OBSERVATIONS UPON ACIDOSIS IN DIABETES MELLITUS.*

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DURING the last twelve years investigations upon the question of acidosis in diabetes have been in progress at Guy's Hospital. The chief practical result of the work has been the demonstration that analyses of the carbon dioxide in the alveolar air of the lungs afford an index of the degree of acidosis, and a guide in treatment and prognosis.

When the work began there was current the theory that in diabetes the blood is unable, owing to its diminished alkalinity, to take up the normal amount of carbon dioxide. The pressure of the gas, therefore, rises in the tissues, and the respiratory centre is stimulated to the great activity seen in the typical "air-hunger" of coma. The accumulation of carbon dioxide leads to a cessation of its production, and, according to Pavy, "death takes place when the non-removal has attained a sufficient height to reduce the occurrence of activity to a point which is no longer consistent with the continuance of life." According to this theory, diabetic coma is a condition of narcosis due to carbon dioxide.

Our first series of observations¹ was concerned with the amount of carbon dioxide in the venous blood and the alkalinity of the serum, as estimated by Wright's method. The blood required for the determination of the gases by the mercurial pump was drawn from a vein in the arm by means of an antitoxin syringe which contained a few cubic centimetres of a solution of potassium oxalate. The following tables (I, I A, I B) give the results:

TABLE I.—Diabetes without Coma.

Case.	Date.	CO ₂ in Venous Blood; vols. per cent.	Alkalinity of Serum.	Urine in c.cm. per day.	Dextrose in grams.	Nitrogen in grams.	N/D	Ammonia Nitrogen in grams.	Percentage Nitrogen as Ammonia.
5	19.xii.02	33.4	N/32						
9	9.ii.03	24.2	N/45						
15	21.ii.03	56.5	N/25						
	6.v.03	52.0	N/25						
	12.v.03	44.6	N/25						
	3.vi.03	30.8	N/40	2280	115.8	15.6	7.4	3.2	20.2
	18.vi.03	45.4	N/27	3930	89.7	13.9	6.5	1.4	10.2
20	2.vii.03	40.0	N/27	3350	112.6	13.8	8.2	0.7	5.2
		70.9	N/25						

* See Table II.

Remarks on Table I.

Case 15.—T. M., male, aged 45. Duration of disease at least four or five years. Discharged from hospital in October, 1903.

TABLE I A.—Diabetic Coma.

Case.	Date.	CO ₂ in Venous Blood; vols. per cent.	Alkalinity of Serum.	Urine in c.cm. per day.	Dextrose in grams.	Nitrogen in grams.	N/D	Ammonia Nitrogen in grams.	Percentage Nitrogen as Ammonia.
1	14.x.02	13.0	N/70						
	15.x.02	16.8							
2	17.x.02	24.0	N/80						
3	2.xii.02	14.8	N/57	1100	40	4.8	7	1.2	23.5
	3.xii.02	13.8	N/45	500	10	0.8	15	0.2	18
4	14.xii.02	13.7							
		22.8	N/60						
		22.1							
7	9.ii.03	20.1	N/90						
11	17.iii.03	14.1	N/45	2620	70	11.3	7	2.0	14.5
		12.2							
13	4.v.03	28.0							
14	4.v.03	17.6	N/40						
21	12.v.04	17.9	N/35						
24	5.ii.05	18.9	N/35						

* After administration of sodium bicarbonate. † See Table II.

Remarks on Table I A.

Case 3.—Female. December 2nd, 1902, sodium bicarbonate intravenously. Died on December 3rd.

Case 11.—C., female, aged 34. Illness began about November, 1902. Died on March 22nd, 1903; bronchopneumonia, hyperpyrexia.

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Case 24.—T. T., male, aged 31. Wasting and thirst during previous twelve months. Coma began on February 3rd, 1905. Recovered from coma after infusion of sodium bicarbonate. Discharged from hospital July 11th, 1905. See Table IV C.

TABLE I B.—Other Diseases (for purpose of Control).

Case.	Date.	Carbon Dioxide in Venous Blood; vols. per cent.	Alkalinity of Serum.	Remarks.
8	11.ii.03	25.5	N/30	Empyema; dyspnoea on this date.
	17.ii.03	43.0	N/27	
	20.ii.03	41.8	N/27	
10	26.ii.03	51.4	N/25	Ascites, malignant.
12	30.iii.03	43.2	N/25	Pernicious anaemia.

It will be seen from the tables that in the cases of diabetes there is a relation between the alkalinity of the serum and the amount of carbon dioxide in the venous blood; the two rise and fall together without being actually parallel. In the non-diabetic cases, which were taken for the purpose of control, the alkalinity of the serum ranged from N/25 to N/30. According to Wright, the average alkalinity of the serum of healthy subjects corresponds to about N/30 NaOH. As regards the amount of carbon dioxide in healthy venous blood the usual figure is between 40 and 50 volumes per cent. In the first determination in Case 8 there was dyspnoea due to empyema, and this probably accounts for the low value of the carbon dioxide in the venous blood.

These results for diabetes confirm those obtained by Minkowski and Kraus, but they do not prove the correctness of the theory of narcosis due to carbon dioxide. The important question is the tension or partial pressure of the carbon dioxide in the blood and tissues. Attempts, therefore, were made to obtain information upon these points. The capacity of venous blood to take up carbon dioxide was determined in cases of diabetes, diabetic coma, and other diseases. Similar estimations were made for the urine, for it was assumed that the tension of carbon dioxide in the renal cells would not be raised without a corresponding increase in that gas in the urine. The results are given in the following table (No. II).

TABLE II.

Case.	Date.	CO ₂ in Venous Blood; vols. per cent.	Alkalinity of Serum.	Total CO ₂ in Urine; vols. per cent.	Saturation Capacity of the Venous Blood for CO ₂ ; vols. per cent.	Saturation Capacity of the Urine for CO ₂ ; vols. per cent.	Disease.
5	19.xii.02	33.4	N/32	7.1	208	99	Diabetic without coma.
	19.ii.03	28.1	N/30	8.9	238	93	
9	21.ii.03	53.5	N/25			87.1	"
3	3.xii.02		N/50		220		Diabetic coma.
		13.8	N/45	5.1		82	"
		13.7					"
4	14.xii.02	22.8	N/60	5.0	301	91	"
		22.1					"
8	17.ii.03	43.0	N/27	11.1			Empyema.
	20.ii.03	38.8	N/27	8.4	212		"
10	25.ii.03	48.5	N/25	6.7	223	139	Ascites, malignant.
12	30.iii.03	43.2	N/25	2.7			Pernicious anaemia.
				2.6			"

* Sodium bicarbonate had been administered for several days before this date.

In addition, attempts² were made to estimate directly the tension of the carbon dioxide in the venous blood by exposing it in a glass sampler to atmospheres of known composition, and kept in a water bath at 37° (98.6°). After an hour or two the composition of the atmosphere and of the gaseous content of the blood was determined. For the analysis of the gases in the small amount of blood the original form of the apparatus introduced by Barcroft and Haldane was used; the difficulty of taking human blood with the ammoniacal solution rendered the results unreliable. The venous blood from a case (No. 15) of

diabetes without acidosis appeared to have a tension between 5 and 7 per cent. of an atmosphere; whereas venous blood from a case of coma with acidosis and an alveolar pressure of carbon dioxide of 2.29 per cent. absorbed carbon dioxide from an atmosphere containing 4.7 volumes per cent.

It is now necessary to consider the errors which may accompany such determinations as these already given. The serum is not the blood; it is not even a normal constituent of the blood. The alkalinity of the serum is not necessarily the same as that of the blood or the plasma. Blood is both alkaline and acid in the sense that it can combine with acids and alkalis. Physico-chemical investigations upon the relative concentrations of acid and basic ions in blood show that in health its reaction is alkaline to such a slight degree that it may be said to be neutral. The blood is a living tissue, and undergoes changes when it is removed from the body; the gases in the blood are affected, carbon dioxide increases, and oxygen decreases. If the bandage upon the arm delays the flow of the venous blood too much before the sample is withdrawn, more carbon dioxide is taken up by the blood from the tissues, and more oxygen is lost by the blood to the tissues. These sources of error will raise the percentage of carbon dioxide, and tend to make the values too high. The argument, however, based upon the low values will not be minimized by these sources of error, which are further discounted by the observations on the blood in other diseases taken for the purpose of control. The figures given in Table II show that the venous blood from patients in diabetic coma will absorb 200 to 300 volumes per cent. of carbon dioxide at the temperature of the room when pure carbon dioxide is passed through it. Although it is probable from this experiment that the blood circulating in the body of the patient has a great capacity for taking up carbon dioxide, it is necessary to prove it by actual observation. This was done in the following way; by means of a tight bandage upon the arm the flow of the venous blood was stopped for a minute or two before the sample of blood was withdrawn into the syringe. This retardation of the flow caused the blood in the small vessels to be exposed for a longer time to the action of the tissues in which the carbon dioxide is produced. The results, as shown in the following table (No. III) prove that the blood in the body of a diabetic patient has a great capacity for absorption.

TABLE III.

Case.	Date.	CO ₂ in Venous Blood; vols. per cent.	Alkalinity of Serum.	Urine in c.cm. per day.	Dextrose in grams.	Nitrogen in grams.	$\frac{N}{D}$	Ammonia Nitrogen in grams.	Percentage Nitrogen as Ammonia.	Acidity.
15	8.ix.03	61.8	N/25	4550	399	12.2	32.4	0.6	4.9	3
22	13.vi.04	39.9* 43.2†	N/30	3430	113.5	22	5.1	5.8	26.5	32.8

* Loose bandage.

† Tight bandage.

Remarks on Table III.

Case 15.—T. M.; diabetes. See Tables I and IV.

Case 22.—D., male; recovering from diabetic coma; alveolar carbon dioxide=2.7 per cent. See Table IVc.

It was desirable in the next place to determine the tension of the gases of the blood circulating in the body, for, apart from the sources of error in the exposure of blood to known atmospheres, it is not often possible to obtain samples of blood. Moreover, blood withdrawn from a vein in the arm is not a fair sample of the mass of the venous blood. The mixed venous blood from the right side of the heart contains carbon dioxide which has been taken up from the various tissues of the body, and it is probable that the pressure of the gas is below that which obtains at the seat of production. In passing through the lungs the blood gives off carbon dioxide and takes up oxygen; an analysis therefore of the air in the alveoli of the lungs will afford an estimate of the pressure of those gases in the arterial blood. The exact value of the estimate will depend upon the nature of this process of gaseous interchange, whether it be one of simple diffusion or whether there be an active secretion inwards of oxygen and an active excretion outwards of carbon dioxide. The

balance of evidence is in favour of diffusion. If such be the process the pressure of carbon dioxide in the alveolar air may be considered to be a little below that of the gas in the arterial blood, and the oxygen would show a reverse relationship. The alveolar air can be obtained by the method introduced by Haldane and Priestley. In these observations a slight modification was made, the last portion of an adequate expiration was collected in a vacuum sampler and, in the case of unconscious patients in coma, a small mask was placed over the face. The results are shown in the following tables (IV, IVA, IVb, IVc).

TABLE IV.—Diabetes.

Case.	Date.	Alveolar Air.*		CO ₂ O ₂	Urine in c.cm. per day.	Dextrose in grams.	Nitrogen in grams.	$\frac{N}{D}$	Ammonia Nitrogen in grams.	Percentage Nitrogen as Ammonia.	Acidity.
		CO ₂ , vols. per cent.	Oxygen vols. per cent.								
115	10.ix.03	4.98 4.05			5030	426	13.3	31.9	0.3	2.5	6
23	17.vi.04	5.62 5.62 6.12	14.06 13.39 13.04	0.78 0.70 0.73	2560	128.8	24.3	5.3	1.8	7.4	24
	8.vii.04	5.45 5.26 5.48	13.94 14.00 14.13	0.74 0.70 0.76	2140	98.2	23.3	4.2	1.4	6.1	26.4
	11.vii.04	5.71 5.55 4.64	13.55 13.93 14.89	0.73 0.70 0.73	1880	57.7	20.9	2.7			43.8
	14.vii.04	4.53 5.01 5.10	15.52 14.35 14.45	0.81 0.71 0.75							
	19.vii.04	4.51 4.90	15.44 14.85	0.79 0.77	2270 2410	65.1 119.3	20.8 19.4	3.1 6.1	2.8 2.9	13.3 15.1	31.3 26.9
M.30	21.vii.13	5.15 4.55 5.22	14.30 16.13 15.07	0.73 0.93 0.87							
E.15	3.ix.13	4.26 4.03 5.39									
	9.x.13	4.91 5.21 4.46									
Mi.30	20.x.13	4.79 6.99 6.77									
A.47	21.vii.13	6.77 6.54 6.44	12.16 12.58 12.68	0.76 0.77 0.76							
	22.vii.13	6.44 5.73 5.25	12.65 12.56 14.60	0.73 0.63 0.79							
	23.vii.13	5.48 5.16 4.83	14.72 14.52 15.10	0.85 0.76 0.79							
	25.vii.13	5.01 4.93 4.64	14.68 14.01 14.89	0.76 0.65 0.73							
	28.vii.13	4.63 4.34 4.43	14.85 14.93 14.47	0.71 0.68 0.63							
	1.viii.13	4.99 5.61 5.36	14.24 14.82 14.40	0.69 0.90 0.78							
	6.viii.13	5.31 4.77 5.13	14.81 15.95 15.58	0.83 0.94 0.95							
	11.viii.13	5.08 5.31 5.22	15.00 15.00 15.00	0.82 0.82 0.82							
	18.viii.13	4.51									
	20.viii.13										
	21.viii.13										

* Not reduced to 0° and 760 mm.

† See Tables I and III.

TABLE IVA.—Diabetic Coma.

Case.	Date.	Alveolar Air.		CO ₂ O ₂	Remarks.
		Carbon Dioxide, vols. per cent.	Oxygen, vols. per cent.		
21	12.v.04	2.55 2.18 2.01	17.37 17.66 17.89	0.65 0.61 0.61	L., male; milk diet. See Table I.
24	3.ii.05	1.16 1.09 1.13 1.13 1.13 1.08	19.40 19.54 19.37 19.47 19.42 19.52	0.71 0.74 0.73 0.73 0.70 0.71	See Table I. Milk and beef-tea. Infused with sodium bicarbonate.
	4.ii.05	1.26 1.24 1.24	19.34 19.16 19.31	0.75 0.65 0.71	See Table I. Milk and beef-tea. Infused with sodium bicarbonate.
27	11.vi.06	1.59 1.77 1.37 1.52	19.08 18.57 19.93 19.19	0.83 0.70 0.83 0.84	E., male; milk diet.
E.17	20.viii.13	1.14			Female. Three hours after onset of coma and six hours before death.
Mi.30	23.x.13	1.55 1.15			Female. A few hours before death.

Remarks on Table IV.

Case 23.—B., male, aged 25. Onset of illness about ten weeks before admission to hospital on May 27th, 1904. On July 8th he was given diabetic diet and 90 grams of starch; on the 11th diabetic diet and 50 grams of laevulose. Diabetic diet was also given on July 14th, 19th, and 20th, on the latter date 90 grams of starch being also given. The patient was discharged on July 26th, 1904, in improved condition, and with a gain of 6 lb. in body weight. See also Table V.

Case M.30.—H., female; mixed diet.

Case E.15.—Female; mixed diet.

Case M.30.—L., female.

Case A.47.—C., male. (For details of urinary examination see reference 5.) Over 100 grams of sodium bicarbonate were given on July 19th, 1913, and also on July 20th; from July 22nd to August 6th 23 grams were administered daily; and from August 9th to 19th, 46 grams daily.

TABLE IV B.—Passing into Coma.

Case.	Date.	Alveolar Air.		Remarks.
		Carbon dioxide, vols. per cent.	Oxygen, vols. per cent.	
E. 17	18.viii.13	3.63		Female. Three hours after onset of coma and six hours before death.
		3.65		
	20.viii.13	1.14		
Mi. 30	20.x.13	4.46		Female. A few hours before death.
		4.79		
	23.x.13	1.55		

TABLE IV C.—Recovery from Coma.

Case.	Date.	Alveolar Air.		CO ₂ in urine in c.c. per day.	Dextrose in grams.	Nitrogen in grams.	D N	Ammonia Nitrogen in grams.	Percentage Nitrogen as Ammonia.	Acidity.
		CO ₂ vols. per cent.	Oxygen vols. per cent.							
24	3.ii.05	1.16	19.40	0.71						
		1.09	19.54	0.74						
		1.13	19.37	0.66						
		1.13	19.47	0.73						
		1.13	19.42	0.70						
		1.08	19.52	0.71						
	4.ii.05	1.26	19.34	0.75						
		1.24	19.16	0.65						
		1.24	19.31	0.71						
	5.ii.05									
	7.ii.05	3.21	17.27	0.85	6135	139.6	11.9	11.7		
	8.ii.05	3.07	17.60	0.90						
22	8.ii.05	3.22	17.56	0.94	5590	174.4	10.3	16.9	1.5	15
		3.00	17.57	0.86						
		3.19	16.89	0.75	3060	209.5	9.7	21.6	1.6	17.3
					6520	437.6	10.8	40.5	1.1	10.2
		4.62	15.31	0.78	5530					
		2.69	16.87	0.60	3430	113.5	22	5.1	5.8	26.5
	13.iii.05	2.64	17.22	0.66						
		2.64	17.11	0.63						
		2.74								
		2.92	17.96	0.97	2570					
		2.46	17.88	0.76	2350					
		3.93	15.57	0.68	2880					
	14.vi.04	4.41	15.05	0.70						
		4.46	14.60	0.65						
		4.74	14.14	0.65						
		3.42	15.44	0.56	4080	153.4	25.9	5.9	5.2	19.9
		3.38	16.32	0.68						
		3.28	16.08	0.63						
	1.vii.04	3.61	15.52	0.62						
		3.47	15.51	0.59	4400	166.8	27.4	6	5.0	18.4
		3.86	14.55	0.54						
		5.72	13.08	0.68	3410	125.5	19.3	6.5	0.29	1.5
		5.82	12.66	0.65						
		5.76	12.76	0.65						
	9.vii.04	5.67	13.50	0.71						
		4.69	14.40	0.66	3630	127.3	25.1	5.1	1.2	4.8
		4.88	13.72	0.63						
		4.91	13.59	0.62						
		4.05	15.45	0.69						

* Alkaline.

Remarks on Table IVc.

Case 24.—T. T., male, aged 31. February 3rd, 1905: Onset of disease about twenty months before this date. Diabetic diet was started on January 27th, 1905. Coma began; infusion with solution of sodium bicarbonate.

February 4th: Infusion continued.

February 5th: Venous blood contains 18.9 vols. per cent. of carbon dioxide.

February 7th: Patient conscious. β -oxybutyric acid (Ryffel's method) = 9.8 grams.

February 8th: Venous blood contains 32.6 vols. per cent. of carbon dioxide. β -oxybutyric acid = 8.9 grams.

February 21st: Abscess formed at site of infusion. β -oxybutyric acid = 8.5 grams.

March 13th: β -oxybutyric acid = 11.9 grams. Sodium bicarbonate and carbohydrate given in diet.

The patient was discharged on July 11th, 1935, much improved.

Case 22.—D., male, aged 45. Illness began about October, 1903. Diabetic diet began on June 9th, 1904; coma threatening (see Table III).

June 14th, 1904: Diabetic diet.

June 15th: Diabetic diet; body weight 52 kilos.

June 17th: Diabetic diet; alveolar air after holding breath for twenty-five seconds = 3.55 per cent. CO₂ and 13.92 per cent. O₂.

June 24th. Diabetic diet.

June 27th: Diabetic diet, with 65 grams of starch and 42 grams of sodium bicarbonate. Weight of patient 54 kilos.

July 1st: Diabetic diet and 90 grams of starch.

July 7th: Fifth day of diabetic diet and 56 grams of sodium bicarbonate. Weight of patient 56.5 kilos. On this day 90 grams of starch and 25 grams of sodium bicarbonate given.

July 9th: Diabetic diet, with 50 grams of laevulose and 14 grams of sodium bicarbonate.

July 16th: Sixth day of diabetic diet. Alveolar air after holding breath for twenty-five seconds = 4.61 per cent. CO₂ and 13.14 per cent. O₂.

The patient died on August 13th, 1904, from pneumonia.

For the better understanding of the foregoing tables it is necessary to give the average values for the composition of the alveolar air of healthy subjects. The means of fifty observations upon ten men are 5.57 volumes per cent. of carbon dioxide and 14.89 of oxygen; the maxima are 6.11 and 15.59, the minima 4.87 and 13.91. In women and children the mean alveolar pressure of carbon dioxide is, according to Fitzgerald and Haldane, about 8 per cent. lower than in men.

Diabetic patients may have alveolar pressures of carbon dioxide, which are within the normal limits, although they are passing large quantities of sugar in the urine. When there is acidosis the carbon dioxide falls and in diabetic coma reaches as low a figure as 1 or 2 volumes per cent. If under treatment with sodium bicarbonate the patient recovers, the pressure of carbon dioxide may gradually rise to the normal level, as is well shown in Case No. 22. Moreover, in diabetic patients massive doses of sodium bicarbonate may raise the pressure to a height beyond the normal range; this is shown by the observations on Case A.47 in whom the highest figure was 6.99 volumes per cent.

To determine more closely the conditions as regards the carbon dioxide, observations were made upon the composition of the alveolar air before and after the patient had held his breath as long as he could.

TABLE V.

Case.	Date.	Alveolar Air Before Holding Breath.		Alveolar Air After Holding Breath.		Duration of Holding Breath in Seconds.
		Carbon Dioxide, vols. per cent.	Oxygen, vols. per cent.	Carbon Dioxide, vols. per cent.	Oxygen, vols. per cent.	
A.B.*		5.77	15.12	7.35	9.67	40
22†	15.vi.04	2.92	17.96	3.55	13.92	25
	18.vi.04	2.46	17.88	4.01	15.18	20
	16.vii.04	4.05	15.45	4.61	13.14	25
23:	14.vii.04	4.53	15.52	5.70	11.00	23
		4.64	14.89			
	19.vii.04	4.51	15.44	5.41	10.75	42

* Healthy man. † Recovering from diabetic coma (see Table IVc).
‡ Diabetes (see Table IV).

The "breaking point" on holding the breath was determined by the discomfort, which, as observations on healthy men show, is produced by the accumulated carbon dioxide rather than by the fall in the amount of oxygen. In these patients the pressure of carbon dioxide was raised, but in no case did it reach normal figures. This result indicates that other substances, in addition to carbon dioxide, were stimulating the respiratory centre. The low values in the patient recovering from coma would suggest that it is due to the condition of acidosis. If this interpretation be correct it would be expected that the pulmonary ventilation would not correspond with the pressure of the alveolar carbon dioxide. The amount of

air breathed by a patient was determined by means of a mask provided with inspiratory and expiratory valves and connected with a meter of low resistance. The following table (VI) shows that the volume of air breathed was greatest when the pressure of the alveolar carbon dioxide was least.

TABLE VI.

Case.	Condition.	Date.	Alveolar Air.		Volume of Air Breathed per Minute in Litres at 15°.	Respirations per minute.
			Carbon Dioxide, vols. per cent.	Oxygen, vols. per cent.		
24*	Diabetic coma	4.ii.05	1.26	19.34	9 9	19 18
	Recovering from coma	7.ii.05	3.21	17.27	3.75 3	18 18
	Recovered from coma	14.iii.05	4.62	15.31	5.3 5.2	20 20

* See Table IVc.

Soon after the first observation the comatose patient was given to breathe a mixture containing 3.9 volumes per cent. carbon dioxide and 18.42 volumes per cent. oxygen; the volume breathed was 8 and 10 litres with 22 and 20 respirations per minute; the pulse became more forcible, although not increased in rate, and a tendency to struggle complicated the result. Ten days later, when the patient had recovered from coma, the ordinary volume of air breathed, 5.3 litres, was increased to 7.65 and 8 litres in two consecutive minutes, when he inspired a mixture containing 5.92 volumes per cent. carbon dioxide and 20.08 volumes per cent. oxygen. The mixture made him breathe more deeply at a rate of 14 and 15 respirations per minute, and the alveolar air taken directly after contained 5.48 volumes per cent. carbon dioxide. The patient himself said that the gas caused a feeling of suffocation.

To remove any effects due to a decrease in the amount of oxygen further observations were made upon the same patient. The alveolar air contained 3.19 volumes per cent. carbon dioxide and 16.89 oxygen on February 21st, 1905; the patient then breathed in and out of a big gas-bag containing 5.78 volumes per cent. carbon dioxide and 84.45 oxygen until his breathing became much deeper. A sample of alveolar air taken directly after contained 4.83 volumes per cent. carbon dioxide, and 52.67 oxygen and the bag 5.82 carbon dioxide and 79.03 oxygen. On the same day the patient breathed in and out of a small bag of oxygen until his breathing was deeper; a sample of his alveolar air was then taken for analysis; it contained 3.96 volumes per cent. carbon dioxide and 39.58 oxygen and the bag 0.82 volumes per cent. carbon dioxide and 77.21 oxygen. The first of these observations shows that the blood in the lungs absorbed carbon dioxide from the mixture when the pressure of that gas was above that present in the patient's ordinary alveolar air (3.19 volumes per cent.). The tension of the gas in the arterial blood was probably between 3 and 4 per cent. of an atmosphere. This was confirmed by the second observation; the breathing became deeper when the alveolar carbon dioxide was raised to 3.96 per cent. by rebreathing. In both cases the oxygen was present in great excess.

A large number of observations have been made upon the composition of the urine at different stages of the disease and under various methods of treatment. Only a few of the data have been given in this paper. The total respiratory exchange was determined in only one case, and further observations are necessary before it would be possible to discuss the significance of the respiratory quotients contained in the tables. The research has been continued and extended by Dr. Poulton, who is communicating some of his results in this number of the JOURNAL.

REFERENCES.

Beddard, Pembrey, and Spriggs: ¹ Some Observations on the Blood Gases in Diabetes, *Lancet*, May 16th, 1903; ² The Quantity and Pressure of Carbon Dioxide in Venous Blood and in Alveolar Air in Cases of Diabetes and Diabetic Coma, *Proc. Physiol. Soc., Journ. Physiol.*, xxxi, 1904; ³ Further Observations, etc., *ibid.*, xxxvii, 1908; ⁴ The Relation of Acidosis to the Carbon Dioxide of the Blood in Diabetic Coma, *Lancet*, June 19th, 1909. ⁵ Kennaway, Pembrey, and Poulton: Observations on Acidosis, *Proc. Physiol. Soc., Journ. Physiol.*, xlvii, 1913.

THE SIGNIFICANCE OF ALVEOLAR CARBON DIOXIDE DETERMINATIONS IN THE TREATMENT AND PROGNOSIS OF DIABETES.*

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THE study of the phenomena of respiration was put on a firm basis when Haldane and Priestley¹ introduced a simple and accurate method of obtaining samples of air from the alveoli of the lungs. By this method Beddard, Pembrey, and Spriggs^{1,2} first showed that in diabetes the partial pressure of the carbon dioxide in the alveolar air falls with increasing acidosis, and during coma reaches a very low point, and when low can be raised by the administration of sodium bicarbonate.

The true explanation of these facts is based on the theory of neutrality regulation—that is, the power of the organism to preserve the neutral or very slightly alkaline reaction of its arterial blood at a nearly constant level. In diabetes where there is an increased production of unusual acids at least three mechanisms are brought into play to counteract their effects:

1. The acidity of the urine is increased.
2. There is an increased formation of ammonia.
3. The partial pressure of CO₂ in the alveolar air is lowered.

It is the last factor which is particularly important in the present connexion, and which has only lately been realized, owing to the work of Haldane, Barcroft, and Hasselbalch.

The venous blood gives off into the alveoli of the lungs its excess of CO₂, and this is prevented from accumulating by the respiratory ventilation. In health the latter is so adjusted that the percentage of CO₂ remains at a constant value, between 5 and 6 per cent. The arterial blood leaves the lungs saturated with CO₂, corresponding to its partial pressure in the alveoli. By the simple expedient of increasing the pulmonary ventilation the percentage of CO₂ in the alveolar air will be diminished without necessarily altering very much the actual quantity given off by the lungs, which depends on the body metabolism. Inasmuch as the alveolar CO₂ is lowered by this means, the amount contained in the arterial blood will be diminished, that is, the arterial blood will become more alkaline.

In diabetes, when the acidosis is severe, the respiratory centre is stimulated by excess of acid, so that the pulmonary respiration is increased, and the diminution of CO₂ in the arterial blood compensates for the quantities of aceto-acetic acid and β -oxybutyric acid in the circulation. Hence the amount of CO₂ in the alveolar air changes inversely as the amounts of these unusual acids present, and thus it can be taken as a measure of the acidosis.

The original observations of Beddard, Pembrey, and Spriggs were carried out on 13 patients. These included 6 fatal cases of diabetic coma, which gave very low values for the alveolar CO₂, namely, about 1 to 2 per cent. The 7 cases which were not fatal showed acidosis of varying intensity; the alveolar CO₂ pressures were normal in the 3 mild cases, that is, 5 per cent. and over. In the 4 remaining cases, the values ranged between 2 per cent. and 5 per cent., depending on the severity of the acidosis.

Porges, Leimdorfer, and Markovici¹² published results somewhat similar in 1910. The method used was that described by Plesch. The patient breathes backwards and forwards into a small rubber bag for about 30 seconds. The air in the bag is then analysed. This method certainly does not give true alveolar values; the CO₂ is too high. As a matter of fact, the results correspond to the CO₂ pressures in the venous blood; whereas the true alveolar air is the gas in equilibrium with the arterial blood.

These authors have been given the credit of being the pioneer workers in this field of inquiry.¹⁵ They even claim the priority for themselves,¹³ as they dispose of Beddard, Pembrey, and Spriggs's work by saying that they only investigated the carbon dioxide pressure in diabetic coma.

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