CLINICAL STUDIES ON THE RESPIRATION

II. THE ACIDOSIS OF CHRONIC NEPHRITIS *

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Since it has been established that under normal conditions the respiratory center is controlled by the reaction of the blood, and that any increase in blood acidity raises the pulmonary ventilation, the clinical conditions associated with acidosis have assumed a new significance. This is especially true of chronic nephritis, a disease in which dyspnea is not infrequently one of the most disturbing symptoms. Lewis and his associates,¹ and Peabody,² have already discussed the association of acidosis and dyspnea in the group of clinical cases which is often classified under the term "cardiorenal disease," but the relation between the two is as yet by no means absolutely clear. In order to get more light on the subject it seemed to be of fundamental importance to obtain rather detailed information as to the mechanism which causes the acidosis, the period at which it begins to develop, the degree to which it attains, and in general the relation which acidosis bears to the clinical course of chronic nephritis.

A considerable body of evidence has already been accumulated to show that acidosis, of a more or less high degree, is apparently a constant accompaniment of uremia. Much, indeed, has been written regarding the possible etiologic relationship between the two conditions. Following the first description of acidosis in uremia by von Jaksch³ who based his work on the titration of blood, there have been published a large number of observations on the carbon dioxid tension of the alveolar air by Straub and Schlayer;⁴ Porges and Leimdorfer,⁵ Poulton and Ryffel,⁶ and Peabody,² as well as more limited series of observations on the hydrogen-ion concentration of the blood by Kreiblich,⁷ Rolly⁸ and Peabody.² The result of all these studies has been,

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1. Lewis, Ryffel, Wolf, Cotton and Barcroft: *Heart*, 1913, v, 45; Lewis and Barcroft: *Quart. Jour. Med.*, 1915, viii, 97.

2. Peabody, F. W.: *Studies on Acidosis and Dyspnea in Renal and Cardiac Disease*, *THE ARCHIVES INT. MED.*, 1914, xiv, 236.

3. Von Jaksch: *Ztschr. f. klin. Med.*, 1888, xiii, 350.

4. Straub and Schlayer: *München. med. Wchnschr.*, 1912, lix, 569.

5. Porges and Leimdorfer: *Ztschr. f. klin. Med.*, 1913, lxxvii, 464.

6. Poulton and Ryffel: *Proc. Physiol. Soc.*, June 28, 1913, *Jour. Physiol.*, 1913, xlv, 47.

7. Kreiblich: *Wien. klin. Wchnschr.*, 1911, xxiv, 1419.

8. Rolly: *München. med. Wchnschr.*, 1912, lix, 1201.

in general, to show that uremia, at least in its advanced stages, is very frequently, if not always, associated with an acidosis which is sufficiently marked to alter the normal composition of the blood, and to produce a lowering of the carbon dioxide tension. In cases of chronic nephritis without uremia, on the other hand, these investigations of the blood and alveolar air showed little evidence of an acidosis. The whole subject has been approached from a much more fundamental aspect by Sellards,⁹ and in a most important series of investigations in which the so-called "alkali tolerance" test was used, he not only describes the acidosis of uremia, but demonstrates beyond doubt the fact that acidosis "is present in an appreciable degree in ordinary grades of nephritis." He shows, furthermore, that the acidosis depends on a retention which is due to imperfect excretion by the kidneys, since the extent of acidosis is roughly parallel to the signs of renal suppression. Palmer¹⁰ has also brought forward evidence of the early interference with the excretion of acids in chronic nephritis.

The question of acidosis may be studied from several points of view. Thus, in ordinary clinical work, the examination of the urine is usually regarded as giving all the information that is necessary. Qualitative tests for abnormal acids, such as the acetone bodies, and determinations of the ammonia excretion are the methods most generally in use. The results of these urinary tests are, however, not infrequently far from satisfactory, for they give information only as to the amount of acid that is being excreted by the organism, and leave one wholly in the dark as to the actual conditions existing in the blood and tissues. That the examination of the urine shall have any great diagnostic significance presupposes the fact that the increased acids are being excreted, while it is the failure to excrete acids—whether formed in normal or abnormal amounts—that forms the danger of acidosis. In chronic nephritis, in which interference with the renal function is the most essential element, the usual methods of studying the urine would, of course, be wholly unreliable for giving an index of the formation or retention of acids in the body. Much more significant information can be obtained from the blood. In spite of the large amount of acid that passes into the blood as a result of the ingestion of food and of the processes of metabolism, the normal reaction of the blood remains constant. This preservation of its normal reaction is upheld by the excretion of acids through lungs and kidneys, as well as by the chemical composition of the blood. The latter is peculiarly well adapted to the taking up of a maximum of acid with a minimum change of reaction. When, however, there is a great

9. Sellards: *Bull. John's Hopkins Hosp.*, 1912, xxiii, 289; *ibid.*, 1914, xxv, 141.

10. Palmer: *Med. Communicat., Massachusetts Med. Soc.*, 1913, xxiv, 133.

abnormal increase in the formation of acids, or when the acids are not properly excreted by the kidneys, so that large amounts accumulate in the blood, the blood will necessarily become more acid in reaction. Such a rise in acidity will stimulate the respiration, the carbon dioxid tension of the blood will be reduced and the normal reaction of the blood will be maintained. Thus a diminution of the carbon dioxid tension of the blood, or, what is the same thing, a diminution of the carbon dioxid tension of the alveolar air, will be an index of the increase of the nonvolatile acids in the blood. Such an index will be of infinitely greater value as a guide to the condition within the body at any given time than can be obtained from the urine, and is of primary significance when one is considering the subject from the point of view of the control of respiration. Of more fundamental importance would be a means of studying acidosis in the cells or tissues, for it is the preservation of the normal reaction of the cells that is really essential to the organism. Enzyme activities, and in all probability the majority of metabolic processes, proceed best at certain definite reactions, and many can only take place within certain narrow limits of reaction. Unfortunately, methods have not yet been devised which allow us to gain much insight into the obscure field of cellular metabolism, and the problem of tissue acidosis can only be approached indirectly. Probably the most delicate index of acidosis is obtained by the use of the so-called "alkali tolerance" test, first described and studied by Sellards,⁹ but simultaneously worked out by Palmer.¹⁰ In a normal individual the ingestion of 5, or at most 10 grams of sodium bicarbonate suffices to change the reaction of the urine from acid to alkaline, but if there is any acidosis, either from excessive formation or from simple retention of acid, a much larger amount of alkali is required. It seems probable that during the gradual development of an acidosis the organism draws on the reserve supply of base in the tissues to neutralize the acids, and when, subsequently, an excess of base is provided, as by giving sodium bicarbonate, it is used to replenish the exhausted stores in the tissue before it is allowed to pass out in the urine. A comparison of various methods for detecting acidosis shows that the amount of sodium bicarbonate which is needed to change the reaction of the urine is a delicate index of the extent of the acidosis. Moreover, in spite of its simplicity, it gives perhaps the earliest evidence of the development of an acidosis, for it apparently tells when even a small inroad on the reserve supply of bases in the tissues has been made. The "alkali tolerance" test may thus be quite safely considered as a general, rough guide to the degree of acidosis in the tissues. Only at a later period, when a considerable amount of acid has been accumulated in the tissues and in the blood,

does the composition of the blood change so that the alveolar carbon dioxid tension begins to fall. It is of course this latter point—the time at which a shift in hydrogen ion concentration of the blood stimulates the respiratory center and causes an increase of pulmonary ventilation with a consequent lowering of alveolar carbon dioxid tension, that is of special significance from the point of view of studies of the respiration.

In the series of cases of chronic nephritis reported on in the present paper an attempt has been made to correlate what may be considered as two stages in the development of the acidosis, with the course of the disease as indicated by renal function tests. The “alkali tolerance” test has been applied to find the earliest indication of acidosis, and the carbon dioxid tension of the alveolar air has been determined to show when the acidosis has begun to affect the balance between volatile and nonvolatile acids in the blood. The usual method for the “alkali tolerance” test has been to give 5 grams of sodium bicarbonate by mouth every two hours until the urine becomes alkaline to litmus paper. This rather rough method has given results that are in general wholly satisfactory. The high normal limit is taken as 10 grams of sodium bicarbonate. In most normal persons the urine becomes alkaline after 5 grams. The carbon dioxid tension of the alveolar air was determined by the Plesch-Higgins¹¹ method, which has been extensively used in this laboratory, and has proved itself most satisfactory for clinical work. As an indication of the severity of the nephritis the functional capacity of the kidneys was studied by the phenolsulphonephthalein test, and in some instances, by the determination of nitrogen retention. Dr. J. P. O'Hare has been kind enough to give me his figures for the total nonprotein nitrogen, or for the urea nitrogen of the blood in the cases which were studied by him in another connection.

Since cardiac insufficiency may of itself cause an acidosis, it is of importance from the present point of view that the cases of nephritis to be studied should be as free as possible from any involvement of the heart. Ideal cases are, of course, very difficult to find, as so large a proportion of all cases of chronic nephritis are associated with cardiac hypertrophy, and, in the later stages at least, with evidences of cardiac weakness. By careful selection, however, a group of cases has been accumulated in which the cardiac element could be fairly safely ruled out. Many gave in their histories symptoms suggesting myocardial weakness, such as dyspnea on exertion, and others had passed through periods of more or less definite cardiac decompensation, but when they were investigated for the present purpose the cir-

11. Boothby, Walter M., and Peabody, F. W.: A Comparison of Methods of Obtaining Alveolar Air, *THE ARCHIVES INT. MED.*, 1914, xiii, 497.

culatory element was absent, or, in a few instances, wholly secondary in importance.

The cases fall naturally into three groups. The first (Table 1) consists of patients in whom there was evidence of a definite, but not particularly severe nephritis. The diagnosis was based on the urinary findings and usually on an associated hypertension and cardiac hypertrophy. In all of these cases the phenolsulphonephthalein output, and the determinations of blood urea, with one exception, indicate that the action of the kidneys was functionally sufficient. The alkali tolerance test was normal in every case in which it was tried, and the carbon dioxide content of the alveolar air was found to be normal. Thus, in this series of patients with comparatively mild chronic nephritis, no evidence of acidosis was found.

TABLE 1.—CASES SHOWING NORMAL PHTHALEIN OUTPUT AND NORMAL ALVEOLAR CARBON DIOXID TENSION

Case No.	Hospital No.	Blood Pressure mm. Hg.	Phthalein Output in Two Hrs. Per Cent.	Urea Nitrogen in Blood mg.	Alkali Tolerance Gm. NaHCO ₃	Alveolar Carbon Dioxid Tension mm.
1	2552	110	58		10	50.3
2	2324	90	52	9.25	10	42.3
3	2548	140	65	9.4	10	43.5
4	M'D.	178	63		10	49.9
5	2077	210	50	22.5	10	43.4
6	17319	220	55		5	
7	428	195	70		..	44.1
8	2081	160	52		..	40.0 *
9	426	100	55		..	42.7
10	2237	160	60	12.3	10	

* Cardiorenal compensated.

Table 2 consists of a group of rather more severe cases. The phenolsulphonephthalein test and the nitrogen retention determinations show that in all of them the functional capacity of the kidneys was below normal. The degree to which renal efficiency was impaired varied considerably, being slight in some instances, but great in others. The alveolar carbon dioxide determinations were always normal, indicating that there was no great accumulation of nonvolatile acid in the blood. "Alkali tolerance" tests were done in only five cases, but in all of these there was an increase above normal in the amount of sodium bicarbonate required to make the urine alkaline in reaction. One patient became nauseated after taking 50 grams, and it was not possible to complete the test. It is worth noting that the increase in "alkali tolerance" runs exactly parallel to the decrease in phenolsul-

phonephthalein elimination. Thus in this group of patients with chronic nephritis of higher grade, and with kidneys which are more or less inefficient functionally, the "alkali tolerance" test shows that there may be a loss of base to the body, an early stage in the develop-

TABLE 2.—CASES SHOWING LOW PHTHALEIN OUTPUT AND NORMAL ALVEOLAR CARBON DIOXID TENSION

Case No.	Hospital No.	Blood Pressure mm. Hg.	Phthalein Output in Two Hrs. Per Cent.	Nonprot. Nitrogen in Blood mg.	Alkali Tolerance Gm. NaHCO ₃	Alveolar Carbon Dioxid Tension mm.
1	2611	195	23	25 *	25	43.6
2	2429	160	39	18.75 *	15	40.3
3	2124	250	36	33.13 *	..	45.1
4	621	280	Traces	90	..	40.3
5	2111	180	10	55.5	50 +	42.8
6	477	200	35		..	41.4
7	2202	245	18	71.9	..	41.9
8	762	192	25	50.0	..	40.2
9	590	145	29		..	42.7
10	2762	260	28	32.5 *	35	41.6
11	655	230	0	279.0	..	41.3
12	2739	200	12	42.7 *	20	41.4

* Urea nitrogen.

TABLE 3.—CASES SHOWING LOW PHTHALEIN OUTPUT AND LOW CARBON DIOXID TENSION

Case No.	Hospital No.	Blood Pressure mm. Hg.	Phthalein Output in Two Hrs. Per Cent.	Nonprot. Nitrogen in Blood mg.	Alkali Tolerance Gm. NaHCO ₃	Alveolar Carbon Dioxid Tension mm.
1	2564	240	Trace	101.5 *	80	31.1
2	2567	195	Trace	57.5 *	55	35.8
3	2006	200	Trace	90.9	50 +	19.1
4	2111	180	6	55.6 *+	50 +	35.8
5	673	205	0	200.0	..	33.8
6	2108	160	15	55.5	80	33.7
7	573	230	0	90.5	..	31.7
8	132	170	0		..	6.0
9	2730	168	27	48.0 *	50	35.3

* Urea nitrogen.

ment of acidosis, but the alveolar air determinations are normal and do not suggest that the nonvolatile acids are increased in the blood.

The nine patients in the third group (Table 3) had very advanced chronic nephritis. Six of them died within a few days or weeks of

the time when these observations were made, and the three who were discharged from hospital were given a bad prognosis. The phenolsulphonophthalein test, and the nitrogen retention figures both indicate that the functional efficiency of the kidneys was extremely low. Even in the two instances showing an output of 27 and 15 per cent. of phenolsulphonophthalein, the high values for the nonprotein nitrogen and for the urea nitrogen in the blood are evidence of severe nephritis. "Alkali tolerance" tests in six cases show a marked acidosis, the figures being on the whole considerably higher than in the previous group of less severe cases. The alveolar carbon dioxid tension was below normal in every case, and in two instances reached extremely low values. There is, however, no strict parallelism between the clinical condition and the fall in carbon dioxid tension, for while the lowest figures occurred during the days just before death, a tension of 33.8 mm. was found in one patient who died in uremia within twenty-four hours. In most of these cases the carbon dioxid tension has been low when the patient entered the hospital, but occasionally it has been possible to follow the development of the acidosis in its relation to the course of the disease. Thus in Case 2111 the patient was in fairly good condition when he came into the hospital. The phenolsulphonophthalein output was 10 per cent. in two hours, the nonprotein nitrogen in the blood 55.5 mg., and the alveolar carbon dioxid tension was 42.8 mm. Two weeks later his "alkali tolerance" was tested and found to be 50 grams $\pm$. One month after admission the clinical picture had changed and the patient was going down hill rapidly. The phenolsulphonophthalein output was 6 per cent. and the alveolar carbon dioxid tension was only 35.8 mm. In two days more it had dropped to 33.4 mm., and in five days he died. In this group of patients, then, with very advanced chronic nephritis, and with kidneys whose functional capacity is greatly reduced, there is evidence of a marked acidosis, involving not only a loss of base from the tissues, but the accumulation of considerable amounts of nonvolatile acid in the blood.

The facts which have been brought out here all bear out the theory that the acidosis of renal disease is due to retention. This is in accordance with the views held by Sellards¹² and with the opinions of Porges and Leimdorfer¹³ regarding the cause of the acidosis of uremia. Apparently, so long as the functional capacity of the kidney is unimpaired, or is so slightly decreased that there is no demonstrable retention of phenolsulphonophthalein or of nonprotein nitrogen, there are no signs of acidosis. As soon as there begins to be any retention, it

12. Sellards: *Bull. Johns Hopkins Hosp.*, 1914, xxv, 141.

13. Porges and Leimdorfer: *Ztschr. f. klin. Med.*, 1913, lxxvii, 464.

is frequently found that an acidosis is developing. Sellards¹⁴ says that "in all cases in which the tolerance to bicarbonate is markedly increased, the phenolsulphonephthalein output is very low. On the other hand the excretion of bicarbonate is practically normal in some of these cases in which the phenolsulphonephthalein test shows a functional insufficiency."

An interference with the excretion of acids runs roughly parallel to the interference with the excretion of phenolsulphonephthalein, and the retained acids draw on the reserve supply of base in the body. These reserves suffice to protect the body from the development of a serious grade of acidosis for a long time, for it is only when excretion is very markedly limited that this protective mechanism fails and acids begin to accumulate in the blood. If large amounts of base are supplied to the body, even after a severe acidosis has developed, the alveolar carbon dioxid will rise, and conditions will become normal again. It may then be quite a long time before this new reserve is used up and before the carbon dioxid tension begins to fall again. The situation is very different in severe diabetic acidosis in which abnormally large amounts of acids are being formed, and correspondingly large amounts of base are required. In chronic nephritis the formation of acids is probably not increased, but the body gradually goes into bankruptcy, as they are not excreted, and the organism loses the advantage of the mechanism by which the kidney excretes acid and retains base for further use. There is, of course, the possibility that the amount of acid substances formed in chronic nephritis is somewhat more than the normal. Mosenthal's work¹⁵ showing a specific increase of protein metabolism, bears on this subject. This, however, would not be a large factor, and in general, the acidosis of chronic nephritis may be considered as being due to the retention of the normal acid products of metabolism.

Having shown that during the later stages of chronic nephritis a sufficient grade of acidosis may develop to cause a depression of the carbon dioxid tension of the alveolar air, it is now of importance to consider in more detail how great the acidosis actually is, and what relation it bears to uremia. In most cases the acidosis does not seem to be particularly great. The alveolar carbon dioxid tension usually runs from 25 to 35 mm. during the days in which uremia is developing and even after coma has set in. The significance of these figures may perhaps be best understood by comparing them with the results found

14. Sellards: Bull. Johns Hopkins Hosp., 1912, xxiii, 289.

15. Mosenthal, H. O.: Nitrogen Metabolism and the Significance of the Non-Protein Nitrogen of the Blood in Experimental Uranium Nephritis, THE ARCHIVES INT. MED., 1914, xiv, 844.

in diabetes, in which it has been quite definitely established that while a tension of 30 to 20 mm. indicates a serious acidosis, the condition is usually not critical until it drops below 20 mm. During diabetic coma the carbon dioxid tension is apt to be about 10 mm. or less. This comparison of the alveolar air in diabetes with that in nephritis suggests, of course, that in many cases of uremia acidosis plays a very subordinate part. There is, however, a well-defined group of cases of advanced chronic nephritis in which the whole clinical picture simulates closely that of diabetic acidosis. These patients are at first somnolent, and then pass into a deep sleep or coma. The respiration becomes deeper, and when the case is fully developed, there is typical "air hunger." Acetone and diacetic acid are present in only small amounts in the urine, or they may be absent. In this group of cases the onset of severe, terminal, uremic symptoms is associated with a fall of the carbon dioxid tension to values as low as are found in diabetic coma. In one instance the tension was 4.59 mm. during coma. Another was of unusual interest in the response shown to alkali therapy. The patient was a woman, 45 years old, with a history of nephritis extending over several years. Her blood pressure was about 200 mm. and the nonprotein nitrogen in her blood had risen to 90 mg. per 100 c.c. of blood. For over a month the phenolsulphone-phthalein test had shown practically no elimination of the dye in her urine. Her general condition, however, remained rather remarkably good, and except for headaches there was no evidence of uremia until January 11. On this day she first began to complain of being short of breath. The alveolar carbon dioxid tension was 19.1 mm. Two days later, on January 13, she was unconscious and her respiration was slow but so deep as to be quite typical of "air hunger." The alveolar air was not taken at this time, but 300 c.c. of 4.7 per cent. sodium bicarbonate solution were given intravenously. On the following morning the carbon dioxid tension was 23.4 mm. This indicated a marked acidosis, and as the "air hunger" persisted, a further intravenous injection of 700 c.c. was given later in the day. On the following morning the clinical picture had entirely changed. The patient was conscious and recognized every one, but she was greatly nauseated and still looked very sick. The "air hunger" had disappeared and the respiration was of the shallow, slow, and irregular type with rather prolonged periods of apnea such as is commonly seen in advanced nephritis. The alveolar carbon dioxid tension had risen to the normal value of 41.5 mm. On the next morning it had fallen to 36.9 mm. Respiration was slightly deeper, with occasional sighing respirations, but it did not suggest "air hunger." She was conscious and responded fairly well to questions but was very dull. An attempt was

made to ward off the further development of acidosis by giving 375 c.c. of 5 per cent. sodium bicarbonate intravenously, but it was unsuccessful, for on the next day the alveolar carbon dioxid tension had dropped to 25.1 mm., her respiration was deeper and more rapid, and she was becoming unconscious. On January 17 she was comatose, and had begun to have convulsions. Another intravenous alkali injection was without effect and the patient died January 18. Sellards has described similar cases of uremia in which "air hunger" was a prominent symptom, and indeed the clinical picture is one that is generally recognized.

The investigations described here agree well with those of other observers, and make the relation between acidosis and uremia quite clear. It seems certain that some degree of acidosis is present in all cases of uremia. Usually it is marked enough to cause a lowering of the alveolar carbon dioxid tension, but often it is not of high enough grade to be of itself an important element in the symptomatology of the case. In a limited number of cases the onset of severe uremia is associated with the development of an acidosis which is extensive enough to produce coma and "air hunger" and which may dominate the clinical picture.

The therapeutic results obtained by the administration of alkali in uremia confirm this point of view. In the case just described the sodium bicarbonate was undoubtedly beneficial in its action, for it relieved dyspnea and restored consciousness. The improvement was only temporary, however, for acidosis is certainly only one factor in uremia, and the patient was necessarily doomed to succumb to the other results of renal suppression. Similar and even better results are reported by Sellards after the administration of alkali in this type of case. The evidence is thus good that in the group of uremic patients with signs of marked acidosis, alkali therapy is indicated, and may produce great temporary improvement. In the group of cases in which the acidosis only produces a slight fall in the alveolar carbon dioxid tension, and in which there are no symptoms directly due to the acidosis, the results obtained by giving alkali are much more questionable. The fact that the body has lost part of its reserve supply of base, and that it is on the edge of a severe acidosis makes the administration of alkali a logical indication. The effect is hard to determine, as there are so few definite symptoms to go by.

The respiration in advanced cases of chronic nephritis is not typical of acidosis even when there is a slight depression of the carbon dioxid tension. As in diabetes, the evidences of "air hunger" usually begin to appear only when the carbon dioxid tension drops below 20 or at most 25 mm. Most cases of advanced nephritis have an irregular, shallow,

periodic type of respiration, with a tendency to the development of Cheyne-Stokes respiration particularly when they begin to sleep. The irregularity or periodicity of the breathing is frequently not very evident on casual examination, but it comes out as soon as pneumographic tracings are taken. At night, with the general depression of nervous excitability, the periodicity becomes more marked, and in many instances the distressing attacks of nocturnal dyspnea are due to Cheyne-Stokes respiration. Even when the periods of apnea and dyspnea are not definitely demarcated, a pneumographic tracing may show that a period of very shallow breathing, followed by a short interval of apnea, precedes the dyspneic attack which arouses the patient from his sleep to severe physical and mental distress. This periodic type of respiration is not a result of acidosis, for, in a number of cases, pneumographic records have shown that it exists after enough alkali has been given to bring the alveolar air back to its normal value, in exactly the same way that it did before the acidosis was overcome. It was also interesting to notice in the case of nephritis with acidosis described above, that when enough alkali had been given to raise the carbon dioxid tension and overcome the "air hunger," the respiration became shallow and irregular, just as it is in most advanced cases of chronic nephritis. It was thus possible to separate the type of respiration characteristic of nephritis itself from that which depended on the acidosis occurring during the nephritis. On the other hand, some patients with milder acidosis seem to be distinctly more comfortable and to have much better nights after they have received alkali. Inasmuch as patients with acidosis are rendered dyspneic more easily than are normal persons by the inspiration of carbon dioxid,¹⁶ and are thus apparently peculiarly susceptible to dyspnea, it would seem wholly likely that overcoming the acidosis in patients with advanced nephritis might increase their comfort by diminishing the tendency to dyspnea.

When chronic nephritis is associated with cardiac weakness the question of acidosis becomes much more complicated, as a new element is added. There is not only the acidosis of nephritis, due to inefficient renal excretion, but there may also be an accumulation of acid metabolic products which are the result of an inadequacy of the supply of oxygen reaching the tissues. Such patients may show a lowering of the alveolar carbon dioxid tension when they are first seen, and while their hearts are more or less decompensated. If, however, the kidneys are not too badly involved, the acidosis will disappear shortly. As the circulation becomes compensated, the production of acids due to circulatory insufficiency will cease, oxidations will go on normally, and the kidneys will excrete the accumulated acids. Since the reserve supply

16. Peabody: *THE ARCHIVES INT. MED.*, this issue, p. 955.

of base may be decreased in patients with chronic nephritis, so that they are constantly nearer than normal to the development of an acidosis, it is quite probable that a degree of cardiac insufficiency which will produce dyspnea in them would not affect a person who could neutralize and excrete acids normally.

CONCLUSIONS

In mild cases of uncomplicated chronic nephritis, in which the phenolsulphonephthalein test shows a normal renal function, there is usually little or no acidosis.

More advanced cases, showing moderate or even extreme decrease in the phenolsulphonephthalein output, show an acidosis by the "alkali tolerance" test, but there may be no fall in the alveolar carbon dioxide tension.

Only in very advanced cases is the acidosis usually so marked as to cause a decrease in the alveolar carbon dioxide tension. Most cases in which the alveolar carbon dioxide tension is below normal show a phenolsulphonephthalein output which is below 10 per cent. in two hours. On the other hand cases showing a phenolsulphonephthalein output of "traces" or less may have a normal alveolar carbon dioxide tension.

The acidosis of chronic nephritis is due to a retention, resulting from inefficient renal excretion.

Acidosis is probably a very constant feature of uremia, but only in a limited number of cases is it of sufficient grade to cause definite clinical symptoms analogous to those seen in advanced diabetes. In these cases the symptoms caused by the acidosis may be relieved by alkali therapy.