THE CHEMISTRY OF THE URINE IN DIABETES MELLITUS.

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The following article is the result of almost daily analysis of the urine in a typical case of diabetes mellitus, extending from the recognition of the disease to the death of the patient, a matter of eight months. On account of the confusion existing in the literature bearing on this subject it has been deemed best to synthetically prepare several of the abnormal bodies present in the urine of this case for the purpose of an experimental study of their properties.

Aceto-acetic acid.—The true history of this body begins with Gerhardt's discovery in 1865 that certain diabetic urines yielded a Bordeaux red on the addition of a solution of ferric chlorid. He did not, however, attribute this reaction to the presence of aceto-acetic acid but believed it to be due to the presence of ethyl aceto-acetate, an allied body responding to this test, since he observed that the distillate of such an urine contained certain quantities of acetone and alcohol, probably in the following reaction:

The alcohol present in this distillate, however, was probably a product of the sugar fermentation and its occurrence thus led to an erroneous conclusion. This theory of Gerhardt has not been confirmed by later investigators. Following Gerhardt's discovery, Rupstein, in a series of experiments, claimed to have isolated a substance apparently identical with aceto-acetic acid, which body has since been considered to give the reaction with ferric chlorid in diabetic urine. In 1885, V. Jaksch ("Ueber Acetonurie und Diaceturie," Berlin) made more extended investigations and published his methods and conclusions, bringing out many new facts with regard to the occurrence of aceto-acetic acid and acetone. He also claimed to have isolated this acid in the form of various basic salts, but the analytic results given by these salts did not confirm his claims, as they by no means closely agreed with the theoretic analyses. Although unknown to him, beta-hydroxybutyric acid, a body allied to, and isolated in practically the same way as, aceto-acetic acid, is nearly always present in urines which yield the ferric chlorid reaction. This body unites with cases in much the same proportions as aceto-acetic acid and has nearly the same molecular weight, a difference of only two hydrogen atoms. No method of separating these two bodies in the form of basic salts was as yet discovered and Jaksch's claim as to his isolation of diacetic acid can hardly be admitted.

Concerning the properties of diacetic acid but little is known. According to Ceresole (*Berichte der Deutsch. Chem. Gesellschaft* B. xv. S. 1326) it is a thick, colorless liquid of strong acid reaction and is miscible with water in all proportions. It decomposes easily below 100 C. breaking up in the production of acetone and carbon dioxid. According to Jaksch (loc. cit.) it decomposes in the urine on standing in 12 to 18 hours and a dissociation of its salts takes place on

bringing it down to dryness. It dissolves calcium and barium carbonates and if treated with nitrous acid gives carbon dioxid and nitroso-acetone. It never occurs free or in combination in nature except in the urines of patients suffering from diseases involving great tissue waste. It may be artificially prepared according to the method of Ceresole. (loc. cit.) Dissolve 4.5 gm. ethyl aceto-acetate (free from acetic acid) in a solution made by dissolving 2.1 gm. metallic potassium in 80 c. c. of water. Let stand for twenty-four hours and then slightly acidulate with sulphuric acid. It is then shaken with ether several times and this ethereal extract shaken with a fresh mixture of barium carbonate and water. The barium aceto-acetate at once goes into solution, the ethyl aceto-acetate remaining in the ether. This barium salt is very hygroscopic and is not crystalline. It does not give a precipitate with silver nitrate but yields a violet red color on the addition of ferric chlorid. The salt has the same properties. This reaction with ferric chlorid does not take place in the presence of free mineral acids. Aceto-acetic acid is a derivative of the fatty acid series and its relationship to propionic and butyric acids is as follows:

It is closely related to acetone, which is one of its decomposition products according to the following reaction:

to beta-hydroxybutyric acid, from which it is directly produced by oxidation

and to ethyl aceto-acetate, its ethyl salt, bearing the same relationship to this body that acetic acid does to acetic ether.

These several bodies are so intimately related it is evident that no violent chemic action is required to convert one into another, a mere oxidation or the decomposition of an unstable compound being sufficient to effect this change.

It was at first supposed that aceto-acetic acid was produced in some inexplicable way in the oxidation of sugar and several writers, among them Minkowski (*Arch. f. Exp. Path. u. Pharm.*, Bd. 18, S. 41) attempted to demonstrate a relationship between the ferric chlorid reaction and the sugar excretion.

Among other attempts at explanation the following series, which is chemically possible outside the body, was offered by Hugounenq (quoted in *Am. Jour. Med. Sci.*, October, 1887). Starting with glucose, he suggested stages consisting of alcohol, aldehyde, aldol, beta-hydroxybutyric acid, diacetic acid and acetone, the last body being very stable and incapable of further oxidation.

Further investigations showed conclusively that the oxidation of sugar was not the source of this body and V. Jaksch ("Ueber Acetonurie und Diaceturie," Berlin, 1885) advanced the theory that in this oxidation the acetone was directly produced and, if in excessive quantity, united with some fatty acid present in the system, perhaps formic acid, in the production of diacetic acid.

That the source of the diacetic acid is in the sugar is opposed by the fact that not every case of sugar in the urine is accompanied by an acetonuria or a diaceturia, and further that the presence of sugar in the urine does not appear to be essential since diacetic acid has been repeatedly demonstrated in the urines of various fevers, carcinoma and other affections characterized by excessive tissue waste. In the case upon which this work has been based the acid first appeared upon placing the patient upon a diet from which all carbohydrates were excluded, at once greatly diminished upon a return to a mixed diet—this diminution being permanent—and was markedly greater after a diet composed almost entirely of meats.

These points would show that the acid is not produced from sugar, but is produced by a splitting up of albumin. Wolpe (*Jahresbericht der Gesamten Medicin*, 1887) believes that the albumin breaks up into a number of bodies, one of which is beta-oxybutyric acid, this acid being converted into diacetic acid by a process of oxidation. This is the explanation which is most generally received. It has been thought by the writer that its origin might be found in leucin, a body formed in the cleavage of the proteid molecule, splitting up in the direct production of oxybutyric acid and other bodies. This theory is favored by the fact that no acid body from which oxybutyric acid can be readily derived has ever been found in urine. The formation of diacetic acid is by the oxidation of the oxybutyric acid, while the diacetic acid itself decomposes in the production of carbon dioxid and acetone. Should the production of the fatty acids exceed certain limits it is possible that the oxidation can no longer be carried on to acetone, with the result that they are excreted in the urine as diacetic or even oxybutyric acid.

Many of the following results are based upon experimental work upon the barium salt, which responds to the various tests for the free acid and is a much more stable and manageable body. It was found to be fairly stable, requiring six minutes of vigorous boiling to produce complete dissociation, while the free acid stood for several weeks in solution and in ethereal extraction without decomposition. On the addition of the barium salt to urine there was an immediate precipitation of the barium with a decomposition of the acid. On evaporation of this salt

decomposition occurs. Both the free acid and salt are readily soluble in ether, less so in alcohol and water. It was found to be fairly soluble in acetic ether and amyl alcohol, less so in benzol ether and chloroform. It gives a bordeaux red on the addition of ferric chlorid, yields iodoform by treating with sodium hydrate and Lugol's solution and also with ammonium hydrate and tincture of iodine, the so-called acetone test. The ferric chlorid reaction is therefore a decisive test in diagnosing an acetonuria from a diaceturia. The writer has found that diacetic acid gives the "diazotization reaction" of Ehrlich, while acetone, oxybutyric acid and ethyl acetoacetate do not. This is a ready and reliable test for differentiation. A free mineral acid decomposes diacetic acid, thus destroying the ferric chlorid and "diazotization reactions." Ferrous sulphate gives a similar reaction to ferric chlorid with diacetic acid and is preferable since it can readily be made up in neutral solution. That the reaction with ferric chlorid lost by boiling is due to an actual decomposition rather than volatilization was proved by placing a portion of this acid in a hermetically sealed tube and keeping in steam for half an hour. On cooling and treating with ferric chlorid no reaction could be obtained.

The method of V. Jaksch for isolating diacetic acid from the urine is as follows: "Urine giving a strong reaction with ferric chlorid is slightly acidulated with sulphuric acid and directly extracted several times with ether, until the ethereal extract on evaporation no longer gives a violet reaction with ferric chlorid. These ethereal extracts are shaken with barium carbonate in water, when the acid goes into solution. The ether is then removed and the aqueous solution of barium diacetate filtered clear and evaporated down to dryness in vacuo over sulphuric acid." This method fails if oxybutyric acid is also present in the urine. To eliminate the possibility of the presence of ethyl acetoacetate in this urine, 63 liters of fresh urine were distilled, it being known that this body splits up in the formation of acetone, alcohol and carbon dioxid. A large amount of acetone was present in the distillate but no alcohol. This practically proved the presence of diacetic acid, since there are probably no other bodies which yield acetone on distillation except propyl alcohols, which have never been found in urine. Since all determinations of the diacetic acid by isolation can be by no means quantitative, through the facility with which it decomposes, its comparative insolubility in any extracting body and the synchronous occurrence of oxybutyric acid, no accurate estimations of the quantity of this acid present in the urine have heretofore been possible. The following method, which has been devised during the course of these experiments, can however be recommended as an easy and accurate way of making a quantitative determination. This method is as follows: Make up a solution of barium diacetate and determine its strength by adding to a known quantity an excess of sulphuric acid. The barium sulphate thus formed is precipitated out and weighed, the percentage of barium diacetate in the solution being readily calculated from this. Dilute this solution up to a known amount with water until only a moderate reaction is given on the addition of ferric chlorid. Add 1 c. c. of the urine to be tested to 9 c. c. of water and find out the least quantity of ferric chlorid required to bring out the maximum intensity of the reaction. Now tritrate in 9 c. c. of water a sufficient quantity of

the standard barium diacetate solution so that the reaction produced in each exactly matches in color. From the reading on the burette the proportion of diacetic acid in the urine can be exactly determined. By this method a quantitative estimation of six hours urine, amounting to 3.5 liters, was made. This specimen of urine contained 76.495 gm. of diacetic acid, an enormous quantity which well substantiates the theory that diabetic coma is due to an acid intoxication. In this connection experiment as to the delicacy of the ferric chlorid reaction showed it to occur in the presence of .0000973 per cent. of diacetic acid, while the reaction was strong in the presence of .00038397, as seen in a ten inch column. For clinical purposes, therefore, a urine in which .0005 to .001 per cent. of aceto-acetic acid occurs should be readily recognized. Careful experimental work upon known solutions of diacetic acid have shown that the test based upon the production of iodoform on treating with sodium hydrate and Lugol's solution or with tincture of iodine and ammonium hydrate can not be made quantitative.

Beta-hydroxybutyric acid was first chemically prepared and described by Morkownikoff and Wislicenus ("Watt's Dictionary of Chemistry") about 1870. It is, according to them, a slightly colored, viscid syrup, which shows no tendency to crystallize and readily abstracts moisture from the atmosphere. It volatilizes rather easily in water vapor and at once decomposes on heating to 120 to 130 degrees C., yielding a thickish acid distillate which, on cooling, deposits snow-white crystals having the composition $C_4H_6O_3$, and exhibiting all the properties of crotonic acid. It never occurs in nature except as a constituent of the urine in certain pathologic processes. It is best prepared by treating ethyl aceto-acetate with water and sodium amalgam, when the sodium salt of this acid is at once produced in the following reaction:

By slightly acidulating with hydrochloric acid, neutralizing with sodium carbonate, evaporating to a syrup, separating out the sodium chlorid formed, extracting with strong alcohol and allowing to cool, the sodium oxybutyrate is obtained. This may be still further purified by repeated alcoholic extractions. By adding sulphuric acid, shaking with ether and pouring off and evaporating this ethereal extract the free acid is obtained. The sodium salt forms anhydrous crusts made up of soft, sharply-pointed crystals, which are soluble in water and alcohol and are very deliquescent. The silver salt separates, on mixing the sodium salt with silver nitrate, in the snow-white capillary and interlaced crystals. The calcium, copper, lead and zinc salts, which are all very soluble and amorphous, are obtained by boiling the acid with the corresponding carbonates. The oxybutyric acid excreted in the urine has the same properties as above and in addition possesses the power of rotating polarized light to the left, the synthetically prepared body being optically inactive. A quantity of the sodium salt was prepared for experimental purposes. This salt was light brown in color and extremely hygroscopic—so much so that it was necessary to expose it to 115 to 120 degrees C. for half an hour and then

keep in a dessicator over sulphuric acid. This salt, with the free acid, gave neither the iodoform test nor the reaction with ferric chlorid although it had been claimed by Minkowski (*Zeitschrift für Biologie*, 1887) that it responded to the latter test. Oxybutyric acid and diacetic acid are frequently present in the urine at the same time and while the reaction with ferric chlorid is not a test for the former body its occurrence renders the presence of oxybutyric acid probable. Neither this acid nor its salts give the "diazo reaction" of Ehrlich. Stadelman (*Zeitschrift für Biologie*, 1887), Minkowski (*Zeitschrift für Biologie*, 1887) and Külz (*Arch. für exp. Path. und Pharm.*, 3, XVIII, S. 41) have all formulated methods for isolating oxybutyric acid from the urine as a salt. The method of Minkowski, probably the best and the simplest, is essentially as follows: A large quantity of urine (several liters) is thoroughly fermented and evaporated to a syrup. It is extracted with alcohol, this alcohol distilled off, the residuum dissolved in water and extracted with ether after the addition of a little sulphuric acid. The ether is then evaporated off and the remaining brown syrup treated with concentrated solution of silver nitrate, when the silver salt, in long shining needles, should precipitate out. Various other salts may be made by substituting solutions of the carbonates of these metals for the nitrate of silver solution. By this method, after adding 3 grams of sodium oxybutyrate to 1 liter of normal urine only 1.1286 gram of the same salt could be recovered. Külz's method (*loc. cit.*) of dehydration into alpha-crotonic acid proved to be uniformly successful. This method is as follows: "Take fresh urine which gives the ferric chlorid reaction, ferment thoroughly and precipitate with lead acetate. Filter clear and evaporate the filtrate to syrup. To this syrup add an equal volume of concentrated sulphuric acid and heat in a retort, collecting the distillate in test tubes packed in a freezing mixture. If oxybutyric acid be present in the urine alpha-crotonic acid will distill over and crystallize out in white plates in cooling. It will be recognized by its melting point, odor, etc. He believes that 100 c.c. is a sufficient quantity of urine to employ, but it has been found necessary in these experiments to use a very much larger quantity. This test is based upon the following reaction:

This method is by no means quantitative, fully 66% per cent. of a known quantity of oxybutyric acid being lost in its conversion into crotonic acid. A determination of the amount of oxybutyric acid in the urine can also be made by the polariscope since this body—the product or cell activity—rotates the plane of polarized light to the left, while the artificially made body is optically inactive. This property may be explained by the presence of an asymmetric carbon atom in the composition of this body and has been taken as a test for its presence in the urine by Minkowski (*Zeitschrift für Biologie*, 1887) and Wolpe (*Jahresberichte der Gesamten Medicin*, 1887). They take 100 c.c. of the twenty-four hours urine, remove the albumin and thoroughly ferment. After fermentation is complete, precipitate with lead

acetate and filter clear, examining the filtrate with the polariscope for the acid. It was found that this acid is optically weak and must be present in considerable quantity to answer this test. In the urine of this case the largest amount of this acid found was 4.513 grams in the twenty-four hours' excretion. This is far smaller than the enormous amounts observed by Stadelman (*Deutsche Medicinische Wochenschrift*, Nov. 14, 1889), Kirstein (*Deutsche Medicinische Wochenschrift*, April 11, 1889) and others, where the twenty-four hours excretion ranged from 75 to 90 grams.

While the most reliable means of detection is actual isolation as a basic salt, its occurrence in very small quantities or the presence of other organic bodies may render such isolation difficult or impossible. Dehydration into alpha-crotonic acid furnishes the best clinical method for the detection of oxybutyric acid. Very small amounts of this body are easily recognized by it, the strong pungent odor of even a minute quantity of crotonic acid being unmistakable. An evaporation of an ethereal extract gives the best results in this respect. The use of the polariscope, owing to the weak rotatory power of this acid, is but a rougher test by which additional confirmation of its presence can be obtained.

Ethyl aceto-acetate, it is now believed, never occurs in urine, although early investigation seemed to point to it as the cause of the ferric chlorid reaction. It is a liquid with an agreeable, sweet odor. It is slightly soluble in water, the liquid giving the reaction with ferric chlorid. It boils at 180 C. and is very stable. It behaves like a monobasic acid, which property is probably due to the position of the group CH_2 between two CO groups. It reacts with ferric chlorid and also with tincture of iodine and ammonia and with sodium hydrate and Lugol's solution. The reaction with ferric chlorid remains after boiling, while with diacetic acid this is not the case. Ethyl aceto-acetate does not give the "diazo reaction" of Ehrlich, while diacetic acid does. Its sodium salt can be extracted with ether from an alkaline solution, while diacetic acid can not. These two bodies can never be confounded with ordinary care, although considered as the same by Halliburton ("Chemical Physiology and Pathology") and Talamon (*La Médecine Moderne*, No. 14, 1891).

Alpha-crotonic acid never occurs as a constituent of the urine, but may result from the dehydration of oxybutyric acid. It is a body which on melting crystallizes out in white shining trimetric plates, which are sparingly soluble in cold water but are extremely so in alcohol and ether. These crystals melt at 72 C. and ebullition takes place on rising to 160.5 C. It unites with most metals to form salts which are permanent at ordinary temperatures but which decompose under 100 C. It is very volatile and possesses a powerful, unpleasant odor, which is quite permanent.

Acetone has long been recognized as occurring in certain cases of diabetes, and more recently has been found to be an urine constituent in other diseases also, especially such as are characterized by nervous or cerebral disturbance or are accompanied by high temperature and excessive tissue waste. To it was long attributed the production of various nervous and cerebral symptoms and even coma. Later experiments have shown, however, that this body possesses but slight toxic properties and that it is improbable that its presence could produce such grave symptoms. The

true history of acetone begins in 1857, when Petters (*Präger Vierteljahrsschrift*, xv, 6, S. 61), described a fatal case of diabetes in the urine of which he detected a body which gave the tests for acetone. In 1860, Kraulich (*Präger Vierteljahrsschrift*, xvii, Bd. 3, S. 58) made further investigations and, like Petters, arrived at the conclusion that acetone was formed by an abnormal intestinal decomposition. During the next twenty-five years experimental work on this subject was carried on by Lieben (*Annalen der Chemie und Pharmacie*, Bd. vii, S. 236), Kouska (Diss. Griefswald, 1873), Küssmaul (*Deutsch. Arch. f. klin. Med.*, Bd. xiv, S. 99) and others, but no satisfactory conclusions were reached. In 1885, however, a careful study of its occurrence was made by von Jaksch ("Ueber Acetonurie und Diaceturie," Berlin), who also discovered the presence of diacetic acid in diabetic urines. It was believed by Petters and Kraulich that acetone was formed by an abnormal fermentation in the intestines. Küssmaul, however, showed that this could not be the case. Jaksch and Kobert believed that acetone is never formed in the alcoholic fermentation, but is produced in the lactic acid fermentation. This is not the conclusion arrived at in this article. As has been previously stated, it is believed that an abnormal decomposition of albumin yields oxybutyric acid; this splits up into diacetic acid and this, on further oxidation, gives acetone—a diaceturia or oxybutyruria occurring when the acids produced in this excessive albumin decomposition are present in larger amount than the system is capable of completely oxidizing to acetone. Acetone is a very clear, mobile, colorless fluid which boils at 56.3 C. It possesses a sweet, ethereal odor which is very characteristic. It is chemically prepared by the dry distillation of wood and the acetates, and is also a product of the oxidation of various organic compounds. It is a rather stable body, but under certain conditions may decompose in the production of acetic and formic acids. It yields iodoform on the addition of tincture of iodine and ammonia, and will produce indigo blue in alkaline solution on treatment with ortho-nitro-benzaldehyde. With a solution of sodium nitroprussid and sodium hydrate it turns red, the color soon fading, but reappearing on the addition of acetic acid. It will also dissolve the red oxid of mercury. Jaksch ("Ueber Acetonurie und Diaceturie") believes that acetone is only slightly toxic, but adds that under certain conditions it may produce severe symptoms of poisoning. Lewin ("Toxicologie") calls 5 to 8 gm. per kilo the fatal dose for the dog. He finds that a man may ingest 10 to 20 gm. in the twenty-four hours without producing serious discomfort. In the course of these experiments 10 gm. of acetone each were given to four healthy persons. No subjective symptoms of any sort were induced, nor could tests for acetone be obtained from the urine. There was an acetone odor to breath for twenty-four hours. Doses of 16 grams were administered to two persons without any effects. No acetone could be obtained from the urine. Twenty-five grams were given during two hours without effect. In one instance 36 gm. were given during two hours with the production of slight intoxication and a temporary rise in the pulse rate from 88 to 112. In this case the acetone odor to the breath persisted for forty-eight hours, while a test for this body could be obtained from the distillate of the urine. It is concluded that by itself acetone can be productive of no dangerous or

marked symptoms, but is of importance as showing a pathologic katabolism of the system and as being the forerunner of the much more dangerous diacetic and oxybutyric acids which in a steadily progressive diabetes must ultimately appear. Jaksch ("Ueber Acetonurie und Diaceturie") claimed that acetone was always to be found in normal urine and was consequently a product of normal metabolism. He claimed to have isolated an appreciable quantity by distilling 300 liters of normal urine. On the other hand, Moscatelli (*Archivio per le Scienze Mediche*, Vol. x, p. 231) has been unable to find acetone in healthy urines. He used 25 liters of urine from healthy persons and distilled, saving only the first few cubic centimeters that came over. These were then mixed and redistilled. The first five c.c. which came over were used for testing. By this method no acetone was found, although tests were used which were sensitive to half a milligram of pure acetone. Salkowski (*Jahresbericht der Gesamte Medicin*), has recently shown that any healthy urine distilled with sulphuric acid yields minute quantities of a body which gives all the reactions of acetone. He does not find this body on distilling such urines without the addition of sulphuric acid. In the course of these experiments 50 liters of healthy urine were distilled, without the addition of any acid, without giving the faintest reaction for acetone in the distillate. Acetonuria, in this case, only existed for a few days. Following the institution of an anti-carbohydratic diet, a diaceturia was produced which continued until the death of the patient seven months later. The amount of acetone present was at no time very large, in fact, a large acetonuria will probably never occur, since the system will probably not be able to decompose a large amount of oxybutyric acid in the production of acetone. After the occurrence of the diaceturia several attempts were made to find free acetone in the urine, but without success. This agrees with Jaksch, who never was able to find free acetone in an urine giving the ferric chlorin reaction. It has been claimed by Kallay ("Ueber Diabetes Mellitus"), Talamon (*La Médecine Moderne*, July, 1891), and others, that acetone in the urine is the cause of the ferric chlorid reaction. Acetone, either in the urine or synthetically prepared, gives no reaction with ferric chlorid. It has also been stated by Landois ("Physiologie"), and Kallay (loc. cit.), that the ingestion of acetone causes the presence of albumin in the urine, and that an acetonuria may be responsible for this frequent concomitant of diabetes. In the eight persons who were given acetone in amounts varying from 10 to 36 gm. no albuminuria could be detected, although frequent tests were made. Such an albuminuria is probably due to an over-excitation of the kidneys through the increased amount of work thrown upon them. Should acetone occur in considerable quantity, it will be recognized by its characteristic odor. It was found that 1 per cent. of acetone in a distillate of healthy urine, made with or without the addition of sulphuric acid, was readily perceptible to smell. Since a certain amount of acetone is yielded on distilling an urine containing diacetic acid, all tests for an acetonuria must be applied to fresh urine. It must be emphasized that diacetic acid gives the usual tests for acetone. A diaceturia is therefore to be recognized by the occurrence of either the ferric chlorid or the diazo reactions, since neither of these tests is responded to by acetone. The best method for the recognition of this body is that

of Gunning, the production of iodoform in the presence of acetone on the addition of tincture of iodine and ammonium hydrate.

All observers have found the excretion of urea in diabetes to be far above that of health, Cohnheim ("Vorlesungen ueber allgem. Pathologie"), and Strümpell ("Lehrbuch der spec. Path. u. Ther."), reporting cases in which the excretion rose as high as 125 to 150 gm. in the twenty-four hours. This increase may in great part be accounted for by the excessive amount of proteids which form the usual dietetic treatment of diabetes. A more important factor, and one which is but little considered, is the abnormal breaking down of the body tissues, it having been demonstrated that the excretion of urea is far in excess what could possibly be produced from the nitrogenous foods ingested. The urea in this case, on a mixed diet, remained at about three times the normal amount.

It has long been known that the excretion of ammonia in the urine is greatly increased in certain morbid processes, especially diabetes. In 1872 Frerichs noticed that the urine of diabetic patients previous to or during the occurrence of coma contained an extraordinary amount of ammonia. He therefore attributed the production of these cerebral symptoms to the poisonous action of this body, which he believed was produced by the action of an abnormal ferment upon the urea, decomposing it in the production of ammonium carbonate. This idea, as the so-called theory of "ammonemia" at one time gained wide credence, but has more recently been shown to be erroneously grounded. In 1889 Stadelman and Kierstein, working independently, published (*Wochenschrift für Klinische Medicin*) reports of work done on this subject. Starting with the observation that the ingestion of acids increased the ammonia excretion and that they exactly kept pace with one another, the reasoning was extended to those diseases in which there was a noticeable increase in the acid excretion. It was found by them that the quantity of oxybutyric acid excreted in diabetes ran exactly parallel with the excretion of ammonia. The theory of an "acid intoxication" was therefore proposed by them, believing that severe nervous and cerebral symptoms appeared only when the production of acid was excessive, and that coma supervened when the neutralization of these acids could no longer be effected by the quantity of ammonia available in the economy. They therefore recommend the determination of the twenty-four hours ammonia excretion as an easy clinical way of arriving at an approximate idea of the amount of acid excreted. The average ammonia excretion of a healthy individual being about .8 gm., they believe that an ammonia excretion of more than one gram may induce serious symptoms, while a rise to 2, 4 or 6 gm. denotes a dangerous condition and a marked liability to coma. On a diet composed exclusively of proteids the patient upon whom these experiments were based excreted an average of 8.4 gm. per diem. On a mixed diet the ammonia excretion fell over 25 per cent. One sample of urine, passed while the patient was on a rigid meat diet, gave an enormous yield of ammonia, far exceeding the maximum quantities given by Stadelman and Kierstein. This specimen was passed between 9 A.M. and 3 P.M. and amounted to 3.5 liters. In this were found 16.635 gm. of ammonia associated with an excretion of 76.435 gm. of diacetic acid and a total urine acidity of 142.8. This amount of ammonia should theoretically be able to neutralize some 90 gm.

of diacetic acid, and there was evidently an excess beyond what could combine with this body. The probable presence of oxybutyric acid would account for this discrepancy. Unfortunately, the full twenty-four hours' excretion could not be obtained, but had this proportion obtained for the usual urine excretion of ten liters the ammonia would have amounted to 42.32 gm., a quantity capable of neutralizing about 125 gm. of concentrated sulphuric acid.

Frequent determinations of the percentage of urine acidity were made in this case, and all examinations of the twenty-four hours' excretion showed an acidity far above normal. The percentage of acidity was about 25 per cent. less while the patient was on a mixed diet than while there was a rigid exclusion of the carbohydrates. It was also noticed that urine passed several hours after meat meals was much more acid than urine passed fasting or shortly before eating. All determinations of urine acidity should be accompanied by estimations of the ammonia, as according to Stadelman and Kierstein it is probable that the acids do not exist free, but in the form of ammonium salts.

OXYGEN INHALATIONS AND HYPODERMIC MEDICATIONS IN THE LUNG AFFECTIONS OF INFANCY.

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The difficulty encountered in procuring a supply of oxygen in the treatment of pulmonary affections leads me to believe that its efficacy is not appreciated by the profession at large. The text-books of recent date recommend oxygen inhalations in such cases, but in so vague a manner as to leave the average practitioner unwilling to undertake the trouble and expense necessary for its utilization. It is for the purpose of urging upon the more conservative members of the profession the extreme value of these remedial agents that the following case is reported:

I. L., infant daughter of Lieutenant L., aged six weeks, was attacked with broncho-pneumonia, with involvement of large lung area. The severity of the attack may be best expressed by relating that a very distinguished specialist called in consultation on the fourth day of her illness gave the gravest prognosis and recommended euthanasia. Up to this time the treatment consisted of oil-silk cotton-batting jackets, steam and medicated vapor inhalations, ammoniacal and alcoholic stimulation. The condition of the patient was that of marked cyanosis, Cheyne-Stokes respiration, carbon-dioxid narcosis, pulse weak, rapid and irregular. After the grave prognosis of the above-mentioned specialist the writer was left alone with the case. Two suitable rubber bags were procured, and with the means at hand afforded by the laboratory of the post hospital, Jackson Barracks, La., a sufficient quantity of pure oxygen was administered almost continuously to the infant, with the most marked and gratifying results. The previous cyanotic condition gave place to a healthy color, with a disappearance of carbon dioxid narcosis. The respiration became deeper and more regular, the pulse slower and stronger and a general tonic effect was noted. In addition to the oxygen inhalation and *pari passu* with its administration, hypodermic injections of digitalin, strychnin and atropia were employed as often as indicated, with an occasional injection of codein to control excessive coughing.

The method of administration was as follows: One-half a tablet of digitalin 1-100 grs., strychnin 1-60, atropia 1-100 were dissolved in a syringeful (30 m.) of water, 5 minims of which were injected at a dose. By plunging the needle boldly in over the region of the hip the infant will not experience pain, provided the needle is small and sharp.

The writer wishes to call attention to the accuracy of dosage and promptness of effect noticed with this form of therapeutic administration, and especially with these agents and to express his conviction that by these means the mortality of uncomplicated cases of broncho-pneumonia, even in the very young, can be brought very low. By this method the digestive apparatus is not interfered with, a point in connection with regular and sufficient nourishment of the highest import. The writer takes this occasion of urging extreme caution in the use of opiates and to express his preference for codein.

SURGERY ONE HUNDRED YEARS AGO.

AN HISTORICAL STUDY

BY DR. GEORGE FISCHER.

DEDICATED TO THE GERMAN SURGICAL ASSOCIATION.

TRANSLATED FOR THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

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CHAPTER V.—SURGICAL INSTRUCTION AND LITERATURE.

Schools of surgery in Germany and Russia; Practical instruction at universities, polyclinic, clinic; Surgical instruction in Paris: Desault, Ecole de Santé, Pensions, visits to Pelletan, French students, Boyer; Surgical instruction in London: John Hunter, Edinburgh; Book-making of German surgeons, servilism, Latin or German; Mutilation of the German language by the French; Translation craze, esteem for foreign countries; Surgical periodicals, reviews; Text-books, prices of books.

With the sharp separation between medicine and surgery in Germany, and the wide gulf which between doctor and barber in respect to scientific acquirements and social position, it could not happen otherwise than that the study of surgery was a very different matter for the physician from what it was for the barber. The universities where the physicians heard surgical lectures, did not exist for the barber; he lacked both the money and the preliminary training of the gymnasium. The state had to provide for its higher education in other ways, since the beginning and the end of the wisdom which the barber apprentice took with him from the home of his master, was the noble art of shaving, bleeding and putting on plasters. With this object in view, special institutions of learning called *Collegia medico-chirurgica*, were founded. In these schools, with which an anatomic amphitheater was connected, various teachers lectured in anatomy, surgery, pathology, materia medica, chemistry, botany, and so forth; also the barbers were examined there, before they were given permission to practice.

One of the oldest institutions was that founded in Hanover in 1716, which was under the direction of the physicians-in-ordinary and court physicians. It received as students the journeyman barbers and the apprentices of the city. Upon payment of a certain amount (two thalers from the apprentices), they were given the bodies of criminals to dissect. Berlin followed and, according to a plan of Holtzendorff, instituted a collegium medico-chirurgicum, which was an enlargement of the anatomic amphitheater, at that