XXXI. STUDIES IN THE ACETONE CONCENTRATION IN BLOOD, URINE, AND ALVEOLAR AIR. II: THE PASSAGE OF ACETONE AND ACETO-ACETIC ACID INTO THE URINE.

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(Received February 10th, 1920.)

THERE is a great difference between the conditions of diffusion in the tissues in the case of the two components of the total acetone, the acetone and the aceto-acetic acid. The aceto-acetic acid occurs within the organism as a largely dissociated salt. Of the salts of the organic acids we know that they possess only to an inconsiderable degree the power of penetrating the living cell. The tissue cells therefore constitute a certain obstacle to the free diffusion of the salt. On this account a difference in concentration may arise and remain on the two sides of a tissue membrane. Acetone on the other hand belongs to a group of substances which can with the greatest ease penetrate the living cell. It can therefore, on its appearance within the organism, diffuse without any hindrance from cells or cell membranes.

This difference appears clearly in the passage of these two substances into the urine.

The aceto-acetic acid is concentrated through the action of the kidneys. The acetone passes into the urine by means of diffusion, and no concentration of the free acetone in the urine can be brought about by the action of the kidneys.

In the urinary bladder the concentration of the aceto-acetates is considerably greater than the concentration of these substances in the blood; diffusion through the walls of the bladder is not probable. The acetone on the other hand is very readily diffused through the walls of the bladder.

In this part we give details of a number of experiments intended to throw light upon these facts.

THE ELIMINATION OF ACETONE THROUGH THE URINE.

The idea that substances soluble in lipoids pass into the urine solely through diffusion was formulated more than ten years ago by Overton [1907]. He writes: "Wenn Amphibien in nicht tödlichen Konzentrationen von Alkohol, Aceton u.s.w. suspendiert werden, so enthält der Harn nach Ablauf einiger Zeit [die zur Einstellung des Gleichgewichts zwischen dem Gehalte

der Verbindungen im Blute und der Aussenlösung erforderlich ist] diese Stoffe in annähernd gleicher Konzentration wie die Aussenlösung [nach eigenen, noch nicht publizierten Versuchen]. Auch bei den Säugetieren fand Gréhant nach Einführung von Alkohol in den Magen fast die gleiche Alkoholkonzentration im Blute und im Harne. Wegen der schnellen Verbrennung des Alkohols bei warmblütigen Tieren ändert sich die Alkoholkonzentration im Blute recht schnell, und bei dem ungünstigen Verhältnis der absorbierenden Oberfläche der mässig oder stärker gefüllten Harnblase zu deren Volumen [namentlich bei grösseren Tieren] kann sich die Alkoholkonzentration jenes Harnes, der zu einer Zeit abgesondert wurde, wo sich viel Alkohol im Blute befand, nicht mehr ausgleichen mit der Konzentration im Blute, nachdem dieses an Alkohol arm geworden ist. Wenn umgekehrt viel Harn in der Harnblase vorhanden war, ehe die Alkoholkonzentration im Blute ihr Maximum erreicht hatte, muss zu einer bestimmten Zeit die Alkoholkonzentration in der Harnblase hinter derjenigen im Blute stehen. Ähnliches gilt natürlich für andere Vertreter dieser Gruppe von Stoffen.

“Dass viele Verbindungen, die in den Lipoiden leicht löslich sind, im Organismus durch Paarung mit anderen im Körper gebildeten Stoffen oder auf anderen Weise in Substanzen übergehen, die nicht mehr in den Lipoiden merklich löslich sind, und einer aktiven Exkretion durch die Drüsenzelltätigkeit unterliegen, ist einer Sache für sich, die in keinem Widerspruch mit dem vorher Gesagten steht. Solche organische Verbindungen die nur schwer löslich in den Lipoiden sind, wie Glycerin und Harnstoff, sind ebenfalls in gewissen Drüsen der aktiven exkretorischen Zellentätigkeit unterworfen.”

No further detailed researches have yet been published by Overton.

The passage of ethyl alcohol into the urine was investigated in detail some years ago by the author [Widmark, 1915]. Comparative estimations were then carried out between the alcohol percentage in the blood and in the urine simultaneously secreted. The results showed that the concentrations in blood and urine very nearly coincided with one another. The alcohol concentration in the urine was not affected by diuresis; an increase in diuresis caused by the taking of a quantity of water did not in any way change the alcohol concentration in the urine.

The agreement between the concentrations in the blood and in the urine has more recently been demonstrated, independently of the author, by Chabanier and Ibarra-Loring [1916], whose experiments were concerned with ethyl and methyl alcohols.

Experimental.

The experiments with acetone were carried out as follows:

The subject first completely emptied his bladder. He then drank a certain quantity of dilute acetone solution. Blood estimations were at once carried out, with a few minutes interval after each. Every 15th minute the bladder was emptied, the quantity of urine measured, and the acetone concentration

determined. In certain experiments this series of estimations began immediately after the taking of acetone; in other cases the comparative estimations were not begun until after the acetone concentration in the blood had become something like constant. In order to demonstrate the influence of diuresis, or more properly speaking to show that diuresis has no influence upon the acetone concentration in the urine, a quantity of water was taken at a certain point in the experiment, the variation in the quantity of urine secreted during the periods of 15 minutes was measured, and the acetone concentration estimated.

Experiment 1. Subject of experiment: the author. Acetone taken: 8 grams in about 200 cc. of water. First blood test 7 minutes after taking, first urination 15 minutes after taking. During the sixth 15-minute period 300 cc. of water at room temperature were taken. The results of the experiment are shown by Table I and Fig. 1.

Table I.

Time (Periods of 15 min.)	URINE		BLOOD Concentration of acetone ‰
	Concentration of acetone ‰	Rate of excretion cc./min.	
I	0.01	2.3	0.04
II	0.12	2.8	0.15
III	0.16	9.2	0.12
IV	0.16	10.7	0.12
V	0.14	4.5	0.12
VI	0.14	3.2	0.12
VII	0.14	5.7	0.11
VIII	0.13	10.7	0.12
IX	0.14	3.6	0.12
X	0.13	3.7	0.10
XVII	0.10	2.9	0.08

The table and figure show that the acetone concentration of the blood at first rises more rapidly than that of the urine; the highest values in the blood were obtained sooner than the highest values in the urine. The connection between the two cannot be ascertained more closely, because the periods during which the urine was collected in the bladder are too long for the estimation of the concentration in the portions obtained to express accurately the course of the curve. When the blood acetone has shown itself to be at a certain fairly constant level, the urine acetone also remains fairly constant, as far as the concentration is concerned. The concentration of acetone in the urine remains throughout somewhat higher than that in the blood. This is probably due to the fact that the acetone in the urine has about the same concentration as that in the plasma, which is somewhat higher than that of the total blood. Possibly the concentration in the urine may be even a little higher than in the plasma, on account of the fact that acetone is perhaps more easily soluble in urine than in plasma. The saltiness of the urine does not seem to play any part worth mentioning. During the experiment the excretion curve reached two maxima: the first due to the

quantity of fluid taken in connection with the taking of the acetone, the second to the quantity of water taken during the sixth period. The concentration in the urine in no way follows the variations in the excretion, but seems to proceed in complete independence of these.

Fig. 1. — = excretion.

---- = concentration of acetone in urine.

o—o = concentration of acetone in blood.

Abscissa: periods of analysis.

Ordinate: acetone concentration in ‰, excretion in cc. per min.

Experiment 2. Subject: the author. On March 16 at 10.45 a.m., 9.6 g. of acetone were taken in 500 cc. of water. The comparative estimations of the acetone concentration in blood and urine were begun at 1.15 p.m. At 1.45 p.m. 500 cc. of water were taken. The result is shown by Table II and Fig. 2.

Table II.

Time	URINE		BLOOD	
	Concentration of acetone ‰	Rate of excretion cc./min.	Time	Concentration of acetone ‰
1.15-1.30	0.160	1.33	1.35	0.127
1.30-1.45	0.160	1.80	2.20	0.127
1.45-2.00	0.160	2.13	2.25	0.124
2.00-2.15	0.160	8.40	2.50	0.115
2.15-2.30	0.160	7.33	—	—
2.30-2.45	0.156	2.87	—	—

This experiment shows, even better than the preceding, how completely the acetone concentration of the urine is independent of the amount excreted. Here too the concentration of acetone in the urine is somewhat higher than in the blood. The lowest value for the rate of excretion is 1.33, the highest is 8.4; although therefore the volume of the urine becomes more than six times as great, the concentration of the acetone is not in the slightest degree influenced by this fact.

In this graph, for the sake of clearness, both the excretion and the estimations of the acetone concentration of the urine are represented by points lying in the middle of the period in question.

Experiment 3. Subject: the author. On March 7, 1917 at 9.45 a.m., 16 g. of acetone were taken in 600 cc. of water. The comparison between the acetone concentration in blood and urine was begun at 1.15 p.m. At 2.35 p.m. 500 cc. of water were taken.

Table III.

Time	URINE		Time	BLOOD
	Concentration of acetone ‰	Rate of excretion cc./min.		
1.15-1.30	0.28	1.87	1.15	0.22
1.30-1.45	—	1.67	—	—
1.45-2.00	0.29	1.80	—	—
2.00-2.15	—	1.87	—	—
2.15-2.30	0.27	1.67	—	—
2.30-2.45	0.27	1.87	—	—
2.45-3.00	0.25	3.73	—	—
3.00-3.15	0.26	9.67	3.14	0.21
3.15-3.30	0.25	10.53	—	—
3.30-3.45	0.23	5.73	4.0	0.18

Experiment 4. Subject: B. J. Body weight, 63 kg. At 11.40 a.m. 8 g. of acetone were taken in 500 cc. of water. The comparison between the acetone concentration in blood and in urine was begun at 2.30 p.m. At 2.35 p.m. 500 cc. of water were taken.

Table IV.

Time	URINE		Time	BLOOD
	Concentration of acetone ‰	Rate of excretion cc./min.		
2.30-2.45	0.15	1.60	2.12	0.15
2.45-3.00	0.16	4.93	3.15	0.13
3.00-3.15	0.17	8.80	4.12	0.12
3.15-3.30	0.16	8.40	—	—
3.30-3.45	0.17	8.67	—	—

This experiment, carried out on a different subject from the preceding, shows the same facts as have been already described.

THE ELIMINATION OF ACETO-ACETIC ACID THROUGH THE KIDNEYS.

If an experiment in the same direction as those recorded above is made with a diabetic patient with acidosis—*i.e.* if he is allowed to drink a certain quantity of water, and comparative measurements are then taken of the total acetone concentration in the blood and in the quantity of urine passed during each 15-minute period—quite a different result is obtained. We know that by far the greatest part of the total acetone of the urine occurs in the form of aceto-acetates. Only a small part is free acetone. It has already been pointed out that the conditions of diffusion for these salts are quite other than for the acetone. The salts are not diffused through the kidneys but may evidently be subjected to an active excretion, through which the concentration of these substances in the urine may become many times greater than their

concentration in the blood. With an increased quantity of urine resulting from the resorption of a certain amount of water by the subject, the amount of the aceto-acetates secreted is not increased in the same proportion as the amount of urine. The consequence of this is that with a water-diuresis the total acetone concentration sinks rapidly, to rise again later as soon as the rate of excretion of urine returns to its normal value. This is shown by the two following experiments.

Experiment 5. August 16, 1916. Subject: Mrs L., diabetic with pronounced acidosis. 1 litre of water was taken on an empty stomach. The total acetone concentration was then estimated in portions of urine obtained every quarter of an hour. The estimations were carried out according to the method of Embden and Schliep. The reaction of the urine was alkaline or amphoteric.

Table V.

Time (Periods of 15 min.)	Total acetone concentration of urine ‰	Rate of excretion of urine cc./min.
I	0.696	0.53
II	0.658	0.60
III	0.482	0.93
IV	0.189	2.73
V	0.193	3.60
VI	0.244	1.80
VII	0.310	1.67

As soon as the rate of excretion is increased, the total acetone concentration in the urine simultaneously falls to a considerable extent. After the rate has reached its maximum and has begun to sink, the total acetone concentration rises.

Experiment 6. Subject: J. N., diabetic with acidosis. At 1.45 p.m. on March 14, 1917, one hour after a meal, 500 cc. of water at room temperature were taken. The reaction of the urine was alkaline or neutral. The results are given in Table VI and Fig. 3.

Table VI.

Time	URINE		BLOOD Total acetone ‰
	Total acetone ‰	Rate of excretion cc./min.	
1.45-2.00	—	0.60	—
2.00-2.15	> 0.95	0.86	2.20 { 0.109 0.103
2.15-2.30	0.31	4.26	—
2.30-2.45	0.19	7.73	—
2.45-3.00	0.25	6.40	3.20 { 0.126 0.121
3.00-3.15	0.72	1.60	—

This experiment shows that the total acetone concentration in the urine is throughout considerably higher than in the blood. When the diuresis sets

in the concentration in the urine at once sinks to a considerable extent, and rises again as soon as the quantity of urine is diminished. There is therefore no correlation between the acetone curves in the blood and in the urine, and the passage of the aceto-acetic acid into the urine is determined by the incidental secretive activity of the kidneys¹.

Fig. 3. Relation between the excretion of urine and the total acetone concentration in the urine in diabetes, according to Exp. 6. o-o = excretion of urine; o-o = total acetone concentration in urine; — = total acetone concentration in blood.

¹ It is possible that the *reaction* of the urine may also play a certain part in the elimination of aceto-acetic acid. The free acid may possibly be more easily diffused than the salt through the kidney epithelium; a difference in concentration will in that case less easily arise. In this circumstance may perhaps lie the explanation of the fact which many writers claim to have demonstrated, that the acetone bodies pass over into the urine in greater quantities if the patient is given bicarbonate.

ON THE RELATION OF THE ACETONE TO THE WALLS OF THE
URINARY BLADDER.,

It was formerly believed that the walls of the healthy urinary bladder are, practically speaking, impermeable to the substances which pass into the bladder by way of the kidneys, and that these substances can only leave the bladder by one way, viz. through the urethra [compare Cohnheim, 1909].

Novicka [1913] has however quite incontestably shown that alcohol is diffused with great ease through the walls of the bladder, the direction of diffusion depending upon the higher concentration. For this substance therefore the rule does not always apply that the amount of alcohol found in the daily quantity of urine is also the daily quantity of alcohol coming from the kidneys. The following cases, for instance, may be imagined to occur:

(a) The alcohol concentration in the bladder and the blood is the same during the period between two urinations. The quantity of alcohol which has come from the kidneys is not altered in the bladder by diffusion.

(b) The alcohol concentration is lower in the blood than in the bladder during the time that elapses between two urinations. The quantity of alcohol which has come from the kidneys is diminished in the bladder by diffusion from bladder to blood.

(c) The alcohol concentration is higher in the blood than in the bladder during the period between two urinations. The quantity of alcohol which has come from the kidneys is increased by direct diffusion from blood to bladder.

If the time between the urinations is short, the difference in concentration between blood and urine will be inconsiderable, because the alcohol, as we have previously emphasised, passes into the urine in the same concentration as into the blood, and no considerable fluctuations in concentration can appear. If the time between two urinations is long, it may happen that the alterations in the concentration of the blood are of so high a degree that cases (b) and (c) may occur.

It is evident that this property possessed by ethyl alcohol of diffusion through the walls of the bladder is merely an evidence of its power to penetrate the living cell and organic tissues in general. It is therefore to be expected that all substances having the same properties as alcohol will form an exception to the rule as to the impermeability of the walls of the bladder¹.

In the following we shall show that the relation of acetone to the walls of the bladder is exactly the same as that of alcohol.

¹ Thus, for example, methylene blue diffuses with the greatest ease through the bladder walls. If the ureters of a rabbit are bound up and a dilute solution of methylene blue is injected into vena jugularis, it will be found very soon—18 minutes after the injection—that the urine is coloured deep blue.

Demonstration of the diffusion of acetone from bladder to blood.

Experiment 7. August 24, 1916. Rabbit ♂. A half-solid catheter was introduced into the bladder and allowed to remain throughout the experiment. 45 cc. of urine were drawn off. 50.5 cc. of 2.42 ‰ acetone in physiological salt-solution—i.e. 122 mg. of acetone—were then introduced. After one hour the bladder was tapped and rinsed out three times with 5 cc. of physiological salt-solution. In the mixed quantity the acetone was determined according to Messinger-Huppert and the amount found to be 71.4 mg.

<i>Result:</i>	Introduced	122 mg.
	Found	71 mg.
	Quantity lacking after one hour	51 mg. = 41.8 %

The blood contained 1.54 mg. of acetone per 100 cc. Post mortem examination showed an intact bladder mucous membrane. Otherwise nothing pathological.

Experiment 8. March 5, 1917. Rabbit 1330 g. ♂. At 11.10 a.m. a few cc. of a 5 ‰ acetone solution were injected by means of a catheter into the animal's bladder. A series of blood estimations was then undertaken. The result is shown by Table VII.

Table VII. The passage of acetone from the contents of a rabbit's bladder into the blood.

Time	Total acetone of blood ‰
11.0 a.m. before the injection	0.010, 0.012 = 0.010
12.15 p.m.	0.10
1.25	0.11
2.25	0.13
3.20	0.09

The experiment shows that acetone introduced into the bladder can be demonstrated in the blood as soon as one hour afterwards.

Even though it is highly probable that there is no important dissimilarity between the conditions of diffusion in the urinary bladder of rabbits and of human beings, the demonstration of the diffusion in human beings is nevertheless of importance. For the introduction of a definite amount of acetone into the bladder of human beings a modification of Janet's method is used. The arrangement of the apparatus is shown by Fig. 4. *A* is a vessel that can be raised and lowered, attached by a tube to the pressure-flask *B*, communicating with the burette *C*, which has a glass tap at either end. The discharging-tube of the burette is provided with a perforated rubber cone, which can be introduced into fossa navicularis penis so as to close the orifice of the urethra. At the beginning of the experiment all the vessels contain sublimate solution (1 : 2000). By lowering *A* beneath the level of *B* and giving *C* a suitable position with the fluid above the tap *b*, the sublimate

solution can be conveniently sucked out of the burette and sterile acetone solution sucked in up to a certain height. When the pressure has been equalised by raising *A*, the taps are closed, and the level in the burette is read off. The burette is now brought into contact with the urethra, the taps are opened once more, and *A* is gently raised to a suitable height. When a sufficient quantity of fluid has passed into the bladder, *A* is lowered and the amount of fluid present in the distended urethra flows back into the burette, with the exception of a very small quantity (0.5–1.0 cc.), which can be caught and measured when the burette is removed from the penis. Before this is

Fig. 4.

done the taps are closed and the burette is read off. By this arrangement an accurately measured quantity of fluid can be introduced into the bladder without pain or any appreciable discomfort. The fluid in the burette can be kept at body temperature. After the injection the concentration of the acetone in the burette is determined. The burette has all the time been completely closed, except during the injection. This removes the possibility of an error which might arise owing to the evaporation of the acetone solution from an open vessel.

Experiment 9. Subject: E. W. August 25, 1916. 37 cc. of a 1 % solution of boracic acid containing 0.74 % acetone were introduced into the bladder. An hour after this the bladder was emptied. In order to wash out as much as possible of the acetone remaining, the bladder was emptied a couple of times more, with 5-10 minutes' interval between. The total quantity of urine amounted to 294 cc. It contained 22.8 mg. of acetone.

<i>Result:</i>	Introduced	27.4 mg. acetone
	Found	22.8 „
	Amount lacking after one hour	4.6 „ = 16.8 %

This experiment suffers from two deficiencies: (1) the amount of acetone introduced is too small, and (2) the experiment was carried out immediately after a meal, so that the excretion of urine was comparatively great. For both these reasons the pre-formed iodine-binding substances present in the urine give rise to a relatively great source of fallacy. The result of the experiment may therefore easily lead to the conclusion that a less complete re-absorption takes place than is actually the case. The following experiment, in which a larger quantity of acetone was introduced during a period of low rate of excretion, gives a clearer idea of the diffusion.

Experiment 10. Subject: E. W. August 26, 1916. 57 cc. of a 2.77 % acetone solution were introduced. After one hour the bladder was emptied as in the previous experiment. The total quantity of urine, 178 cc., contained 114 mg. of acetone.

<i>Result:</i>	Introduced	158 mg.
	Found	114 mg.
	Amount lacking after one hour	44 mg. = 27.8 %

The experiments show that acetone is able to pass quite easily through the walls of the human bladder also. It should however be pointed out that a certain quantity of acetone may have diffused into the blood in the passage through the urethra during the introduction of the liquid. The walls of the ureters are of course permeable to a far higher degree, for many substances, than the walls of the bladder. Nevertheless, that there is a diffusion through the walls of the bladder can hardly be denied.

*Demonstration of the diffusion of acetone from blood to urine
with tied ureters.*

Experiment 11. August 23, 1916. Rabbit ♂. Weight 2640 g. Narcosis with ethylene urethane. After ventral incision in the middle line both ureters were brought forward and tied immediately above the bladder. The wound was provisionally closed. A half-solid catheter was then introduced through the urethra and 46 cc. of urine were drawn off. 50 cc. of physiological salt-solution were introduced.

Now, for a period of ten minutes, 15 cc. of about 50 % acetone in physiological salt-solution were injected drop by drop through the vena jugularis

externa. The rabbit showed strong dyspnoea during the injection. Five minutes after the injection was over Legal's acetone test on 2 cc. of the contents of the bladder showed uncertain reaction. After five minutes more the test was clearly positive, and 15 minutes after the injection strongly positive: 30 minutes after the injection a blood sample was taken and the urine left in the bladder drawn off. Acetone estimations on both samples according to Messinger-Huppert showed:

In the blood: 3.2 ‰ acetone.

In the contents of the bladder: 1.1 ‰ „

Section showed an intact bladder mucous membrane. In other respects nothing noteworthy.

These experiments show therefore that free acetone can pass with considerable ease through the walls of the urinary bladder. The direction is determined by the side of the bladder walls on which the greater concentration prevails. The quantity diffused will depend on the concentration and the extent of the absorbing surface.

In diabetes the changes in the percentage of free acetone in the blood probably take place somewhat slowly. In all probability no considerable difference in concentration occurs between the free acetone of the blood and that of the bladder, nor, consequently, is there any considerable change in the amount of acetone in the urine owing to diffusion through the walls of the bladder. On the other hand it is conceivable, especially if the urine is strongly acid, that part of the aceto-acetic acid is already decomposed in the bladder. On account of the higher acetone concentration which thus appears in the bladder, a diffusion of acetone into the blood may take place. The extent of the decomposition of the aceto-acetic acid under such circumstances is not known. No kinetic measurements of the decomposition of the acid under different circumstances are yet forthcoming. We cannot decide, therefore, how great a diminution is undergone by the amount of aceto-acetic acid secreted by the kidneys as a result of the fact that part of it is already decomposed in the bladder and the acetone arising therefrom diffused through the bladder walls.

I have performed no experiments with regard to the relation of aceto-acetic acid to the walls of the urinary bladder. From the fact that the total acetone concentration of the urine is usually higher than that of the blood we may conclude that diffusion through the walls of the bladder cannot take place to any considerable extent.

FORMULA FOR THE ELIMINATION OF ACETONE THROUGH THE KIDNEYS.

Free acetone is eliminated—as soon as more violent variations in the acetone concentration of the blood have ceased to take place—in a concentration which lies very near to that of the acetone concentration in the plasma. This concentration remains unchanged even though the amount of urine excreted during the unit of time varies.

The amount of acetone, M_u , coming from the kidneys in the unit of time depends therefore upon the following three factors:

The concentration of free acetone in the plasma, a ,

The partition coefficient urine/plasma, κ ,

The rate of excretion, quantity of urine per unit of time, v ,

or
$$M_u = a.v.\kappa.$$

If free acetone exclusively is present in the blood, the quantity eliminated may be approximately estimated from the above factors. With constant blood acetone concentration the amount of acetone eliminated will be increased proportionally to the increase in the quantity of urine. If this quantity of urine is increased to twice as much, *e.g.* because the subject of the experiment drinks a certain quantity of water, the amount of acetone eliminated will also be doubled. With a constant quantity of urine the amount of acetone eliminated increases proportionally to the increase in the concentration in the blood, provided that this increase does not proceed too quickly.

κ for urine/plasma is in all probability very nearly 1. For urine/total blood—according to calculation from the values given by the published experiments—it is 1.235, with $E = \pm 0.0670$ and $e_1 = \pm 0.0186$.

If, as well as the free acetone, aceto-acetic acid simultaneously occurs, the total quantity of acetone eliminated through the urine cannot be calculated in the same simple fashion. The amount of aceto-acetic acid secreted depends not only on the aceto-acetic acid concentration in the blood but also on the capacity of the kidneys, a factor which cannot at present be determined. The formula for the elimination of the total acetone, M_t , in the unit of time may (for a purpose to be mentioned later) be written:

$$M_t = a.v.\kappa + c,$$

where c is unknown.

By throwing light on this proposition we shall be able to arrive at some explanation of the relations between the acetone and the aceto-acetic acid in the urine.

As is well known, Folin [1907] and Embden [1907] have found that the pre-formed acetone in the urine generally constitutes a quite inconsiderable proportion of the total acetone of the urine. From Folin's measurements we take the following table in which all the values are reckoned in ‰.

Table VIII. Some of Folin's estimations concerning the relation between acetone and aceto-acetic acid in the urine of diabetics. All the values are expressed in ‰.

Nc.	Total acetone	Free acetone	Acetone from aceto-acetic acid
I	0.67	0.16	0.51
II	0.68	0.25	0.43
III	2.83	0.36	2.47
IV	0.79	0.24	0.55
V	2.15	0.26	1.89
VI	1.67	0.22	1.45
VII	1.02	0.10	0.92

Embden finds that often only aceto-acetic acid occurs in the urine. In general the amount of acetone in his estimations constituted less than 25 % of the total acetone, and most frequently considerably under 10 %.

Now we know that the free acetone—provided that no very considerable decomposition of the aceto-acetic acid takes place in the bladder—can never reach values lying appreciably higher than the concentration of the free acetone in the blood. It is only in very rare cases that the total acetone in the blood of diabetics is as much as 0.40 ‰; the free acetone therefore has still lower values. Hence it follows that the acetone in the urine can never reach any very high concentration. But the aceto-acetic acid, which is secreted by the kidneys, may on the other hand be present in the urine in a concentration many times greater than that of the blood.

SUMMARY.

Acetone passes into the urine by way of diffusion. The concentration in the blood and in the urine is therefore usually the same.

Aceto-acetic acid passes into the urine by way of the concentrating activities of the kidneys. The concentration in the urine is therefore higher than in the blood.

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