly than normally. The serum was alkaline to litmus in the only case tested. Spectroscopic examination in several cases showed only the absorption bands of oxyhemoglobin or hemoglobin. Methemoglobin was not found. Hemoglobin estimations on several cases ruled out the possibility of the low oxygen-combining power being due to anemia.

The explanation of the striking changes shown in the oxygen content and in the oxygen-combining power of the blood in the terminal stage of fatal cases of pneumonia is to be found by turning to experimental studies. Butterfield and Peabody[10] have shown that when the pneumococcus grows in a mixture containing red blood cells, there is a gradual conversion of the hemoglobin into methemoglobin, and coincident with this a decrease in the extent to which the blood can take up oxygen. There is, moreover, a marked fall in the oxygen-combining power of such mixtures, even when no methemoglobin absorption bands can be distinguished spectroscopically. Peabody[11] has also found that similar changes take place in rabbits with a severe pneumococcic bacteremia. When the infection in rabbits becomes advanced, there is a gradual fall in the oxygen content of the arterial blood and also in the oxygen-combining power of the blood. The fall both in the oxygen content of the arterial blood and in the oxygen-combining power is a gradually progressive one up to the time of death. At the time of death the combining power is usually only between 60 and 75 per cent. of its original value. In some animals the oxygen content of the blood falls more rapidly than the oxygen-combining power, so that the arterial blood is less completely saturated with oxygen than under normal conditions. The suggestion was thus made that, besides a fall in the actual combining power of the blood, there is also a slowing in the rate of the reaction.

Conditions similar to those produced experimentally in rabbits are found in the fatal cases in man. In both there is a progressive decrease in the oxygen content of the blood. This has only been demonstrated for the venous blood of man, but it occurs in the arterial blood of rabbits and probably also in the arterial blood of man. In man and in the rabbit there is also a progressive diminution in the oxygen-combining power of the blood, reaching its minimum at the time of death. In the experimental infections and usually in the fatal cases in man there is a severe bacteremia. The conditions in man and in the rabbit are so similar to those in the test-tube that it seems logical to explain all three in the same way

[10] Butterfield, E. E., and Peabody, F. W., *loc. cit.*

[11] Peabody, F. W., *Jour. Exper. Med.*, 1913, xviii, 1.

and to account for the changes in the blood by the growth of the pneumococcus. In solutions of laked hemoglobin the pneumococcus produces amounts of methemoglobin that are easily found with the spectroscope. In mixtures of unlaked red cells the change goes on much more slowly and is less complete. In the human body and in experimental animals death occurs before enough methemoglobin has been formed to be visible spectroscopically, but the falling off of the oxygen-combining power of the blood indicates that such a change is probably taking place. Case 8 never had any demonstrable bacteremia, but it has been shown that if a bouillon culture of the pneumococcus be passed through a Berkefeld filter, the filtrate will have the same effect on blood as does the organism itself. It may thus be assumed, with comparative certainty, that the changes in the blood in this case are due to the passage into the blood stream of the products of the growth of the organism in the lungs. Case 11, the only fatal case not showing changes in the oxygen of the blood, died suddenly. It is possible that had he lived longer, the organisms would have developed and produced the characteristic changes in the blood.

The progressive fall in the oxygen content and in the oxygen-combining capacity of the blood in fatal cases of pneumonia is thus undoubtedly the direct result of the growth of the pneumococcus. An interference with the respiratory exchange of gases in the lungs, or a circulatory effect could not explain the conditions, for the low oxygen was associated with a low carbon dioxide content of the blood,[12] and any condition which interfered with the taking up of oxygen would also interfere with the excretion of carbon dioxide. Moreover, an abnormal respiratory exchange would not affect the oxygen-combining power of the blood. The same change is also present in the arterial blood of rabbits infected with the pneumococcus, and in these animals the lungs are not involved. In how far the changes produced in the blood are the actual cause of death, it is impossible to say, but that they are a factor, and probably an important one, can hardly be denied. The terminal symptoms,—toxemia, cardiac failure, polypnea, pulmonary edema, and cyanosis,—run parallel to the changes in the blood and may well

[12] Peabody, F. W., *loc. cit.*, 1912, xvi, 701.

be due in part to a deficient oxygenation dependent on these changes. It is interesting that in case 8 the temporary rise in the oxygen values was associated with a marked clinical improvement. While not attempting to assign a rôle that is all important to the changes in the blood, it would seem correct to consider that in many cases of pneumonia the terminal symptoms and death are in part dependent on the changes produced in the hemoglobin molecule by the growth of the pneumococcus.

CONCLUSIONS.

In most cases of uncomplicated lobar pneumonia the decrease of respiratory surface is completely compensated for, and the oxygen content of the blood is within normal limits. Occasional cases of uncomplicated pneumonia have an oxygen content of the venous blood which is below normal. In the two cases reported here, this was associated with a carbon dioxide content of the blood which was higher than normally, and the condition was apparently due to an interference with the respiratory exchange of gases.

In the terminal stage of the fatal cases of pneumonia in which death does not occur with great suddenness, there is often a progressive diminution in the oxygen content of the blood. Synchronous with this is a progressive decrease in the oxygen-combining capacity of the blood. These changes are usually seen in patients in whom an intense bacteremia has developed and are analogous to those found in the arterial blood of infected rabbits, and to those resulting from the growth of the pneumococcus in blood *in vitro*. In all three conditions there is probably a change of oxyhemoglobin to methemoglobin. This change of the hemoglobin molecule, so that it no longer takes up and gives off oxygen readily, is probably a factor in the immediate cause of death in many cases of pneumonia.