

STUDIES ON ACIDOSIS AND DYSPNEA IN RENAL AND CARDIAC DISEASE *

FRANCIS W. PEABODY

BOSTON

The present study was undertaken to obtain information concerning the cause of dyspnea in cardiac disease, with especial reference to the possibility of changes in the nature of the stimulus to respiration. Recent progress in our knowledge of the physiology of respiration and of its exciting stimulus, together with the development of certain physiological and chemical methods, have opened new pathways for the study of pathologic conditions.

The pioneer work of Haldane and Priestley seemed to establish the fact that the exciting stimulus to the respiratory center is the carbon dioxid content of the blood. This conception, however, has been broadened by such subsequent investigators as Winterstein¹ and Hasselbalch,² who have shown that the essential stimulus is the hydrogen-ion concentration of the blood. The variations in the carbon dioxid content of the blood, and consequently of the alveolar air, are but the result of the attempt on the part of the organism to keep the hydrogen-ion concentration of the blood at a constant value. The carbon dioxid in the blood rises as the amount of non-volatile acid falls, and the carbon dioxid falls as the production of other acids rises. L. J. Henderson³ has been chiefly instrumental in showing the enormous biological importance of the constancy of the reaction of blood and other body-fluids, and in explaining the mechanism by which this constancy is maintained. In the living organism large amounts of the acid products of metabolism are continually being poured into the blood, but the constancy of the reaction of the blood is normally maintained, in part by the regulatory mechanism of certain remarkably adapted chemical equilibria (sodium carbonate—sodium bicarbonate, monosodium phosphate—disodium phosphate and the proteins) which allow the maximum amount of acid to be added with the minimum change in the reaction of the system, and in part by the process of elimination. The rôle played by the kidney has been especially studied by Henderson,⁴ who has called attention to the remarkable specific

* Submitted for publication, March 13, 1914.

* From the Medical Clinic of the Peter Bent Brigham Hospital.

1. Winterstein: Arch. f. d. ges. Physiol., 1911, cxxxviii, 167.

2. Hasselbalch: Biochem. Ztschr., 1912, xlv, 403.

3. Henderson, L. J.: Science, 1913, xxxvii, 389.

4. Henderson: Jour. Biol. Chem., 1911, ix, 403.

action by which this organ is enabled to separate acid from its combined base, excrete the acid and save the base to the body so that it may again combine with and neutralize acid. The lungs form the second excretory channel of importance, for by means of them carbon dioxid is excreted. Any tendency to the production of an acidosis in the body is immediately compensated for by an increase in respiration and a washing out of carbon dioxid. It seems probable that the kidney is the fundamental regulator of the reaction of the blood, but the lungs, acting more quickly in response to sudden calls, serve as the more delicate balance-wheel of the regulatory mechanism.⁵

The question of the regulation of respiration has, however, been fundamentally widened by the writings of the two Danish physiologists, Hasselbalch and Lindhard, who have shown that there are two factors which must be considered. The first of these, and the one to which attention has hitherto been generally directed, is the nature or size of the stimulus to respiration. The second is the excitability of the respiratory center. This has been usually accepted as being a constant, and the possibility of its varying has been rather overlooked. To quote Hasselbalch's own words:²

The two factors, regulation of neutrality and excitability of the respiratory center, together govern the chemical regulation of respiration, and therefore the amount of the alveolar carbon dioxid tension is a function of the two factors, and cannot be regarded as a physiologic constant."⁶

Hasselbalch states that a diminution in the carbon dioxid tension of the alveolar air is thus not necessarily due to an increase of the acids in the blood, since this condition may be present when the respiratory center is hyperexcitable and responds to a hydrogen-ion concentration of the blood that is lower than normal. In such a case the threshold for the excitation of the center has become lowered, but the composition of the blood as far as acids other than carbon dioxid go may remain unchanged. That variations in the excitability of the respiratory center do actually occur has been shown. The excitability may be tested by the method of Lindhard⁷ in which the subject is given mixtures containing various percentages of carbon dioxid to breathe, and the increase in alveolar ventilation which results from a given increase in the inspired carbon dioxid is measured. Lindhard⁷ has shown that the excitability of the respiratory center varies inversely as the oxygen tension of the blood. The excitability

5. Campbell, Douglas, Haldane and Hobson: *Jour. Physiol.*, 1913, xlvii, 301.

6. Die zwei Faktoren: Neutralitätsregulation und Reizbarkeit des Atemzentrums beherrschen zusammen die chemische Atmungsregulation, so dass die Grösse der alveolaren CO₂—Spannung als Funktion der beiden Faktoren hervorgeht und nicht als physiologische Konstante betrachtet werden kann.

7. Lindhard: *Jour. Physiol.*, 1911, xlii, 337.

is furthermore increased by exposure of the person to ultra-violet light (Hasselbalch²), and in pregnancy (Hasselbalch⁸), but it is decreased by the action of morphin (Hasselbalch²). The decrease in the alveolar carbon dioxid tension described by several observers as occurring at high altitudes has been asserted by Hasselbalch and Lindhard⁹ to be the result of an increase in the excitability of the respiratory center which is probably associated with the action of ultra-violet rays. Haldane and his coworkers⁵ have criticized the experimental methods used by Lindhard in his work on the effect of oxygen tension on the excitability of the respiratory center. Their own experiments show no changes of excitability corresponding to variations in the oxygen tension, and they conclude that the excitability appears to be constant during health.

Inasmuch, then, as blood, urine and alveolar air are all more or less directly related to the control of respiration, it is evident that in studying the complicated processes at work under pathologic conditions, all three of these factors should be considered.

In a consideration of the subject of cardiac dyspnea, one has various clinical types of patients under observation, and it is important to separate and simplify the types as far as possible. Perhaps the broadest lines that can be drawn are in the recognition on the one hand of the cases of uncomplicated cardiac disease, and on the other, cases of so-called "cardiorenal" disease in which the kidneys may be assumed to be the essential or at least an important underlying factor.

It is quite possible that different causes for the dyspnea in various types of uncomplicated heart-disease may be ascertained, and the study of large numbers of cases may lead to the recognition of definite groups of functional derangement. Of more immediate importance, however, is the determination of the rôle played by renal disturbance. It has long been known that certain types and stages of nephritis may be associated with the development of a considerable degree of acidosis, and since there is a direct relationship between acidity and respiratory control, it is logical to give some attention to this factor, and to determine if possible whether renal insufficiency has any bearing on the production of dyspnea. The first group of cases to be reported are, therefore, instances of renal disease in which cardiac involvement was either absent or of secondary importance. The second group of cases are instances of heart-disease with either no renal disturbance except passive congestion, or else a very moderate degree of nephritis.

It is to be regretted that the number of cases reported is not great, but some of them have been studied rather extensively, and as further

8. Hasselbalch: *Skandin. Arch. f. Physiol.*, 1912, xxvii, 1.

9. Hasselbalch and Lindhard: *Skandin. Arch. f. Physiol.*, 1911, xxv, 361.

investigation has necessarily been temporarily postponed, the work is reported in its present state.

METHODS

Alveolar Air.—The samples of alveolar air were almost always taken by the Plesch method. A comparative study of various methods of taking samples of alveolar air by Boothby and Peabody¹⁰ showed the simplicity and reliability of this method for work with patients. Subsequent use has fully confirmed their opinion. Three separate samples were taken, and almost always a very satisfactory agreement within 2 mm. was found. Occasionally the carbon dioxid tension in one tube fell so far below the others that it was obviously an error, and this figure was discarded. The gas analyses were made with the small Haldane gas-analysis apparatus. The tension of the carbon dioxid in the alveolar air in normal persons usually ranged between 39 mm. and 44 mm.

Hydrogen-Ion Concentration of the Blood.—This was determined by means of the concentration cell, since titration and colorimetric methods do not give satisfactory results with blood. The general arrangement of apparatus was exactly like that described by Sørensen.¹¹ A platinum wire, calibrated in the physical laboratory of Harvard University, and a standard cell whose voltage was checked in the same laboratory, were used. An Edison nickel accumulator, and a Lippmann capillary electrometer were used. The hydrogen was generated in a Kipp apparatus and passed through a pyrogallie acid-potassium hydroxid solution, sulphuric acid, calcium chlorid tube and water before it entered the electrode vessel. All parts of the apparatus were mounted on paraffin blocks to prevent trouble from poor insulation. The electrodes were controlled by the use of the Sørensen standard phosphate solutions.

The measurement of the electromotive force, and thus of the hydrogen-ion concentration of simple solutions is comparatively easy by means of the concentration cell. The problem is, however, much more difficult when one is working with blood. This is on account of two features—the high albumin content of blood and the important part played by the carbon dioxid. The albumin content of blood apparently affects both the accuracy with which the readings can be made, and the rapidity with which an end-point is reached. The carbon dioxid is of even greater significance, for the reaction of blood varies according to the carbon dioxid tension at which it is tested.

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

11. Sørensen: *Ergebn. d. Physiol.*, 1912, xii, 393.

Hasselbalch¹² has done an important service in calling attention to the error inherent in the previous work of most investigators of the reaction of blood, in that they neglected the escape of carbon dioxide, and he proposed a method by which it was possible to measure the hydrogen-ion concentration of blood saturated with carbon dioxide at a known tension. By the use of an ingeniously devised electrode vessel he is able to introduce, one after another, several samples of blood. Each new sample is shaken up in the atmosphere of hydrogen which is present in the electrode. Carbon dioxide escapes from the blood into the atmosphere above, but after several changes of blood, the atmosphere has a carbon dioxide tension equal to that of the blood, so that on the admission of a new sample, there is no loss of carbon dioxide. This form of electrode was used in the earlier work here, but it was found impossible to get constant results. After each change of blood there would be a fall in the reading and it was extremely difficult to get a constant end-point. Hasselbalch's¹³ latest modification of his method, which is supposed to obviate some of the difficulties, was not tried, as it seemed much simpler to change the apparatus so as to be more on the principle of the method described by Michaelis and Rona.¹⁴ The essential feature of this consists in the use of an electrode vessel which shall contain a large amount of blood and a small volume of hydrogen. With this arrangement only a comparatively small proportion of the carbon dioxide in the blood will pass out into the hydrogen atmosphere, and after a single filling of the vessel, a reading is obtained which is to all intents and purposes accurate. This does away with the changing of the blood necessary in the Hasselbalch vessel, in which the volume of blood is very small in proportion to the volume of hydrogen atmosphere. In the form finally adopted, the electrode vessels were shaped something like small Florence flasks with a tube for the inlet of blood set into the bottom, and a tube for the inlet of hydrogen set into the side of the neck. When ready for use, the bulb contains about 5 c.c. of blood and the neck about 1 c.c. of hydrogen. The neck is closed by a tightly fitting rubber stopper, through which is passed a piece of glass tubing with a short platinum wire, to serve as the electrode, fused into the end of it.

The blood used was taken from a vein at the elbow and defibrinated. Lundsgaard¹⁵ has shown that the hydrogen-ion concentration is the same in defibrinated as in herudinized blood. The blood was then filtered and placed in a bottle through which was passed a rapid

12. Hasselbalch: *Biochem. Ztschr.*, 1910, xxx, 317; Hasselbalch and Lundsgaard: *Biochem. Ztschr.*, 1912, xxxviii, 77.

13. Hasselbalch: *Biochem. Ztschr.*, 1913, xlv, 451.

14. Michaelis and Rona: *Biochem. Ztschr.*, 1909, xviii, 317.

15. Lundsgaard: *Biochem. Ztschr.*, 1912, xli, 247.

stream of a mixture of carbon dioxide and air. The mixture was analyzed for every experiment, so it was known at what tension of carbon dioxide the blood was saturated. After thorough saturation by running in this mixture for thirty minutes, and after thorough shaking, the blood was transferred by means of a glass syringe, and with constant care to prevent loss of carbon dioxide, into the electrode vessel. This vessel had previously been filled with the same mixture of carbon dioxide and air, so that there was no opportunity for the blood to lose carbon dioxide while it was being passed into the electrode vessel. The vessel and the side tube were completely filled with blood so that no bubbles of air remained. Then the side tube was connected with the hydrogen apparatus and blood allowed to run out of the lower end of the vessel until the neck of the vessel was filled with hydrogen, and the platinized electrode was just dipping into the blood. After shaking for ten minutes to promote a more rapid diffusion of gases, the electrode was allowed to stand. Readings were then made from time to time until a constant end-point was reached. Sometimes this occurred quickly, but usually it took two or three hours. All observations were made in duplicate, and at room temperature. The results were calculated and the temperature corrected to 18 C. (64.4 F.), using the formulas which are given in Sørensen's article.¹¹ The results are expressed in the now familiar terms of Sørensen as the *ph*.¹⁶ It is to be remembered that the more alkaline a solution, the higher the *ph*., and the more acid, the lower the *ph*. When saturated at 40 mm. carbon dioxide the *ph*. of normal blood is approximately 7.45. Taking the high and low limits the extreme variations are between 7.40 and 7.50.

In all instances the *ph*. of the blood was determined when it had been saturated with a mixture containing carbon dioxide at about 41 mm. tension. This carbon dioxide tension may be considered as that at which the blood is saturated in the body when the alveolar carbon dioxide is normal. In normal individuals, therefore, it gives the actual *ph*. of the blood. If, however, the carbon dioxide in the alveolar air is below normal, as in cases of acidosis, the saturation at 41 mm. carbon dioxide will give a more acid value for the blood than is actually present. This is at least true in the majority of instances, for we

16. "Aus Zweckmässigkeitsgründen, die besonders bei graphischen Darstellungen der Abhängigkeit zwischen dem Verlauf biologischer Prozesse und der Wasserstoffionenkonzentration des Mediums hervortreten hat S. P. L. Sørensen vorgeschlagen als Mass für die Grösse der Wasserstoffionenkonzentration einfach der numerischen Wert des Exponenten der oben erwähnten Potenz von 10 zu benutzen und die Bezeichnung PH. anzuwenden. . . ." "Unter dem Wasserstoffionenexponenten, PH., einer Lösung ist der Brigg'sche Logarithmus des reziproken Wertes des auf Wasserstoffionen bezogenen Normalitätsfaktors, der Lösung zu verstehen." Sørensen: *Ergebn. d. Physiol.*, 1912, xii, 401.

know that the reduction of the alveolar carbon dioxide is usually an indication of the compensatory mechanism by which the blood-reaction is kept constant with a ph. of 7.45. The ph. of the blood saturated at 41 mm. carbon dioxide will thus be an index of abnormal acid formation. As such an index, it confirms what the determination of the alveolar carbon dioxide gives us, but it is also of especial value in cases in which it is not possible to obtain samples of alveolar air. Moreover, at present there has not been sufficient correlation of the alveolar carbon dioxide findings with the hydrogen-ion concentration of the blood in pathologic conditions for us to know in how far they correspond, as they do in normal conditions. In many instances, determinations of the ph. were also made on the same specimens of blood saturated with carbon dioxide at or about the tension at which it was found in the alveolar air. This would tell the actual reaction of the blood in the lungs. Usually this gives, of course, a ph. of the value of normal blood, about 7.45. Occasionally, however, in terminal conditions there is evidence of a failure of the compensatory mechanisms and of a true change in the reaction of the blood toward the acid side.

Urine.—The nitrogen was ascertained by Kjeldahl's method, and the ammonia determinations were made by the method of Folin.¹⁷ The hydrogen-ion concentration of the urine was found by the colorimetric method described by Palmer.¹⁸ The "retained base" and "total acidity" were determined by Adler and Blake's method.¹⁹ To save space a great part of the urinary analyses are omitted, as they contribute little that is not shown by the other methods.

Blood.—I am indebted to Dr. C. Frothingham, Jr., and to Dr. W. G. Smillie, who kindly made the determinations of the non-protein nitrogen in blood by the method of Folin.²⁰

CHRONIC NEPHRITIS

From the point of view of this study, the factor of importance in chronic nephritis is the development of acidosis. The cases examined fall clearly into two groups—those of uncomplicated nephritis and those of nephritis with uremic manifestations. Palmer²¹ and others have shown, and studies in this hospital have confirmed the fact, that a very mild grade of acidosis is a frequent accompaniment of chronic

17. Folin: *Am. Jour. Physiol.*, 1905, xiii, 45.

18. Palmer, Walter W., and Henderson, Lawrence J.: *Studies Upon Acid Base Equilibrium and the Nature of Acidosis*, *THE ARCHIVES INT. MED.*, 1913, xii, 153.

19. Adler, Herman M., and Blake, Gerald: *The Retention of Alkali by the Kidney with Special Reference to Acidosis*, *THE ARCHIVES INT. MED.*, 1911, vii, 479.

20. Folin and Denis: *Jour. Biol. Chem.*, 1912, xi, 527.

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

nephritis. This is shown by the high hydrogen-ion concentration of the urine, by the total acid excretion, and by Palmer's sodium bicarbonate tolerance test. Apparently, however, in uncomplicated cases this degree of acidosis is taken care of by the kidneys. The increased excretion of acids in the urine serves to prevent any accumulation in the blood, and there is no decrease in the tension of the carbon dioxide in the alveolar air as there would be if the regulatory mechanism of the kidney were unable to compensate for the increased formation of non-volatile acids. Table 1 gives the alveolar carbon dioxide in a few cases of uncomplicated nephritis. It will be noted that the phthalein output in some of them indicates a nephritis of considerable severity.

TABLE 1.—ALVEOLAR CARBON DIOXIDE IN CHRONIC NEPHRITIS WITHOUT CARDIAC DECOMPENSATION OR UREMIA

Case	Date	Non-Protein Nitrogen in Blood	Alveolar CO ₂ mm.	Phthalein Output in Two Hours Per Cent.)
V. R.....	11-13	44.1	
	12- 6	42.0	
J. J. B.....	12-19	42.7	
G. U.....	2-2	38.5	
J. J. F.....	2-3	47.6	40.2	25
	2-4	39.3	
	2-5	39.3	
	2-7	56.1	38.1	18
G.....	2-5	28.4	42.3	

The second group of renal cases consists of those in which there were definite manifestations of uremia. The majority of these ended fatally. In some of them it was possible to obtain observations over a more or less protracted period, during which the development of a marked acidosis could be followed. In these cases the determination of hydrogen-ion concentration of the blood was of great value, for after the patients became very sick, or developed coma, it was not possible to obtain samples of alveolar air.

CASE 1.—H. G. M. (medical No. 621), woman, aged 28, was admitted to the hospital, Dec. 9, 1913, discharged Dec. 16, 1913. Diagnosis: chronic nephritis. There was no history of any previous illness, but the patient gave an indefinite account of rheumatic fever a few years ago. Onset of present illness is somewhat obscure, but apparently she had had disturbance of vision for over a year. During the summer she was well enough to play tennis several times, but had to give it up owing to "flashes" before her eyes. Two months before admission she had a severe attack of nausea and vomiting, and she has had some nausea since. There has been no edema other than a slight swelling of the eyelids.

Physical examination was generally negative, except for a hypertrophied heart. Blood-pressure: systolic 280 +. The eye-grounds show several hemorrhages and marked albuminuric retinitis.

Urine: acid, specific gravity 1.012, albumin, 0.3 per cent.; sediment, few hyaline, many granular and blood-casts.

Blood: hemoglobin 81 per cent.

The phthalein test was made twice during her stay in the hospital, and on both occasions only traces appeared in the urine.

December 10: Uncoagulable nitrogen in the blood, 90 mm. per 100 c.c. The ph. of the urine varied from 5.7 to 7.

During her stay in the hospital the patient vomited frequently and had several severe headaches. It was quite apparent that these were early symptoms of uremia. After leaving the hospital she developed marked muscular twitching and slowly lost ground. She died about ten days after leaving the hospital.

The ph. of the blood determined at 41.8 mm. tension of carbon dioxide December 11 was 7.44. This day the carbon dioxide tension of the alveolar air was 40.3 mm. Carbon dioxide tension of alveolar air December 12, 41.7 mm. and December 13, 40.4 mm.

This case then, at the beginning of what proved to be a terminal uremia, showed a perfectly normal carbon dioxide tension of the alveolar air and correspondingly a normal hydrogen-ion concentration of the blood.

CASE 2.—L. F. C. (medical No. 655), man, aged 30, admitted Dec. 19, 1913, died Jan. 10, 1914. Diagnosis: chronic interstitial nephritis. This patient has been admitted to the hospital three times for chronic nephritis. The only etiological factors in the past history are malaria and dysentery, which he had in the Philippines ten years ago. For nine years he has had headaches, but these have been more severe in the last year and a half. On each occasion he has entered the hospital with a history of morning headaches, polyuria, moderate edema, poor vision, and slight dyspnea. Only on the final admission was there any evidence of grave cardiac insufficiency. At the last admission he was having marked dyspnea and orthopnea. The urine always showed a large amount of albumin and a low specific gravity. On the first admission the phthalein output was 20 per cent. in three hours, on the second admission 8 per cent. in two hours, and on the last admission it was zero in two hours. Blood-pressure has ranged from 200 to 240. Since the first admission there has been an albuminuric retinitis. There was cardiac hypertrophy but there were no murmurs except for a loud systolic murmur best heard in the aortic area, which developed under observation a few days before death. The dyspnea and orthopnea which were evidences of cardiac insufficiency and were present on his final admission, disappeared shortly after he was put to bed. After the first few days the heart was apparently completely compensated. Thus, December 21, the note states that "the dyspnea which was marked on entrance has disappeared. He breathes easily and sleeps lying almost flat. There is marked pallor of the skin and mucous membranes. Respiratory rate is 21. There is slight irregularity in rhythm and depth. Lungs are negative except for scattered râles, especially at the bases. Heart-sounds are loud and clear; no murmurs heard."

December 24, the patient began to be restless and his mind became clouded. From that time he gradually failed with increase of mental clouding. He vomited frequently and was at times definitely delirious.

January 9: "The patient seems very doxy at this time but responds when told to put out his tongue. There is marked pallor. There is no dyspnea and no orthopnea. Respirations are irregular but there are no definite periods of

apnea. Lungs are clear on percussion, but the breath-sounds are distant. Heart is enlarged. There is no edema. Pulse-rate 88. There is constant muscular twitching."

January 10: Patient sank into unconsciousness and died. Diagnosis of chronic nephritis confirmed by necropsy.

TABLE 2.—FINDINGS IN CASE 2. CHRONIC NEPHRITIS ENDING IN UREMIA

Date,	Volume Urine c.c.	Ph. in Urine	Non- Protein Nitrogen in Blood mg. per 100 c.c.	H-ion Concentration of Blood		Tension of Alveolar CO ₂ in mm.	Remarks
				Tension of CO ₂ in mm.	Ph.		
1913 12/19	...	5.5	42.7	7.37	36.3	Marked dyspnea. Pallor. Phthal- ein = 28 per cent. in two hours.
12/20	2,100	5.25	96.1	35.8	
12/21	2,420	4.9					
12/22	3,110	4.85	39.0	Blood-pressure = 230 mm.
12/23	2,300	5.00	37.7	
12/24	1,930	5.05	35.6	
12/25	5.05		
12/26	1,065	5.1	42.0	7.45	35.4	
12/31	1,150	4.9	37.7	
1914							
1/ 1	1,430	4.7	38.9	
1/ 2	1,590	4.8	129.8				
1/ 3	500	4.8					
1/ 4	1,160	4.9					
1/ 5	920	39.1	Phthalein output = 0.
1/ 6	0	41.3	Blood - pressure = 230 mm.
1/ 7	750	4.7	278.9	40.7	7.45	38.8	
1/ 8	560	4.7*	330.0	45.4†	7.15	No dyspnea.
			41.0‡	7.21	36.8	Blood - pressure fallen to 180 mm.
1/ 9	347.0	41.0	7.04	Too sick to get alveolar air.
1/10	Died at 4 a. m.

* Below; † a. m.; ‡ p. m.

The studies of the urine during the first few days show little that is significant. During the last days it was impossible to collect twenty-four-hour specimens, so that the figures are not of great value. The hydrogen-ion concentration, however, as one would have expected, tended at all times toward low limits. The non-protein nitrogen of the blood shows a progressive increase, reaching at the end the extremely high value of 347 mg. per 100 c.c. blood. The determinations of the

hydrogen-ion concentration of the blood and of the carbon dioxide tension of the alveolar air are of considerable interest. On admission when there was marked dyspnea the alveolar air was slightly below normal, and the ph. of the blood also indicated a very slight degree of acidosis. Following this the carbon dioxide in the alveolar air rises, but the figures are rather irregular and slightly low. December 26, the ph. of the blood was normal. January 7, both the blood and the alveolar air were normal. January 8, however, at about the time at which severe symptoms of uremia developed, there was a slight fall in the carbon dioxide tension of the alveolar air and a marked fall in the ph. of the blood. A comparison of the alveolar air and the blood-findings suggests strongly that at this time the actual reaction of the blood had become abnormally acid. January 9, the patient was so sick that it was impossible to get the alveolar air, but the ph. of the blood showed a very marked acidosis. Perhaps the most striking result of these studies is the fact that at the period when dyspnea and orthopnea were marked, both blood and alveolar air showed very little evidence of acidosis, while at a period when acidosis was extreme there was scarcely any disturbance of the respiration.

CASE 3.—N. H. (medical No. 617), woman, aged 56, admitted Dec. 8, 1913, died Dec. 12, 1913. Diagnosis: chronic nephritis, uremia. The patient was unconscious when she was brought into the hospital. At a subsequent date a history of kidney trouble was obtained. The present condition apparently came on acutely about sixteen hours before admission to the hospital.

Physical examination showed an obese woman, lying in deep coma. Respiration rather difficult and loud. No cyanosis. Heart apparently not markedly enlarged. Pulse 72. Blood-pressure, systolic 120, diastolic 75. Lungs show fine and coarse râles. Abdomen, negative. No edema. Eye-grounds, negative.

Urine, specific gravity 1.021, albumin, trace; sediment, great numbers of hyaline and a few granular casts.

Non-protein nitrogen of the blood: 65.7 mm. per 100 c.c.

December 8: Phthalein test. No urine obtained at the end of two hours by catheterization. Hydrogen-ion concentration of the blood at 40 mm., carbon dioxide tension = 7.39.

December 10: Patient can be roused to answer questions. There is almost complete anuria. Two catheterized specimens of urine were obtained of 35 c.c. and 18 c.c., respectively, during the twenty-four hours.

December 11. Patient is in deeper coma. Blood taken ten hours before death, non-protein nitrogen, 133 mg. per 100 c.c. of blood. The ph. of the blood saturated at 38.7 mm., carbon dioxide tension = 7.29.

December 12: At 8 p. m. last evening the patient lapsed into deeper coma with stertorous respiration. This morning she had general convulsions and died. Necropsy showed chronic nephritis.

Urine examinations could not be made on this patient as the output was so small. It was impossible to obtain specimens of alveolar air. The hydrogen-ion concentration of the blood, however, was determined on two occasions. When the patient was admitted the hydrogen-ion concentration was practically normal, but December 11 there was evidence of well-marked acidosis. Shortly after this determination was made the patient developed a deep, slow respiration, somewhat suggestive of the respiration seen in diabetic acidosis.

CASE 4.—J. W. D. (medical No. 673), man, aged 32, admitted Dec. 26, 1913, died Jan. 4, 1914. Diagnosis: chronic nephritis, uremia, pericarditis. Complaint, vomiting. Past history negative, except for osteomyelitis of the tibia twelve years ago. For six months he has had frontal headache in the morning. This has been often associated with vomiting. During the last three weeks he has been short of breath on exertion and has had to prop himself up in bed at night. He has also been very drowsy; has had epistaxis for two months. No edema. Vision is normal. He worked as usual until four days ago.

Physical examination shows a fairly well-developed young man lying propped up in bed breathing rapidly with some effort. Skin, pale; heart: left border of dullness in the fifth space, 11 cm. from the midsternal line. There is a high-pitched systolic murmur at the apex. Aortic second sound is rather weak. Blood-pressure: systolic 180, diastolic 125. There is moderate effusion in the pleural cavities. Reflexes very active; no edema.

Urine acid, specific gravity 1.026, trace of albumin. Sediment negative.

December 30: Output of phenolsulphonephthalein is zero for two hours. This has been repeated twice. Non-protein nitrogen of blood is 209 mg.

January 1: Pericardial rub noticed. Patient is perfectly clear mentally. Output of urine 800 c.c.

January 2: Mind is clear, no headache. Nausea and vomiting continue.

January 3: Respiration 12 per minute, regular, slightly deep but not abnormally so. There is muscular twitching. Mind perfectly clear. Urine output 350 c.c. Carbon dioxide tension of alveolar air, 33.8 mm. The ph. of the blood measured at 39.8 mm., carbon dioxide tension, 7.32. Non-protein nitrogen of the blood 285.7 mg. per 100 c.c.

January 4: Patient became unconscious during the night and died early in the morning. Necropsy showed a chronic nephritis, acute pericarditis and edema of the lungs.

In this case it was impossible to make complete urinary examinations. The alveolar air and the hydrogen-ion concentration of the blood determined January 3, correspond extremely well and indicate a moderate degree of acidosis. At this time the respiration was slow and regular and there was no evidence of dyspnea.

CASE 5.—L. C. M. (medical No. 573), woman, aged 38, admitted Nov. 29, 1913, died Dec. 7, 1913. Diagnosis: chronic nephritis, uremia. With the exception of an attack of measles as a child, the patient has never had any illness confining her to bed. For the past five years she has had headaches. These began as mild attacks once a month, and have gradually increased in frequency and severity, now occurring weekly. She has been dyspneic on exertion for the past five years, but has never had to leave work. One week before admission she had a severe "bilious" attack, with pain in the epigastrium and vomiting. She has had continued nausea since the onset of this attack, but no other disturbance until three days before admission. At this time she noticed that she could not see objects clearly. On admission she could not count fingers at a distance of four feet. She has noticed that she has passed very little urine during the last week.

Physical examination shows a small, undersized, poorly nourished woman. There is no marked dyspnea. Eyes and pupils are normal; the pupils are equal and react normally. There is a conjunctival hemorrhage on the temporal side of the right eye. Mucous membranes are pale. Breath is foul. Heart: apex indefinitely localized in the sixth space, 7 cm. from the midsternal line; left border is 12 cm. to the left of the midsternal line in the sixth space, and the right border is 3.5 cm. to the right of the midsternal line. There is a loud, blowing systolic murmur at the apex. Aortic second sound is markedly accentuated.

ated and there is a long systolic murmur heard over the aortic area. Pulse-rate 90. Blood-pressure, systolic 230, diastolic 130. Lungs show a few râles at the right base; slight dulness with râles at the left apex. Examination of the eye-grounds shows well-marked albuminuric retinitis.

Urine acid, specific gravity 1.012; albumin, large trace; sediment contains many hyaline and a few granular casts, rare red blood-corpuscle.

Blood: Hemoglobin, 66 per cent.; leukocytes, 14,600.

November 30: During the night the patient was bled about 450 c.c. Although her mental condition was perfectly clear, it was feared that uremia was impending owing to the condition of the eye-grounds and the urinary findings, together with the absence of any output of phenolsulphonephthalein. The patient has been put on a milk diet of 1,500 c.c.

TABLE 3.—FINDINGS IN CASE 5. CHRONIC NEPHRITIS TERMINATING IN UREMIA

Date, 1913	Volume Urine c.c.	Ph. in Urine	Non-Protein Nitrogen in Blood mg. per 100 c.c.	H-ion Concentration of Blood		Tension of Alveolar CO ₂ in mm.	Remarks
				Tension of CO ₂ in mm.	Ph.		
11/29	90.5	Headache, vomiting. Albuminuric retinitis. Phthalein = 3 per cent. in two hours.
11/30	210	7.4 +	Phthalein = 0 in two hours.
12/ 1	250	7.4 +	32.9	Phthalein = 0 in two hours.
12/ 2	260	Menses	31.4	
12/ 3	150	Menses	117.0	29.1	Eyesight almost gone.
12/ 4	170	Menses	200.0	26.1	Mind clear.
12/ 5	200	7.4	42.5	7.22	
			34.4	7.27		
12/ 6	58 *	7.4	43.7	7.10	Blood taken six hours before death. Mind cloudy at 6 p. m. Unconscious at 11 p. m.
			21.8	7.23	24.4	
12/ 7	Died at 2:50 a. m.

* Catheter specimen.

December 1: The patient complains only of general weakness. Headache is less and there is no edema.

December 2: Patient mentally clear and does not complain of headache.

December 3: Vision is, if anything, decreased. There is practically no dyspnea and no edema. During the past twenty-four hours the urine output has not risen above 200 c.c. in spite of two doses of theocin.

December 4: The patient was bled about 400 c.c. last night. Following this, 600 c.c. of normal salt solution was introduced per rectum. Warm bath and later a hot pack given. Patient seemed somewhat better. There are no subjective symptoms whatever at this time other than the blindness, which is now almost complete.

December 7: The patient's condition up to 6 p. m., December 6, was unchanged. At that time her mental condition was somewhat clouded. In spite of venesection and enteroclysis, her condition became worse during the early part of the evening and at 11 p. m. she became unconscious. Death occurred at 2:50 a. m.

The preceding case is thus one of pure chronic nephritis terminating in uremia. During the whole of her stay in the hospital the excretion of urine was very small. The non-protein nitrogen in the blood was markedly increased and rose progressively. In the last two tests there was no output of phenolsulphonphthalein in two hours. The urine examination shows a high ammonia percentage, which would suggest acidosis. It is interesting, however, that the hydrogen-ion concentration of the urine was at all times low. There was nothing in the diet or medication to account for this unusually low acidity. Analyses of the alveolar air showed a progressively falling carbon dioxide content. The ph. of the blood was determined on the last two days and on both occasions shows evidence of marked acidosis. Indeed the determination December 6, of blood taken six hours before death, shows evidence of a true shift in the reaction of the blood toward the acid side. It is to be noted that at no time during the course of the disease was dyspnea noticed.

DISCUSSION OF FOREGOING CASES

The foregoing cases confirm the work of von Jaksch,²² who, from results obtained by a rather crude titration method, was the first to describe the acidosis of uremia. More recent investigators, using more accurate methods, have added little that is of essential importance. Straub and Schlayer,²³ studying the carbon dioxide tension in samples of the alveolar air, obtained by the Haldane method, found a decreased tension in eight cases of uremia. Slightly low values were found in a number of cases showing only moderate uremic symptoms. The lowest tension occurred in the most advanced cases. These authors go so far as to assume a causal relationship between the acidosis and the uremic condition. Cases of nephritis without evidence of uremia showed normal carbon dioxide tension. Similar results were obtained by Porges and Leimdorfer,²⁴ who also made determinations of the carbon dioxide of the alveolar air. Poulton and Ryffel²⁵ found the alveolar carbon dioxide tension between 14 and 25 mm. in four cases of uremia. The urea-content of the blood was high, and the lactic acid in the blood slightly increased. The blood of these patients took

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

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

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

25. Poulton and Ryffel: *Proc. Physiol. Soc.*, June 28, 1913, published in the *Jour. Physiol.*, 1913, xlvii, p. xlvii.

up oxygen with abnormal difficulty in spite of the low pressure of carbon dioxid present. "This effect would be produced by the presence of excess of acid in the blood." These authors add that "as there was the possibility that the *meionexy** in these cases might be directly connected with the high percentage of urea in the blood, a control experiment was made in which 0.39 per cent. urea was added to normal blood." The results showed that the addition of urea to blood does not cause the dissociation curve to shift to the right.

There are also a number of direct determinations of the hydrogen-ion concentration of the blood in nephritis with and without uremia. Thus Kreiblich²⁶ found that in uncomplicated nephritis the reaction of the blood was within normal limits, while in uremia there was an acidosis. Rolly²⁷ also found that the hydrogen-ion concentration of the blood was normal in nephritis without uremia. In four cases of terminal uremia there was evidence of acidosis, but in three cases with temporary uremia the blood was normal. He believes that an acidosis of the degree found in uremia may be present in the agonal stages of many conditions. The findings of these last two observers are open to the criticism that the determinations of the hydrogen-ion concentration of the blood were not made in blood which had previously been saturated at a known carbon dioxid tension. We have already seen that this is essential in order to obtain accurate values.

The present studies confirm in general the work of previous investigators, but they also give more accurate information as to the relation of the acidosis to some of the associated conditions. The evidence is certainly against the theory adopted by Straub and Schlayer that acidosis is a cause of uremia. Several of the cases show that marked symptoms of uremia may exist without any evidence of acidosis as manifested by the alveolar air or by the blood. That slightly low figures for the carbon dioxid tension in the alveolar air may be obtained in some mild cases of uremia, as found by Straub and Schlayer, and by Porges and Leimdorfer, is certain; but all the evidence goes to show that acidosis of any great importance is rarely found except in severe and usually terminal cases. Even in cases in which the blood was examined within twelve hours before death, the acidosis is not so marked as is found in advanced diabetic coma. In one case of diabetic coma in this hospital the blood saturated at 43.2

* Lewis, Ryffel, Wolf, Cotton and Bancroft: The condition in which the blood takes up less than its usual share of oxygen is called *meionexy*; the opposite condition, that in which it takes up more than its usual share, is called *pleonexy-meionexy*, indicates a shifting of the reaction in the acid direction," Heart, 1913, v, 45.

26. Kreiblich: Wien. klin. Wchnschr., 1911, xxiv, 1419.

27. Rolly: München. med. Wchnschr., 1912, lix, 1201.

mm. carbon dioxid had a ph. of 7.07. The development of acidosis in renal disease bears little or no relation to the amount of non-protein nitrogen in the blood. The latter may be extremely high without signs of marked acidosis being present. This is confirmatory of the experiments of Poulton and Ryffel.²⁵ Furthermore, the relation is slight between the output of phenolsulphonephthalein and the development of acidosis. In several instances the phthalein output had fallen to zero some time before evidence of acidosis arose. It is thus only after the excretory power of the kidney has been reduced to a minimum for a somewhat prolonged time that the signs of acidosis begin to develop in the blood. Finally there is apparently little relation between the occurrence of acidosis in nephritis and that of dyspnea. Dyspnea on exertion was observed in some of these cases a long time before there was any development of acidosis, and on the other hand, at the time when acidosis was present, respiratory disturbance was certainly not a prominent feature. Occasionally a type of deep, slow respiration is seen, resembling the respiration of typical diabetic acidosis. It bears, however, little relation to the type of breathing in cardiac dyspnea. It seems thus fair to conclude that in combined cardiorenal disease, the dyspnea is essentially a circulatory feature, and the renal condition plays an accessory part.

CARDIAC DYSPNEA

There are many researches concerning the nature of cardiac dyspnea, but comparatively few deal specifically with the nature of the stimulus to respiration. Beddard and Pembrey²⁸ found the carbon dioxid in the alveolar air reduced in decompensated cardiac cases. They are uncertain whether the stimulus to rapid respiration is chemical or nervous in origin. Lack of oxygen appeared not to be the cause, as the administration of oxygen had little effect. Fitzgerald²⁹ also studied the alveolar air in cardiac disease and found values that are rather low in most of the causes in which dyspnea is noted.

A much more extensive study was made by Porges, Leimdörfer and Markovici.³⁰ These authors found that the carbon dioxid in the alveolar air in cases of cardiac disease without dyspnea is normal. In cases with dyspnea they found that the tension of alveolar carbon dioxid is usually diminished. In a few instances, a normal tension was found and this they explain by the presence of an associated pulmonary condition, for their observations go to show that in dyspnea due to pulmonary disease the tension of alveolar carbon dioxid is

28. Beddard and Pembrey: *Brit. Med. Jour.*, 1908, ii, 580.

29. Fitzgerald: *Jour. Path. and Bacteriol.*, 1910, xiv, 328.

30. Porges, Leimdörfer and Markovici: *Ztschr. f. klin. Med.*, 1913, lxxvii, 446.

increased. The average tension in thirty-six cases of cardiac disease without dyspnea was 43.5 mm. if the barometric pressure is assumed to be 76.5 mm. The results are given only in percentages. The average of thirty-one observations on cases with dyspnea was 33.0 mm. Porges assumes that the low carbon dioxid in the alveolar air is the result of an abnormal formation of acid bodies and concludes that the dyspnea in cardiac disease is due to an acidosis.

A much more complete study of dyspnea in cardiac and renal patients has lately been published by Lewis, Ryffel, Wolf, Cotton and Barcroft.³¹ They call attention to the fact that while patients with congenital heart-lesion may have marked cyanosis without dyspnea, the majority of patients with definite breathlessness are not particularly cyanotic. The degree of cyanosis certainly does not correspond with the degree of dyspnea, so they conclude that the dyspnea is not wholly accounted for by lack of oxygen. In the cases without marked cyanosis they believe that the cause of the dyspnea is a relative acidity of the blood—an acidity which is not due to excess of carbon dioxid. In the cases with deeper cyanosis, the acidosis is an etiological factor acting in addition to the lack of oxygen. The group of cases in which dyspnea occurred with only slight or moderate cyanosis were for the most part those in elderly persons with enlarged hearts, with or without valvular disease, often with arteriosclerosis or renal involvement. This group they term the “special cases” in contradistinction to a group of three “cardiac cases.” In only one of the latter does the record state that there was “deep cyanosis.” In the other two it was said to be “very slight” and “slight or moderate”—descriptions also found applied to some of the “special cases.” Studies of the oxygen-combining power of the blood showed an acidosis (meionexy) which is more often definitely present in the “special cases.” The determinations of the carbon dioxid in the alveolar air fall into two groups. In the nine “special cases” the values are below normal. Of the two “cardiac cases” one had a normal and one a rather increased carbon dioxid. They feel that the meionexy in the “cardiac cases” may be accounted for by carbon dioxid, but that in the “special cases” it must be due to an increase of non-volatile acids. With a special test for the determination of non-volatile acids, they found that all the “special cases” gave evidence of an increase, while the two “cardiac cases” examined did not. It is to be noted, however, that five of the eleven “special cases” showed as little or less increase in non-volatile acids than did two of the three “special control cases” which had “no dyspnea but little reserve.” The table also shows that this test

31. Lewis, Ryffel, Wolf, Cotton and Barcroft: *Heart*, 1913, v, 45.

for non-volatile acids does not always run parallel to the depression of carbon dioxid tension in the alveolar air. Thus, for example, Patient 1 had a lactic acid equivalent of 0.15 per cent. and an alveolar carbon dioxid of 26.0 mm. Patient 3, with a lactic acid equivalent of 0.15 per cent., had an alveolar carbon dioxid of 13.0 mm., and Patient 5, with a lactic acid equivalent of 0.007 per cent. had alveolar carbon dioxid tension of 28.0 mm. Improvement of general conditions with lessening of dyspnea in the same case was associated with a diminution of the acidosis. Determinations of urea, non-protein nitrogen and chlorids in the blood showed that these substances had little relation to acidosis. An increase of lactic acid in the blood was present in only two terminal cases, and there was no evidence of increase of lactic acid in the urine. No connection was found between the acidosis and urinary excretion of ammonia or total acid. Since the urine examinations were negative these authors believe that the "acidosis appears to be another instance of the same phenomenon of retention of acids in excess of bases which is shown during residence at high altitudes." "During residence at an altitude of 10,000 feet or more the alveolar carbon dioxid falls progressively until accommodation is established. An excess of non-volatile acid is retained in the blood to compensate for this loss of carbonic acid, with the result that the dissociation curve of the blood is slightly displaced in the acid direction. The slight increase of lactic acid which is observed in the blood is not adequate to account for more than a small part of this retention of acid and no increase of lactic acid is excreted in the urine, so that this change appears to be an instance of the second cause of acidosis, namely, altered excretion of acids and bases by the kidney, which is beneficial at high altitudes, as the pressure of oxygen in the lungs is thereby increased."

CASE 6.—J. W. (medical No. 828), man, aged 37, admitted Feb. 7, 1914. Diagnosis: chronic valvular disease, mitral insufficiency, mitral stenosis, aortic insufficiency, auricular fibrillation. This patient had previously been in the hospital for the same condition. Five days after having been discharged from the hospital, the patient was admitted again on account of intense dyspnea, precordial pain, and pain in the right hypochondrium.

There is marked cyanosis of the lips and lobes of the ears. Lungs: negative except for a few moist râles at both bases. Heart: left border 17 cm. to the left of the midsternal line in the sixth space; right border is 5.5 cm. to the right. At the apex there is a blowing systolic murmur following the first sound and a faint diastolic rumble. Along the left border of the sternum there is a distant blowing diastolic murmur. Pulse is absolutely irregular. Blood-pressure: systolic 130, diastolic 85. Liver dulness extends from the sixth rib to 8 cm. below the costal margin. There is tenderness over the liver. No ascites, no edema of the extremities.

February 9: Patient is still slightly dyspneic and there is a little cyanosis of lips, ears and fingers. Examination of the heart is essentially as on admission. Urine: specific gravity, 1.021; albumin, trace; sediment, rare hyaline cast.

February 11: Dyspnea has almost entirely disappeared. Patient complains of no subjective symptoms. Urine: specific gravity 1.014; albumin, 0; sediment negative.

February 16: Under digitalis the pulse-rate fell to 40 per minute. Since then it has increased in rate to 60. Dyspnea has entirely disappeared.

February 20: Patient was suddenly seized with intense sharp pain, which was referred to both lower legs. Subsequent examination showed evidence of an embolus of the posterior tibial artery.

CASE 7.—J. T. (medical No. 787), man, aged 16, admitted Jan. 26, 1914, discharged Feb. 9, 1914. Diagnosis: chronic valvular disease, mitral insufficiency, mitral stenosis, auricular fibrillation. This patient has been in the hospital twice before. He was readmitted on account of marked dyspnea.

Physical examination shows considerable cyanosis. Lungs: negative except for a few râles in the left axilla, and at each base posteriorly. Heart: left border 14 cm. to left of the midsternal line in the fifth space, right border 5 cm. to the right in the third space. At the apex both sounds are replaced by murmurs. There is a loud, blowing, systolic murmur transmitted to the left axilla and a rumbling diastolic murmur. Toward the sternum in the sixth space there is a louder, higher-pitched systolic murmur. The pulmonic second is greatly increased. Pulse is absolutely irregular and 96 at the apex. Liver: lower border is indefinitely made out 8 cm. below the costal margin in the right nipple line. There is great tenderness on pressure over the liver. There is no ascites. Slight edema over both shins. Urine: acid; specific gravity 1.025; albumin, large trace; sediment, rare hyaline cast.

January 30: Cyanosis has almost disappeared. Respirations are 14 per minute. Patient has no dyspnea and feels perfectly comfortable.

CASE 8.—H. N. (medical No. 719), woman, aged 46, admitted Jan. 10, 1914, discharged Feb. 7, 1914. Diagnosis: chronic valvular disease, mitral stenosis, mitral insufficiency. Patient has had two attacks of rheumatic fever, which were followed by heart-trouble. During the last two years she has had three breaks in compensation, which compelled her to go to bed. She has been short of breath for two years. She is not able to walk a block without getting "purple"; has been in bed for three weeks. Orthopnea at night.

Physical examination: lips, ears and mucous membranes are very cyanotic. Heart: left border 16 cm. to the left of the midsternum in the fifth interspace and 4 cm. to the right in the fourth interspace. There is a presystolic thrill at the apex. The first sound is followed by a systolic murmur which is transmitted to the axilla. Second sound is scarcely audible and is followed by a loud, rough, diastolic murmur ending with a presystolic accentuation. Over the tricuspid area the systolic murmur is much higher pitched and of different character than that heard at the apex. Pulmonic second sound is accentuated. Pulse is regular. Lungs: numerous crackling râles on inspiration and expiration. Abdomen: definite shifting dullness. Liver dullness extends from the sixth rib to 5 cm. below the costal margin. There is edema of the legs. Blood-pressure, systolic 128, diastolic 80.

January 11: Patient has marked cyanosis of face and hands. Respiration is not rapid. There is no dyspnea while she sits propped up. Examination of the heart is as at admission.

January 29: Patient is sitting up in a chair. There is very little shortness of breath and no edema. Lungs are practically clear.

January 10: Urine, specific gravity, 1.025; albumin, trace; sediment no casts, many white blood-cells. Blood hemoglobin: 95 per cent.; red cells, 4,570,000.

January 21: Urine, specific gravity, 1.020; albumin, very large trace; sediment, rare hyaline cast, many white blood-cells.

CASE 9.—A. M. (medical No. 865), woman, aged 46, admitted Feb. 9, 1914. Diagnosis: chronic valvular disease, mitral stenosis, mitral insufficiency, auricular fibrillation. The patient had rheumatic fever at 14 years of age. For twelve

years she has had heart-trouble, including many periods of broken compensation. She was discharged from this hospital Jan. 3, 1914, after a stay of seven weeks. Her condition is now about what it was at the previous admission. For the last week she has been extremely short of breath, with orthopnea and a sense of smothering at night. Abdomen and legs have swollen rapidly.

Physical examination shows very little cyanosis, but marked dyspnea. Respiration about 40 per minute. Heart: left border of dulness is 15 cm. to the left of the midsternal line in the fifth space; right border is 4 cm. to right. Action is absolutely irregular. The first sound at the apex is followed by a loud, harsh systolic murmur, and the second is followed by a loud, blowing, diastolic murmur. At the base both sounds are weak. Lungs: dulness to percussion at both bases with some diminution in the intensity of the breath-sounds; a few scattered râles. Liver: lower border 3 cm. below costal margin. Liver pulsating and very tender. Slight edema of legs.

Blood: hemoglobin, 97 per cent.; leukocytes, 6,600.

February 20: Urine, specific gravity, 1.020; albumin, large trace; sediment, many casts.

February 21: Patient feels very much more comfortable. Respiration easier. Color is good. Respiration is still rapid.

February 23: Looks much better. Respiration remains rapid. Blood-pressure, systolic, 135; diastolic, 80.

February 24: Urine, specific gravity, 1.018; albumin, slightest possible trace; sediment, rare hyaline cast. Phthalein output in two hours, 40 per cent.

CASE 10.—I. J., man, aged 50, admitted Feb. 15, 1914. Diagnosis: acute rheumatic fever, chronic, valvular disease, mitral insufficiency, aortic stenosis (?). This patient gives a history of three previous attacks of acute articular rheumatism. For two years he has been troubled with dyspnea on exertion. He has had frequent attacks of what he terms "asthma" at night. When admitted to the hospital he had considerable dyspnea.

There was no cyanosis. Heart: left border in the sixth interspace is 18 cm. to the left of the midsternal line, right border is 3.5 cm. to the right. Action is rapid and absolutely irregular. The first sound at the apex is followed by a systolic murmur. The pulmonic second sound is accentuated. In the aortic area there is a rough systolic murmur, followed by a loud, snapping second sound. There is a coarse systolic thrill over the aortic area. Lungs: a few râles posteriorly. No emphysema. Liver not enlarged. There is an acute inflammation of the joints of the first finger on the right hand.

February 15: Urine, specific gravity, 1.025; albumin, slightest possible trace; sediment, few hyaline casts. Blood: hemoglobin, 80 per cent.; leukocytes, 13,000.

February 17: Dyspnea is very much less to-day; no cyanosis.

February 19: Urine, specific gravity, 1.026; albumin, 0; sediment negative.

CASE 11.—M. R. (medical No. 837), man, aged 53, admitted Feb. 11, 1914, discharged Feb. 21, 1914. Diagnosis: chronic valvular disease, mitral stenosis. The past history has no bearing on the present condition. For three months the patient has noticed dyspnea on exertion. This has gradually increased in severity until at present any slight exertion practically exhausts him. He has had no edema.

On examination there is slight cyanosis of the lips and marked dyspnea, although the patient is able to lie flat on his back. Heart: left border 11.5 cm. to the left of the midsternal line in the fifth space; right border is at the right sternal margin. The action is regular. The first sound at the apex is loud and snapping, no definite systolic murmur heard. Second sound is distant and followed by a long, rumbling diastolic murmur with presystolic accentuation. Both sounds are weak at the base. Lungs: numerous fine, moist râles at both bases posteriorly. Liver not enlarged or tender. No edema.

Urine, specific gravity, 1.010; albumin, trace; sediment, occasional hyaline cast.

Blood, hemoglobin, 105 per cent.; leukocytes, 15,000.

The dyspnea disappeared gradually in a few days, and on discharge the patient's respiration was normal except for dyspnea on exertion.

CASE 12.—A. J., man, aged 52, admitted Feb. 17, 1914. Diagnosis: chronic myocarditis. There is nothing in the past history of the patient which has any relation to the present disease. He was first admitted to this hospital Oct. 31, 1913, at which time he had very severe dyspnea. The dyspnea had persisted for about six weeks. There was no edema. November 11, the phthalein output in two hours was 55 per cent. He was discharged much improved November 12. Since his discharge he has become progressively more short of breath, and when admitted the second time was dyspneic and had Cheyne-Stokes respiration.

Heart: Left border 18.5 cm. to left of midsternal line in sixth interspace, right border 3.5 cm. to right in fourth interspace; action regular; rate 90. At the apex the sounds are fairly well audible, and there is a systolic murmur. Sounds are distant at the base. Lungs: moderate dulness with diminution in intensity of breath-sounds and a few râles at both bases posteriorly. Liver: edge felt 7 cm. below the costal margin. It is not tender. Much edema of legs. Blood-pressure: systolic, 130; diastolic, 98.

February 18: Urine, specific gravity, 1.026; albumin, trace; sediment, rare cells and granular casts. Blood: hemoglobin, 108 per cent.; leukocytes, 10,200. Phthalein output in two hours, 27.0 per cent.

February 23: The patient has had no cyanosis. He is rather pale. He has orthopnea. Cheyne-Stokes respiration has persisted and is rather more marked.

DISCUSSION OF CASES 6 TO 12

The number of cases reported here is not large, but the findings are all of the same general type and of the same order of magnitude as are reported in other analogous studies, so that they represent fairly well-recognized types of cases. It is comparatively easy to classify them according to the laboratory findings and by such a procedure they fall into two main groups. One of these is somewhat analogous to the "special" group of Lewis, especially in that the patients show a decreased alveolar carbon dioxide. In this series, however, the attempt has been made to rule out or take account of any renal element in the cases. The second group corresponds more or less to Lewis' "cardiac cases." Group 1 consists of Cases 6, 7 and 12, in which on the whole the highest grade of dyspnea occurred. Cases 6 and 7 are certainly as pure cardiac cases as one sees. Patient 12, with a slightly decreased phthalein output, probably has some renal involvement and arteriosclerosis. This group is characterized by a low tension of the alveolar carbon dioxide during the dyspnea period, which is followed by a rise when compensation is regained. The determinations of the pH in the blood, however, show that the actual hydrogen-ion concentration of the blood is at or below the low limits of normal. Certainly the reaction of the blood does not tend to shift toward the acid side, although the considerable drop of the alveolar carbon dioxide in the cases makes it probable that there is some increase of non-volatile acids in the blood. The urinary ammonia was neither relatively nor absolutely increased. In one case there was a mod-

TABLE 4.—NEPHRITIS WITH CARDIAC DECOMPENSATION

Case	Date, 1914	Non-Protein Nitrogen mg. per 100 c.c.	H-ion Concentration of Blood		Alveolar CO ₂ mm.	Phthalein Output in 2 Hours. Normal from 40 to 60 Per Cent.	Remarks
			Tension of CO ₂ in mm.	Ph.			
J. W....	2/7	28.9	41.9	7.38	30.9	61.0	Marked cyanosis. Dyspnea. Blood-pressure, systolic 130, diastolic 85.
	2/8	30.8	Dyspnea and cyanosis less, but distinct.
	2/9	23.1	42.8 33.4	7.34 7.44 33.6	Slight cyanosis. Much less dyspnea.
	2/10	36.4	Much more comfortable.
	2/11	18.1	44.6 37.7	7.44 7.51 36.0	Respiration 17.
	2/12	39.4	Practically no cyanosis or dyspnea.
	2/15	40.9		
	2/17	22.1	41.1		
J. F.....	1/26	34.0	42.0 35.0	7.50 7.53 34.7	50.0	Considerable cyanosis. Moderate dyspnea.
	1/30	43.5	7.47	41.9	Slight cyanosis. Respiration 14. No dyspnea.
H. N....	1/13	37.8	40.0	Marked cyanosis. Respiration quiet 26. Dyspnea on exertion.
	1/14	38.3		
	1/15	37.7		
	1/16	39.3		
	1/19	37.4		
	1/20	31.4	39.7	7.45	38.4		
A. M....	2/19	20.7	43.5	7.45	4.44	Very marked dyspnea. Slight cyanosis. Respiration 30, labored.
	2/20	41.5	Very marked dyspnea. Very slight cyanosis.
	2/21	38.2	Respiration easier. Color is normal. Still has considerable dyspnea.
	2/23	42.3	7.50	41.2	40.0	Respiration still rapid, but not labored. No cyanosis. Blood-pressure = sys. 135, dias. 80.

TABLE 4.—NEPHRITIS WITH CARDIAC DECOMPENSATION — (Continued)

Case	Date, 1914	Non-Protein Nitrogen mg. per 100 c.c.	H-ion Concentration of Blood		Alveolar CO ₂ mm.	Phthalein Output in 2 Hours. Normal from 40 to 60 Per Cent.	Remarks
			Tension of CO ₂ in mm.	Ph.			
I. J.....	2/16	35.7	42.0	7.40	46.0	48.0	Dyspnea. Respiration 35. Lies flat on back. No cyanosis. No especial pallor.
	2/17	42.1	Dyspnea less. No cyanosis. Has received 6.0 gm. NaH CO ₃ since yesterday.
M. R.....	2/11	31.0	46.4	7.40	46.5	49.0	Moderate dyspnea, much increased by moving. Lies flat on his back. Slight cyanosis.
	2/12	46.7	Very little dyspnea or cyanosis. Blood - pressure, sys. 110, dias. 70.
A. J.....	2/18	44.6	7.44	35.0	27.0	Very marked dyspnea and orthopnea. Very slight cyanosis. Moderate Cheyne-Stokes respiration.
	2/19	29.9	Cheyne - Stokes respiration.
	2/20	44.2	43.0	7.42	31.2	Cheyne - Stokes respiration.
	2/23	31.8	Cheyne - Stokes respiration. Has been given NaHCO ₃ .

erately high hydrogen-ion concentration of the urine (ph. = 4.6) and a slight increase of "retained base" which fell as compensation was established. The urine, however, showed no evidence of marked acidosis.

The second group consists of Cases 9, 10 and 11. These are characterized by a normal or very slightly increased carbon dioxide tension of the alveolar air. In two of the patients there was a tendency of the carbon dioxide to fall as compensation occurred. There was not enough involvement of the lungs to account for this rise in carbon dioxide

on the basis of an interference with respiratory exchange. Cyanosis was not marked in any of them. The hydrogen-ion concentration of the blood saturated at the tension of alveolar carbon dioxide was normal. There was no evidence in either the blood or alveolar-air determinations of an increase in non-volatile acids in the blood. The rise in alveolar carbon dioxide which may possibly be regarded as abnormal was compensated, so that reaction of the blood was normal. In other conditions a much higher alveolar carbon dioxide may be found without causing dyspnea. Thus in a case of emphysema the alveolar carbon dioxide tension was 52.6 mm., the ph. of the blood saturated at 44.0 mm. was 7.56 and saturated at 53.4 mm. was 7.45. The patient showed no dyspnea.

Case 8 was one of mitral stenosis with considerable cyanosis, but little dyspnea, except when the patient moved. Both the alveolar air and the hydrogen-ion concentration of the blood were normal. Thus in the group of cases in which the severest dyspnea occurred, although the alveolar carbon dioxide is low, the hydrogen-ion concentration of the blood tends to be lower than normal. In spite of the fact that there is evidence of some increase of non-volatile acids, the respiratory center is responding to a stimulus that is apparently less than normal. The increased formation of non-volatile acids seems to be overcompensated by the decrease in carbon dioxide. In the second group of cases which showed more moderate dyspnea, the alveolar carbon dioxide is somewhat increased, but the hydrogen-ion concentration of the blood is normal. There was thus no evidence of an increase of non-volatile acids in the blood.

It is quite striking that in neither group of cases is there any evidence of a very high grade of acidosis. The same degree of depression of alveolar carbon dioxide is frequently seen in other conditions—uremia, diabetes—without producing any particularly obvious effect on the respiratory center. Thus in one case of diabetes, in which there was an ammonia output of 5 gm. in twenty-four hours, the alveolar carbon dioxide tension was 32 mm., while in a second case, in which there was a similar ammonia output, the carbon dioxide tension was only 26 mm. Neither of the patients had any disturbance of respiration which was evident on a routine clinical examination.

The degree of cyanosis makes it improbable that lack of oxygen is an important factor in the direct stimulus to this type of dyspnea. Since, then, there is apparently no very great change in the nature of the stimulus, one must seek some other condition which may play a part in causing this profound change in respiration. It is of course possible that the underlying factor is some as yet unknown substance which affects the stimulus. We have, however, already seen

that in considering the mechanism of the control of respiration, it is necessary to take into account not only the stimulus to respiration, but also the excitability of the respiratory center. Porges³⁰ discards this latter factor, as he says that even Hasselbalch calculates that hyperexcitability of the respiratory center would not practically produce a fall in the alveolar carbon dioxide tension of over 5 mm. In the second group of cases, however, there is no fall in the alveolar carbon dioxide, and no especial change in the pH. of the blood so that here the theory of a hyperexcitability is quite tenable. In the first group of cases there is certainly evidence of some acidosis, not such a degree as would greatly affect the respiration normally, but one which, in the presence of a hyperexcitable respiratory center, might produce much more marked change in breathing.

There is nothing inherently untenable in the conception of a variable excitability of the respiratory center. Variations in the excitability of all nervous mechanisms are continually seen in both physiological and pathological conditions. Indeed, it is almost impossible to imagine the excitability of the controlling center of any physiological mechanism as being a constant. The experimental studies showing variations in the excitability of the respiratory center have already been referred to. It is certainly much more than probable that similar and perhaps greater variations may exist under pathological conditions. Moreover, certain simple clinical facts point to the existence of such variations in decompensated heart-disease. Thus the dyspnea produced by moderate exertion can hardly be the result of a change in the stimulus alone. Similarly morphin, one of the most definite effects of which is to depress the excitability of the respiratory center, is certainly the most efficient drug in the control of cardiac dyspnea. A general consideration of the clinical facts and laboratory findings makes it highly probable that, while in some cases of cardiac dyspnea the stimulus to respiration is increased by the production of a moderate grade of acidosis, another important causative element is an increase in the excitability of the respiratory center.

It is hardly possible at present to offer an adequate explanation of the cause of an increase in excitability of the respiratory center. If, as Lindhard⁷ considers to be proved, a diminution of oxygen tension increases the excitability of the center, one might consider that with a slowing of the circulation due to cardiac insufficiency the oxygen tension in the respiratory center becomes decreased, and the center becomes hyperexcitable so that it responds to a lesser stimulus than normally and more actively to a given stimulus. In very severe cases of cardiac insufficiency with a greater slowing of blood-flow there would be, added to this factor, a change in the stimulus itself due to

the passage into the blood of acid substances—the partially oxidized products of metabolism. In a similar way, renal disease would be a contributing factor in the causation of dyspnea, for as soon as the kidney begins to fail in its function of acid excretion, the regulatory mechanism controlling the constancy of blood-reaction is upset, and there will be a tendency to call on the respiration to counteract the threatened acidosis. Haldane and his associates⁵ have lately laid much stress on the fundamental function of the kidney in replacing the hydrogen-ion concentration of the blood and thus of indirectly influencing respiration. In so-called “cardiorenal” disease, the weakening of the myocardium would produce less adequate, slower circulation. One result would probably be an increased excitability of the respiratory center due to diminished oxygen tension in it. A second result would be an interference with renal excretion (as shown by the decreased output of phthalein during the period of decompensation) and the tendency to retain acids in the blood. The resulting acidosis while not necessarily of a grade to affect respiration in a normal person, may produce profound dyspnea in a patient with a weak heart. In cases of pure cardiac disease with decompensation and slowing of the circulation the lowered oxygen tension would increase the excitability of the respiratory center, and in more severe failure of the heart with the production of passive congestion there will be a temporary upset of renal function in the same way, although perhaps in a less degree than when kidneys are themselves organically diseased. Thus in simple cardiac disease, failure and slowing of the circulation may cause a disturbance in renal excretion, as well as an incomplete oxidation of abnormal acids. Both of these tend to produce an acidosis. The resulting change in the stimulus to respiration, even if it is slight, when acting on a respiratory center rendered hyperexcitable by an inadequate blood-flow, may well cause dyspnea.

In a somewhat similar manner Boothby³² has recently suggested a slowing of the blood-flow as an explanation of the unusual condition of hyperpnea after forced respiration. He believes that the slowing may bring about a condition of oxygen-want, and in consequence, the presence of lactic acid or some similar exciting substance, which, in conjunction with the carbon dioxid, keeps the respiratory center excited so that the normal apnea does not appear. The only essential difference between this theory and the one put forward above is as to whether the oxygen-want resulting from an inadequate circulation shall be regarded as acting directly on the respiratory center by increasing its excitability, or as causing the presence of partially oxidized substances in the blood which are themselves added to the

32. Boothby: *Jour. Physiol.*, 1912, xlv, 328.

stimulus to respiration. It is to be remembered that in the cases of dyspnea studied by Lewis,²⁰ only a very slight increase in the lactic acid content was found, in other than moribund patients.

The direct determination of the excitability of the respiratory center under pathological conditions is planned as the next step in this investigation. It is quite possible that the excitability of the respiratory center may be an index of the functional adequacy of the circulation.

CONCLUSIONS

The mild grade of acidosis which is often associated with uncomplicated chronic nephritis is compensated for by the increased excretion of acids by the kidney.

It is only in uremia and usually only in very advanced uremia that non-volatile acids accumulate in the blood in an amount sufficient to cause depression of the tension of carbon dioxide in the alveolar air.

In the terminal stage of uremia there may be a high grade of acidosis.

The development of acidosis bears little relation to the accumulation of non-protein nitrogen in the blood or to the output of phenolsulphonephthalein. Determinations of both of these may show extreme abnormalities before any marked degree of acidosis develops.

The development of acidosis is not the direct or sole cause of dyspnea associated with cardiorenal disease. A high grade of acidosis may exist without causing a change in respiration which is evident on the ordinary clinical examination.

In some cases of cardiac disease accompanied by dyspnea there is evidence of a slight accumulation of non-volatile acids in the blood. In other cases there is no evidence of such an accumulation.

The tension of the carbon dioxide in the alveolar air is normal or very slightly increased.

The hydrogen-ion concentration of the blood remains normal.

In neither group of cases is the degree of acidosis sufficient to account for the dyspnea on the basis of an increase in the stimulus to respiration alone.

It seems probable that an important factor in the causation of dyspnea in cardiac disease is an increase in the excitability of the respiratory center. Such a change in excitability may well be caused by a lowering of the oxygen tension, and be dependent on an inadequate blood-flow.

I wish to express my gratitude to Miss B. I. Barker for her unfailing assistance in carrying out much of the analytical work on which this paper is based.