

THE CARBON DIOXIDE CONTENT OF THE BLOOD IN PNEUMONIA.*

By FRANCIS W. PEABODY, M.D.

(From the Hospital of The Rockefeller Institute for Medical Research, New York.)

As a result of experimental study and of a limited amount of clinical investigation, it has long been known that fever, or more accurately infection, is very generally associated with a diminution in the carbon dioxide content of the blood. This low carbon dioxide content has been accepted, probably correctly, as an index of acidosis. Apparently the values for carbon dioxide in the blood in fever are not infrequently within the range which is found in the more typical acidosis of diabetes. The object of the present study was to determine more accurately than has yet been done the constancy and extent of the variations in the carbon dioxide content of the blood in pneumonia, the possible relation of such variations to the course or severity of the disease, and more especially the relation of the carbon dioxide content to certain changes in the urine in this disease. Analysis of arterial blood, would, of course, be of much more value than of venous blood, but it is quite impossible to obtain samples of arterial blood from patients except under unusual circumstances. It will be noted, however, that the experimental studies on arterial blood agree well with the clinical studies on venous blood. On account of the recognized bearing of the carbon dioxide content of the blood on acidosis, the nitrogen and ammonia of the urine were quantitated. Determinations of "alkali retention" (Henderson and Adler) were also made, as this method is stated to be an index of acidosis. The relation between chlorine retention and carbon dioxide was studied, and observations were also made on the "total acidity" (Folin), phosphorus, and acetone in the urine.

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The first observations on the gases of the blood in fever were made by Pflüger in 1868 in the course of a series of experiments on dogs. Small operations were performed and the wounds healed with pus formation. Analysis of the blood showed a diminution in the contents of both oxygen and carbon dioxide. Senator¹ made determinations of the gases in the blood of a dog injected with pus. Four hours after injection the temperature had risen to 38.7° C., and the arterial blood showed a fall of 5.6 per cent. in the content of carbon dioxide. The oxygen had remained normal. Reynard's² experiments gave variable results. In one instance fever was produced by the injection of putrifying urine, and a fall in the oxygen and rise in carbon dioxide content of the arterial blood were noted. In two experiments the oxygen was increased and the carbon dioxide diminished. The latter he considered due to the accelerated respiration. In a dog in which septicemia was produced by injecting putrified blood into the femoral vein a fall of both oxygen and carbon dioxide occurred. Geppert³ made a more extensive study of the arterial blood in fever in dogs. The oxygen content he found not to vary from the normal. The carbon dioxide content, on the other hand, dropped considerably, and the diminution appeared to run approximately proportional to the height of the fever. The fall in carbon dioxide even after the onset of a very intense fever was somewhat delayed. Geppert explained the results by supposing that in fever there is a diminution in the alkalinity of the tissues and a subsequent corresponding change in the composition of the blood. He cites as an analogous condition the low carbon dioxide content, associated with a rise of temperature, caused by severe muscular exertion. "As a result of prolonged contractions, the muscle becomes acid, allows acid products to get into the blood, diminishes its alkalinity, and thus explains the fall in carbon dioxide."

Minkowski⁴ made extensive contributions to the subject. Geppert's results had been criticized on the ground that the low carbon dioxide was dependent on rapid respiration. Hence Minkowski first confirmed his observations as to the constancy of the low carbon dioxide in fever, and then showed that the change is quite independent of respiratory rate. Minkowski suggested, as did Geppert, that the essential factor is a change in the composition of the blood,—a diminution of the substances which bind carbon dioxide. Indirect evidence of acid formation in fever is given by the high ammonia output, the frequency with which acetone is found in the urine, and the finding by Minkowski of lactic acid in small amounts in the blood of febrile dogs. Minkowski repeated the experiments of Walter⁵ who found a diminution in the carbon dioxide of the blood of animals fed on mineral acids. Rabbits, which on account of their herbivorous diet have little ammonia at their disposal with which to neutralize acids, showed a greater fall of carbon dioxide than did dogs which were fed on a meat diet. In fever the fall in the carbon dioxide content of the blood is greater in rabbits

¹ Senator, H., *Untersuchungen über den fieberhaften Process und seine Behandlung*, Berlin, 1873.

² Reynard, *Recherches expérimentales sur les variations pathologiques des combustions respiratoires*, Paris, 1879.

³ Geppert, J., *Ztschr. f. klin. Med.*, 1880-1, ii, 355.

⁴ Minkowski, O., *Arch. f. exper. Path. u. Pharmacol.*, 1885, xix, 209.

⁵ Walter, F., *Arch. f. exper. Path. u. Pharmacol.*, 1877, vii, 148.

than in dogs. The organism in fever is consuming its own tissues and is thus essentially on a meat diet,—a diet associated with a high ammonia output in which the alkali present is not sufficient to cover the overproduction of acids formed. Another factor suggested for the withdrawal of available alkali for transporting carbon dioxide is the passage of alkali from the serum into the tissue cells, where it is bound by the acid products of decomposition. The retention of sodium in fever was cited. Finally Minkowski found a similar low value for the carbon dioxide in the rise of temperature produced artificially in overheated animals. While probably in part due to increased respiratory rate, other factors, notably metabolic changes and muscular rigor, play an important part, in which again the essential feature is a diminution in the alkalinity of the blood.

That the carbon dioxide content of the blood is diminished during fever had been definitely established by animal experimentation when Kraus⁶ made the first observations on man. His studies embraced a series of fourteen patients with fever of various types. Typhoid and tuberculosis composed the long fevers, and erysipelas, scarlet fever, and pneumonia the short ones. The blood was obtained from the median vein. In general the results were a confirmation of those obtained in animals. While the normal percentage of carbon dioxide in the blood varies, according to him, from 26 to 40.3 per cent. by volume, most of the normal figures run between 31.34 and 35.96 per cent. During fever, however, the carbon dioxide content was between 9.84 and 20.34 per cent. An exception to this was formed by two cases of pneumonia. One of these, on the fifth day of the disease, had a carbon dioxide content of 22.16 per cent., and the other, on the sixth day, a content of 29.2 per cent.,—thus within normal limits. Kraus suggests that the relatively high carbon dioxide content of the blood in the cases of pneumonia may be due to the fact that the sudden lessening of available respiratory surface by the formation of the pneumonic exudate interferes with the excretion of carbon dioxide in the lungs. He found no especial relation between the height of temperature and the diminution of carbon dioxide and suggested that temperature is in general no index of the severity of an infection, but possibly the low carbon dioxide, indicating the more essential metabolic changes in fever, might be some measure of the severity of the disease. In the majority of his cases one analysis of the blood was made but in one instance of pneumonia a second analysis was made a few hours after the crisis, and in three cases of typhoid fever analyses were made at a time when the temperature had been brought down to normal by administering antipyretics. As in none of these was there any marked rise in the carbon dioxide, he concluded that the fall of the fever is not immediately followed by a return of the carbon dioxide to normal. In two cases of erysipelas, however, the second analysis was made after one day without fever, and after the patients had begun to take nourishment. In both the carbon dioxide had risen to normal. Kraus agreed with the former investigators that the diminished carbon dioxide content of the blood in fever is the expression of a lowered alkalinity of the blood. This view, he believed, received support from his method of direct titration of the blood.

⁶ Kraus, F., *Ztschr. f. Heilk.*, 1889, x, 106.

METHODS.

For the purposes of a study in which it was intended that frequent analyses of the blood of patients should be made, and in which very small variations in the results would be of little or no importance, it was desirable to have a method which allowed accurate blood-gas determinations in small amounts of blood, and which was simple enough to be applicable for clinical use. The method described by Barcroft and Haldane⁷ fulfills these requirements. The apparatus and the method of using it have been described so well by its originators that nothing need be added on this point. In general it is as follows: About 1 c.c. of blood, taken under precautions to exclude contact with air, and prevented from coagulating, is put into a small glass bottle which connects with a water manometer. The blood is laked by ammonia solution. By a special device inside the bottle, potassium ferricyanide is added to the laked blood and the oxygen set free. The increase of pressure caused by the gas is measured by the manometer. After resetting the manometer, tartaric acid is added to the blood mixture and the carbon dioxide set free. From the change of pressure shown by the manometer and from the previously determined volume of the bottle and manometer, the volume of gas liberated is calculated. Corrections are made for the solutions used, for temperature and barometric pressure, and for the absorption of carbon dioxide by the fluid mixture in the bottle. The results are then reported in volumes of gas reduced to a pressure of 760 mm. and a temperature of 0° C.

In this work some of the modifications of the original apparatus as devised by Brodie⁸ were used. The "modified blood-gas apparatus" is easier to work with than the original form, and the substitution of a solution of bile salts for water in the manometer greatly simplifies the problem of keeping the manometer absolutely clean. Brodie's method for collecting, measuring, and delivering the blood was tried, but proved rather too complicated for use in connection with patients. Glass syringes provided with metal cases, of the form described by Barcroft and Haldane, were therefore used. In these syringes the blood is mixed with a known amount of 2 per cent. potassium oxalate solution and an accurately measured quantity of blood and oxalate delivered into the gas apparatus. In nearly every instance two separate samples of blood were taken. One disadvantage of this method is that it involves puncturing the skin twice, but with sharp needles the discomfort is slight. Another possible disadvantage is suggested by the experiments of Pfüger,⁹ who obtained somewhat varying results in his sets of blood-gas analyses, unless the samples of blood were taken simultaneously. He states that the difference might be as great if the second sample was taken immediately after the first as if the two samples were taken some hours apart. The blood was taken from one of the veins at the bend of the elbow. On account of the effect of stasis on the blood-gases, it was a general rule that no compression of the arm or obstruction of the circulation should be caused. In the rare cases in which it was not possible to enter the vein

⁷ Barcroft, J., and Haldane, J. S., *Jour. Physiol.*, 1902, xxviii, 232; Barcroft, J., and Morawitz, P., *Deutsch. Arch. f. klin. Med.*, 1908, xciii, 223.

⁸ Brodie, T. G., *Jour. Physiol.*, 1909-10, xxxix, 391.

⁹ Pfüger, E., *Arch. f. Anat. u. Physiol.*, 1868, i, 61.

without some distension of it, compression was made for a very short time, and released as soon as the needle was in the vein. The blood was then withdrawn slowly and only after enough time had elapsed for the circulation to readjust itself.

The application of this method of blood-gas analysis to clinical work presents some difficulties at first, but the results obtained are, for the most part, very satisfactory. The two controls usually checked accurately and almost always gave results within the necessary limits of accuracy of the experiment. Of sixty-five consecutive pairs of analyses of the carbon dioxide in the blood, twenty-four agreed within less than 1 per cent. by volume, forty-three within 2 per cent., and fifty-one within 3 per cent.

According to Loewy,¹⁰ the arterial blood of man contains between 39 and 43 per cent. of carbon dioxide at a tension of 30 to 40 mm. of mercury, while venous blood contains from 43 to 50 per cent. of carbon dioxide at a tension of 40 to 50 mm. of mercury. The figures obtained in this investigation for the normal carbon dioxide content of the venous blood are somewhat higher than those given by Loewy, but they are very constant, both in healthy individuals and in the patients after their metabolic processes had returned to normal. In general, the normal carbon dioxide of the venous blood varied between 54 and 58 per cent.

The methods used in the analysis of the urine were as follows: "Alkali retention" was determined according to the method of Henderson and Adler.¹¹ A definite quantity of urine, under standard conditions, is titrated with one-tenth normal sodium hydrate solution, using neutral red as an indicator, until it is of the same reaction as a standard solution which is made up to the reaction of blood. This titration is supposed to give an index of the amount of acid excreted by the kidney, and corresponds to the amount of base saved to the body. To this figure is added the ammonia excretion, expressed also in terms of one tenth normal solution. The sum of the two measures "the effective work of the kidney in saving basic substances for the further neutralization of acid and transport of carbonic acid." The other determinations were done by the usual methods,—total nitrogen by Kjeldahl's, ammonia by Folin's,¹² chlorine by the Volhard method,¹³ phosphorus by titration with uranium nitrate solution,¹⁴ acetone by Lieben's test, and "total acidity" by the method of Folin.¹⁵

THE CARBON DIOXIDE CONTENT OF THE VENOUS BLOOD.

Observations on the carbon dioxide content of the venous blood were made on twenty-six cases of pneumonia. Of these, eleven

¹⁰ Loewy, A., in von Koranyi, A., and Richter, P. F., *Physikalische Chemie und Medizin*, Leipzig, 1907, i, 255.

¹¹ Henderson and Adler, *Jour. Biol. Chem.*, 1909, vi, p. xxxviii; Adler, H. M., and Blake, G., *Arch. Int. Med.*, 1911, vii, 479.

¹² Folin, O., *Am. Jour. Physiol.*, 1905, xiii, 45.

¹³ Harvey, S. C., *Arch. Int. Med.*, 1910, vi, 12.

¹⁴ Neubauer-Huppert, *Analyse des Harns*, 11th edition, Wiesbaden, 1910, i, 138.

¹⁵ Folin, O., *loc. cit.*

were fatal cases. In all, ninety-one analyses were made. With the exception of two cases, which will be discussed later, the carbon dioxide was found to be regularly diminished during the febrile period. In most cases the carbon dioxide content ran from 40 to 50 per cent. in the acute stage of the disease, but not infrequently it was from 50 to 53 per cent., or only very slightly below normal. The lowest observation made was 29.01 per cent.

No definite relationship could be made out between the carbon dioxide content of the blood and either temperature, pulse, or respiration, except that the lowest values for carbon dioxide were apt to be found associated with very rapid respiration. Nor was there any clear-cut relation between the carbon dioxide and the extent of lung involved or the severity of the disease. Four cases, however, in which observations were made within two hours of death, are of considerable interest, as they show that the tendency is for the carbon dioxide content to be very low in the terminal stage of the disease. When, however, circulatory disturbances or local processes in the lungs interfere with the respiratory exchange of gases, the carbon dioxide may be relatively higher. In case XIX the chest was free from râles two hours before death, and the oxygen content of the blood was normal. Gaseous exchange in the lungs was thus apparently unaffected. The carbon dioxide content was 29.01 per cent., the lowest value found in the whole series. Case XVI was very cyanotic and had a general edema of the lungs one hour before death. An exceedingly low oxygen content of the venous blood suggests that oxygen was being imperfectly taken up in the pulmonary capillaries, and makes it probable that the excretion of carbon dioxide was similarly interfered with. In spite of this, the carbon dioxide was only 35.53 per cent. The same conditions, pulmonary edema and low oxygen content, prevailed in case XII two hours before death, and here again the carbon dioxide value was one which would be considered low, even if there were no hindrance to the excretion of carbon dioxide in the lungs. Similarly, case XXIV had, on clinical examination thirty minutes before death, marked cyanosis and many coarse tracheal râles. At this time the oxygen content of the venous blood was only 2.07 per cent., and the carbon dioxide content was

40.46 per cent. Thus the three last cases show a carbon dioxide content which is absolutely low and may be considered to be relatively very low. Beyond this, there is little association between the severity of the disease and the carbon dioxide of the blood, except that the mild cases with a short course usually showed the least marked deviations from the normal.

The relation of the carbon dioxide content of the blood to the course of the disease is somewhat variable. Unfortunately, no observations were made on the first or second days. Several cases, however, notably Nos. III, VIII, IX, and XXI, show that the carbon dioxide is, in general, nearer normal in the first days of the disease, and then gradually sinks, so that the minimum is at about the height of the disease or at the time of the crisis. After the crisis the carbon dioxide usually begins to show a rise towards normal, but occasionally very low, and even the lowest figures are found some days after the patient has become afebrile. Thus case XXI had a carbon dioxide content of 43.08 per cent. four days after the crisis, and case III one of 45.23 per cent. on the fifth day of normal temperature. Both of these patients had been taking a good amount of nourishment for several days, so that the low carbon dioxide can scarcely be referred to a starvation acidosis. These cases bring out the fact that the low carbon dioxide content of the blood may persist for a considerably longer period after the fall of temperature than was noticed by Kraus, and they show definitely that the changes in the carbon dioxide bear no direct relation to temperature itself, but are rather in line with the other metabolic changes which are associated with infection and which are sometimes more marked after the fall of temperature than during the febrile period itself. Chief among the evidences of these changes, as shown in the urine, are the high nitrogen and ammonia excretion ("epicritical excretion") and the low chloride excretion.

THE RELATION OF THE CARBON DIOXIDE CONTENT OF THE BLOOD TO
THE EXCRETION OF AMMONIA AND CHLORINE IN THE URINE.

The high excretion of ammonia and the low excretion of sodium chloride are two of the most characteristic features of the urine during fever. The diminution of the carbon dioxide in the blood

is apparently as constant an accompaniment of fever. It would be of some interest, then, to see in how far these three changes run parallel to one another. This is especially so since Hamburger¹⁶ has attempted to explain the chloride retention on the basis of a febrile acidosis.

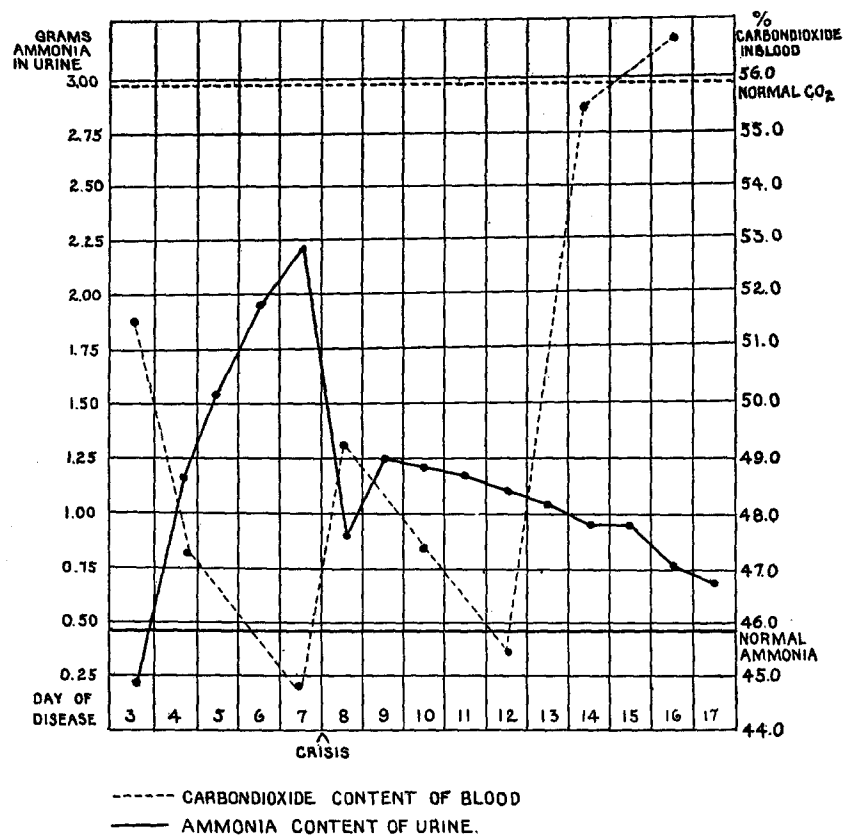
In general, of course, the excretion of ammonia and the excretion of chlorides are in inverse ratio during fever. When the ammonia excretion is high, the chlorine excretion is low. After the fever is over, the ammonia excretion falls to normal and the chlorine excretion rises to normal or above. The curves of excretion of the two substances, however, do not run strictly parallel to one another. The ammonia runs fairly well parallel to the total nitrogen excretion,—so much so that the percentage of ammonia nitrogen is usually not far from normal. Occasionally it is somewhat high during the febrile period. That the changes in chloride and in ammonia excretion do not always run strictly parallel is shown by cases III and VIII (table I), in which the chlorides began to be excreted two days after the crisis, and the ammonia only reached a normal level four or five days later. The same tendency for the ammonia metabolism to readjust itself more slowly than the chloride metabolism is seen, but less strikingly, in other cases.

Kraus¹⁷ has already shown that the carbon dioxide content of the venous blood does not necessarily rise to normal immediately after the fall of temperature. His examinations were made after one or two days of apyrexia. Moreover, we have already seen that in this series of cases the carbon dioxide may persist at a low level for a considerably longer period after the fever has gone. In case III (text-figure 1) it was as low as 45 per cent. five days after the crisis. Two days later it had risen to a normal value. The return of the carbon dioxide to normal was in this instance at just about the period at which the ammonia excretion in the urine was becoming normal. Retention of chlorine had ceased some days before. Case IV shows similarly a lack of relation between the carbon dioxide content and the chlorine excretion. The carbon dioxide was 47.1

¹⁶Hamburger, H. J., *Osmotischer Druck und Ionenlehre in ihrer Bedeutung für die Physiologie und die Pathologie des Blutes*, Berlin, 1912.

¹⁷Kraus, F., *loc. cit.*

per cent. on the eighth day after the crisis, nearly a week after chlorine retention had ceased. The ammonia excretion was irregular but only became constantly normal after this time. In case VIII the carbon dioxide was still low at the time when the chlorine was just beginning to come out.



TEXT-FIG. 1. The relation between the carbon dioxide content of the blood and the ammonia content of the urine in case III.

It is thus only in the few cases in which there is a very definite difference in the time at which the metabolism of ammonia and that of chlorine readjust themselves, that the relation of the carbon dioxide to each of them can be studied. The evidence, however, goes to show that the carbon dioxide in the blood follows much more

closely the curve of ammonia excretion than it does that of chlorine. In view of the known relation between ammonia excretion and carbon dioxide in typical acidosis (experimental acidosis, diabetic acidosis), this is, of course, what one would have expected *a priori*. Hopkins and Davis¹⁸ have brought out the interrelation of carbon dioxide and ammonia from a different point of view by showing experimentally that asphyxiation, by increasing the carbon dioxide content, causes a decrease in the ammonia content of the blood. Case XVII (table II) shows this relationship even more definitely. At a time when the carbon dioxide was 43.64 per cent. in the blood, the patient was given sodium bicarbonate in such amounts that the urine was made alkaline. In the forty-eight hours preceding his death, six specimens of urine were obtained by catheter. Examinations of the blood were made to correspond to each specimen of urine. It will be seen that the administration of alkali caused an increase in the carbonates of the blood (the carbon dioxide pressure was higher than could be read on the manometers), a change in the reaction of the urine, and a great fall in the ammonia excretion. When the sodium bicarbonate was discontinued, the carbon dioxide in the blood fell and the ammonia in the urine rose nearly to its former value. The chlorine excretion showed no rise with the administration of alkali, but rather a gradual falling off until death. The acetone reaction was very strong in all specimens and showed no relation to the carbon dioxide in the blood, the ammonia or reaction of the urine. In the alkaline specimen of urine the amount of albumen was much less than in the acid specimens.¹⁹

Case XXVI (table III, text-figure 2) shows the same condition. On the third day of the disease, control observations were made on the blood and urine. The carbon dioxide in the blood was moderately low, and the urinary ammonia only slightly high, as is typical of the first days of the infection. The patient was receiving ten grams of sodium chloride by mouth daily in addition to the salt in his food. Of this he was retaining about two-thirds. For the following two and a half days, sodium bicarbonate was given by

¹⁸ Hopkins, R., and Davis, W., *Jour. Biol. Chem.*, 1911, x, 407.

¹⁹ von Hösslin, R., *Deutsch. Arch. f. klin. Med.*, 1912, cv, 147.

TABLE II.
Case 17.

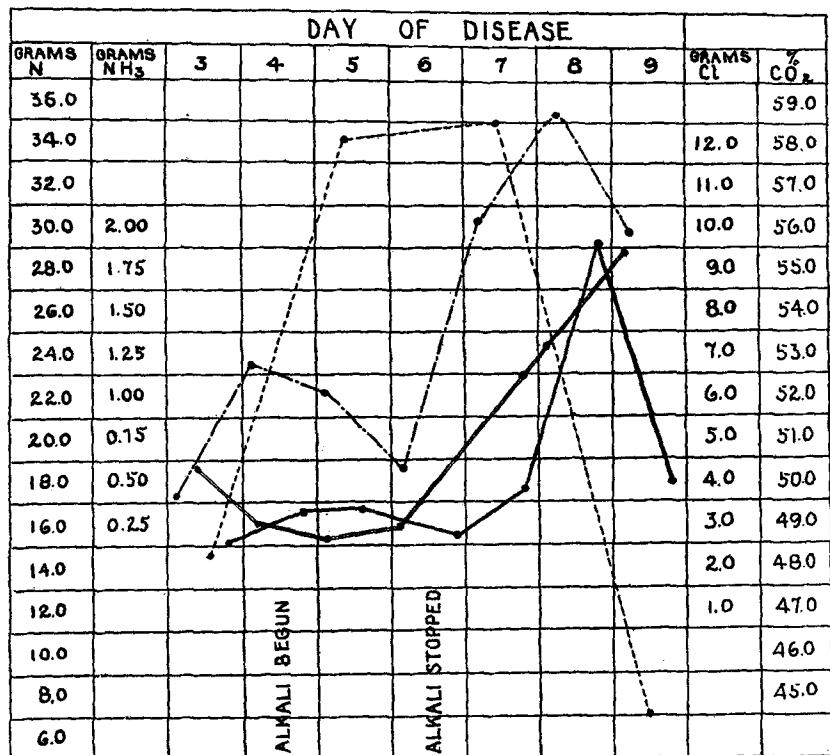
Num-ber of speci-men.	Time.	Hours.	Amount in c.c.	Reaction.	Specific gravity.	Albu-men.	Nitro-gen.	Am-monia.	Percent- age of am-monia.	Chlo-rine.	Percent- age of chlo-rine.	Acce- tone.	Time.	Carbon dioxide.
I	9:00 A. M. to 6:00 P. M.	9.0	600	Acid	1.021	++	10.36	0.280	2.7	0.42	0.070	++	10:00 A. M.	43.64
II	6:00 P. M. to 5:00 A. M.	11.0	770	Alkaline	1.020	++	7.97	0.033	0.4	0.14	0.018	++	4:30 A. M.	74 +
III	5:00 A. M. to 10:30 A. M.	5.5	640	Alkaline	1.015	++	4.97	0.005	0.1	0.16	0.025	++	9:30 A. M.	74 +
IV	10:30 A. M. to 4:30 P. M.	6.0	490	Alkaline	1.017	++	4.65	0.022	0.4	0.12	0.025	++	2:30 P. M.	62.95
V	4:30 P. M. to 10:00 P. M.	5.5	340	Slightly acid	1.016	++	4.18	0.084	2.0	0.06	0.018	++	8:45 P. M.	55.27
VI	10:00 P. M. to 9:00 A. M.	11.0	355	Acid	1.017	++	4.57	0.271	6.1	0.00	0.000	++	10:00 A. M. 1:00 P. M.	64.62 62.10

TABLE III.
Case 26.

Day of disease.	Total amount.	Reaction.	Nitro-gen.	Am-monia.	Percent- age of am-monia.	Chlo-rine.	Albu-men.	Carbon dioxide.	Remarks.
3	1,320	Acid	18.04	0.70	3.8	3.19	Very slight	48.92	Sodium bicarbonate 5 gm. every two hours, 9:00 A. M. Sodium bicarbonate 5 gm. every four hours, 8:30 P. M. Sodium bicarbonate discontinued, 11:30 P. M.
4	2,390	Alkaline	24.65	0.37	1.5	3.74	Slight	—	
5	2,555	Alkaline	22.92	0.34	1.4	3.93	Slight	58.51	
6	2,250	Alkaline	19.79	0.42	2.1	3.33	Very slight	—	
7	2,580	Alkaline	30.70	1.29	4.2	4.38	Very slight	59.15	
8	3,740	Neutral	36.50	1.45	3.9	10.20	Very slight	—	
9	2,320	Acid	30.07	1.96	6.5	4.64	Very slight	45.00	

The patient received 10 gm. of sodium chloride daily.

mouth in rather large doses. The urine became alkaline, the carbon dioxide in the blood rose, the ammonia fell to a low absolute, and a very low relative figure. In spite of a greatly increased diuresis, there was very little change in the chlorine excretion except



----- TOTAL NITROGEN IN URINE ——— AMMONIA IN URINE
 ——— CHLORINE IN URINE ----- CARBONDIOXIDE IN BLOOD

TEXT-FIG. 2. The effect of feeding sodium bicarbonate upon the carbon dioxide content of the blood and the ammonia content of the urine in case XXVI.

on the eighth day, after the administration of sodium bicarbonate had been stopped, and when the urine had become neutral once more. On this day, with much the largest total amount of urine, the chlorine rose to over ten grams. The ninth day served as a further

control. The urine was again acid, the ammonia was absolutely very high and relatively slightly high, the chlorine excretion was a little higher than before and the carbon dioxide content of the blood was once more low. In none of the specimens was there more than a faint cloud of albumen. Thus the question of chloride retention was not complicated by acute nephritis.

In these two cases, then, with great variations in the carbon dioxide content of the blood, exactly corresponding changes were found in the ammonia output in the urine. No similar interrelation was to be found between the carbon dioxide and the excretion of chlorine.

So far, then, the evidence points against the theory that the retention of sodium chloride in fever depends on the acidosis. Further evidence against such a theory is given by the conditions found in more typical varieties of acidosis. In diabetic acidosis and in experimental poisoning by mineral acids, there is not a retention of bases as there is in pneumonia, but a marked increase in the excretion of bases. The conditions, then, with regard to the excretion of bases are diametrically opposed to one another.

THE RELATION OF THE CARBON DIOXIDE CONTENT OF THE BLOOD
TO THE PHOSPHATES, THE "TOTAL ACIDITY," AND TO THE
"ALKALI RETENTION" OF THE URINE.

Phosphates.—In agreement with the usual results in fever, the excretion of phosphates was rather irregular. In general, however, the urine contained larger amounts after the temperature had fallen than in the febrile period. There is apparently no especial relation between the carbon dioxide content of the blood and the excretion of phosphates. The latter frequently rises after the crisis, quite irrespective of any change in the carbon dioxide.

"Total Acidity."—This term is applied by Folin²⁰ to the value which is obtained by titrating the urine with sodium hydrate after the addition of neutral potassium oxalate, phenolphthalein being used as an indicator. It is expressed in cubic centimeters of decinormal sodium hydrate solution. According to Folin,²¹ "the phosphates in

²⁰ Folin, O., *loc. cit.*

²¹ Folin, O., *loc. cit.*, p. 66.

clear acid urine are all monobasic, and the acidity of such urines is ordinarily greater than the acidity of all the phosphates, the excess being due to free organic acids." The acidimetric value of the free organic acids is thus obtained by subtracting the acidimetric value of the phosphates from the "total acidity." "If the acidity calculated from the total phosphates is greater than the titrated acidity, then there are practically no free organic acids present, and the titrated acidity represents the amount of phosphates present in the diacid form."²² Magnus-Alsleben²³ used this method in the examination of the urine of children with scarlet fever, and found a considerable increase in the organic acids during the febrile period. After the temperature became normal, the phosphate acidity usually exceeded the "total acidity." The children were on a milk and vegetable diet. He believes that the method gives a simple means of obtaining a numerical value for the abnormal excretion of acids during fever.

Pick²⁴ has described a similar condition in the urine of pneumonia. In forty-two out of fifty-four cases there was a change in the reaction of the strongly acid urine, so that in thirty-six to forty-eight hours after the crisis it became less acid, amphoteric, or alkaline to litmus. This was associated with a drop in the proportion of monobasic phosphates as calculated by him. A simultaneous rise in the excretion of dibasic phosphates occurred, and this he considered to be associated with an increased excretion of bases which had presumably been absorbed from the pulmonary exudate. The importance of the rôle of the exudate is, however, somewhat lessened by the fact that the same condition may be found in scarlet fever.

In the present series of cases the results of Magnus-Alsleben are to a considerable extent confirmed. Values representing a rather high excretion of organic acids were practically constant during the febrile period. In several cases (Nos. II, III, and VII) after the fall of temperature, the urine contained no organic acids and the acidimetric value of the phosphates exceeded the "total acidity."

²² Folin, O., *loc. cit.*, p. 55.

²³ Magnus-Alsleben, E., *Ztschr. f. klin. Med.*, 1911, lxxiii, 428.

²⁴ Pick, F., *Deutsch. Arch. f. klin. Med.*, 1900, lxxviii, 13.

In other cases, however (Nos. V, VI, and VIII), the excretion of organic acids was apparently as great after the fall of temperature as during the fever. No parallelism could be found between either the "total acidity" or the excretion of organic acids, as determined by this method, and the carbon dioxide content of the blood.

"*Alkali Retention.*"—The method of determining "alkali retention" has been discussed above. The result is supposed to give a more accurate index of the degree of acidosis present than does the determination of ammonia alone. In the present cases of pneumonia the values which represent "retained bases," and which were obtained directly by titration of the urine to the reaction of blood, were variable and not particularly suggestive. The results obtained for "alkali retention" were, in general, somewhat higher during the fever than after it, but the variation is chiefly due to the ammonia excretion. The relation of the "alkali retention" to the carbon dioxide content of the blood is less definite than is that of the ammonia alone.

ATYPICAL CASES.

It has been stated that two cases (Nos. II and V) were atypical in that the carbon dioxide content of the blood was normal or above normal during the febrile period. One of these (No. V) was a case of influenzal pneumonia with involvement of the right lower lobe, and the other a case of pneumococcus pneumonia with solidification of the left lower lobe. The first observation on the carbon dioxide of each case was slightly below normal, but all subsequent observations were normal or above normal. Both were fairly severe cases. The urinary analyses gave results which do not differ from those in ordinary cases of pneumonia,—a moderately high ammonia output, and a marked or moderate retention of chlorides. The diet was essentially the same as in the other cases, and contained nothing which would raise the carbonates in the blood. The cause of this unusually high carbon dioxide is suggested by the analyses of the oxygen content of the blood made at the same time. In uncomplicated cases of pneumonia the diminished respiratory surface is compensated for, and the amount of oxygen in the venous blood re-

mains fairly well within the normal limits of 11 to 12 per cent. In no other uncomplicated cases were oxygen values found which were nearly as low as in these two cases. Both cases, moreover, showed clinically a cyanosis which was more extreme than was seen in any of the other cases. Cyanosis, a low content of oxygen, and a high content of carbon dioxide, suggest, of course, an interference with the respiratory gas exchange, an incomplete absorption of oxygen and an incomplete excretion of carbon dioxide. In case II, at the first observation, the oxygen content of the blood was normal and the carbon dioxide was, as one would expect, low. On the following days, when the oxygen was low, the carbon dioxide had risen markedly, and only when the oxygen rose again to normal did the carbon dioxide fall. Practically the same association of low oxygen and high carbon dioxide is seen in case V.

Such an imperfect aeration of the blood might conceivably depend on an incomplete compensation for the diminution of respiratory surface caused by the pneumonic exudate, although it is scarcely possible that the throwing out of one lobe should produce so profound a change. According to Loewy and von Schrötter,²⁵ the occlusion of the main bronchus to one lung, without change in rate of respiration or circulation, would only lower the oxygen content of the venous blood to 8 per cent. Moreover, in case V the low oxygen and high carbon dioxide persisted for some time after the chest was perfectly clear. That the low oxygen was due to an inability of the blood to take up oxygen normally was disproved in case V at least by finding, on three occasions, that the combining power of the blood for oxygen was normal. That the time of the reaction might be slowed, however, cannot be excluded. In neither case was there any reason to believe that improper aeration depended on too shallow respiration. In case V the pulse rate was not rapid, but in case II it was about what one would expect with the amount of fever present. An unusual slowing of the rate of circulation would increase the amount of oxygen given off in the capillaries, and also the amount of carbon dioxide taken up, and thus account for the changes found in the venous blood. Wolff²⁶ has

²⁵ Loewy, H., and von Schrötter, H., *Ztschr. f. exper. Path. u. Therap.*, 1905, i, 197.

²⁶ Wolff, E., *Arch. f. exper. Path. u. Pharmakol.*, 1885, xix, 265.

shown that in rabbits the circulation in fever is actually slower than normally. More recently Hewlett²⁷ has concluded from studies on man that "the flow is exceptionally slow when the temperature rises during fever and is moderately accelerated when the temperature falls during fever." If this be so, then in the great majority of cases of pneumonia, the slowing of the circulation, as well as the diminished respiratory surface, must be compensated for by changes in respiration. From the facts at hand, however, it would be impossible to determine whether the unusual condition of the blood in these cases is due to a slowing of the circulation or to an interference with respiratory exchange of gases due, possibly, to some local change in the lungs, as of the capillary walls or the alveolar cells, or to the effect of a change in the chemical constitution of blood cells or of serum. Kraus found that the carbon dioxide content of the blood was considerably higher in pneumonia than in other acute fevers, and he explained this by the pulmonary involvement which complicates the conditions in pneumonia. According to him, the local conditions interfere with the ready excretion of carbon dioxide. In the presence of a normal oxygen content, as is found in most cases, this would be difficult to prove, but the explanation seems worth considering in these atypical cases.

CONCLUSIONS.

A diminution in the carbon dioxide content of the blood is a constant feature in pneumonia. Occasional cases, however, may fail to show low carbon dioxide.

The carbon dioxide in the blood bears little definite relation to the severity of the disease, except that it tends to be lowest in severe cases and in the terminal stages of the disease. There is less deviation from the normal in short or mild cases.

The diminution in the carbon dioxide in the blood bears no immediate relation to temperature, as it may persist for some days after the patient is afebrile. The diminution in carbon dioxide corresponds to the other evidences of metabolic changes in infection and, like them, may be even greater after than during the febrile period.

²⁷ Hewlett, A. W., *Heart*, 1910-11, ii, 230.

The changes in the carbon dioxide content of the blood run parallel to the output of ammonia in the urine. The carbon dioxide appears to bear no relation to chlorine excretion.

In two unusual cases the carbon dioxide content of the blood was normal or above normal. This was associated with a very low oxygen content of the venous blood.