for the sake of comparison I have arranged these data along with my own by decades according to the age of the individual at the onset of the disease.

TABLE II.—DURATION OF FATAL CASES OF DIABETES IN MASSACHUSETTS FOR 1915 COMPARED WITH AUTHOR'S TOTAL FATAL CASES.

Decades.	MASSACHUSETTS.		JOSLIN.	
	No. of Cases.	Yrs. Duration.	No. of Cases.	Yrs. Duration.
0-10	17	0.79	33	2.39
11-20	22	1.77	50	2.62
21-30	25	1.21	41	5.28
31-40	41	4.16	55	6.82
41-50	59	5.36	83	6.87
51-60	77	4.82	108	6.46
61-70	86	3.83	56	5.47
71-80	34	2.01	16	5.06
81-90	6	1.11	1	0.83

It will be seen that the greatest difference in mortality between the statistics of the state and my own lies in the early decades. And a further startling difference, not obvious in this table, lies in the number of cases in each group who succumbed during the first year to the disease. This is best illustrated by another table, which is of special interest because it includes the data of the Massachusetts General Hospital for two different periods. In it I have also included statistics given by Naunyn for his own practice.

TABLE III.—THE FATALITY OF DIABETES MELLITUS DURING THE FIRST YEAR OF THE DISEASE.

Sources of Statistics.	Number of Cases.	Percentage of Total Fatal Cases Dying First Year.
Massachusetts 1915*.....	370	27.9
Boston 1915†.....	117	27.3
Massachusetts General Hospital		
1824-1898	47	67.5
1898-1913	69	40.6
Naunyn	66	30.0
Joslin	408	16.9

It may not be out of place to add that of 490 cases of diabetes on my list, 94% have already passed the first year of the disease,—the danger-zone of the diabetic.

In a study of the causes of death of 408 cases of my series, it was found that two out of every three (66%) died of coma, that 87% of all those who succumbed during the first year of the disease died of coma, and that this was the case in 100% of the fatal cases in children. Therefore, if the mortality of diabetes is to be reduced, our energies should be directed first toward the avoidance of coma, because the treatment of coma is so unsatisfactory; and, second, particular attention should be exercised in the management of cases of diabetes in the first year following the detection of the disease.

*The total number of fatal cases of diabetes mellitus in Massachusetts for 1915 was 648, but of this number the duration is recorded as less than one day in two, and not recorded at all in 278, thus leaving only 370 available for statistics; only 367 were used in Table II, three cases with duration of 22, 29 and 51 years being omitted in first three decades.

†The total number of fatal cases of diabetes in Boston for 1915 was 191, but the duration is not recorded in 74, thus leaving 117 available for statistics.

Furthermore, all cases should be persistently followed up, and the good effects of treatment not be allowed to lapse by indifference or neglect.

FATAL CASES.

May 1, 1915, to May 1, 1916.

Cause of Death.	New Cases.	Case. Nos.	Old. Cases.	Case. Nos.
Coma (within 24 hrs.)..	3	(1004, 865 893)		
Coma (broke treatment)	4	(927, 740, 901, 868)		
Coma (died within 24 hrs., suppression urine)	1	(1015)		
Coma	4	(906—not seen since diabetes developed; 909, 887, 937)	7	(723, 181, 269, 530, 363, 813, 733)
Cardiac	1	(929)	1	(848)
Cardio-renal	1	(859)		
Thyroid	1	(869)		
Gangrene	2	(900, 1010)		
Operation on prostate or bladder drained.....	3	(939, 1042, 1019)		
Tuberculosis	2	(861, 862)		
Cancer			1	(474)
Appendicitis			1	(753)
Carbuncle			1	(513)
Pneumonia			1	(527)
Angina pectoris			1	(355)
Unknown			2	(823, 582)
Total	22		15	

DEFINITION AND DETECTION OF ACIDOSIS IN DIABETES MELLITUS.

By ALBERT A. HORNOR, M.D. BOSTON.

[From the Clinic of Elliott P. Joslin, M.D.]

SINCE Kussmaul described the deep breathing and coma of diabetic patients approaching death, and acetone diacetic acid and B. oxybutyric acid were associated with this condition by Petters, Gerhardt, and Minkowski, and an increase of the elimination of ammonia was pointed out by Stadelman, this state has been termed by Naunyn one of acid poisoning or acidosis.

By observation of the patient, it is easy to note the drowsiness, exaggerated respiration, and dry skin, so characteristic of the diabetic about to die in coma. So seldom does a patient recover and so temporary are the few recoveries recorded that it is manifestly necessary for us to recognize precomatose conditions if we would save our patients.

Consider the demonstrable differences between the metabolism of a comatose diabetic and the metabolism of a healthy individual. Until recently these were limited to the changes demonstrable in the urine. Of late, however, changes in the blood and in the expired air have been recognized. The changes in the urine are

the excretion of glucose and increased quantities of diacetic and B. oxybutyric acid and ammonia. The changes in the blood are a reduced amount of carbon dioxide and an increased amount of acetone bodies; the change in the expired air consists in a reduced percentage of carbon dioxide. The reason for this will be discussed later.

Among diabetics who are exhibiting no undesirable condition, one finds the condition of the urine essentially normal; in other words, an absence of glycosuria and no increased excretion of acetoacetic acid, B. oxybutyric acid or ammonia. Prior to the development of acidosis by a diabetic, there will always be a recurrence of glycosuria. Further, in none of the cases on which this study is based has there been any evidence of extreme acidosis where the amount of glucose excreted in the urine was less than the amount of carbohydrate ingested in the corresponding twenty-four hours; in other words, no extreme acidosis in the presence of a positive carbohydrate balance.

After the occurrence of glycosuria, there may quickly follow an increased urinary excretion of acetone bodies. This can usually be detected qualitatively and roughly estimated quantitatively by the addition of a few drops of a strong solution of ferric chloride (the Gerhardt test for diacetic acid, familiar to you all). It happens in rare instances, however, that a patient presents all other symptoms of diabetic coma without showing any marked ferric chloride reaction in the urine. In such instances, the presence of abnormal quantities of acid bodies may be inferred by the demonstration of an increase in the urinary ammonia, a part of the urea nitrogen being converted to ammonia, so that the acetone bodies may be excreted as salts of ammonia. In acidosis, the urinary ammonia may rise from the normal, 0.75 gr. in twenty-four hours, to 7.5 gm. or even more in twenty-four hours. At the same time, there is a change in the ammonia-nitrogen ratio of 1:12 to 1:3, or in extreme cases even 1:2. Consequently, if a twenty-four hour amount of urine be not available, one may estimate the degree of acidosis by determining urinary ammonia and urinary nitrogen and their ratio in a single specimen of urine. This, of course, involves the apparatus and ability to determine urinary nitrogen. The ammonia-nitrogen ratio serves as an index of acidosis save when alkali, for example, sodium bicarbonate, is being administered, under which condition some of the acetone bodies may be excreted in combination with the alkali administered. The determination of urinary ammonia may be done satisfactorily either by the method of Folin¹ or that of Malfatti.² The simpler, though less accurate, method of Malfatti (as described in the more recent text-books on physiological chemistry) is probably better adapted to the use of the general practitioner than that of Folin, involving,

as it does, only the mixture of urine with potassium oxalate and a titration with formalin. Actual quantitation of acetone bodies in urine is best done by the Schaffer-Marriott method. This, however, requires more apparatus and time than is available, save in highly specialized laboratories.

As already stated, in acidosis there occurs a reduced percentage of carbon dioxide in the expired alveolar air, which is consequent to a reduced carbon dioxide tension in the blood. Before discussing this fact, however, it is probably best to say a few words about the mechanism through which it is affected. By the micro method for quantitating acetone bodies in blood, described by Marriott,³ it has finally been shown that in certain, if not all, cases of diabetic coma, there is an increase in the quantity of acetone bodies in the blood. This, however, does not affect the reaction of the blood either by increasing acidity or, what would be the same thing, decreasing alkalinity, though all the acetone bodies are acid in character. The present conception of the wherefore of this fact is chiefly due to the work of Dr. Lawrence J. Henderson.⁴ His studies have shown definitely that the relation of blood to neutrality is that of slight alkalinity, and varies only within extremely narrow limits, and is capable of accurate determination only by the use of electrochemical methods. The reaction of the blood is maintained by the large amount of weak acids and their salts in the blood,—carbon dioxide and sodium bicarbonate, monosodium phosphate and disodium phosphate, and somewhat by the amphoterics acids from proteins. Carbonates and phosphates possess, so far as is known, the highest power to preserve neutrality in solution. Under normal, as well as under abnormal, conditions this is quite essential, for acid substances are continuously being poured into the blood in the course of normal metabolic processes. The maintenance of neutrality of the blood is further facilitated by excretion of volatile acids through the lungs, chiefly in the form of carbonic acids and the excretion of non-volatile acids through the kidneys, chiefly in combination with ammonia and other bases. Under normal conditions, the amount and kinds of acid poured into the blood by metabolic processes are such that the amount of carbonic acid present in the blood is practically constant. The acetone bodies in the blood of diabetics may be and frequently are in such great quantities that in order to maintain its constant relation to neutrality the blood must lower the normal tension of other acids. This is done by lowering the tension of carbonic acid. To do this, more carbon dioxide must be excreted through the lungs, inasmuch as carbon dioxide is excreted from blood capillaries until, and only until, the carbon dioxide tension and alveolar air is the same as that of the blood, it is necessary to increase lung ventilation. This

has been shown to be regulated by the reaction of the blood. In other words, lung ventilation will keep carbon dioxide at a level necessary to maintain the normal reaction of the blood. It was reasoned, and later shown, that since carbon dioxide is excreted from blood into alveoli up to the point where the tension of carbon dioxide in alveoli equals the tension of carbon dioxide in blood, the estimation of carbon dioxide tension in expired alveolar air would furnish an estimate of the tension of carbon dioxide in blood and, consequently, an indirect estimate of quantity of acetone bodies in blood. Recently, Van Slyke, Stillman, and Cullen⁶ of the Rockefeller Institute have devised a method of determining directly the carbon dioxide tension of the blood. Theirs is an admirable and accurate method and requires no coöperation on the part of the patient and, consequently, is suitable for use even in comatose patients. The method is easily learned, but requires considerable apparatus and more time than does the estimation of carbon dioxide tension in alveolar air, which has been found to run parallel, at least among diabetics.

For the determination of carbon dioxide in alveolar air many methods have been described. In 1914, Boothby and Peabody, after careful study of the various methods, recommended that of Plesch as modified by Higgins, the collection of sample being simple, but requiring considerable apparatus for analysis of gas collected. Quite recently Marriott⁶ has described a method which is probably simpler than any other, when once the standard solutions have been prepared. The method employed in this work has been that described by Fridericia.⁷ The method is simple, involves the use of inexpensive apparatus, which may be easily transported to the bedside, and the complete test requires less than fifteen minutes. The objection raised to this method is that it requires coöperation on the part of the patient. This is, of course, regrettable, but among diabetics who cannot coöperate, the clinical evidence of acidosis is so striking that an estimation of carbon dioxide tension would be desired only for academic reasons. On the other hand, observations made upon one comatose patient agreed with that obtained by direct determination of carbon dioxide tension in the blood.

The determination is made by collecting in a specially constructed U-shaped glass tube the last hundred cc. of a forced expiration after a normal inspiration, and then absorbing at room temperature the carbon dioxide in this 100 cc. of expired alveolar air with a strong alkali (20% potassium hydrate), thereby causing a partial vacuum, which is later replaced by water at room temperature and atmospheric pressure. (A detailed description of apparatus and method is appended.)

By a study of the carbon dioxide content of alveolar air it is found that normally the ten-

sion of carbon dioxide varies between 38 and 45 mm. of mercury. Among diabetics with slight acidosis, the carbon dioxide tension varies between 32 and 38 mm. of mercury; with moderate acidosis between 28 and 32 mm. of mercury; severe acidosis less than 25 mm. of mercury. Nineteen mm. of mercury is the lowest tension observed in a patient ultimately recovering from acidosis. Nine mm. of mercury is the lowest observed in this present study. That was in a comatose patient only a few hours ante mortem.

In an analysis of three hundred observations of carbon dioxide tension in alveolar air recently made upon cases from Dr. Joslin's Clinic, and reported by me at the Peter Bent Brigham Hospital, it was found that patients with carbon dioxide tension less than 25 mm. of mercury all had three grams or more urinary ammonia in twenty-four hours, and a negative carbohydrate balance. When the carbon dioxide tension varied between 25 and 33 mm. of mercury, urinary ammonia was between 3.7 gm. and 1.5 gm. in twenty-four hours, and in three-fourths of the cases the carbohydrate balance was positive. With carbon dioxide tension greater than 33 mm. of mercury, the urinary ammonia in twenty-four hours was less than 2 gm. The carbohydrate balance was usually positive and always so when the carbon dioxide tension was above 36 mm. of mercury. Ferric chloride reaction varies from negative to strongly positive at 36 mm. tension and also at 23 mm. tension, and, consequently, must be a very rough index of the degree of acidosis.

With the determination of the so-called alkali tolerance as an index of acidosis by the administration of sodium bicarbonate until the urine becomes alkaline, I have had no experience. This has been due chiefly to the fact that this study has been made entirely within the past year, and that now some of us are in doubt as to whether administration of alkali may not do harm. Consequently, it has not been deemed right to attempt a study of this sort from a purely analytical standpoint.

In conclusion, therefore, the acidosis of diabetes mellitus, aside from its clinical picture of exaggerated respiration, drowsiness and rapid pulse, may be defined as a condition in which the carbon dioxide tension in the blood and, consequently, in the alveolar air is reduced; the acetone bodies in the blood and urine are increased and associated with this is a rise in the excretion of ammonia; glycosuria is marked, and, saving exceptional cases, toward the end of prolonged coma, the carbohydrate balance is markedly negative. All these factors are important in determining the degree of acidosis, and, where time and facilities permit, should be ascertained. The detection of glycosuria, the demonstration of a positive ferric chloride reaction, and the determination of a diminution in the alveolar carbon dioxide tension are the procedures suitable for

bedside use. The carbohydrate balance is also a valuable indication and one surely to be determined, but, unfortunately, it must always furnish information in part, at least, a day late.

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APPENDIX.

Fridericia Method. This method possesses the advantage of being simple and involving the use of apparatus which may be easily transported to the bedside. One hundred cubic centimeters of alveolar air are collected in a closed chamber and then cooled from the temperature of the body to that of the room. The carbon dioxide in this air is then absorbed with a 20% aqueous solution of potassium hydrate, thereby creating a partial vacuum, which in turn is equalized with water. This water is then subjected to atmospheric pressure, when the amount of carbon dioxide replaced by water can be read in per-

centage of atmospheric air by reading the height in centimeters to which the column of water has risen in the closed 100 cc. chamber. This percentage may be changed to millimeters of mercury pressure by multiplying by the difference between barometric pressure at the time of the test, and this varies in Boston between 770 mm. and 750 mm., and the tension of aqueous vapor at 37.5° Centigrade, which is 48 mm. mercury. This will make a factor which lies between 718 and 702. As the reading of 760 is much the more common at sea level, for clinical purposes the factor 715 may be used satisfactorily. The

patient should be in the same position and quiet for ten minutes prior to the performance of the test.

After a normal inspiration, the end, A, of the apparatus is inserted between the lips, and the patient is instructed to expire forcibly through the apparatus, with cocks C and D open, so that there is a free passage from A to B. The tube remains in the mouth throughout the entire expiration and the cock C is then closed, thus retaining between cocks C and D the last 100 cc. of expired air. (As the exchange of air in the upper respiratory passage is 200 cc. and the exchange of air from the alveoli is 800 cc., it is plain that with any care at all a sample of alveolar and not upper respiratory air will be obtained.) The apparatus is now immersed in a glass tank of water at room temperature and allowed to remain there five minutes. The best way to obtain water at room temperature is simply to keep the glass tank in the room with the patient for several hours before the test, though with an ordinary thermometer one can easily adjust the temperature of the water to that of the room. At the end of five minutes about 10 cc. of 20% aqueous solution of potassium hydrate is poured into the apparatus through the orifice B. A little of this potassium hydrate will leak through the hole in cock D to chamber CD. Now cock D is turned to the left so that chamber CD is closed and chamber BD is also closed. The small amount of potassium hydrate in chamber CD is shaken in the chamber for a moment. Then with apparatus in upright position, cock D is turned so that there is a continuous passage from C and B, and the amount of potassium hydrate which will run into the chamber CD is allowed to do so. Now cock D is turned to the left until BDE is a continuous passage, and in this way potassium hydrate is allowed to escape into the water tank. Chamber CD still contains 2 or 3 cc. of potassium hydrate solution and should be thoroughly washed with this solution. Every point in the surface of chamber CD must be touched by the alkaline solution. This is accomplished by shaking very thoroughly the potassium hydrate in chamber CD. The apparatus is again immersed in the tank of water, cock D is turned to the left until water rises into CD through EDC, and the apparatus left in the water five minutes. At the end of this time, the apparatus is raised until the bottom of the meniscus of the water in chamber CD is level with the top of the water in the tank. Now cock D is turned to the right until water runs through EDB to the level of water in chamber CD, which is now closed. Then cock D is turned further to the right until CDB is a continuous chamber. The apparatus is then again immersed to the bottom of the glass tank and the water in the arm BD of the apparatus should be at the same level with the water in the chamber CD and continuous with it. If this is not so, then the amount of water in BD should be changed

until it reaches the height of the column of water in CD. The reading is now taken in centimeters of the height to which the column of water stands in CD, and this is so graduated as to represent the percentage of CO₂ which was absorbed by alkali and replaced by water. This completes the test.

The apparatus is prepared for the next test by opening cock C so that A to B is a continuous passage. The fluid in the apparatus is allowed to escape. Orifice B is put under the faucet and cold water allowed to run through the apparatus, taking care to shake sufficiently at the time so that water touches all of the inside of the apparatus. Repeat. Then pour through orifice B about 10 cc. of 4% solution boric acid. Rinse the apparatus very thoroughly with the acid so that there shall be no alkali remaining adherent to its sides. Wash again with cold water. Leave the apparatus so that orifices A and B are down, thereby allowing any water in the apparatus to drain out.

From the above it will be seen that the apparatus necessary is, first, the Fridericia appliance, a glass tank, whose depth is equal to the length of the Fridericia apparatus, a wash bottle containing 20% solution of potassium hydrate and another wash bottle containing 4% solution of boric acid. It is convenient to add an indicator, such as alizarin, or litmus, to the alkaline and acid fluids.

OBSERVATIONS ON THE BLOOD SUGAR IN DIABETES MELLITUS.

By ORVILLE F. ROGERS, JR., M.D., BOSTON.

[From the Medical Services of the Massachusetts General Hospital.]

THE aim of this paper is to present some conclusions as to the value or necessity of determining the blood sugar in treating diabetes, either from a prognostic or therapeutic standpoint.

There have been in the past many methods for the estimation of blood sugar, but most of them have necessitated the use of such large quantities of blood that they were not practical for frequently repeated determinations, and therefore not suitable for clinical work. Another objection has been the complicated procedures involved, capable of being carried out only in a well equipped laboratory, and by a trained chemist. In the past few years there have been a number of methods brought forth which can be carried out on small samples of blood, notably the Bang micro-method,¹ in which the amount necessary is only a few drops, and the Lewis-Benedict method,² in which 2 cc. of blood are required. At the Massachusetts General Hospital we are using the Lewis-Benedict method* with a modification described by Myers and Bailey.³ There are several other modifications

in which only a few drops of blood are used, but the accuracy of these is rather doubtful.

The normal blood sugar varies between 0.06% and 0.11% according to the various authors. With the method that we use, the average is around 0.09% to 0.10%, and the high limit of normal about 0.11%. There are many factors that influence blood sugar besides diabetes. The sugar in the blood seems to be in a very labile state, and may be much influenced by a number of causes. Excitement, infections, the ingestion of food, and nephritis may all raise the blood sugar values above normal for a greater or smaller period of time, and to a greater or less degree. Lately the influence of damaged kidneys in raising the blood sugar in both normal and diabetic individuals has been emphasized more and more.

Diabetes is the most common cause of increased blood sugar and it also causes the highest values. Those rather rare cases of renal diabetes are the only ones in which there is not some elevation of the blood sugar while sugar is being excreted.

The blood sugar among those patients treated at the Massachusetts General Hospital who had diabetes but who had had no previous treatment, or whose treatment had not been efficient, that is, they were still excreting considerable sugar, was about 0.26% for an average, with variations from 0.76% to 0.16%. The highest value that was found (0.76%) was in a man in coma and the next highest was 0.36% in a very severe diabetic on the verge of coma. Values above 0.30% seem to be uncommon unless there is some difficulty on the part of the kidneys in accomplishing excretion.

On the other hand, the blood sugar determinations done on patients at the time they left the hospital, when they were sugar-free, and had been so generally for some days or weeks, showed variations from 0.07% to 0.18%, and averaged 0.12%. This is a decided drop in the blood sugar, but only six or seven of the values were actually within normal limits.

This brings up the question of the relation of glycaemia to glycosuria, and the permeability of the kidneys to sugar. The level of sugar in the blood does undoubtedly determine in a general way in normal or diabetic individuals, with normal kidneys, the presence or absence, or the amount, of glycosuria, but it is also true that the level which blood sugar must reach in order to cause a glycosuria of any given intensity varies greatly in different diabetics and in the same diabetic at different times. Recent work by Hamman and by Foster reported at Washington in May, 1916, seems to show that for normal individuals there is a fairly constant threshold for sugar excretion. However, for diabetics this threshold was more variable.

McLean,⁴ Epstein,⁵ and Myers and Bailey⁶ have published papers tending to show a direct relationship between glycaemia and glycosuria, especially when there is no renal element, and

* I wish to express my thanks to Dr. W. Denis and Miss Anna Minot, by whom almost all of the determinations have been done.