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.

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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.

* The expenses of this investigation were defrayed by a grant from the British Medical Association.

They add, "In four diabetics who were not comatose they (Beddard, Pembrey, and Spriggs) obtained in opposition to our findings, absolutely normal CO₂ pressures." A true examination of Beddard, Pembrey, and Spriggs's published figures, summarized just above, shows that this statement is absolutely incorrect. These authors established all the facts concerning the behaviour of the alveolar CO₂ in diabetics, and published them before the Viennese authors started working at the subject at all.¹⁴

Straub¹⁴ and Fridericia,⁵ and Kennaway, Pembrey, and Poulton,¹¹ using the Haldane-Priestley method, quite recently published results which confirm the original observations of Beddard, Pembrey, and Spriggs.

A brief examination of all these results makes it quite obvious that the method of measuring the alveolar CO₂ should become of the greatest importance in estimating the acidosis in the severer types of diabetes, and it has been regularly employed for this purpose during the last year and a half at Guy's Hospital.

In all the results so far published the alveolar air has been analysed by means of some type of gas analysis apparatus. Such an apparatus is only suitable for the laboratory; for clinical work it is essential to have some simple method of analysis. Collingwood and Buswell³ have described a simple apparatus which has given satisfactory results in the hands of students.

Fridericia⁶ has introduced a modification for clinical work which makes the operation even simpler, and possesses the additional advantage that after the CO₂ has been absorbed the percentage amount can be read off, without any calculation at all being necessary.

This method of Fridericia's seemed at first sight to be the most satisfactory means of obtaining and analysing the alveolar air for clinical purposes. Experience has borne this out fully. It is an extremely simple instrument to use. The results obtained are surprisingly accurate, considering that it is purely a clinical instrument.

The object of this paper is to describe Fridericia's instrument in some detail and to bring forward observations on several diabetics which will indicate the importance of alveolar CO₂ determinations as a guide to prognosis and treatment, and to show at the same time that the instrument gives trustworthy results. The actual dimensions of the instruments used in these investigations have been chosen by the writer with a view to combining accuracy and practicability.

Fridericia's Carbon Dioxide Tensimeter.

This instrument is shown in the figure. M is the mouthpiece through which the patient blows; A is an ordinary two-way tap of wide bore; B is a three-way tap so arranged that (1) X and Y can be put into communication with one another through a channel of wide bore, C being shut off (Position I), (2) by turning the tap through 90 degrees Y is made to communicate with C, X being shut off (Position II), or (3) by turning the tap through another 180 degrees, X communicates with C, Y being shut off (Position III). The volume of X between the taps A and B, including the wide bore of B, is 100 c.cm., and percentages of this volume up to 7 per cent. are marked on the narrow stem of X.

The subject whose alveolar air is to be analysed must sit quietly in a chair and breathe naturally, holding the apparatus in front of him with the tap A open and B in

Tap B is
hereshown
in Position
III.

Fridericia's carbon dioxide
tensimeter*: a clinical appa-
ratus for measuring the
CO₂ pressure in the alveolar
air. The scale in X shows
percentage of CO₂. Tap B
is shown in Position I.

Position I. After taking a normal inspiration he puts the mouthpiece into his mouth and blows as hard and as quickly as possible through the apparatus, thus washing out the whole apparatus and leaving it filled with alveolar air; the tap A is at once closed, and the whole apparatus is placed in a pail of water for five minutes. By this means the alveolar air in X and Y is cooled to a temperature which remains constant throughout the experiment, and the contraction in volume will cause the alveolar air in the lower part of Y to be drawn back into X, and any diffusion with the outside air at the top of Y will not reach down to the bottom of the tube owing to its length. At the end of five minutes the tap B is turned into Position II. By this means we have in X 100 c.cm. of alveolar air at atmospheric pressure, and at the temperature of the water in the pail, which remains constant throughout the experiment.

The apparatus is now removed from the water, a rubber ball is fitted over the end of Y, and the tube C is placed beneath some 10 per cent. caustic soda in a porcelain dish, and, by squeezing and releasing the rubber ball, soda is sucked up into Y; B is then turned into Position I, and the soda forced into X by squeezing the ball. During this operation the instrument is held with Y rather depressed, so as to prevent any small bubbles of air from escaping from B along the tube Y; B is at once turned back into Position II, and the remainder of the potash in Y forced out again at C. The vessel is turned up and down several times, and all the CO₂ is absorbed; half a minute is sufficient for this.

The instrument is then put back into the pail of water, which rises through C into Y; B is then turned through 180 degrees into Position III. The apparatus is left in the water for five minutes to equalize the temperature. It is then raised rapidly until the level of the water in the pail is the same as that in the narrow tube X. The gas in X will now be at the same pressure and temperature as before. The reading of the bottom of the meniscus of the fluid in X is taken, and this represents without any further calculation or correction the percentage of CO₂ in the alveolar air.

Before the apparatus is put away it should be completely freed from alkali by washing out with water and dilute acid.

It has been pointed out that when any one breathes out forcibly through a tube, the expired air travels along the axis of the tube and tends to leave the air at the sides unmixed. Obviously this fact will not produce any perceptible error in this clinical instrument, as the volume of the instrument is only 100 c.cm. and the volume of a forced expiration is 2 litres, which is sufficient to wash out the whole apparatus several times over. This fact can also be observed experimentally by filling the instrument with tobacco smoke and noticing how long it takes for the smoke to be expelled on forcibly breathing out through the tube. The smoke disappears almost instantaneously.

The accuracy of the instrument has been tested on several occasions by performing duplicate determinations with the apparatus and with the Haldane-Priestley method, or the modification of this method described by Hasselbalch and Lindhard;⁹ the latter is an excellent method for use with patients.

The following results have been obtained. The Haldane-Priestley method is so well known that it requires no description here.

Subject.	Fridericia's CO ₂ Tensimeter. Sample Obtained after Normal Inspiration.	H.-P. Method after Normal Inspiration.*
E. P. P. ...	5.4 5.6 5.35 5.15 average 5.38	5.50 5.20 5.10 average 5.27
A. B. ...	5.6 5.5 5.8 6.1 5.7 6.0 average 5.78	5.54 5.33 5.28 5.69 average 5.46

* Throughout this paper the CO₂ pressures are given in percentages of the dry alveolar air. The actual pressures of CO₂ in the lung alveolar air are a little lower, because the alveolar air is saturated with moisture at 37°C. (the body temperature). For purposes of comparison in clinical work at sea level, it is unnecessary to apply this correction.

* This apparatus can be obtained from Siebe, Gorman and Co., 187, Westminster Bridge Road, London, S.E.

The results obtained by the clinical method agree quite well among themselves; but with these two subjects the mean result is slightly higher than the results obtained by the H.-P. method after a normal inspiration. They seem to approximate towards the mean alveolar CO₂ pressure, which is calculated by Haldane by taking the mean of end-inspiration and end-expiration samples. This is probably due to the fact that it takes a little longer time to breathe out through the instrument owing to the slight resistance of the taps. Hence the CO₂ has a little longer time in which to accumulate in the lung alveoli.

On many occasions the clinical method has been compared with the Hasselbalch-Lindhard modification, which is carried out as follows: The patient is told to breathe absolutely quietly into a closely-fitting mask, having inspiratory and expiratory valves attached to it. Towards the end of each expiration a minute quantity of air is withdrawn from just in front of the lips and nose of the patient. The small samples are collected together over mercury, and analyzed by a Haldane's gas analysis apparatus.

It is of course necessary to be certain that the patient is breathing sufficiently deeply to wash out all the dead space completely at each breath.

The very close agreement of the results obtained by this method can be seen from Hasselbalch's own figures.⁸ It is particularly suited to cases of diabetes, as the tidal air is larger in volume than usual in serious cases, and the results are usually very concordant. Unfortunately, the use of some form of gas analysis apparatus is essential, which at once limits its use to the laboratory.

It is the great advantage of Fridericia's instrument that the whole analysis is made as simple as the ordinary urea determination in urine. However, the instrument cannot be used when the patients are actually comatose. Under these circumstances it is best to use the Hasselbalch-Lindhard method.

Diagram I shows the effect of a rigid diabetic diet on the alveolar CO₂ of a perfectly healthy individual. It also affords a comparison between the results obtained by the

Diagram I.—Dr. G. G.

Notes on Diagrams.—O denotes alveolar CO₂ determination by the Hasselbalch-Lindhard method. ● denotes alveolar CO₂ determination by Fridericia's clinical method. C denotes the onset of coma. In Diagram IV and in Diagram VII (case P. S.), and in Diagram VIII (cases L. W., W. B.), the alveolar CO₂ determinations were made by the Haldane-Priestley method, the actual samples in coma being taken by means of a mask and valves.

clinical and the H.-L. methods respectively. They agree very closely. It will be noticed that the acidosis produces a perceptible lowering of the CO₂ after thirty-two hours. This reaches a maximum in the next twenty-four hours and diminishes again towards the end of the next two days. Straub has pointed out that the alveolar CO₂ in mild diabetes behaves in a similar manner if the patient is put on a rigid carbohydrate-free diet.

On many other occasions in diabetic subjects the clinical method and the H.-L. method have been compared (see Diagram IX especially). The result is usually quite satisfactory. On the whole there is a tendency for the clinical apparatus to give the lower value, again approximating towards the mean alveolar CO₂ pressure, as it has been pointed out by Hasselbalch that his method gives results identical with end-expiration samples of the Haldane-Priestley method.

However, there are two errors in the Fridericia method that must be guarded against. In the first place there is a

tendency to take a deep inspiration before making the forced expiration. This is the natural thing to do, and it requires some patience to get the subject to take only a normal inspiration before blowing out. The result of this error is to dilute the air in the lungs abnormally, just before the sample is obtained, and so the values are too low. In the second place the subject, after correcting the first error, is apt to hold his breath before making the forced expiration. This makes the results too high. Of course, these errors may also be present in the Haldane-Priestley method, especially when the subject has had but little practice. The magnitude of these two errors is shown by the following figures:

Subject E. P. P. (Clinical Method Used.)

	Percentage of CO ₂ .	
Normal alveolar samples	5.6	5.8
Alveolar samples immediately after taking a large inspiration	4.9	4.9
Alveolar samples after holding the breath for five seconds	6.5	6.2

Alveolar CO₂ Pressures in Diabetes.

Before considering the values of the alveolar CO₂ pressure in diabetes it is necessary to state what variations occur in normal individuals. The following figures were obtained by Fitzgerald and Haldane,⁴ using the Haldane-Priestley method, and they will serve as a standard for comparison in pathological cases.

	Number of Individuals Examined.	Maximum CO ₂ per Cent. of the Series.	Minimum CO ₂ per Cent. of the Series.	Mean CO ₂ per Cent.
Men ...	27	6.25	4.58	5.51
Women ...	32	5.76	4.26	5.10
Boys ...	16	5.92	4.30	5.21
Girls ...	11	5.62	4.37	4.94

As a contrast, the following table shows the values obtained by the writer in diabetic coma; the Hasselbalch-Lindhard method was mostly used.

		Age.	CO ₂ per Cent.	CO ₂ Pressure in mm. Hg Corrected for Pressure of Aqueous Vapour.
W. B. ...	Man	35	0.86	6.9
P. S. ...	Man	22	1.23	8.8
J. O. ...	Man	47	2.49*	17.8
E. S. M. ...	Man	24	1.01	7.3
M. N. ...	Woman	47	1.51	10.8
R. S. ...	Woman	61	2.13	14.1
B. K. ...	Woman	40	1.66	11.7
E. H. ...	Woman	61	1.14	8.1

* Shortly before death, patient not actually comatose.

The alveolar CO₂ pressures of the various cases of diabetes examined are shown in the Diagrams II to IX. Every single observation made has been plotted on these diagrams. This plan has the advantage of showing the trustworthiness of the method. It will be noticed that occasionally values were obtained which were obviously incorrect, because they lie a long way away from the curve in the particular case. In Diagram VI, for instance, two of these fallacious results are seen; one of them was proved to be incorrect by carrying out two concordant determinations by the Hasselbalch-Lindhard method at the same time. It is obviously necessary to treat the results with a certain amount of discrimination and reject those obviously wrong. It would probably be safest to do duplicate determinations in a case seen for the first time. However, these obviously erroneous results are not met with very often.

These cases of diabetes fall roughly into two groups; in

one the acidosis* was mild and the alveolar CO₂ pressures were normal; in the other the alveolar CO₂ pressures were diminished and these cases usually terminated fatally.

Diagram II.—H. S., aged 44.

The mild cases (Diagrams II to IV) consisted of 5 patients, all men. In each case the amount of carbohydrate in the diet was restricted. In spite of this, in the

Diagram III.—R. E., male, aged 45.

case of H. S. the sugar excretion was roughly 8 oz. a day (227 grams), while in the case of R. E. it had practically disappeared after a fortnight. Acidosis was slight in all cases. The alveolar CO₂ was in the neighbourhood of 5 per cent. It is noteworthy that, in two cases—C. G. M. and R. E.—investigated soon after admission, the alveolar CO₂ was distinctly low—that is, 4.2 per cent. in each case (mean of two determinations), and rose subsequently. In the case of R. E., this low value was associated with a slightly raised ammonia index—namely, 7.7 per cent. It is a well-known fact that diabetics often become comatose very soon after admission into hospital, whether due to the excitement of the journey or their unusual surroundings. Probably, in these two cases, the abnormally low CO₂ values were due to the same cause, the acidosis subsequently disappearing. In the case of A. J. T. there was no obvious diminution in the CO₂ pressure on admission.

The next two cases (Diagrams V and VI) are of special interest, as the patients sometimes exhibited a mild degree of acidosis, with a normal alveolar CO₂, whereas at other times the acidosis became severe, and the alveolar CO₂ pressure became lowered.

*It has been pointed out by Hurlley¹⁰ that the nitro-prusside reaction is a far more delicate test for aceto-acetic acid (diacetic acid) than for acetone. In fact, in acidosis there is probably very little acetone present if the urine is fresh. This fact has been taken into account in this paper. The strength of the nitro-prusside reaction has been used in drawing inferences as to the presence of smaller or larger amounts of aceto-acetic acid.

F. R., a boy aged 11 years, was a marked example of this kind. For about a month the alveolar CO₂ consistently gave normal values of about 5 per cent. On March 23rd a

Diagram IV.

steady decline in the CO₂ began. For ten days remarkably constant values of 3.8 per cent. were obtained, and then the patient went rapidly downhill and died in coma. This decline was associated with a very marked aceto-acetic reaction and ammonia excretion, and with a rise in the output of sugar.

The case of B. R., a woman aged 42, was of particular interest as showing the value of the method from the point of view of prognosis. When admitted she was drowsy, and had severe headache. The ammonia index was 14 per cent.—that is, distinctly raised. Coma was thought to be imminent. Alveolar determinations, however, gave values ranging from 4.4 per cent. to 5.2 per cent. A good prognosis was given, and she rapidly improved. The carbohydrate in the diet was restricted, but the acidosis remained very slight until February 26th, when she had a bilious attack, accompanied by abdominal pain and vomiting. Acetone was smelt in her breath, and she was thought to be going into coma. In fact, when the writer was to make the alveolar determination, he was told that the case was hopeless. However, the CO₂ was

Diagram V.—F. R., male, aged 11.

Diagram VI.—B. R., female, aged 42.

found to be 3.7 per cent., and again a hopeful prognosis was given. On the next day it had risen to 4.6. Undoubtedly the acidosis had been suddenly increased by the bilious attack, but, as the alveolar analysis showed, the acidosis was not sufficient in amount to indicate the immediate onset of coma. The patient was eventually discharged feeling much better.

Diagrams VII and VIII show the results obtained from analyses on patients who all died in coma.

P. S., a man of 22, is a particularly instructive case. It was one of the earliest of the series to be investigated. On admission he was not looked upon as one of the

Diagram VII.

gravest cases. Only 0.8 oz. (23 grams) of sugar was being passed, though the aceto-acetic reaction was marked. He was feeling perfectly fit. His alveolar CO₂, however, gave a value of 3.8 per cent., which is considerably below the minimal value for a healthy adult. The carbohydrate in his diet was reduced to 80 grams per diem; it was further reduced to 23 grams eight days later, and he began to get up and walk about, still feeling quite well. Three days later the alveolar CO₂ began to diminish. On July 7th

Diagram VIII.

the pressure was 2.5 per cent., and coma started shortly afterwards.

The other 6 cases do not require separate description, but it is noteworthy that in most of them abnormally low values were obtained several days before the onset of coma. Thus with S. S., E. S. M., and R. H. values of about 3 or 4 per cent. were obtained two days before the onset of coma, while the values just before coma were under 2 per cent.; at this stage typical air hunger was present.

The case of J. O. (Diagram IX) merits a rather fuller

Diagram IX.—J. O., male, aged 47.

description. His was a different type of case in several particulars. He was lipaemic, the blood containing fat in a finely divided state, and he retained consciousness to the end, although the breathing was obviously somewhat increased. The most noticeable thing about the CO₂ chart is its extreme irregularity; on one occasion the pressure

* The total acetone bodies were determined by Dr. E. L. Kennaway.

varied from 5 to 2.5 per cent. in the course of two days. To make sure that these variations were real, and not simply due to errors of experiment, the Hasselbalch-Lindhard modification was also used on January 22nd to 30th. The values obtained by these two methods correspond well together, the H.-L. values being usually somewhat higher for the reason already explained. The patient was given large doses of sodium bicarbonate every day, and at one time there was some temporary oedema.

Discussion of Results.

The object of alveolar CO₂ determinations is to measure severity of acidosis. Hence it is useless to apply the method when the urine, in a case of diabetes, gives a negative result with the nitro-prusside test. Under these circumstances the alveolar CO₂ pressure will always fall within normal limits. However, when the urine contains acetone bodies, it is usually impossible, from the nitro-prusside or ferric-chloride tests alone, to say how severe the acidosis is. In any of these cases the alveolar CO₂ pressure is a sure guide.

By its means cases can readily be divided into two categories: (1) *The mild cases*, where the alveolar CO₂ pressure falls within normal limits; in these cases the prognosis with regard to coma is relatively good. (2) *The severe cases*, where the alveolar CO₂ is definitely lower than normal; here the utmost care must be taken to prevent the onset of coma. All the time the CO₂ is below normal the patient is, as it were, on the edge of a precipice, and any disturbance, such as sudden excitement or worry, or the administration of too rigid a diet, may push him over the edge.

In these cases the actual CO₂ pressure observed will give the measure of the danger. A value of 2 per cent. means that coma may supervene within twenty-four hours. A value of 3 per cent. or 4 per cent. is less dangerous; in the worst event, coma will not come on for at least two or three days.

A sudden drop in the alveolar CO₂ is also of significance; it means that acidosis is increasing, and, though the immediate danger may not be great, there is always the possibility of a further increase until coma sets in. The cases E. S. M., L. W., and P. S., all of whom died in coma, illustrate this point. This sudden drop in the CO₂ pressure may be unaccompanied by symptoms, such as drowsiness, abdominal pain, or air-hunger; for these only appear when the CO₂ reaches a very low value—that is, about 2 per cent. Hence the alveolar CO₂ gives by far the earliest warning

of approaching danger.

Again, it is possible to be misled if reliance is placed on symptoms alone, without determining the alveolar CO₂, because it not infrequently happens that the rapid onset of coma may be suspected from symptoms, even when the alveolar CO₂ still remains relatively high. Case B. R. illustrates this point. On two occasions—namely, December 8th and February 26th—coma was suspected from her symptoms, but the alveolar CO₂ was too high for her drowsiness, etc., to be really due to oncoming coma, and the patient improved.

Of course, it does not necessarily follow that the chance of averting coma is hopeless because a very low CO₂ pressure is obtained. It may be kept off for a considerable time by judicious treatment. In the case of J. O. death did not occur for a month, in spite of several very low CO₂ results. Beddard, Pembrey, and Spriggs have published similar cases.

There are various other methods commonly employed for measuring acidosis in diabetes, such as estimating the amount of ammonia or total acetone in the day's urine. The disadvantages of these methods are the labour involved in the determinations and the fact that it is necessary to get the patient to collect his urine for a period of twenty-four hours. However, the greatest disadvantage of all is that it is impossible to obtain the result at once. This is especially the case if the patient is being seen for the first time.

A device for overcoming this difficulty is to determine the ratio of the ammonia nitrogen to the total nitrogen in a specimen of urine. This ratio, the so-called ammonia index, is usually about 3 per cent. or 4 per cent. in health;

in severe acidosis values of about 12 per cent. to 30 per cent. are obtained. These analyses, of course, take some little time to perform, and they are essentially methods for the laboratory; but even so, the results are apt to be uncertain, because the total amount of protein consumed by the patient is unknown.

It would be possible to draw quite incorrect conclusions from this ratio in some cases. For instance, in the case of B. R., on February 26th, when she had a sharp attack of vomiting accompanied by drowsiness, the ratio was 13 per cent. This might suggest coma, but it has been pointed out from the alveolar CO₂ results that coma was not imminent. Again, in the case of R. H., on March 12th, while the ratio was only 6.4 per cent., the alveolar CO₂ on the next day was 2.7 per cent., and coma came on the day after; and even when the patient was actually comatose the ratio had only risen to 10 per cent.

The great advantage of the alveolar CO₂ pressure is that it affords a measure of the actual acidosis of the blood at the time of the observation. Its sensitiveness as an indicator depends on the sensitiveness of the respiratory centre to changes in hydrogen ion concentration of the arterial blood. This sensitiveness is very high.

On the other hand, an increase of substances excreted in the urine does not necessarily mean an increased production of these substances in the organism; it may mean increased excretion alone. The two processes, production and excretion, do not necessarily run parallel to one another. Suppose sodium bicarbonate is given to a diabetic in a state of acidosis, the excretion of acetone bodies may be increased, their production in the body remaining the same; hence the actual acidosis of the blood will be diminished, whereas, from an analysis of the urine alone, the erroneous conclusion would be drawn that the acidosis had increased.

Apart from this theoretical advantage, alveolar CO₂ determinations by the tensimeter method present many practical advantages. The apparatus is easy to use. It can be readily carried about from case to case. The method requires but little practice. The results are of a high degree of accuracy, and they are of the greatest significance in the treatment and prognosis of diabetes; in fact, to any one who has once used the method it would appear absolutely impossible to treat satisfactorily a severe case of diabetes without it.

The writer's thanks are due to his colleagues on the medical and surgical staff of Guy's Hospital for allowing him to investigate the cases under their care, and to Mr. J. H. Ryffel for letting him quote extensively the urine analyses made by him, and to Mr. J. F. Venables, who kindly undertook some of the observations when he was away.

Clinical Notes on Cases.

H. S., a porter aged 44, was admitted January 23rd, 1914, and discharged March 18th. He had been in Guy's Hospital five years previously with diabetes. He subsequently had jaundice and was operated on for gallstones. Chronic pancreatitis was diagnosed. Two months previous to admission he noticed wasting, and also that he passed large quantities of urine. He had some bronchitis. A test meal showed hyperchlorhydria. While in hospital carbohydrate was restricted to 120 grams per diem. He was given 3 oz. olive oil per diem in addition to his diet. He passed about 1 lb. (227 grams) of sugar daily, but put on 4 lb. in weight during his stay. Most of the time small amounts of aceto-acetic acid were present in the urine. The alveolar CO₂ remained between 5 and 6 per cent.

R. E., a postman aged 45, was admitted February 12th, 1914, and discharged March 3rd. He had a gonorrhoeal orchitis. He had had rheumatism. He became ill five weeks previous to admission, and had since lost 32 lb. in weight. Treatment while in hospital—carbohydrates 142 grams, sodium bicarbonate 6 grams per diem. His weight remained about the same—that is, 11 st. He passed about 3 oz. (85 grams) of sugar at first; this gradually diminished, and finally only traces were passed. Aceto-acetic acid disappeared after ten days. The ammonia index was 7.7 per cent. on admission. This was associated with an alveolar CO₂ of 4.2 per cent. The alveolar CO₂ subsequently rose and remained about 5 per cent.

C. G. M., a boy aged 19 years, was admitted March 12th. He was given a strict diabetic diet with occasional starvation days. He had sodium bicarbonate 6 grams per diem. Aceto-acetic acid present. Sugar about 1 oz. (28 grams) per diem. Alveolar CO₂ about 5 per cent.

A. S., a man aged 30, admitted March 11th, 1913, discharged May 22nd. He had peripheral neuritis and an enlarged liver. Diet, strict diabetic. Aceto-acetic acid present. Sugar about 1 oz. (28 grams) per diem. Alveolar CO₂ 5 per cent.

A. J. T., a man aged 64, admitted January 6th, 1913, discharged February 6th. He had peripheral neuritis. Diet, etc.: Carbohydrate 57 grams, olive oil ½ oz. per diem. Traces of

aceto-acetic acid present. Sugar excreted about 4 oz. (113 grams) per diem. Alveolar CO₂ 5 per cent.

F. R., a schoolboy aged 11 years, was admitted February 2nd, 1914, and died March 20th, 1914. There was a month's history of hunger, thirst, and frequent micturition. On admission apart from his diabetes he was normal. Carbohydrates were restricted to 102 grams. Total calorie value of diet, 2,150; sodium bicarbonate 21 grams per diem. The sugar remained about 110 grams, but rose to 230 grams towards the end of February. Aceto-acetic reaction marked. Ammonia N, 1 gram per diem. Alveolar CO₂ about 5 per cent. On March 2nd the carbohydrate in the diet was increased to 173 grams including a small quantity of cane sugar. Subsequently the amount of sugar in the urine increased to about 300 grams; the aceto-acetic reaction increased and the ammonia nitrogen output increased to 3.2 grams. The alveolar CO₂ remained fairly constant at 3.8 per cent. from March 5th to 14th; it then sank in three days to 2.2 per cent., and the patient subsequently died in coma. *Post mortem*: Pancreas small (28 grams).

B. R., a woman aged 42 years; admitted December 6th, 1913; discharged March 18th, 1914. She had neuritis in the legs. On admission she was drowsy, and had headache. Her limbs were painful and wasted; the aceto-acetic reaction was marked. The ammonia index 14 per cent.; alveolar CO₂ 4.8 per cent. Diet: Carbohydrates 68 grams, protein 106 grams, olive oil 3 oz.; total calorie value, 2,259. On February 4th a period of restricted protein intake was begun: protein 45.3 grams, carbohydrates 40 grams per diem; calorie value, 2,502. On February 23rd the diet was relaxed. On February 26th the patient became very sick, vomiting bile-stained fluid. She had abdominal pain. Acetone was smelt in the breath. The urine contained albumin and much aceto-acetic acid; ammonia nitrogen 1.2 grams; index 13 per cent.; alveolar CO₂ 3.7 per cent. Next day she was better. Urine contained traces of albumin; ammonia nitrogen 1.9 grams; index 13.4 per cent. aceto-acetic reaction conspicuous; alveolar CO₂ 4.7 per cent. Two days later the acidosis was still less; ammonia nitrogen 0.5 gram; index 3.4 per cent. The rest of her stay in hospital was uneventful.

S. S., a woman in domestic service, aged 22. Admitted February 28th, 1914; died March 7th, 1914. Symptoms of the disease were first noticed before Christmas, 1913. On admission: Diet, light, full; no restriction of carbohydrates. Sodium bicarbonate 9 grams per diem. On March 3rd sugar excretion was 15.6 oz. (443 grams), subsequently falling. Marked aceto-acetic reaction.

	Mar. 1st.	Mar. 2nd.	Mar. 5th.	Mar. 6th.
Ammonia N (grams) ...	2.07	1.35	2.18	1.78
Ammonia index ...	12.2%	12.9%	12.4%	24.4%

Alveolar CO₂ 3.5 per cent. two days before coma. *Post mortem*: Pancreas soft, smaller than usual, 37 grams.

P. S., a man aged 22; admitted June 23rd, 1913; died July 9th, 1913. Diet: Carbohydrates at first restricted to 80 grams a day; on July 2nd to 23 grams; on July 8th 102 grams were given. Sodium bicarbonate, on admission, 5.8 grams per diem; on July 8th 87 grams. Sugar excretion rather small in quantity, rising to 3.3 oz. (94 grams) on July 6th. Aceto-acetic reaction marked. Alveolar CO₂ at first 3.8 per cent.; while in coma 1.23 per cent.

E. S. M., a chauffeur aged 24; admitted January 2nd, 1914; died January 7th, 1914. Diabetes had been diagnosed four years previously. He had been dieted for three months before admission. On admission, diet light, full. Sodium bicarbonate 7 grams. He was passing 15 oz. sugar (420 grams) in the day. On January 6th the ammonia N was 5.8 grams, and the index 11.7 per cent. The alveolar CO₂ fell rapidly after January 5th. On January 6th, 7.20 p.m., the patient's breathing was increased, but he was perfectly sensible; alveolar CO₂ 2.2 per cent. Coma supervened the next day, and at 5 p.m. the alveolar CO₂ was 1.01 per cent.

L. W., a man aged 40, was admitted May 22nd, 1913, for a septic scalp, and died on June 2nd. On May 27th the alveolar CO₂ was 5.8 per cent. A strict diabetic diet was then begun. The alveolar CO₂ fell to 4.3 per cent. on May 30th. A guarded prognosis was given. Coma supervened three days later.

W. B., a man aged 35, was admitted March 8th, 1913, and died on March 13th, 1913. On admission an ordinary full diet was given with 28 grams sodium bicarbonate daily. On March 11th carbohydrates were restricted to 43 grams. The urine showed a strong aceto-acetic reaction. The ammonia index, 12 per cent.; sugar 241 grams; alveolar CO₂ 1.9 per cent. Coma came on the next day, the CO₂ in the alveolar air being 0.86 per cent. *Post-mortem*: Pancreas, 35 grams; appeared normal; atheroma of aortic valves; subpleural and subpericardial haemorrhages.

M. N., a woman aged 47, suffering from diabetes, was admitted February 2nd, 1914, for a surgical operation. She became comatose. Alveolar CO₂ 1.5 per cent.

R. H., a woman aged 24; admitted March 6th, 1914; died March 14th. On admission, ordinary full diet; sodium bicarbonate 71 grams per diem. Marked aceto-acetic reaction. On March 11th, ammonia N was 0.29 gram, and the ratio was 6.4 per cent. On March 12th the alveolar CO₂ was 2.7 per cent. On March 13th she became comatose; ammonia nitrogen 0.34 gram; index 10 per cent.

J. O., a painter aged 47; admitted January 5th, 1914; died January 29th, 1914. He had had diabetes since March, 1913. Since then he had been on a strict diet. For the last fortnight he had complained of great lassitude. His eyesight had become bad. He had weighed 11 st. previously. On admission his weight was 8 st. 8 lb.; he was rather drowsy; his breath smelt of acetone. There was a small haemorrhage in the right retina, with some retinitis. The ferric chloride reaction was strongly positive. A diet containing 113 grams carbohydrate was given and sodium bicarbonate in large doses by the mouth and rectum (78 grams on January 7th). On January 9th ammonia N was 4.4 grams, index 13.6 per cent. He passed about 8 oz. (227 grams) sugar daily. On January 11th the urine was faintly alkaline. On January 13th ammonia N was 2.6 grams. He was now walking about the ward. The large doses of sodium bicarbonate were still continued. On January 22nd the patient's legs began to be oedematous. The sodium bicarbonate was diminished to 51 grams for three days, and it was then increased again to the previous amount. The oedema disappeared in twenty-four hours. On January 26th a normal full diet was given, with porridge and milk *ad lib.* On January 29th, 2 a.m., the patient suddenly had an attack of abdominal pain. He became delirious. He regained consciousness, and remained conscious right till his death, the next morning at 4 o'clock. While in hospital the alveolar CO₂ showed large variations—that is, between 2 and 5 per cent.

Post mortem.—Lipæmia, due to a finely divided suspension of fat. General wasting. Atrophied pancreas.

METHODS OF ANALYSIS EMPLOYED.

Sugar.—Benedict's method.

Ammonia.—By formal titration.

Ammonia Index (that is, the ratio between the ammonia nitrogen and total nitrogen).—The total nitrogen was calculated from the amount of urea, determined by Duprès's method, assuming that the urea nitrogen was always 96 per cent. of the total nitrogen. This is approximately the case under ordinary conditions of diet, and the results are accurate enough for clinical purposes. The Duprès method is much simpler than Kjeldahl's, and takes less time to perform.

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PAROXYSMAL HAEMOGLOBINURIA.

BY

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As the condition known as paroxysmal haemoglobinuria is of extreme rarity, and recorded observations may assist in its elucidation, I venture to set out some of the results obtained in an investigation of a case that has recently come under my notice.

The man, an ex-soldier, 42 years of age, who had re-enlisted for home service during the period of the war, was sent to me by the medical officer of his battalion on July 8th, in order to have his blood and urine examined, with a view to ascertaining if he was suffering from secondary anaemia and, if so, to what cause it could be assigned.

Well built and of keen intellectual capacity, he was, when I saw him, pale and bloodless, and his sclerotics were tinged yellow. He stated that he joined the army at the age of 19 years, and after six months' home service and six months at Malta was drafted to India, where he served eight years. He left India at the age of 28, and was then transferred to the army reserve. Whilst in India, at the age of 25 years, he contracted malaria—benign tertian—and also syphilis; for the latter he received oral mercurial treatment for a period of three months. After leaving the army he started work as a coal miner, and became successively a mine official and an inspector of mines. At the age of 33 he married, and six years later a girl was born, whom I have seen. She is now over 3 years of age, and appears perfectly healthy.

His general health has been excellent. Eight years ago, at the age of 34, he had an attack of what was diagnosed as influenza, with symptoms of pain in calves and thighs, and headache, but no rigors or "port-wine" urine.

In October, 1913, he formed one of an exploration party after the Senghenydd explosion. At one time, whilst returning to the base of operations, a distance of 1,000 yards, he and his companions were exposed for over two hours to smoke and gases. He himself felt great difficulty in breathing, and was unable to travel more than ten yards at a time. A fellow explorer suffered chiefly from pains in the head, calves, and thighs, with weakness of the legs—symptoms characteristic of CO poisoning.

Whether the effect of this exposure has played any part in my patient's subsequent illness it is difficult to estimate, but it is of interest to note that thereafter he complained of frequent tingling of the ears, only relieved by the application of warmth. His present illness, he told me, started eight weeks before with loss of appetite, constipation, frontal headache, lassitude, pains in the thighs and calves, some feverishness, and also some pain in the epigastrium. A fortnight later he experienced a slight "shiver," but no vomiting occurred at any time. During the last two weeks definite rigors developed, followed by profuse sweating. These rigors usually started about mid-day every day, and would last from two to five hours; they were not controlled by quinine. He noticed that the first appearance of "port-wine" coloration of his urine synchronized with the first rigor. From then to the time that I first saw him he had become steadily worse. About the time that the rigors started he first noticed that an irritating rash appeared on exposing his arms and legs when getting out of bed. The rash and its attendant irritation would last from twenty to thirty minutes, and on returning to bed and keeping closely covered the skin would assume its normal condition.

The specimen of urine he brought with him (July 8th) presented the following characters: "Port-wine" colour, acid, gave strong positive reaction with tincture of guaiacum and ozonic ether; high albumin content. On centrifuging, a heavy deposit containing very many granular casts, a few granular-leucocytic casts, and much detritus, all tinged a brownish colour. A few isolated leucocytes and urinary epithelial cells were seen. Some calcium oxalate crystals were present, but there were no red blood corpuscles.

I now proceeded to obtain some blood from the tip of the right ear. This procedure was immediately followed by a rigor. It will be noted that the blood taken on this occasion represented a sample of his circulating blood during the period of his haemoglobinuria. As subsequent events proved, this was the only sample I was able to obtain while he was in this condition, as, when I next saw him, he had improved so much that his immediate symptoms had ceased.

The blood withdrawn clotted quickly, and the resultant serum was large in amount. The serum was tinged a smoky-brown colour, with the very merest trace of a reddish tint. The Wassermann reaction was positive. A differential count of 300 leucocytes, performed at the same time, gave the following result: Polymorphonuclears, 70 per cent.; large mononuclears and transitionals, 7 per cent.; lymphocytes, 9.6 per cent.; eosinophiles, 10 per cent.; mast cells, 3.3 per cent. The leucocytes appeared greatly in excess of the normal ratio to the red corpuscles. There were a few dead leucocytes, chiefly polymorphs, eosinophiles, and mast cells. Blood platelets were present in slight excess. The red corpuscles stained lightly, rouleaux formation was fair; macrocytes, microcytes, poikilocytes, and many phantom cells present; polychromatosis abundant. No nucleated red corpuscles and no malarial parasites seen.

Four days later (July 12th), after his removal to the local military hospital, I was enabled to make continuous estimations of his urine over a period of eight days. Each time he micturated the total amount was measured, and a sample submitted to examination, in order to ascertain the question of acidity, specific gravity, general appearance and colour, and the presence or absence of haemoglobin, bilirubin, albumin and crystalline deposits. In this way it was possible to estimate the total for each successive twenty-four hours, and any changes that might occur.