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Helen Eastman Martin, Arne N. Wick

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Research Article

QUANTITATIVE RELATIONSHIPS BETWEEN BLOOD AND URINE KETONE LEVELS IN DIABETIC KETOSIS

By HELEN EASTMAN MARTIN and ARNE N. WICK

(From the Departments of Physiology and Medicine of the University of Southern California, and the Department of Medicine of the Los Angeles General Hospital, Los Angeles, and the Scripps Metabolic Clinic, La Jolla, California)

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In the study of ketosis in diabetic patients, certain problems have gone largely unanswered due to the lack of sufficiently accurate methods for blood ketone determinations. With the development of blood ketone methods accurate at low as well as high blood concentrations, it has been possible to study the problems of (*1*) the renal threshold for the ketone bodies, and (*2*) the quantitative relationship between the urinary ketone excretion and the blood ketone level.

The studies to be presented summarize the results obtained on (*1*) 13 diabetic patients in mild ketosis, produced by withdrawing insulin for 12 to 24 hours, a ketogenic diet for 12 to 24 hours, or a combination of a ketogenic diet and insulin withdrawal; and (*2*) 7 patients entering the Los Angeles County Hospital in moderate to severe ketosis (several in diabetic "coma"). In both types of patients, after initial levels of blood and urine ketone bodies were obtained, insulin and fluids were given as required by the individual case, and blood and urine ketone levels were followed until ketosis, as indicated by the qualitative urinary acetone test (modified Lange test), disappeared. The blood ketones [1] were determined by the Barnes-Wick (1) method, and the urine ketones by the Van Slyke (2) gravimetric method in most instances.

Table I summarizes the results obtained in the diabetic patients in mild ketosis, and Table II the results in patients in moderate to severe ketosis. Figures 1 and 2 give the clinical course, during therapy, of two of the most completely studied cases, one in mild ketosis, the other in severe ketosis. These are patients "Ha" and "Wi," from Tables I and II, respectively. The figures illustrate how the data listed in the tables were obtained.

[1] Total blood and urine ketones calculated as beta-hydroxybutyric acid (1).

From the analysis of the data given in these tables and figures, certain facts are apparent. In Table I (record of patients with blood ketone levels between 1 and 30 mgm. per cent), it is seen that even with very low blood ketone levels (5 to 10 mgm. per cent) small amounts of the ketone bodies appeared in the urine. This indicates that the absolute renal threshold for the ketone bodies in diabetic patients is very low—under 10 mgm. per cent—in the majority of cases. While it is evident that the threshold for the ketone bodies is very low in diabetic patients, relatively small amounts appeared in the urine, less than 100 mgm. per hour, until blood levels over 20 mgm. per cent are reached. This gives a ratio under 10 for

$$\frac{\text{urine excretion mgm. per hour}}{\text{blood ketones mgms. per cent}}$$

in 10 of the patients listed in Table I. In one patient ("P"), all the ratios were under 10, with one exception, where there was a marked increase in urine output per hour. In two patients ("Ho" and "St"), there were much higher ratios. Certain variations in the ratios at low blood levels can be explained on the basis of marked variations in urinary output per hour.

The great increase in urinary ketone excretion per hour with blood ketone levels over 20 mgm. per cent is seen in Table II (blood ketone levels from 35 to 150 + mgm. per cent). The amount of urine ketones excreted per hour at comparable blood levels varied greatly from patient to patient. As the amount of the urinary ketone excretion is very small as contrasted to the amount utilized (3), this may partially explain this difference. These results in patients in moderate to severe ketosis indicate a complex relationship between the blood ketone level and the urinary ketone output per hour. When the urinary ketone output per hour is charted against the blood level, a

TABLE I

Ketone excretion in mild ketosis

Patient	Time	Urine volume	Urine ketones*	Urine ketones mgm. per hour / Blood ketones mgm. per cent	Blood ketones
	minutes	*cc. per hour*	*mgm. per hour*		*mgm. per cent*
1. "Ha"†	97	414	101	3.4	30
	86	1,150	58	3.5	16.4
	43	1,310	25	1.6	15.5
	52	559	12.9	1.0	12.8
2. "P"†	166	123	141	7.4	19
	192	106	80.5	4.5	14.7 to 21
	55	933	121	22.4	5.4
	40	630	18.3	4.5	4.1
3. "Du"†	201	128	94	5.9	16
	169	41	10.2	5.1	±2
4. "Ho"	269	118	63.7	3.7	21 to 15.8 to 6.3
	53	386	52	17	3.6 to 2.4
	70	283	39	13	2.4 to 3.6
	65	328	42.5	7.9	3.6 to 7.2
5. "Str"	55	71	32.5	5.7	5.7
	60	276	16.4	2.1	7.9
6. "Hal"	315	210	0	0	8 to 1.2
7. "D"†	57	98	14.4	1.12	12.8
	60	110	4.9	0.83	5.8 to 6
	57	69	6.9	2.7	2.9 to 2.2
	66	74	6.3	2.6	1.7 to 3.1
	51	94	6.1	3.2	3.1 to 0.7
8. "Si"	60	38	51	5.8	8.8
	60	138	64	7.9	8.1
	90	504	0	0	4.7 to 2.4
9. "N"	70	107	55.9	6.8	8.2
	60	180	0	0	5.3
	60	162	0	0	2.7
	60	40	0	0	1.4
10. "Q"	175	63	0	0	7.8 to 3.8
11. "B"†	56	115	4.81	0.8	6.0
	62	420	11.8	1.8	6.6
	64	430	35.7	3.6	10.0
	56	573	3.96	1.59	2.5
	43	725	0	0	1.7
12. "Be"	68	±242	±31.5	±6.2	5.1
	180	55	0	0	4.8
13. "St"‡	60	350	14.6	3.4	4.3
	60	370	24	20	1.2
	58	671	13	18.5	0.7
	62	203	7.5	7.5	1.0

* Calculated for time period listed.

† Urine ketones fractionated into beta-hydroxybutyric acid and acetone. Amount listed represents beta-hydroxybutyric acid.

‡ Urine ketones represent beta-hydroxybutyric acid. (Mercury precipitate dissolved, distilled and reprecipitated.)

hyperbolic type of curve is obtained (Figure 3—patient "St"—Table II). When these data from Figure 3 are expressed as a relationship between blood level and a ratio between urine ketone excretion mgm. per hour and blood ketone level in mgm. per cent, a straight line is obtained, with the point of origin passing through the blood level around 20 mgm. per cent (Figure 4). In the

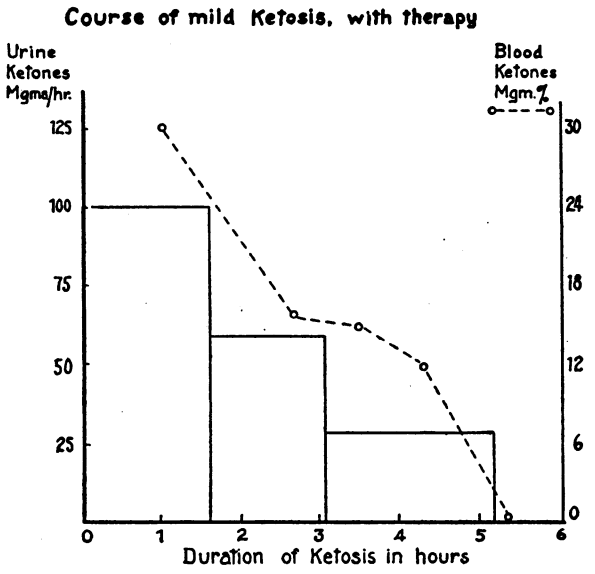

FIG. 1. THE RAPID FALL OF THE BLOOD KETONE LEVEL AND THE SMALL URINARY KETONE OUTPUT AT LOW BLOOD KETONE LEVELS (Patient "Ha," Table I)

majority of the cases, a somewhat similar relationship was found, with a marked falling off of the ratio at blood levels under 20 mgm. per cent.

Studies in 5 patients included the determination of both acetone (including acetoacetic acid and acetone) and beta-hydroxybutyric acid in the urine, at varying blood levels—2 to 78 mgm. per cent. The results are listed in Table III. In patients "Ha" and "K," acetone represented approximately 80 per cent of the ketone bodies in the urine at the lower blood levels. In patient "P," the urinary acetone rose from 11 per cent, at a blood ketone level of 19 mgm. per cent, to 41 per cent, at a blood ketone level of 2.9 mgm. per cent. In patient "B," the urinary acetone rose from 42 to 100 per cent, with corresponding change in blood ketone level from 6 to 1.7 mgm. per cent. In patient "D," there was only a slight increase in percentage of acetone at the lower blood ketone levels.

In studying the data summarized above, certain other points of interest were noted. In all the patients in moderate to severe ketosis, the carbon dioxide combining power was determined repeatedly and synchronously with the blood ketone determinations. The lack of specific correlation in different patients between the carbon dioxide combining power and the blood ketone level is seen in Table IV. (This reaffirms the previous work of many.) In this table it is seen that one patient with a carbon dioxide combining power of 10 volumes per cent had a blood ketone level of 80 mgm. per cent, while another patient with a carbon dioxide combining power of 16 volumes per cent had a blood ketone level over 150 mgm. per cent. Since the carbon dioxide combining power is only a measure of the alkali reserve, and this is determined by many factors other than the degree of ketosis in uncontrolled diabetes, it is obvious why the two determinations are not more closely related.

Table V shows the low urinary ketone output per hour in a patient with uremia and oliguria. In this patient with blood ketone levels over 150 mgm. per cent, 61.7 to 455 mgm. per hour were excreted in the urine.

DISCUSSION

There are few quantitative figures given in the literature on the relationship between blood and urine ketone levels. The impression, however, is given that there is no correlation. As Peters and Van Slyke (4) state: "The relation between blood and urine ketones has not been studied; but the data of Allen, Stillman and Fitz show a peculiar lack of association between the two." In studying the data of these authors (5), it is noted that the total urinary ketone excretion for 24 hours, with varying diets or starvation, is correlated apparently with one or two blood ketone levels. As variations occur during the 24 hours, it is impossible to draw conclusions from their data, although their results do show very small urinary ketone output at low blood ketone levels. Also there are very few references to the renal threshold for the ketone bodies in the literature. The work of Wilder (6) on the injection of beta-hydroxybutyric and acetoacetic acid into dogs, suggested a urinary threshold, since 0.4 gram per kgm. of body weight had to be injected before beta-hydroxybutyric acid appeared in the urine. Briggs and Shaffer (7) conclude from their studies that acetone is a non-threshold substance, and the concentration in the urine parallels the concentration in the blood. These authors, and also Widmark (8), state that under certain conditions acetone can diffuse into the urinary bladder directly from the blood, like alcohol, with-

TABLE II

Ketone excretion in moderate to severe ketosis

Patient	Time	Urine volume	Total urine ketones	Urine ketones	Urine ketones mgm. per hour / Blood ketones mgm. per cent	Blood ketones
	minutes	*cc. per hour*	*mgm.*	*mgm. per hour**		*mgm. per cent*
1. "Wi"	240	589	22,050	5,512	66.5	80 to 86
	250	444	18,120	4,350	58	75
	165	336	9,000	3,270	43.6	75
	260	426	12,560	2,900	39.2	74
	225	613	9,950	2,650	44.2	60
	190	805†	4,630+	1,400+	85.4	16.4
	170	380	1,135	400		
	180	282†	955+	318+		
	170	405	340	120	9.4	12.8
	85	494	0	0	0	1.3 to 2.3
	210	128	136	39	10.4	2.3 to 5.2
2. "St"	290	370	17,305	3,580	70.6	60 to 41.5, av. 50.7
	110	327	2,340	1,270	30.6	41.5
	180	297	1,322	440	16.8	29.9 to 22.9, av. 26
	180	±160(?)	534	±178	±7.7	23.1
	175	284	343	117	6.4	18.3
	125	198	77	37	2.3	16.2
3. "K"‡	240	272	3,014	754	9.7	78
	65	55	56	52	0.8	66
	65	250	116	107	2.1	51.7
	57	137	9	9	0.24	38
	60	200	12	12		
4. "B"	110	292	485	264	7.2	36.9
	130	180	376	174	5.8	29.9
	120	285	237	119	4.9	24.3
	120	365	0	0	0	11.1
	60	110	0	0	0	10
5. "G"	130	128	2,710	1,254	19.6	64
	50	516	922	1,106		
	60	610	397	397	15.9	25
	375	138	311	50	3	
	140	178	40	17	4	4
6. "W"	155	170†	618+	239+	6.6+	36.3
	135	131†	158+	70+	2.7+	26.9 to 25.8
	115	82	98	51	2.2	22.4 to 23.5
	120	121	0	0	0	
	120	21†	0	0	0	5.1
7. "H"§	185	117	977	316		108 to 150+
	135	53	330	147		69

* Calculated for time period listed.
† Some urine lost.
‡ Urine ketones fractionated into acetone and beta-hydroxybutyric acid. Amount listed represents beta-hydroxybutyric acid.
§ Patient in uremia.

out excretion through the kidneys. Widmark further claims that for acetoacetic acid there is no correlation between the blood and urine curves, indicating secretory activity of the kidney. All this early work, however, is open to the criticism of relatively inaccurate blood methods. Shipley and Long (9) in recent years have established evidence that in the rat, there is a definite renal threshold—between 25 and 30 mgm. per cent. Our results give definite quantitative data concerning the renal threshold for the ketone bodies, and the correlation between blood level and the urinary excretion per hour. The urinary excretion of ketone bodies varies with the blood level, but does not act similarly to such substances as urea. When the urinary ketone output per hour is charted against the blood level, a somewhat hyperbolic type of curve is obtained, with a

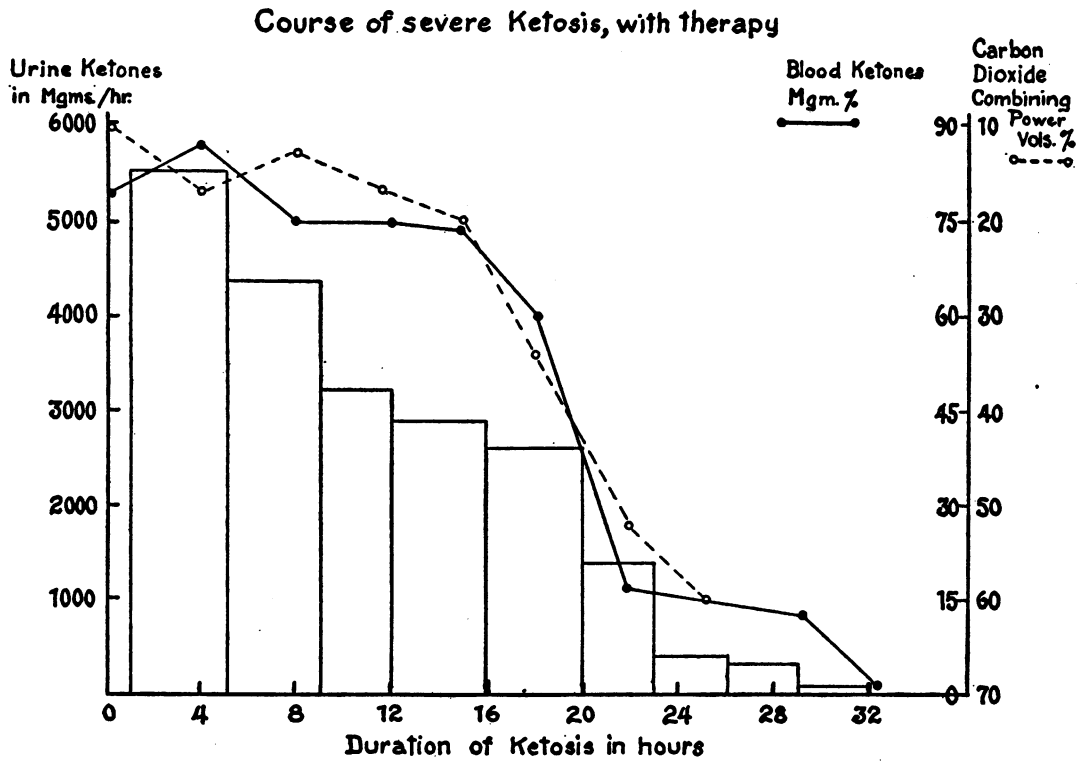

FIG. 2. THE PROLONGED PERIOD OF SEVERE KETOSIS (20 HOURS) WITH THE VERY LARGE URINARY KETONE OUTPUT AT THE HIGH BLOOD KETONE LEVELS (Patient "Wi," Table II)

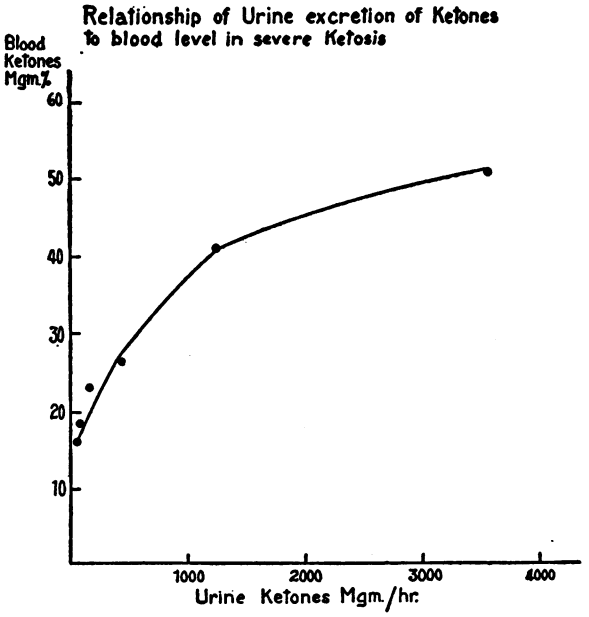

FIG. 3. The INCREASE IN URINARY KETONE OUTPUT PER HOUR WITH RISING BLOOD KETONE LEVELS (Patient "St," Table II)

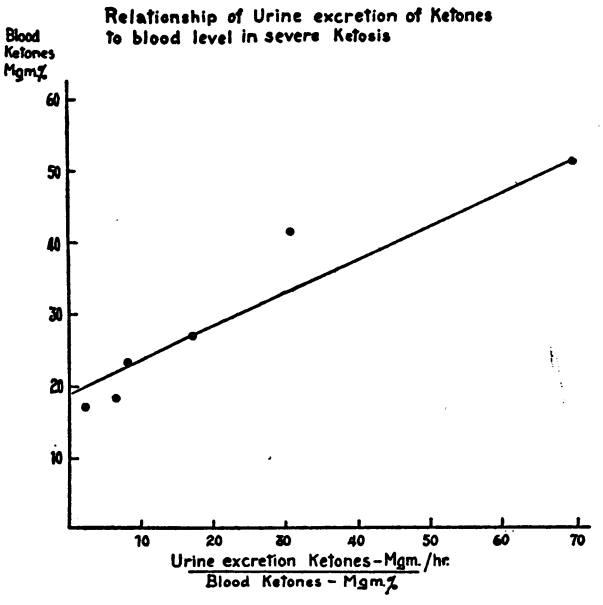

FIG. 4. EXPRESSING THE DATA FROM FIGURE 3 AS A RATIO BETWEEN BLOOD KETONE LEVEL AND THE RATIO BETWEEN URINE KETONES PER HOUR AND BLOOD LEVEL, A STRAIGHT LINE RELATIONSHIP IS OBTAINED (Patient "St," Table II)

TABLE III

*Fractionation of urine ketones into beta-hydroxybutyric acid and acetone**

Patient	Total acetone in urine	Total beta-hydroxy-butyric acid in urine	Acetone	Beta-hydroxy-butyric acid	Blood ketones
	mgm.	*mgm.*	*per cent*	*per cent*	*mgm. per cent*
1. "B"	3.1	4.3	42	58	
	2.3	4.5	33	67	6
	9.6	12.2	44	56	6.6
	18	38.2	32	68	10
	3.4	3.7	48	52	2.5
	6.8	0	100	0	1.7
2. "K"	34	68	34	66	
	35	385	8	92	78
	460	2,300†	17	83	75
	84	329	20	80	78
	34	56	37	63	66
	113	116	50	50	51
	38	9	81	19	38
	68	12	85	15	
3. "Ha"	80	163	33	67	30
	84	76	53	47	
	47	7.1	87	13	16.4
	65	17.9	78	22	15.5
	41.7	17.2	79	21	12.8
	78	28.9	73	27	0.5
4. "P"	48.9	391	11	89	19
	46.9	258	15.4	84.6	21 to 14.7
	18	85	17.4	82.6	5.4
	9.5	26.2	27	73	4.1
	8.4	12.2	41	59	2.9
5. "D"	23.4	270	8	92	
	48.1	314	13.3	86.7	16
	5.3	28.8	15.5	84.5	2

* Acetone represents acetoacetic acid and acetone.
† Bladder not completely emptied before, catheter inserted at this point.

TABLE IV

Lack of correlation between carbon dioxide combining power and blood ketone level

Blood carbon dioxide combining power	Blood ketones
volumes per cent	*mgm. per cent*
10	80
13	75
14	64
16	150+
17	86, 78, 30
20	75, 24
23	37
27	75
28	69, 11
34	51, 60, 25
44	10
46	26

marked fall in output with blood levels under 20 to 30 mgm. per cent. (The exact levels vary from patient to patient.) In contrast, when urea excretion per hour is plotted against the blood urea level, a straight line passing through the point of origin is obtained. When the relationship between blood and urine ketones is expressed as a ratio: $\frac{\text{urinary ketones mgm. per hour}}{\text{blood ketones mgms. per cent}}$ the fact that the ketone bodies are threshold substances is clearly demonstrated, as there is a striking change in the ratio at low and high blood concentrations. This, again, is in distinct contrast to threshold substances, like urea, where the threshold is proportional to the blood concentration. Addis and Drury (10, 11) showed with urea "That under certain special conditions the rate of urea excre-

TABLE V

Ketone excretion in patient with oliguria and azotemia

Time	Blood ketones	Urine ketones	Urine volume	Blood sugar	CO_2 C.P.	Fluid intake
	mgm. per cent	*mgm. per hour**	*cc. per hour*	*mgm. per cent*	*volumes per cent†*	
9:30 A.M.						1000 cc. N.S. i.v.
10:10				930 (N.P.N. = 80	16	
10:10 to 11:25		?	8	mgm. per cent)		
10:40	150+					1000 cc. N.S. i.v.
11:25 to 12:30		61.7	55			
11:45						1000 cc. N.S. i.v.
12:15 P.M.						1000 cc. N.S. subcut.
12:30	150+			740 (chlorides = 335	16	1000 cc. M/6 sodium
12:30 to 2:30		455	150	mgm. per cent)		lactate
1:33	108					
2:30 to 4:45		147	53			
3:42	69			932	28	
4:45						500 cc. blood transfusion
5:55	39					

* All urines gave a positive qualitative acetone test.

† CO_2 C.P.—carbon dioxide combining power.

‡ Just at death.

N.P.N.—non-protein nitrogen.
N.S.—normal saline.
i.v.—intravenously.
subcut.—subcutaneously.
M/6—sixth molar.

tion becomes directly proportional to the blood urea concentration, so that in any one individual the ratio: $\frac{\text{urea in 1 hour's urine}}{\text{urea in 100 cc. of blood}}$ is a constant with only narrow limits of variation, over a wide range of blood urea concentrations." The fact that the percentage of acetone (and hence aceto-acetic acid) increased proportionally to beta-hydroxybutyric acid at a very low blood level suggests that these substances are non-threshold substances, and would account for the majority of ketone bodies found in the urine under blood levels of 20 mgm. per cent. This is further evidence that beta-hydroxybutyric acid is a threshold substance. It thus appears to belong to the group of threshold substances, and behaves similarly to such electrolytes as chlorides (12), substances with "fixed" thresholds.

These results are of significance clinically. The qualitative urinary acetone test, in the majority of cases, roughly paralleled the quantitative total urinary ketone output. The results in one patient with uremia and oliguria suggest, however, that such a gauge of blood level, *i.e.* urinary acetone, can be used only in the presence of adequate renal function. This has been suggested by others (13, 14), although Briggs (15) claims that it is impossible to have ketone bodies in the blood and not in the urine, due to diffusion directly from the blood to urine in the urinary bladder.

SUMMARY

Studies on 20 diabetics in mild and severe ketosis have shown:

1. The low urinary output of ketone bodies (less than 100 mgm. per hour) with blood ketone levels under 20 mgm. per cent. This is probably due largely to the excretion of acetone which appears to be a non-threshold substance.

2. A relationship between blood ketone levels and urinary output:
   a. Increased urinary output per hour with rising blood ketone levels.
   b. A renal threshold for beta-hydroxybutyric acid over 20 mgm. per cent.

3. Impaired urinary excretion with renal failure.

4. A lack of correlation between the blood ketone level and the carbon dioxide combining power.

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