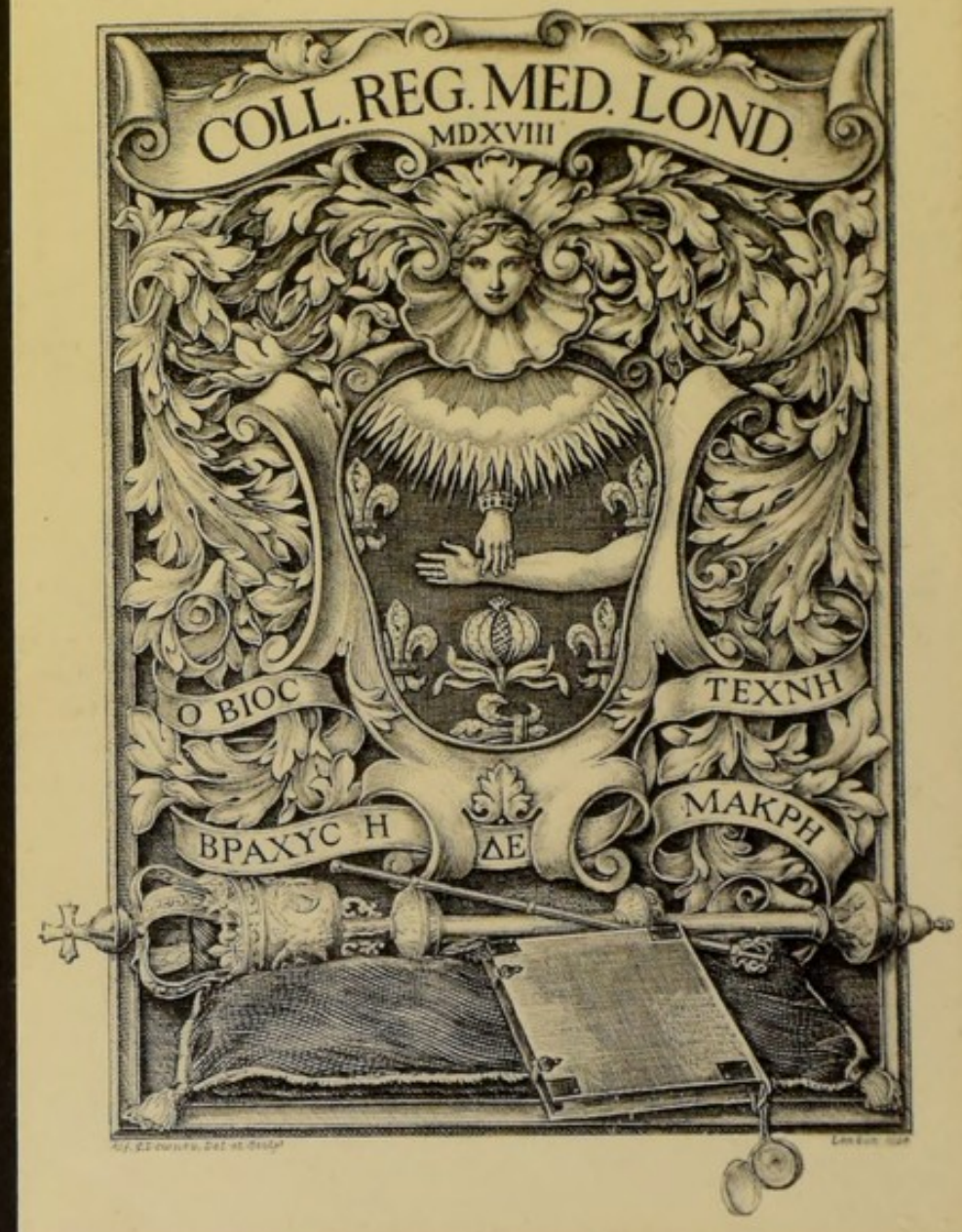
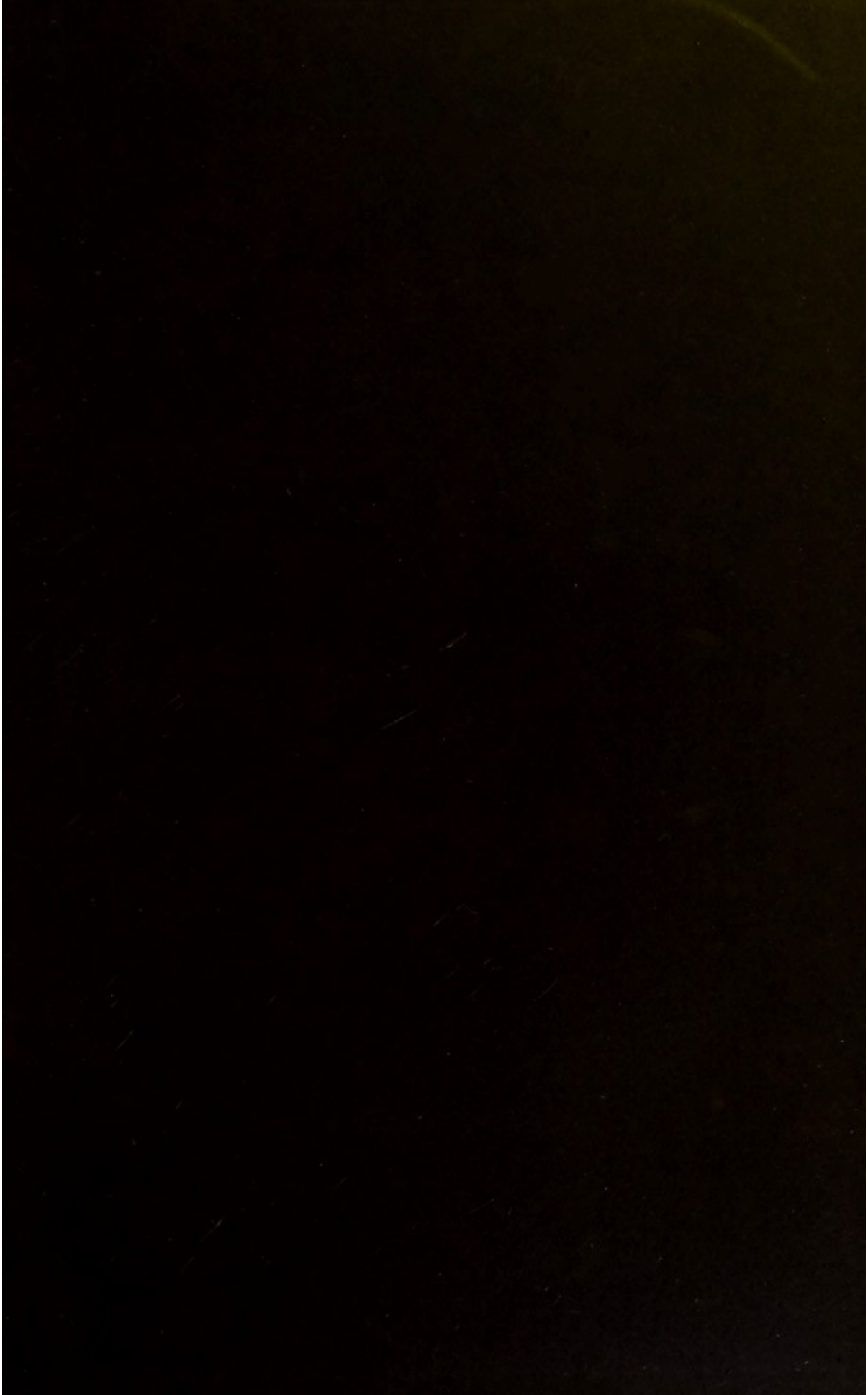
Acid autointoxications / by Carl von Noorden and Dr. Mohr.

DISEASES OF METABOLISM
AND NUTRITION

VON NOORDEN

ACID AUTOINTOXICATIONS





THE ACID AUTOINTOXICATIONS.

ACID AUTOINTOXICATIONS:

BEING PART IV OF SEVERAL

CLINICAL TREATISES

ON THE PATHOLOGY AND THERAPY OF

DISORDERS OF METABOLISM AND NUTRITION.

BY

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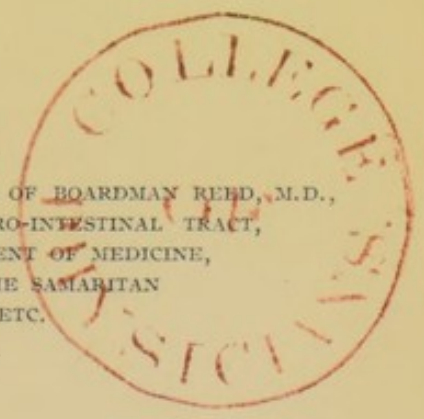

AUTHORISED TRANSLATION UNDER THE DIRECTION OF BOARDMAN REED, M.D.,
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PREFACE BY THE AMERICAN EDITOR.

PROFESSOR VON NOORDEN'S studies into these derangements of metabolism which result in an overproduction of acid, thus endangering the proper degree of alkalinity of the blood, may seem at first more abstruse and of less utility than the subjects of the previous volumes in this interesting series, but in reality they concern the clinician very nearly; moreover, they are in a field which has been hitherto too little explored.

French investigators have until very recently done most work here, the Germans, as our author frankly concedes, having been at first sceptical regarding the whole doctrine of autointoxication; but since becoming convinced of its truth, the latter are studying the subject with their accustomed thoroughness. von Noorden's researches into it have been particularly valuable.

Physicians who treat chronic disease successfully, must keep a close and intelligent watch upon the digestion, excretion and assimilation of their patients. All such will agree with von Noorden, 1, that there are numerous forms or manifestations of self-poisoning; 2, that the acid forms are among the gravest of them, and 3, that those special perversions of metabolism resulting in the excessive production of oxybutyric acid, diacetic acid and acetone, which so greatly endanger diabetics and also complicate at times other diseases more or less seriously, are of the utmost practical importance. Dr. A. C. Croftan, the translator of

the three previous volumes of the series, has performed the same service for this one, and in his customary able and scholarly manner. The author's title may be briefly rendered "The Acid Autointoxications" and the needs of the publishers have led to a further contraction of this into the one word "Autointoxications."

BOARDMAN REED.

1833 Chestnut Street, Philadelphia, Pa.

NOTE.

It is a source of satisfaction to me to announce that Messrs. E. B. Treat & Co., New York, have undertaken to publish the collection of these monographs in English. Particular care will be taken to have them appear as nearly simultaneously in New York and in Berlin as possible; and I hope that this American Edition will meet with the same approbation which I am happy to say has been accorded the German.

PROF. DR. CARL VON NOORDEN.

CONTENTS.

1. GENERAL REMARKS ON AUTOINTOXICATION WITH ACID PRODUCTS OF METABOLISM.

WITHIN recent years the idea has become firmly established in the minds of physicians that a variety of morbid phenomena are due to autointoxication—are, in other words, attributable to certain poisonous metabolic products. This view, it is true, is not new, for it was familiar to the physicians of past generations and was a part of the teachings of the medical folk-lore of long ago. It was not, however, until Bouchard and his pupils published their investigations on the subject of autointoxication that this theory attained the dignity of a scientific doctrine. At first we German physicians were by no means inclined to accept the theory of autointoxication that was being so enthusiastically proclaimed. Of late years, however, our attitude has become more friendly to the doctrine; this change of front is due to the fact that a number of toxic products of metabolism have actually been isolated and their mode of origin in the organism and their pathologic effect determined to the satisfaction of the former critics of the doctrine. We do not, of course, know all that we should properly know about the poisonous metabolic products that we incriminate in so many morbid states; but in a large group of important symp-

tom-complexes we are fortunately in possession of a number of facts that suffice to ground the doctrine of autointoxication on a solid chemical basis.

Acid Products of Metabolism.—One form of autointoxication in particular, namely, intoxication by acid products of metabolism, in other words, acid intoxication,[1] is well understood from the clinical point of view and is also well founded experimentally.

In process of normal metabolism a number of acid products of the disassimilation of proteids, fats and carbohydrates are formed as intermediary bodies that either undergo further degradation or that cannot be oxidized further and are consequently excreted. Of these bodies carbonic acid leaves the body in large quantities through the lungs while sulphuric acid, phosphoric acid, hydrochloric acid, uric acid and others are eliminated through the urine, always combined with alkalies: free acid never appears in the urine. As the carbonic acid is eliminated through the lungs, alkali is liberated in the blood that can be utilized to saturate other carbonic acid affinities. At the same time the organism loses a portion of its alkali in the urine for some of the bases combine with the urinary acids and are eliminated as salts. In general this loss is covered by the ingestion of alkali in the food, and in addition the organism possesses a reserve of alkali that is stored

[1] An exhaustive review of the literature on this subject is given by Kraus in Ergebnisse der allgemeinen Pathol. Morphologie und Physiologie des Menschen und der Tiere, edited by v. Lubarsch u. Ostertag, Part 2, 1895,

in the cells of the blood. Alkalies constitute an integral part of protoplasm, for in the latter substance the different alkalies are combined with albumen in different modifications. The chief of these protoplasmic alkalies are potassium salts, whereas the principal alkalies circulating in the fluids of the body are sodium compounds. The alkalinity of the blood is dependent on several compound :—

First, compounds with an alkaline reaction as sodium carbonate and sodium phosphate.

Second, large quantities of alkali that are combined with mineral acids.

The amount of alkaline substance in the blood is not very great. It is said to correspond to 180 mgr. of Na OH in 100 grm. of blood. The organism has a tendency to maintain its alkalinity, and any reduction in the alkaline reaction of the body is fraught with serious consequence. This we know chiefly from experimental investigations into this subject.

Alkali can be withdrawn from the body in two ways : first the ingestion of the alkali with the food can be reduced or altogether stopped, or ; second, *per contra* large quantities of acid may be exhibited. In the first instance, no particular derangement of general metabolism is noticed, with this exception, of course, that the alkali content of the body gradually decreases. The consequence of even slight loss of alkali in the dog is a morbid derangement of the nervous system and disturbances of food assimilation. At the expiration of a certain time, death results with spasms. In mice the

withdrawal of the alkali causes death sooner than in dogs. According to Bunge,[1] the cause of death is intoxication with sulphuric acid. This acid is a product of the catabolism of proteids and if insufcient alkali is present to combine with it, it necessarily accumulates in the organism. Bunge proved this fact conclusively by causing animals who were in a state of acid autointoxication to live longer than control animals if he administered a certain quantity of alkali.

Much more pregnant symptoms are seen if correspondingly large quantities of acid are given animals by mouth or subcutaneously. In herbivorous animals the administration of acid leads to a rapid loss of alkali in the urine and consequently to a considerable decrease of the alkalescence of the blood. The respiration becomes more rapid in the beginning but grows slower towards the end of life. The pulse rate is also increased and the blood pressure increased in the beginning, but falls off later in the course of the intoxication; the animals become ataxic, fall into convulsions and finally die in coma. In dogs the intoxication runs a different course. Quantities of acid that are three times as great as the fatal dose for a rabbit (tabulating the dose per kilo of animal) are borne by a dog without any particular impairment of the general health. The loss of alkali in the urine is slight and the alkalescence of the blood is only slightly reduced. In the urine the quantity of acid corresponding to the amount administered

[1] Lehrbuch der Physiol. 1901, Vol. II.

appears, and at the same time more ammonia. The organism of carnivorous animals is, in other words, protected against acid intoxication by the power it possesses of manufacturing ammonia from its proteids and of excreting this substance through the urine. Man shares this advantage with carnivorous animals of being able to manufacture ammonia in almost unlimited quantities and of neutralizing acid products in his body. It is due to this fact that human subjects are capable of getting rid of such enormous quantities of acid in certain pathologic conditions.

The doctrine of acid autointoxication in man is founded on the similarity between the most important symptoms of experimental acid intoxication and certain clinical syndromes. The most important features are the reduction in the alkalinity of the blood, the increased excretion of ammonia and the appearance of acids that are not present normally or that at best are found in very small quantities. We can hardly expect, of course, to discover the pronounced picture of experimental acid intoxication in each individual case. At the same time, the syndrome of acid intoxication has occasionally been found as a complication of a variety of primary diseases.

How Acid Autointoxication Occurs.—In cases of perverted metabolism, an abnormal accumulation of acids can occur in two ways, namely, first, the excretion of acids may be reduced, or, second, the formation of acids may be increased, while at the same time their elimination is interfered with. Aside from those cases

of pulmonary and cardio-vascular disease in which the elimination of carbonic acid through the lungs is reduced and aside from acute attacks of gout in which the excretion of uric acid is reduced, the first named possibility is of very small practical significance. At least, interference with the elimination of acid products alone never produces the clinical picture of acid autointoxication. Insufficient elimination, however, may occasionally be combined with over-production of acid, and in this way the danger of intoxication be increased.

The second possibility is pathologically much more important. The acids that must be considered in this connection are, among others, sarcolactic acid, carbaminic acid, aliphatic acids, oxalic acid, uric acid, aromatic oxy-acids, and above all, the acids that interest us here in particular, namely, β-oxybutyric acid, diacetic acid and acetone.

There can be no doubt that these three substances are closely related to one another. The three have been grouped by Gelmuyden [1] and designated by the collective name of "acetone bodies." Until very recently, there was considerable diversity of opinion in regard to the true connection existing between these bodies. Von Jacksch [2] assumed that the appearance of acetone in the organism produced symptoms of intox-

[1] Zeitschr. f. Physiol. Chemie, Vol. XXIII and XXVII and Scandinav. Arch. 1900.

[2] Ueber Acetonurie, u. Diaceturie, Berlin, 1895.
See here also the older literature.

ication. If the tissue fluids contained too much acetone, the latter would combine with certain acids that are formed from the disassimilation of proteids, and in this way produce diacetic acid. In the same manner von Jacksch imagines the genesis of acetone from β-oxybutyric acid. The discoveries of the last few years, however, have taught us to abandon this conception, partly on account of certain chemical considerations, partly on account of certain experimental and clinical findings.

It can readily be shown that outside of the body, in the test tube, the transition of these three substances into one another occurs in a way that is exactly opposite to the teachings of the older chemists. Oxybutyric acid is an oxy acid with a secondary alcohol group. Like all acids of this character, it is readily converted into its keto acid, viz. diacetic acid, by oxidation. The latter can be considered as acetone in which one hydrogen atom is substituted by the carboxyl group. If diacetic acid is warmed or boiled, acetone and carbon dioxide are formed. The following formulas will illustrate my meaning:

β-Oxybutyric acid : $CH_3 - CHOH - CH_2 - COOH$.
Diacetic acid : $CH - CO - CH_2 - COOH$.
Acetone : $CH_3 - CO - CH_2$.

The same process that occurs *in vitro* occurs *in vivo* if β-oxybutyric acid is administered to animals or human subjects. In healthy human subjects and in healthy animals β-oxybutyric acid is completely destroyed and the only evidence of its passage through

the organism is a slight increase of the urinary acetone. In diabetic dogs, after extirpation of the pancreas, and in diabetic human subjects, diacetic acid appears in the urine in addition to a considerable quantity of acetone. Some authors even claim that the acid itself has been known to pass into the urine. The reverse process, namely, the appearance of β-oxybutyric acid or diacetic acid in the urine after the administration of acetone has never been observed, the only urinary change being an increase of the acetone. The fact that the introduction of β-oxybutyric acid is followed by different consequences in healthy and in diabetic animals; the fact, furthermore, that the subcutaneous injection of sodium oxybutyrate in animals which had been poisoned by carbon monoxyde (Araki)[1] does not lead to the elimination of more CO_2 but to the elimination in the urine of an unchanged portion of the injected acid and some diacetic acid and acetone, demonstrates that all three substances owe their origin to some common perversion of oxidation and that this perversion is due to different causes in the two cases quoted above, viz., carbon monoxyd poisoning in the one case (dog) and pancreatic diabetes in the other. In the former case the perversion of oxidation is due to the lack of oxygen; in experiment diabetes, on the other hand, and in diabetes in human subjects there is no lack of oxygen, for diabetic subjects as well as depancreatized dog with diabetes consume all the oxygen that is necessary to promote the

[1] Zeitschr. f. Physiol. Vol. XXV, 16 and 17.

combustion of the ingested pabulum. We cannot, therefore, in these cases, be dealing with a lack of oxygen but merely with some local interference with oxi-'ation.

Acetonuria a Subdivision of Acid Autointoxication.— The clinical interpretation of these three bodies becomes very clear when we adhere to the view just enunciated, namely, that the appearance of the three acetone bodies is due to one common cause, i.e., a peculiar inhibition of the oxidative processes. By studying these acetone bodies we are able to gauge the intensity of the perversion of oxidation; for we are justified in assuming that the excretion of β-oxybutyric acid represents a much more advanced degree of oxidative perversion than the excretion of acetone or of diacetic acid. We know this from the results of the chemical investigations that I have described and from experiments with feeding these substances. A natural consequence of this interpretation is the following: acetonuria, instead of maintaining the dignity of an independent disease symptom, must be included under a more general category of acid autointoxication. At the same time the theories that have been formulated to explain the occurrence and the formation of acetone must be amplified to include its chemical precursors, viz.: β-oxybutyric acid and diacetic acid. The appearance of acetone in the urine has up to now been credited with too much importance, and this is due to the historical development of our knowledge of the pathological appearance of the acetone

bodies in the urine. Petters[1] who was the first to find these bodies in the urine of a diabetic subject, and Kaulisch who studied the excretion of acetone soon after the former author, arrived at the conclusion that subjects excreting acetone were in a state of auto-intoxication and that the poisoning of the organism was due to acetone, a body that had heretofore never been found in the urine. This theory dominated all the investigations into the nature and the significance of acetone that followed. Cantani[2] Betz[2], von Jacksch[2] and Buhl[3] attributed poisonous properties to acetone and formulated the assumption that it was the cause of so-called acetonemia, a disease picture that was constructed more according to symptoms produced in animals by the sub-cutaneous injection of acetone than from clinical observation. In the animal experiments performed by von Buhl[4] von Jacksch[5], Albertoni[6], Buschhaupt[7], and Franz Müller, the injection of acetone into the circulation or the simple inhalation of this body was followed by grave stupor and occasionally a drop of temperature; sometimes glycosuria was also observed. The latter result, however, seems to have been due more to the reduction of

[1] Quoted in von Jacksch, l. c.
[2] Quoted by von Jacksch, l. c.
[3] Zeitschr. fur Biologie, Vol. XVI.
[4] L. c,
[5] L. c.
[6] Arch. f. exper. Path. u. Pharm. Vol. XVIII.
[7] Archiv. f. exper. Path. u. Pharm. Vol. XLIV.
[8] Ibid. Vol. XLVI.

the temperature than to the effect of the acetone itself (Franz Müller). On the other hand, the administration of acetone even in large quantities by mouth (Kussmaul[1], Frerichs[2],) produced absolutely no symptoms in human subjects. Frerichs consequently repudiated the idea that acetonemia was an independent disease picture and that acetone was a determining factor in the production of the symptoms included under this head.

The valuable investigations of Rosenfeld[3] and his pupils and of Hirschfeld[4] demonstrated the connection between the excretion of acetone and the composition of the food. This revelation, as we shall see below, threw a great deal of light upon the subject. The dicta of Hirschfeld in regard to the prognostic significance of acetonuria in diabetes were one-sided and had to be considerably modified as soon as the relationship between acetonuria and the excretion of oxybutyric acid was cleared up and the pathology of acetonuria was better understood.

The Cause of Diabetic Coma.—Hallervorden[5] interpreted the increased excretion of ammonia in diabetes

[1] Zeitschr. f. klin. Med. Vol. VI.

[2] Deutsch Arch. f. klin. Med. Vol. XIV.

[3] Deutsche Med. Wochenschr. 1885, and Centralbl. f. innere Med. 1895 (in this dissertation the investigations of his pupils are also quoted).

[4] Zeitschr. f. klin. Med. Vol. XXVIII and Deutsche med. Wochenschr. 1893. Vol. XXXI.

[5] Archiv. f. exp. Path. u. Pharm. Vol. 10.

to signify the presence of some acid that was hitherto unknown. Later Stadelmann[1] isolated crotonic acid from diabetic urine and later Minkowski[2] and Külz[3] succeeded in isolating β-oxybutyric acid itself from diabetic urine. Since that time the acid has been found in a great many other diseased states, as, for instance, in scurvy, in certain infectious diseases, in carcinoma, in typhoid and dysentery. The appearance of this acid in the urine is by no means a rare event. Owing to the fact that this acid is so closely related chemically to acetone and diacetic acid, one is justified in suspecting its presence in the urine whenever these two bodies are excreted in considerable quantities. As a matter of fact, one always succeeds in finding the acid under these circumstances. (Magnus-Levy[4], Gerhart and Schlesinger[5], Kraus[6], and myself).

The highest values in the excretion of the acid are seen in diabetes, particularly before and during coma, and it is precisely in this state, as we know, that the highest values for acetone are also obtained. This fact has led to the theory that diabetic coma is due to the accumulation of acids in the body (acidosis), and

[1] Ibid. Vol. 17. Also a dissertation by this author in Deutsch Arch. f. klin. Med. Vols. 37 and 38.

[2] Ibid. Vol. 18.

[3] Zeitschr. f. Biol. Vol. 20.

[4] Arch. f. exper. Path. u. Pharm. Vol. 42.

[5] Ibid.

[6] L. c.

it is upon this theory that the alkali treatment of diabetic coma is based.

As a matter of fact, however, β–oxybutyric acid is just as little toxic when taken by mouth as acetone or diacetic acid. This has been demonstrated by numerous experiments in which the acid was administered to healthy subjects and to sufferers from diabetes. In depancreatized dogs with diabetes it is also impossible to produce coma or comatose conditions by the administration of very large quantities of β–oxybutyric acid. The *deleterious effect of β–oxybutyric acid* in coma as a matter of fact, is not due to any specific toxic properties of β–oxybutyric acid but to its acid character in general and to the power it possesses, as an acid, of withdrawing alkali from the organism. Whether only fixed alkalies are removed in this way or whether, as Magnus-Levy [1] claims, the basic components of the proteids are removed, so that the latter in this way become unfit to carry on the life processes, remains to be determined. In view of the fact that the alkalescence of the blood is unquestionably greatly reduced in diabetic coma, it is probable that all these factors are operative at the same time.

The appearance of acetone bodies in the different pathological conditions that I have just enumerated, and that I will sketch in detail below, is rendered more comprehensible when we study the factors that determine the appearance of these bodies in the urine under otherwise normal conditions. Above all, the concep-

[1] L. c.

tion must be abandoned that the secretion of acetone is under all circumstances a morbid phenomenon. This erroneous conception must be made responsible for the formulation of a variety of forms of so-called acetonuria that are more theoretically constructed than well-founded clinically. As our knowledge of the physiology of acid formation in the organism has increased, the old disease pictures that were originally sketched by Peters and Kaulisch, Cantani and von Jaksch have been abandoned. In the first place, it was found that normally the secretions of the body contained a small quantity of acetone that varied within narrow boundaries. The urine in a healthy subject fed on an ordinary diet contains from one to three centigrams of acetone in 24 hours. A still larger quantity (60 to 70 per cent of the total acetone) leaves the body through the expired air (J. Müller[1]), L. Schwarz[2], Gelmuyden.[3] The amount of acetone excreted varies at different hours of the day, and during the night time a larger quantity is excreted than during the day. This indicates that taking food exercises an influence on the excretion of acetone. As a matter of fact, the excretion of acetone rises considerably during inanition. Fr. Müller[4] found 40 times as much acetone on the seventh day of starvation as before the

[1] Arch. f. exper. Path. u. Pharm. Vol. 40.

[2] Verhandl. d. Congr. f. inn Med. 1900. Arch. f. exp. Path u. Pharm. Vol. 40. Centralbl. f. Stoffwechs. Krankh, 1900. No. 1.

[3] L. c.

[4] Virchow's Arch. Vol. 131, Suppl.

period of fasting. In addition, diacetic acid and oxybutyric acid are also excreted in the urine if the period of fasting is still further prolonged (Minkowski and others), whereas, as we know, the latter bodies are always absent in the normal secretions of the body. In addition Biermer showed that the excretion of acetone increased in diabetes if the subjects are put upon a meat-fat diet; and here, too, diacetic acid is occasionally excreted, and moreover in a healthy subject living on a diet consisting exclusively of meat and fat, the same phenomenon is observed. The explanation of this phenomenon seemed easy, for, it was argued that if acetonuria from fasting was due to the diminished ingestion of food, then the same cause (underfeeding) must be made responsible for the acetonuria occurring on a meat-fat diet; for, as we know, the caloric value of the food is usually too small to maintain full nutrition if the patients are fed on meat and fats exclusively.

Lessened carbohydrate Feeding the Sole Cause of Acetonuria. As against this view, Hirschfeld[1] could show that the degree of acetonuria remained the same even if the caloric value of the food was brought up to the normal or above by the addition of fat, and that the excessive ingestion of proteid caused a decrease of the acetonuria. The above explanation, therefore, became very improbable, and as a matter of fact, Hirschfeld finally succeeded in showing that both

[1] L. c.

in healthy subjects and in fasting subjects the increase of acetone in the urine was due solely and alone to the removal of carbohydrates from the food. Simultaneously with Hirschfeld, Friedlander[1] arrived at the same conclusion and the results obtained by the latter investigator have since been corroborated. The power of carbohydrates to prevent the appearance of acetone in the urine is really quite extraordinary. This is not only the case in underfed subjects in whom one might imagine that the acetonuria was due to inanition and that the addition of carbohydrates remedied the deficiency in calories, but also in patients who are eating nothing but very small quantities of carbohydrates, patients who are certainly in a state of inanition and in whom otherwise acetonuria would certainly appear. The following experiment of Dr. Satta, performed on himself at the suggestion of one of us is a striking example of what has been said:

S. ate nothing for two days but 100 grm. of milk sugar (410 calories) and excreted 1 ctgr. of acetone in the urine. Then he lived on a diet consisting of 300 grm. of meat and 300 grm. of butter with a caloric value of from 2700 to 2800, i. e., enough to satisfy the caloric demands of the organism. On this diet the amount of acetone excreted in the urine was 0. 8 grm. on the first day and 1.1 grm. on the second day, and the acetone content of the expired air rose correspondingly. In another experiment S. ate 125 grm. of rice and excreted

[1] Quoted by Rosenfeld, l. c.

1 ctgr. of acetone. As soon as he put himself on a meat fat diet as in the first experiment, the amount of acetone excreted in the urine and the air amounted to 3 grm.

A similar example is quoted by Waldvogel, who had his subject drink 1-½ liters. of beer and eat 750 grm. of white bread, and found that only the physiological quantities of acetone were excreted in the urine, i. e, the same quantity that would have been excreted on an ordinary mixed diet. This effect of the carbohydrates, has certain limitations. Thus Hirschfeld, for instance, determined that the effect of carbohydrates to reduce the excretion of acetone, was lost if less than 80 grm. of carbohydrate were ingested. Very few reliable statements, however, can be found in the literature in regard to the effect of carbohydrates on the acetone excretion in healthy subjects. In pathological cases a large number of data are on record. We shall have occasion to refer to this later on and shall also have occasion to enter into an explanation of this influence that the carbohydrates exercise.

Ingestion of Butter may Increase Acetone. Another phenomenon that demonstrates that acetonuria is largely dependent on the character of the food is the fact that the acetonuria varies with the amount and the character of the fat that is eaten ; this subject has been thoroughly studied in recent years. Gelmuyden[1] was the first to call attention to this relation, for he de-

[1] L. c.

monstrated that the ingestion of butter led to an increased excretion of acetone. This author assumed that the acetonuria in this instance was due to the effect of free fatty acids, and Waldvogel[1], Hagenburg[2], Schwarz[3], Mohr and Löb[4] and others could, also determine that the ingestion of free fatty acids, as for instance, butyric acid, led to an increased elimination of acetone in the urine and in the expired air. The same effect, however, is also exercised by the neutral fats, although not to such a degree. This so-called alimentary acetonuria is dependent on the amount of carbohydrate ingested, just as is the acetonuria that I have described in fasting and on a diet consisting exclusively of meat and fat. This fact must be remembered, particularly as it does not coincide with the observations of Hagenberg and Waldvogel[5], who determined an increased acetonuria on the addition of calcium butyrate to a mixed diet. The variations in the acetone excretion that these authors determine were too slight, however, to positively demonstrate the validity of this statement. As a matter of fact, neither Schwarz in his older experiments nor we in more recent ones, have succeeded in increasing the excretion of acetone above the physiological limits by adding an excessive quantity of fat to an ordinary

[1] Zeitschr. f. klin. Med. Vols. 38 and 42.
Centralbl. f. Stoffw. Krankh. 1900. No. 2.
[3] L. c.
[4] Centralbl. f. Stoffw. Krankh. 1902.
[5] Zeitschr. f. klin. Med. Vol. 42.

mixed diet. Dr. Satta, for instance, could demonstrate in his own case that 300 grm. of butter added to a diet consisting of 125 grm. of rice led to no increase in the excretion of acetone, but that when the rice was excluded from the diet, 300 grm. of butter and 200 grm. of meat caused a considerable increase in the acetonuria. At the same time 1. 3 grm. of oxybutyric acid were excreted on the third day of the experiment. In addition a number of clinical observations were made in subjects who were undergoing a fattening cure. In these cases 200 grm. of butter and more were daily added to a mixed diet without producing acetonuria. We must assume, therefore, that it is not the addition of fat alone but also the absence of carbohydrates from the diet that determines alimentary acetonuria. Even in severe cases of diabetes the same applies. von Noorden[1] recently described a case in which 300 grm. of butter were administered while at the same time the acetone in the urine was reduced to from 1 to 2 ctgr. namely, when the patient was eating considerable quantities of oatmeal.

[1] Berl. klin. Woch. 1903.

II. THE SOURCES OF THE ACETONE BODIES.

WE have demonstrated so far that the excretion of acetone bodies in healthy subjects is dominated by the presence of certain quantities of carbohydrates in the food. We have also called attention to the theory that the appearance of these bodies in the urine is the result of some perversion of oxidation. This leads us to the further assumption that there must be some inter-relationship between the absence of carbohydrates from the food and perversions of oxidation. These hypothetical disturbances of oxidation could, for instance, produce noncombustion of acetone bodies that are normal intermediary products of metabolism, in the sense that in the absence of carbohydrates they would not be burnt to CO_2 and H_2O. This view is favored by the fact that a healthy person living on a mixed diet can destroy β-oxybutyric acid and diacetic acid completely, and can also destroy the greater portion of any acetone that may be administered. Another view would be that in the absence of sufficient carbohydrate metabolism would be perverted in such a way that the acetone bodies would be produced as new bodies, i. e., as abnormal products of metabolism. We have no definite and direct data to prove the latter assumption. The view that the acetone bodies are an intermediary product of normal metabolism seems to agree more with the facts we possess.

Disproved Theories as to the Origin of the Acetone Bodies.—At different times the carbohydrates, the pro-

teids and the fats have all been considered the mother substances of the acetone bodies. The old view that acetone is a product of the fermentation of carbohydrates in the intestine must be considered invalid in the light of what we know nowadays in regard to the effect of the carbohydrates on the excretion of acetone bodies. Still another assumption is improbable *a priori*, namely that the excretion of acetone bodies is due to the abnormal disassimilation of body carbohydrates occurring whenever there is a deficiency of carbohydrates in the food. The chief arguments against this view are certain observations that have been made in diabetic subjects, for it is a well known fact that the latter, as soon as the tolerance for proteids and carbohydrates increases, not only excrete less sugar but also less of the acetone bodies; in other words, act in this respect exactly like healthy subjects who are living on a meat-fat diet and who receive carbohydrates in sufficient quantities.

Until very recently the idea was generally prevalent that the proteids were a source of the acetone bodies. The reason for this was the observation that acetonuria was common when there was much catabolism of proteids. A leading argument against this view, however, was the fact that acetone and β-oxybutyric acid were also frequently excreted when the metabolism of the proteids was normal or even abnormally low. Another idea, namely that acetonuria, etc., was the result of the degradation of the body proteids (Honigmann[1], von

[1] Dissert. Breslau, 1885.

Noorden [1]) was advanced at one time but had to be abandoned as soon as careful metabolic studies were made in diabetic subjects, in whom it was found that proteids might be retained and at the same time β-oxybutyric acid be continuously excreted in the urine. (Weintraud [2], Magnus-Levy, numerous observations by von Noorden.) Some time prior to this Minkowski [4] advanced the theory that the acetone bodies might be due to some qualitative perversion of proteid metabolism, in the sense, namely, that the nitrogenous end products of this catabolism would be normal, but that the catabolism of those parts of the molecule that contained no nitrogen proceeded along abnormal paths so that β-oxybutyric acid, etc., were the result.

The Origin of β-oxybutyric Acid.—More recently Sternberg [5] has formulated the hypothesis that β-oxybutyric acid is formed from proteid *via* amidobutyric acid, and that the latter is a decomposition product of albumen. Feeding with this acid produced a symptom complex that very much resembled diabetic coma. In the urine of such animals diacetic acid could be discovered by Gerhardt's reaction. Magnus-Levy [6] objected to Sternberg's reasoning on the following grounds: in the first place the picture presented in cases

[1] Lehr. d. Path. d. Stoffw. 1893, Berlin.
[2] Arch. f. exp. Path. u. Pharm. Vol. 34.
[3] Ibid. Vols. 42 and 45.
[4] Ibid. Vol. 31.
[5] Zeitschr. f. klin. Med. Vol. 38,
[6] Arch. f. exp. Path. u. Pharm. Vol. 45.

that are intoxicated with amido-butyric acid differs in no way from the disease picture in other forms of intoxication which certain poisons that are in no way theoretically related to oxybutyric acid. In the second place, no one has ever demonstrated conclusively that amido-butyric acid is a product of the disintegration of proteids in the organism.

Finally, the assumption that amido-butyric acid is the mother substance of β-oxybutyric acid becomes altogether improbable when the quantities of β-oxybutyric acid that have been found in individual cases of diabetes are calculated for amido-butyric acid, a calculation that Magnus-Levy has performed in some of his investigations.

The fact, again, that acetone can be manufactured from gelatin (Blumenthal and Neuberg) or from albumen (Zuckelberger and von Jacksch) by active oxidation signifies nothing in regard to the origin of oxybutyric acid and its derivatives from albumen in the organism for the quantities of acetone that can be manufactured from albumen are altogether too small. In addition the fact that oxybutyric acid can be manufactured in this way *in vitro* demonstrates nothing in regard to its origin *in vivo*. We see, therefore, that on the basis of the facts that we possess we are forced to deny the possibility of acetone formation by simple oxidation or splitting of albumen. At the same time, we cannot deny that possibly the nitrogen-free radical of the albuminoids at first splits off atom groups that

contain little carbon and that oxybutyric acid is finally formed from these groups by synthesis (see the formation of acetone bodies from the fatty acids below).

As the carbohydrates in the proteids cannot therefore be considered the mother substance of oxybutyric acid, only two possibilities remain, namely, that oxybutyric acid may be formed from fats (by degradation) or that it may be formed by synthesis from bodies containing two or three carbon atoms; in the latter case it would be immaterial whether these bodies were a product of the disassimilation of albumen or of fat (Magnus-Levy). The following facts seem to speak in favor of the former possibility:

From the investigations of Gelmuyden already quoted above, we know that if a subject is fed on a diet free from carbohydrates, the addition of fat to such a diet, or of fatty acids, increases the excretion of acetone. The original assumption of Gelmuyden that only the lower series of fatty acids are capable of exercising this effect has not been verified, for Schwarz, Mohr and Löb, etc., were able to show that neutral fats possessed the same power, although not to the same degree. The same is demonstrated by a large number of experiments that have been performed in diabetic subjects. (These investigations will soon be published by Dr. Satta from our laboratory.) Other experiments show that the quantity of free fatty acids cannot be the factor that determines the increase in

the excretion of oxybutyric acid or of acetone, for in some of the cases more oxybutyric acid was excreted than butyric acid was administered. Besides, we know that in diabetics the enormous quantities of oxybutyric acid that are excreted cannot possibly be derived from preformed low fatty acids that were introduced with the food. The question therefore rises whether or not the catabolism of the higher fatty acids (of the food or of the organism itself) proceeds in such a way that the chain of atoms containing from 16 to 18 atoms of carbon is split and butyric acid formed in this way. Even if we assume this to be the case, the chemical interpretation of the process is not rendered any more clear, for the assumption that butyric acid is transformed into oxybutyric acid by simple oxydation is chemically inconceivable. It is a little more probable that the fatty acids are disassimilated until the stage of acetic acid with two atoms of carbon is reached and that later certain synthetic processes lead to the formation of oxybutyric acid. Other syntheses occurring with acetic acid, a body that is always present in the organism, are well known, and Cohn[1] has actually assumed that in the case under discussion such a synthesis takes place.

This question has also been investigated by one of us experimentally without obtaining the desired result. Nevertheless, the idea of a synthetic formation of β-oxybutyric acid in the way outlined is much more

[1] Quoted by Magnus-Levy Arch. f. exp. Path. u. Pharm. Vol. 42.

probable than the assumption that the acid is a product of disassimilation of atom complexes containing many atoms of carbon.

According to our view, as already stated, this synthesis could occur either with fragments of the proteids or of the fats that contain few atoms of carbon. It is an altogether one-sided view to consider only the fats or only the proteids in this connection as some authors do. The phenomenon of acetonuria with its many modifications becomes quite comprehensible if we adhere to the views that have just been developed and assume that acetone is a synthetic product derived from certain bodies that contain few carbon atoms and that may be derived from different sources.

Normally the fragments of the proteid and fat molecules that contain few carbon atoms undergo further oxidation but only as has been repeatedly emphasized if a sufficient quantity of carbo-hydrate is present. This is probably due to the fact that the carbohydrates contain so much oxygen. A portion of this oxygen is presumably liberated when the carbohydrates undergo metabolism and is used for the oxidation processes. That the effect of the oxygen must be of a peculiar kind is demonstrated by the fact that there is no lack of respiratory oxygen in diabetes (this has been demonstrated by respiration experiments in diabetic subjects by Voit and Pettenkofer[1], Wein-

[1] Zeitshr. f. Biol. Vol. 3 and 29.

traud and Laves[1], etc.) One might imagine that the influence of the carbohydrates is a contact effect, exercised by the oxygen *in statu nascendi* that is liberated within the cell.

[3] Zeitshr. f. fhys. Chemie. Vol. 16.

III. WHERE ARE THE ACETONE BODIES FORMED?

According to the oldest views, acetone is formed in the intestinal tract from the decomposition of the carbohydrates. The so-called intestinal form of acetonuria and the fact that so-called acetone autointoxication is often accompanied or preceded by gastro-intestinal disorders seem to favor this view. It is true that several investigators have succeeded in finding acetone in the stomach and the intestinal secretions of such patients and that quite recently Magnus-Levy even succeeded in finding β-oxybutyric acid in the gastric contents. The quantities found in the gastro-intestinal tract are, however, so small in comparison with the quantities found circulating in the blood that one is hardly justified in postulating that the acetone bodies are formed in the stomach and intestines. It is much more feasible to assume that *per contra* these bodies are excreted into the intestine from the blood. The fact, in addition, that thorough cleansing of the gastro-intestinal tract by laxatives, does not decrease the acetonuria (F. Müller-Lüthge[1]) and that this procedure occasionally even increases the amount of acetone in the urine of diabetics (von Noorden) militates against the enterogenous origin of this substance. Very recently, J. Müller[2] has again pointed to the gastro-intestinal tract as the source of the acetone bodies.

[1] Verhandl. d. Congr. f. inn. Med. 1898.

[2] Ibid.

He based his view on the discovery that sugar given by mouth reduces the amount of acetone, whereas sugar administered as a clysma or subcutaneously, does not exercise this effect. In addition he demonstrated that fatty acids introduced subcutaneously did not increase the acetonuria, and this too he considers an argument in favor of his view. Neither of these arguments, however, is altogether correct. The amounts of sugar introduced subcutaneously or per rectum are altogether too small. Although J. Müller has undoubtedly proceeded with the greatest care, one can nevertheless imagine that less carbohydrate enters the circulation than is necessary to produce a reduction of the acetonuria. We know from recent respiration experiments (by Reach[1]) that the absorption of carbohydrates is less complete from the intestine than from the stomach, and that consequently the body receives less carbohydrate through the former channel.

The same applies to sugar that is introduced subcutaneously or the fatty acids that are introduced in the same way. Of the latter we do not even know whether they are at all burnt up or whether they are excreted unchanged. At all events, both substances are absorbed into the circulation much too slowly, and much too little of them, moreover, is present in the circulation during each time unit to allow us to conclude that they could be capable, when introduced subcutaneously, of exercising any appreciable effect upon the formation

[1] Arch. f. exp. Path. u. Phar. Vol. 46.

of acetone. The fact, moreover, that such enormous quantities of acetone bodies are excreted in the former case speaks decidedly against the enterogenous origin of this body. All the facts of the case, therefore, particularly when combined with the arguments given above, point definitely to intra-cellular processes. It is of course impossible to determine for the present whether or not all the organs of the body participate in this process. Magnus-Levy,[1] however, discovered that β-oxybutyric acid was a product of the autolysis of the liver, and his observation may, therefore, possibly be considered an argument in favor of the view that the liver has something to do with the formation of acetone bodies.

[1] Hofmeister's Beiträge, z. Chem., Phys. u. Path. Vol. 2.

IV. PATHOLOGICAL NON-DIABETIC ACETONURIAS.

In the course of recent years, as already indicated, a number of so-called pathological acetonurias have been described that properly occupy an independent position. A number of causes have been incriminated with producing the acetone in all of the different forms. A number of these acetonurias were soon recognized to be purely symptomatic, so that they were soon excluded from the number of independent disease pictures that were grouped under the general heading of acetonuria. Some of the symptom complexes, however, in which acetone bodies were excreted are still considered to be independent clinical entities, as, for instance, experimental acetonuria in phlorizin and pancreas diabetes, the acidosis occurring in diabetes in human subjects, the febrile form of acid intoxication and the cryptogenetic form of these intoxications. The primary factors that determine the formation of acetone bodies in these cases are presumably certain poisons that are formed in the intestinal canal and that directly or indirectly lead to the formation of acetone bodies (Kraus). So far no one has succeeded in demonstrating that such primary intestinal toxins exist. As a matter of fact, it does not seem to us necessary to postulate their existence, especially in diseases in which β-oxybutyric acid and its derivatives are excreted. For if we study the connection between the acetone bodies and the decomposition and utilization of the

carbohydrates in the organism it becomes clear that all acetonurias are due to some one-sided perversion of nutrition. From this standpoint the attempt will be made in the following to describe a connected conception of the large series of acetonurias that have been referred to.[1]

The first of this group of acetonurias that was discovered by Lustig[2], after extirpation of the cœliac plexus in rabbits, and that was considered to be an essential acetonuria by this investigator, does not stand the light of critical illumination. Thus Peiper[3] repeated some of the experiments of Lustig and could not completely corroborate them. The animals after the operation suffered serious disturbances of general nutrition, so that the acetonuria might well have been the result of malnutrition. In addition, moreover, acetonuria was not a constant result of the operation. We believe that these cases are instances of so-called "hunger acetonuria." At the same time we call attention to the fact that in these animals it is less the "under feeding" than the lack of carbohydrates that is the most important factor (see above). At all events the experiments of Lustig are in no way fundamental, as far as deciding anything in regard to the acetone question is concerned. The experiments of Claude-

[1] For literature see also Albu, the Autointoxications of the Intestinal Tract, Berlin, 1895.

[2] Quoted in Peiper, Zeitshr. f. klin. Med. Vol. 17.

[3] Ibid. Vol. 17.

Bernard[1] are more important. This investigator discovered acetone in addition to dextrose in the urine after performing piqûre. In this case, however, the connection between insufficient utilization of carbohydrates and excretion of acetone is apparent. In phlorizin diabetes acetone, oxybutyric acid and an increased quantity of ammonia are also found in the urine in addition to dextrose. In one case of Von Mering's a comatose condition even developed. The particular animal was allowed to starve for four days before the phlorizin was administered; in this way Von Mering[2] made the animal carbohydrate-free; as soon as the phlorizin was stopped and the sugar excretion ceased, both the symptoms of coma and the acetonuria also disappeared. Kraus interprets the connection between glycosuria and the formation of acids in these cases as follows: He imagines that phlorizin interferes with the chemical interchange of the different substances in the organism and that β-oxybutyric acid is formed from abnormal splitting of N-free remnants of the proteids—that are undergoing rapid disintegration. On the other hand, we think that the acid intoxication in phlorizin diabetes can be explained very much more simply by assuming that the utilization of the carbohydrates is reduced. This view is borne out by the fact that the ferric chloride reaction appears soon after the operation and that β-oxybutyric

[1] Quoted in F. Kraus, l. c.

acid (in small quantities, it is true) also appears sometime afterwards (Minkowski).

Some Clinical forms of Acetonuria.—We will now discuss clinical acetonurias. The first of these is *febrile acetonuria.* Von Jacksch was the first to determine that considerable quantities of acetone, and at times of diacetic acid, are regularly found in a large number of diseases that are accompanied by high fever, as for instance, scarlatina, typhoid, pulmonary tuberculosis, etc. β-oxybutyric acid has also been frequently found in the urine of patients suffering with these diseases, both during the course of the disease and during convalescence. As a rule there is a certain proportion, though not a regular one between the height of the fever and the amount of acetone that is excreted in the urine; acetonuria has, however, been observed in cases of typhoid fever that ran their course without much elevation of temperature.

In order to illustrate the influence of the diet on the excretion of acetone in typhoid fever, two patients suffering from this disease and both with temperature between 39 and 40 degrees were placed on a different diet. The one received a diet that contained little carbohydrate, the other a diet that contained much carbohydrate. Patient A, on three successive days received ten eggs, $\frac{3}{10}$ths of a liter of cream (with 30% of fat) 50 grm. of oatmeal flour, 100 grm. of butter and in addition a little meat broth and tea (about 82 grm. of albumen, 39 grm. of carbohydrate, 228 grm. of

fat ; all in all, about 2600 calories). The urine gave Gerhardt's ferric chlorid reaction and contained an average of 0.8 grm. of acetone a day. Patient B on three successive days took two liters of milk, 150 grm of oatmeal flour made into soup with milk, 200 grm. of sugar (about 90 grm. of albumen, 70 grm. of fat, 380 grm. of carbohydrate, all in all about 2,600 calories). This patient excreted only about 0.05 grm. of acetone, on an average during the course of these three days. Now the two patients reversed the diet. As a consequence the amount of acetone excreted by patient A dropped to 0.1 grm. a day, whereas patient B excreted 0.7 grm. The food was well absorbed in both cases, there being only one soft evacuation of the bowels a day.

Von Engel [1] who together with Seiffert and others examined the urine of a large number of febrile cases for acetone, states that apparently the location of the disease and the individuality of the patient determines the excretion of acetone more than the height of the fever. A large number of investigators soon formulated objections against the idea that febrile acetonuria was a specific manifestation of fever. Attention was called in particular to the acetonuria occurring in fasting, and Von Noorden [2] was the first to emphasize the fact that insufficient ingestion of food must be considered to be the cause of febrile acetonuria. Hirschfeld later circumscribed this theory of von Noorden's

[1] Zeitschr. f. klin. Med. Vol. 20.

[2] L. c. [3] L. c.

and others by claiming that the absence of carbohydrates from the food of febrile cases was chiefly responsible for the excretion of acetone in these cases. As a matter of fact, one can easily determine that febrile acetonuria and diaceturia disappear in a short time in patients with fever if they are placed on a carbohydrate diet.

Essentially the same applies to *carcinomatous acetonuria* [1] a form of acetonuria that is by no means rare. Sufferers from carcinoma frequently die in a condition that greatly resembles diabetic coma, while at the same time acetone appears in the urine, consequently many investigators have attributed this terminal condition in carcinoma to an intoxication with acetone. It is also claimed that the appearance of acetone and of diacetic acid in carcinoma is a particularly bad prognostic sign, but aside from the fact that the quantities of these bodies that are excreted are so small that they do not compare with the quantities excreted in diabetic coma, there are, moreover cases of coma in carcinoma in which no acetone bodies whatsoever are excreted in the urine. As, in addition, these bodies are never found in the early stages of the disease, when the ingestion of food is still normal, and are only found in the later stages of carcinoma, I am much inclined to the belief that the acetonuria is not related to the carcinomatous process *per se*, but is merely the result of insufficient nutrition —above all of inadequate ingestion and assimilation of

(1) See Albu, l. c.

carbohydrate during the terminal stages of the disease. This view is borne out by a number of cases in which acetonuria and the excretion of β-oxybutyric acid was stopped as soon as a sufficient quantity of carbohydrates was administered. The following is a particularly striking case of this kind: A girl of 26 was admitted to the hospital suffering from constant vomiting. She was greatly reduced in strength. The result of the objective examination of the patient rendered the diagnosis of carcinoma of the pylorus very probable, and this diagnosis was later corroborated by an autopsy. During the first days an average of 3 grm. of acetone, an abundant quantity of diacetic acid and 10 grm. of oxybutyric acid (determined according to the method of Magnus-Levy) were excreted. It was possible on two successive days to administer 120 to 150 grm. of carbohydrates to this patient in the form of clysmata of dextrose, and of oatmeal by mouth. On the third day the excretion of acetone fell rapidly and only 0.6 grm. were eliminated. At the same time the ferric chloride reaction and all traces of oxybutyric acid disappeared from the urine. We have seen a number of such cases and could in addition quote several from the literature (Klemperer, von Noorden and others)

The last named observation is also of fundamental importance in another from of acetonuria, namely, *gastro-intestinal acetonuria.* Lorenz[1] found this form of acetone excretion in a large number of diseases of

[1] Zeitschr, f. klin. Med. Vol. 10.

the stomach and intestine, particularly in acute cases. This fact has recently been repeatedly corroborated, and has been variously utilized in constructing theories on the origin of acetone. But even these observations, studied in the light of our present knowledge, completely lose any symptomatologic or pathognostic importance. In these cases we are apparently not dealing with specific disease processes that lead to the formation of acetone, but with acetonuria from inanition that is produced by loss of appetite, vomiting, diarrhœa and decreased ingestion of food.

Even the rapid appearance of the acetone bodies so soon after the onset of the disease can hardly be considered a specific sign of the intestinal origin of acetone and its congeners. It is remarkable how rapidly acetone appears in the urine as soon as the diet is one sided and insufficient, and the administration of carbohydrates is greatly reduced. We do not think that the appearance of acetone in the vomit and in the intestinal contents speaks in favor of the gastro-intestinal origin of acetonuria in these cases, for the quantity of acetone that is found is rarely larger than the amount normally found in the gastric and intestinal contents. At the same time, one can readily understand how the entrance of a large quantity of acetone and β-oxybutyric acid into the circulation, as described in the above cases, might very well lead to the excretion of more acetone bodies than normal into the stomach and intestine. It is further possible that in catarrhal conditions of the stomach and intestine, in which

there is fermentation of carbohydrates, acetone might be formed in the intestine, just as traces of acetone are occasionally formed as a bi-product in fermentative processes outside of the body. But even this formation of acetone is only very slight, and in the cases quoted by Lorenz in particular no indications are given that large quantities of fermenting carbohydrates were present in the intestines. On the other hand, it has repeatedly been demonstrated—and we have shown this in numerous cases of gastritis, enteritis, carcinoma of the stomach and intestine, poisoning etc.,—that the excretion of acetone bodies is always decreased (even in those cases in which undoubtedly the gastro-intestinal function is greatly perverted) as soon as sufficient quantities of carbohydrate can be administered and absorbed.

On the basis of Lorenz' observations a number of other morbid states that are accompanied by acetonuria have been attributed to intoxication with this body, and the theory has been advanced that here this poisonous acetone was formed in the intestinal canal. Here belong, for instance, certain psychoses that are accompanied by acetonuria and that Wagner has recently designated as acetone autointoxication. In addition, certain spasmodic states that have been described by von Jacksch[1] as epilepsia acetonica and finally certain disease pictures occurring in children and characterized by spasms with acetone excretion;

[1] Arch. f. Kinderheilkunde. Vol. 9.

such cases have recently been described by Baginsky. A number of these observations were published before the colossal influence of the diet on the secretion of acetone was understood. None of the older observers and—remarkable to say—none of the newer ones have paid sufficient attention to this point. It is a well known fact that the ingestion of food is reduced in insane people and in sick children. In the cases of nervous disease, accompanied by somnolence, that von Jacksch has described, the acetonuria is apparently due to the insufficient administration of carbohydrate.

One should be just as skeptical in regard to *asthma acetonicum*, a condition that was first described by Pawinski.[1] His particular case is especially instructive, for it shows how careful one must be in interpreting a symptom complex that is *per se* very complicated. In this patient there was a combination of nephritis with cardiac hypertrophy and apparently stenocardiac attacks that were attributed to the action of acetone by the author. He felt justified in doing this because during the asthmatic attacks the excretion of albumen was slight, while at the same time the excretion of acetone was very considerable, and because, furthermore, in the interims between the attacks the conditions were exactly reversed. This in itself seems to indicate that the nutrition of this patient was the determining factor in the production of the acetonuria, for the increased excretion of albumen and the decrease in the acetonuria can very well be attributed to the increased

[1] Berlin. klin. Wochenschrift, 1888.

ingestion of food. Consequently, the sequence of events in Pawinski's case would seem to be as follows: the primary event was the stenocardiac attack, accompanied, of course, by decreased ingestion of food, i. e., of carbohydrates; the secondary event, then, was the excretion of acetone.

Puerperal eclampsia and the *eclampsia* of *pregnancy* have also been attributed to autointoxication with acetone and the origin of the acetone has been laid in the intestine, according to Lorenz. Recently Stumpf[1] and Stolz[2] have gathered more casuistic material on acetonuria occurring in pregnant women and during labor and have advanced the theory that the relative frequency of acetonuria in such cases must be attributed to an increased destruction of fat in the maternal organism. No very convincing proofs, however, have been adduced in favor of this far-reaching theory, for the reason, chiefly, that the character of the nutrition in these cases has not been sufficiently considered, so that on these grounds alone one is hardly justified in assuming an increased destruction of fat. The same applies to acetonuria in pregnancy in cases in which the fetus is dead. These cases of acetonuria were interpreted to signify toxogenic destruction of fat resulting from the absorption of poisonous products from the uterus (Waldvogel.[3]) This assumption is altogether unjustified, for this form of acetonuria is also directly influenced by carbohy-

[1] Verhandl. d. deutsch. Gesellsch. f. Gynaecologie, 1886.

[2] Arch. f. Gynaekol. Vol. 65.

[3] Deutsch. Arch. f. klin. Chirurgie. Vol. 66.

drates. This may be illustrated by the following two cases observed by von Noorden; both were women with febrile tuberculosis of the lungs, and both were in the eighth month of pregnancy. For fourteen days neither of them had felt any fetal movements nor could any fetal heart sounds be heard. The nutrition of both of these cases was greatly reduced and the ingestion of food had been very small for a number of weeks, and consisted moreover, principally of meat broth, eggs and tea. Legal's test was very positive, also the ferric chloride reaction. In the course of the next few days the nutrition of these patients was improved by the addition of milk and bread to the diet, whereupon the ferric chloride reaction disappeared at once and Legal's test was only slightly positive for a little while and finally disappeared almost completely. No positive ferric chloride reaction could be obtained after this, because the nutrition in these patients was carefully maintained until the macerated fetus was born on the fifth day in one case and the seventh day in the other.

In poisoning with antipyrine, sulphuric acid, atropine, extractum filicis, morphine, lead, etc., and also after chloroform narcosis, another form of acetonuria has been described that is called *toxic acetonuria*. (Becker[1]). A large number of these cases were thought to be due to toxic disintegration of albumen and lack of oxygen—the latter being attributed to the destruction of red blood corpuscles. According to Ebstein, there

1 Centralbl f. Chirurg. 1895, and Virchow's Arch. Vol. 140.

is a condition that he calls "insufficiency of intracellular respiration" due to the action of these poisons. *A priori* one cannot deny that in poisoning with some of these bodies disturbances of oxidation may occur and that the excretion of acetone may be due to deficient catabolism of certain bodies that would ordinarily be oxidized further than the acetone stage. We call attention in this connection to the experiments of Araki on poisoning with carbon monoxide. On the other hand, one must never forget that in the most pronounced forms of toxic acetonuria the patients were in a condition of prolonged somnolence and took little food for long periods of time, and that, further, the acetone was rarely discovered until these patients had been fasting for several days. It is remarkable how naive and indiscriminate the interpretation of some of these cases is, for some of the authors pay no attention whatsoever to the nutrition of the patient. As far as acetonuria after narcosis in particular is concerned, one of us can state from personal experience that the excretion of acetone in these cases disappears after the administration of carbohydrates, or is at least greatly reduced by carbohydrates, so that the same conditions apparently exist here as in acetonuria from fasting.

We can conclude, therefore, from all that we have learned in regard to pathological acetonuria that this form behaves exactly like the experimental form that is brought on artificially by fasting or by feeding a diet that consists exclusively of meat and fat. If we are justified in the experimental forms in concluding

that the absence of carbohydrates produces the acetonuria, then it would appear that we are also justified in concluding that pathological acetonuria may be due to the same cause. One might object that these two forms have merely this in common, that the addition of carbohydrates to the diet causes the acetonuria to disappear, but that in all these different cases the primary cause of the acetonuria is different. One could, therefore, assume, that there are a variety of forms of acetonuria of different etiology. We believe, however, that this assumption is false, particularly in regard to the forms of acetonuria that follow fasting or a one-sided, carbohydrate free diet and in regard to diabetic acetonuria.

V. DIABETIC ACIDOSIS.

The literature on the excretion of acetone in diabetes mellitus is enormous. There was much confusion in the beginning; but light was finally thrown upon this obscure subject when the factors determining the excretion of β-oxybutyric acid were elucidated and when the fact was recognized that β-oxybutyric acid, diacetic acid and acetone were derived from the same mother substance and represented merely different stages of oxydation. Whenever these acetone bodies appear in the urine, we must assume some perversion of oxydation (see above). This perversion one must imagine is greater when all the acetone bodies appear than in cases in which only acetone is excreted. Only if we consider the three acetone bodies as belonging together, and if we remember that they represent different stages of oxidation, can we credit acetonuria in diabetes with practical and theoretical significance. In other words, the excretion of the acetone bodies together in diabetes assumes the same importance that was formerly attached to diabetic acetonuria alone.

The quantity of acetone bodies excreted in diabetes varies greatly. Sometimes the quantities are so small that they barely exceed the physiological quantities that are excreted by a healthy individual living on a meat-fat diet. In other cases several grams a day are excreted. In the latter case the ferric chloride is positive. No definite numerical statements can be made in regard to the quantity of acetone that appears

in cases in which diacetic acid is also excreted, nor can we determine definitely how much acetone must be present in the urine before β-oxybutyric acid appears. We can say, however, that on an average (and we know this purely empirically) 0.5 grm. of acetone must be excreted in the 24 hours before diacetic acid can be determined by the ferric chloride reaction; and again, that oxybutyric is rarely absent when more than 1.5 to 2 ctgr. of acetone are excreted *per diem*. On the other hand, the absence of acetone does not always indicate that oxybutyric acid is also absent. There are conditions in which the oxidative powers of the organism are damaged to such an extent that the β-oxybutyric acid that is formed cannot even be oxidized to acetone. As a matter of fact, cases with diabetic coma are on record in which no acetone was excreted and in which all of the acetone bodies appeared in the form of oxybutyric acid.

The quantity of oxybutyric acid excreted in the urine varies greatly in each individual case. Sometimes only a few grm. are excreted *per diem* and in other cases 30, 40 and more grm. a day may be excreted for weeks. The highest figures have been found in coma or after coma. Magnus-Levy records a daily excretion of 150 to 180 grm. of β-oxybutyric acid a day in cases of comatose diabetics. No one will seriously deny nowadays that the typical coma of diabetes is due to an autointoxication with β-oxybutyric acid and that it is the acid character of this body more than any specific toxic property that determines the syndrome

of coma (see above). Quantities of oxybutyric acid have been found in the urine and in the blood that, to judge from animal experiments, must be considered lethal. In addition a number of symptoms may be mentioned that are common both to diabetic coma and experimental acid intoxication. In the first place, we have the peculiar dyspnœa, then the increased pulse rate, the lowering of the temperature, the decrease in the blood alkalescence and the increased excretion of ammonia that may amount to 10 grm. *pro die*. The question arises now why such large quantities of acetone bodies are formed in diabetes, quantities that by far exceed those excreted in any other form of acetonuria. In this connection we wish again to distinctly emphasize that there is no tangible evidence to demonstrate that there is an enterogenous intoxication as assumed by some authors (Schmitz, Kraus). If we review all the conditions that determine the excretion of oxybutyric acid and of acetone in diabetes we will find that the following important facts may be considered established (von Noorden[1]).

Dangers in Dieting Diabetics too Strictly. 1. Numerous diabetics living on a diet containing at least 60 to 80 grm. of carbohydrate and not passing any sugar on this diet, do not excrete more acetone than a healthy individual. As soon as such cases are placed upon a rigid diet the excretion of acetone increases and diacetic acid also appears in the urine. If the strict

[1] Die Zuckerkrankheit und ihre Behandl. III. Ed. 1901.

diet is continued, the excretion of acetone decreases again and the ferric cloride reaction also disappears.

2. In another group of cases of diabetes of medium severity or of severe diabetes in its initial stages the excretion of acetone amounts to as much as one grm. a day on a diet containing more carbohydrates than these patients can tolerate. At the same time, there is no diacetic acid, or only traces of it, and no oxybutyric acid. In these cases, too, a strict diet causes an increases of the acetonuria, at the same time that the excretion of diacetic acid and oxybutyric acid is also increased. This excretion of acetone bodies may persist if the rigid diet is continued, or may even become greater; or, again, may, as in the first class of cases, be decreased in the course of a few days.

3. The third group of cases comprises patients who show all the symptoms of so-called severe glycosuria; the peculiarities of this group are, however, also occasionally seen in patients in whom the amount of glycosuria, according to our ordinary terminology, is slight, i. e., the glycosuria disappears as soon as the carbohydrates are withdrawn. In this group large quantities of acetone and of oxybutyric acid are continuously formed, and finally so much of these bodies accumulates that diabetic coma may develop. At the same time numerous fluctuations occur in these cases, so that the quantity of acetone bodies may suddenly decrease without determinable cause and then increase again after a time until the same amount as before is excreted.

All these different varieties of acidosis can be greatly influenced by the diet. The carbohydrates play the same role in diabetic acetonuria as in the other forms (see above, Hirschfeld). with this difference, however, that in diabetes the conditions are so complicated that the effect of the diet cannot be determined so readily as in healthy subjects or in patients with fever or with some other disease than diabetes.

The following important points may be enumerated, and they agree essentially with the facts discovered in other forms of acetonuria (see above).

As the tolerance for carbohydrates increases, the excretion of acetone bodies decreases, so that on the same diet not only less sugar but also less acetone, etc., is excreted. We believe that under these conditions more carbohydrate is burnt and consequently the oxidation of acetone bodies is favored.

As the tolerance for carbohydrates decreases, exactly the reverse is seen.

If large and increasing quantities of carbohydrate are administered the excretion of acetone and the other symptoms of acidosis can be reduced, at least for a time; for in nearly all diabetics a certain proportion of the increased quantity of carbohydrates that is administered is destroyed. The oxidation of this part of the food consequently decreases the acidemia. There are certain cases in which this factor can be utilized to advantage. In other cases, again, such treatment would do great harm as far as the primary diabetic taint is concerned.

In those rare cases in which all the carbohydrate that is added to the food reappears in the urine, the acetonuria is not influenced in any way by the addition of carbohydrates to the food.

The fact, furthermore, that in no other disease are even approximately so great quantities of acetone bodies found in the blood and urine, etc., agrees fully with the experience we have in regard to acetonuria in general, for in diabetes mellitus precisely those cells are functionally damaged that are expected to aid in the disassimilation and oxidation of the acetone bodies (see page 66). The combustion of the carbohydrates is reduced partly because the function of these cells is inhibited or destroyed, partly because we administer as little carbohydrate as possible in order to influence the actual condition of the patient or to prevent further trouble in the future. In those cases in which really very large quantities of acetone bodies are formed, the carbohydrates of the food are not destroyed; in addition, moreover, only very little of those carbohydrates undergoes this disintegration that is derived from other substance (albuminoids, fats). This occurs in no other disease, and consequently the values for acetone are never so high as in diabetes.

Although diabetic acetonuria follows the same rules as acetonuria from inanition in all these respects, there are, nevertheless, certain exceptions and peculiarities in diabetes that cannot readily be explained; consequently we must for the present have recourse to hypothetical considerations.

One such exception, for instance, is that only a slight decrease in the acetonuria may be seen in certain cases, in which the utilization of the carbohydrates is greatly increased. We showed above that acetone is not excreted in a healthy person if 80 to 100 grm. of carbohydrate are absorbed and assimilated every day. In cases of pneumonia, moreover, with high fever and in patients suffering from gastric ulcer who receive no other nourishment than 100 to 200 grm. of dextrose, the same fact can be determined (see above). In a number of diabetics, on the other hand, who really disintegrate (not only absorb, but actually assimilate) 120 to 150 grm. of carbohydrates, the excretion of acetone bodies may be found to remain very abundant. Another peculiarity that is difficult to explain is the fact that a diabetic excretes such different quantities of acetone bodies at different times, even though no change is made in the character of the food and no change occurs in the excretion of dextrose (in other words, even if the carbohydrate metabolism remains unchanged). The following is one of the many examples of this kind that I have on record :

The patient O. K., age 55, suffered from diabetes that was recognized two months before his entrance into the hospital (Nov. 14th, 1902). On admission he excreted about 35 grm. of sugar and in addition 0.132 grm. of acetone on a strict diet plus 100 grm. of white bread. After this patient had been on a strict diet for several

days, the sugar disappeared from the urine, but at the same time, as is usually the case, the excretion of acetone rose to 1.232 grm. a day and the ferric cloride reaction, that had been negative up to now, became positive. No oxybutyric acid was discovered. Soon after, the excretion of acetone gradually decreased. The patient during the last week of his sojourn in the hospital received in addition to the strict meat-vegetable-fat-diet, 45 grm. of graham bread, 25 grm. of oatmeal and 100 grm. of apple daily. The urine was free from sugar during this time, and from Dec. 2, to Dec. 8th he excreted an average of 0.405 grm. of acetone. Ferric cloride reaction negative. The patient, who was very conscientious, lived on exactly the same diet for three months longer at home and again received the same diet when he re-entered the hospital on the 12th of March, 1903, for the purpose of further observation. Again no sugar was found in the urine. The quantity of acetone, however, had fallen to 0.060 grm. from 0.4. grm. (average on three days).

As has been said, we have a number of observations on record of cases in which the diet remained the same and the excretion of sugar remained the same, but in which the excretion of acetone varied greatly at different times in the course of the disease.

We need not, therefore, be surprised to find that of 20 diabetics who are living on the same diet and who are excreting the same or approximately the same quantity of sugar, in whom, in other words, according

to our conception, the carbohydrate metabolism is the same, hardly two or three excrete the same quantity of acetone bodies. This phenomenon is most striking in those cases who live on a rigid diet and receive a moderate quantity of albuminates so that the excretion of sugar becomes almost zero. We refer to observations of this kind that von Noorden[1] published some time ago. We have a large number of observations of this kind; in some of them all the acetone bodies were determined for weeks at a time. The following two observations may be quoted here to illustrate our meaning:

Patient Adolph S., age 50, four days of strict diet and disappearance of sugar from the urine; and Miss Anna R., age 25, disappearance of the sugar after ten days of strict diet and two days in which some vegetables were allowed. After the urine was free from sugar for eight days, all the necessary urinary determinations were made as below, while the same strict diet was continued. The figures indicate the average values on ten days.

	Adolph S.	*Anna R.*
Quantity of urine	1530 grm.	1980 grm.
Nitrogen	16. 8 grm.	13. 5 grm.
Sugar	0	0
Acetone	0. 08 grm.	1. 1 grm.
Oxybutyric acid	0.	15. 0 grm.
Ferric chloride reaction	negative	positive
Ammonia	0. 9 grm.	1. 9 grm.

The two examples just quoted show us that two ex-

[1] Von Noorden: Die Zuckerkrankheit und ihre Behandlung. III. Edition, 1901. s. 106.

ceedingly important factors, that are independent of the character of the food, may determine the excretion of acetone bodies in diabetes. These two factors are the individuality of the patients and the fact that they become accustomed to a certain diet. We must remember, however, that both factors may also be operative to a certain extent in non-diabetic acetonuria. There are whole populations that exist exclusively on a diet consisting of albumen and fat, and only rarely, and that only at certain times of the year, ingest a little carbohydrate in the form of milk (Laplanders, Esquimaux). No facts have been reported in regard to the acetone excretion of these peoples and it is not known whether they excrete more acetone bodies than inhabitants of warmer climates who are accustomed to a mixed diet. Von Noorden in his Text Book on the Pathology of Metabolism, called attention to the fact ten years ago that obese subjects who are undernourished in the course of reduction cures, as a rule do not develop acetonuria. This observation was corroborated many times later and it was found that fat people who eat between 50 and 60 grm. of carbohydrates per diem and whose diet consisted otherwise exclusively of albumen and fat (including the fat of their own body which they disintegrate) never excreted more than a few centigrams of acetone except on the first few days of the new diet. Only one of these patients excreted as much as from 2 to 3 dgr. and this patient developed diabetes a year later. The reason why these subjects excrete so little acetone when they

undergo a reduction cure is probably the fact that they have been accustomed for a long time to eating very little carbohydrate. In order to demonstrate the validity of this view, von Noorden recently undertook the following experiment: A fat subject during the first week of the reduction treatment, received in addition to 500 grm. of meat, green vegetables and salad, meat broth, tea and coffee, some 200 grm. of bread (about 130 grm. of carbohydrate). The urine contained only traces of acetone. As soon as the organism had in this way been accustomed to carbohydrate, the latter was suddenly withdrawn and replaced by 80 grm. of butter (about 63 grm. of fat). The excretion of acetone began immediately and on the third day as much as 0.2 grams were excreted. Soon, however, the acetone excretion became smaller, and at the end of a week hardly traces of this body could be detected in the urine. On general principles, therefore, an obese subject reacts exactly like a healthy person, with this difference, however, that habit causes certain variations.

The other phenomenon mentioned, namely the dependence of the acetonuria on the individuality of the patient (compare the last small table) which is so conspicuous and so easily verified in diabetics, is occasionally also observed in subjects who are not diabetic. One of us examined, for instance, the acetone-body excretion in two subjects, the one suffering from a polyneuritis of syphilitic origin, the other one from hysterical disturbances of the stomach. Both were eating the same diet, consisting of 200 grm. of meat and 300 grm. of

butter. The former patient on the second day of this diet excreted 3 grm of oxybutyric acid and 2½ grm. of acetone. At the same time, the ferric chloride reaction of the urine was very strong. The latter patient excreted no oxybutyric acid, only 0.9 grm. of acetone, while the ferric-chloride reaction was negative. I have records of a number of other such cases that are not so pronounced, however. Mention might also be made in this connection that certain differences can be observed in this respect among the mammalian species, for while it is an easy matter, for instance, to produce considerable degrees of acetonuria in human subjects by fasting, this is very difficult to accomplish in a dog. As soon, however, as a dog has once developed acetonuria, the excretion of acetone follows the same laws that we have discussed above, that is, to a great extent it is dependent on the amount of carbohydrate eaten.

The law that the excretion of acetone is due to insufficient metabolism of carbohydrates is not absolute, and while many of the peculiarities just enumerated (the influence of habit and individuality) constitute deviations from this law, we are nevertheless forced to the conclusion that in diabetes certain factors are operative that are not active in normal conditions or in any other pathological state; one of the most important factors is the quantitative difference existing between the acetonuria in diabetes and in other conditions. A diabetic frequently excretes very much more acetone than a healthy subject whose carbohydrate

metabolism is the same or even much smaller. Or again, a diabetic may excrete considerable quantities of acetone under conditions in which a healthy subject would excrete only traces.

The Effect of Fasting.—A subject when fasting completely, possesses no residual carbohydrates after the fifth or sixth day (we know this from animal experiments and from a study of the respiratory quotient). The daily carbohydrate catabolism cannot very well be greater than would correspond to the metabolism of nitrogenous material. The nitrogen metabolism may fall as low as 8 to 9 grm. a day, and about 40 grm. of sugar that are formed from distintegrating body proteids correspond to this amount of nitrogen. Such a fasting individual never excretes more than 20 grm. of acetone—bodies a day (calculated for acetone). On the other hand, there are numerous cases of diabetes—and we, ourselves, have a number of such examples on record,—in which the conditions are as follows: if they live on a strict dict containing much proteid they excrete no sugar. The daily nitrogen metabolism amounts to 25 to 30 grm. The amount of proteid sugar that corresponds to this amount of nitrogen and that is formed and later disintegrated in the organism, is three times as great as the amount one would calculate in a fasting subject. In addition there are at least ten to fifteen grm. of carbohydrate that are ingested with the food, even on a very strict diet. Nevertheless, we often find an excretion of from 40 to 50 grm. of acetone bodies, calculated for acetone, whereas in reality we should

have expected less than in a fasting subject, provided the quantity of destroyed carbohydrate and not certain peculiarities of the diabetic organism determined the excretion of acetone.

It has already been mentioned above that a healthy subject living on a mixed diet containing a sufficient quantity of proteids and fats and at least 80 grm. of carbohydrates does not develop acetonuria. In diabetic subjects, on the other hand, we occasionally encounter cases that disintegrate at least 110 and even 150 grm. of carbohydrates and still excrete acetone, or in which at least the excretion of acetone is only slightly influenced by the addition of this large quantity of carbohydrates to the diet. Cases of the latter kind, it is true, are comparatively rare.

The Acetonuria of Diabetes—This shows that in diabetics acetonuria occupies a peculiar position, although on the other hand it is true that in many diabetics the same factors seem to influence the excretion of acetone as in healthy subjects. Wherever we find these peculiarities in diabetic subjeets it is not so much the quantity of carbohydrate that is disassimilated as the manner in which the carbohydrates or the fats are disassimilated that determine the special features. If we understood what phase of carbohydrate metabolism determines the oxidation of acetone, we would understand the abnormalities better. Unfortunately, however, we know nothing about this. We know, however, that in diabetics the perversion of the carbohydrate metabolism may be manifold, for there may be, first,

interference with the oxidation of the carbohydrates; secondly interference with the power of the body to form fat from carbohydrates; third, interference with the power of the organism to form glycogen from the carbohydrates and to store it. We are not justified in assuming that in all cases of diabetes these three perversions of metabolism are developed to the same degree. On the contrary, there is much evidence to show that these three anomalies of function, any one of which may lead to glycosuria, are more or less independent of one another (see the hypothesis of VonNoorden on diabetogenous obesity). The question now arises, which one of these functions is concerned with the oxidation of the acetone bodies. This question we cannot answer. We can very well imagine, however, that the degree of acetonuria varies if one or the other or all of these functions are perverted. This view would explain the fact that certain diabetics, although they are living on the same diet and are excreting the same amount of sugar, still produce different quantities of acetone, and that many diabetics, even though they do not excrete any sugar, nevertheless excrete much more acetone than a healthy subject living on the same diet.

One other possibility must be considered in this connection, viz.:—the tendency of diabetics to produce quantities of the acetone bodies that are much greater than those excreted by healthy subjects or by patients suffering from any other pathological condition, may also be due to abnormalities of the fat me-

tabolism. We do not refer to the increased disintegration of fats that is so common in diabetes, for this factor, according to universal experience, could only explain the excretion of moderate quantities of acetone but not the excretion of the enormous quantities of acetone bodies that severe cases of diabetes frequently eliminate. We refer, moreover, to those qualitative differences in the catabolism of the fats, that von Noorden first mentioned. For we have much clinical evidence to show that in severe cases of diabetes carbohydrates can be formed from fatty acids; the chemical formula for this conversion, it is true, is still lacking.

This leads us to the question of *intermediary metabolism*, a field that is obscure and more or less hypothetical.

Generally speaking, the following statements can be made in regard to diabetic acetonuria (the excretion of acetone bodies).

Diabetic acetonuria in general follows the same laws as acetonuria in non-diabetic subjects, i. e., it may be attributed to insufficient utilization of the carbohydrates. Whereas, however, the relation between the carbohydrate metabolism and acetonuria in healthy subjects (a few peculiarities excepted) is due to quantitative disturbances, it is due in diabetics to qualitative changes in the metabolism of the fats and carbohydrates.

VI. THERAPEUTIC CONSIDERATIONS.

It may appear daring to speak of a special treatment of intoxication with the acetone bodies, inasmuch as this form of intoxication, according to our views, is no independent disease picture, but is merely a symptom complex that accompanies a variety of morbid conditions and is dependent on the nutritive disturbances that are the result of these conditions. Nevertheless, the toxic symptoms of acidosis occupy a more or less independent clinical position and call for treatment that is not always identical with the treatment of the primary disease. Even the mild forms of acidosis that are seen in non-diabetic subjects are worthy of the most careful study, because this form of poisoning constitutes a source of danger in an organism that is already diseased. The acidosis of diabetics, of course, is still more important, for it constitutes the foundation of future attacks of coma. Very frequently the condition of acidosis must be combated more than the glycosuria, even at the risk of increasing the glycosuria temporarily or even permanently, provided, of course, that this is the only way to obviate the dangers incident to acidosis.

Generally speaking, there are at our disposal:

Two Means for Combating Acidosis.—1. Means directed towards limiting the formation of the acetone bodies, i. e., towards favoring their oxidation.

2. Means directed towards disintoxicating the ace-

tone bodies circulating through the tissues and towards accelerating their elimination.

In all non-diabetic cases the first measure invariably leads to the goal. In all such cases the daily addition of 150 grm. of carbohydrate to the diet suffices to reduce the acetonæmia and to prevent the appearance of Gerhardt's ferric chloride reaction in the urine. Where this reaction is already positive the same amount of carbohydrate is sufficient to cure the acidosis in one or at most two days. We have frequently had occasion to verify the correctness of this statement and have given a few examples of such cases above. If it becomes necessary to work quickly and if in cases, for instance, of severe gastro-enteritis, rapid absorption of the carbohydrates from the stomach cannot be produced, monosacharides may be injected subcutaneously or intravenously (dextrose or levulose); the disacharides (cane sugar and milk sugar) are, as we know, not disintegrated if they enter the organism through other channels than the intestine (F. Voit). As an example, mention may be made of a case of acute gastro-enteritis with violent vomiting and diarrhoea that was treated by von Noorden in the summer of 1903 and in which the ferric chloride reaction of the urine disappeared within three hours after the intravenous infusion of a litre of a physiological salt solution to which had been added 10 per cent. of dextrose.

In diabetes mellitus the matter is much more difficult. There are cases, of course—and happily these constitute the majority—in which the degree of acidosis is

insignificant and in which the ordinary dietetic treatment that is employed to reduce the glycosuria produces the desired result. In other cases, again, in which large quantities of the acetone bodies appear in the urine on a moderately strict diet, or even when the carbohydrates are completely excluded, the problem is more difficult. It is hard to say what amount of acetone bodies one would consider as "large." In the majority of cases one can probably speak of "large quantities" if more than 1 grm. of acetone is continuously excreted every day. Under these circumstances the acidosis is at least as important as the glycosuria. Some authors recommend adding carbohydrates or substances that are similar to carbohydrates to the diet, for in this way, it is argued, the acetonuria is decreased, while at the same time the glycosuria is not greatly increased. A substance answering this purpose would seem to be levulose. Unfortunately, however, as von Noorden has repeatedly shown, this sugar is useful only in mild cases, for in the more severe cases levulose seems to increase the glycosuria as much as other carbohydrates (amylum, etc.). In severe cases, on the other hand, levulose presumably exercises the same effect on the glycosuria as starch, and the latter substance is more useful because it offers more variety to the patient and is more agreeable to take than levulose. For these reasons we employ levulose only in those cases in which we desire a very rapid result and in cases in which—as for instance in incipient coma,—only a liquid diet can be taken. Under these circumstances, levu-

lose frequently exercises a very excellent effect and aids in warding off impending danger. We know from clinical experience that the administration of 50 to 100 grm. of levulose a day rapidly produces a great decrease in the excretion of oxybutyric acid (Weintraud, Hirschfeld, von Noorden, Mohr and Loeb).—Glycerine in doses of from 50 to 100 grm. has also been employed with fair success, but this remedy increases the glycosuria much more than levulose.

Recently L. Schwarz, basing on the idea that certain disintegration products of dextrose are presumably oxidized by diabetic subjects, advised the administration of *saccharic acid* and of *glyconic acid in acidosis*. In his clinical experiments he found that the acetonuria was reduced by the administration of 50 to 60 grm. of glyconic acid. In diabetic coma he witnessed a transitory "recovery" in two cases after the administration of large quantities of glyconic acid together with large quantities of bicarbonate of soda. We have tried this plan in a number of severe cases of diabetes but have been unable to corroborate the prompt effect of glyconic acid described by Schwarz. He has written in another place that the good effects that Schwarz obtained in these cases of coma were presumably due to the large quantities of alkalies that he administered.

A number of authors, basing on recent investigations described above, have advanced the idea that in cases of acidosis the administration of fats must be reduced in order to prevent the accumulation of acetone bodies. This treatment should only be instituted if one could

be persuaded that the reasons for the exclusion of fat were cogent, for fat is of paramount importance in maintaining the nutrition of diabetics. It is, as von Noorden has said, our "sheet anchor" in all severe cases of diabetes. Although it is probable that the acetone bodies are formed from fat and although the production of acetone bodies can be increased by the administration of fat and particularly of fatty acids, we are nevertheless not justified in excluding fats from the diet of diabetics. From a number of investigations that von Noorden has performed in conjunction with Dr. Loeb and Dr. Satta in numerous cases of diabetes, it has been shown that butter, for instance, does not cause an increase of acetone bodies until quantities larger than 150 grm. a day are given. If more than this amount is administered, the total quantity of acetone bodies excreted in the urine is increased, but only by a few grm., and much less rapidly than would correspond to the increased amount of fat that is administered. Butter gives the highest values for acetone excretion of all the fats that we eat. von Noorden has called attention to the fact that this deleterious influence that large quantities of butter exercise can be reduced if the butter is first thoroughly washed with cold water, for in this way the lower fatty acids are removed and they exercise the greatest influence on the acetonuria (paper read before the Association of Naturalists in Carlsbad, 1902). If the butter is thoroughly washed, quantities as large as 180 or even 200 grm. can be given without causing any appreciable

increase in the acetone excretion and we will hardly ever be tempted to give more fat than this. The practical question, therefore, whether or not fat is to be administered is hardly touched by the interesting and important studies on the origin of acetone bodies from fat.

The most efficient means for combating acidosis in diabetes is the abundant *administration of carbohydrates.* The best plan of all, of course, is to promote an improvement in the diabetic condition in general—an improvement that is quite commonly brought about. von Noorden has repeatedly recommended allowing diabetics with much acidosis a certain amount of carbohydrate during certain periods irrespective of the fluctuations in the glycosuria that result. During the carbohydrate periods the acidosis decreases, and the external sign of this improvement is the disappearance of the ferric chloride reaction from the urine. This improvement is often maintained for a long time, for weeks or even months, after the amount of carbohydrates is gradually reduced to the old low standard. A very important method of treatment, particularly in severe and obstinate cases of acidosis is the institution of the so-called oatmeal cure that von Noorden recently warmly recommended (Berl. klin. Wochenschrift, 1903).

Von Noorden's Oatmeal cure.—This treatment is carried out as follows: The patient for one or two weeks eats nothing but oatmeal gruel daily, 250 grm. of oat flour, 250 to 300 grm. of butter, 100 grm.

of Roborat or of some other vegetable albumen; this mixture is prepared as a soup and given at intervals of two hours. It is a remarkable fact that on this diet the excretion of sugar almost without exception falls below the quantity that was excreted on a mixed diet free from carbohydrates. We shall not enter into an elaborate discussion of this theoretically and practically important fact and refer for the details to the article by von Noorden on the Dietetic Treatment of Diabetes in Von Leyden's Handbook of Dietetic Therapy (Second Edition 1903) and the fourth edition of his monograph on Diabetes that will presently appear. We shall only mention the fact in this place that notwithstanding the administration of such exceptionally large quantities of butter, the excretion of acetone falls rapidly, so that in two or three days the total acetone secretion is about one-tenth of what it was before. If one resumes the ordinary diabetic diet afterwards, that is, after the acidosis has been done away with, one must be very careful to increase the quantity of food albumen very gradually, for otherwise the acidosis may suddenly return. It requires a certain amount of skill and experience to gradually resume the old diet without causing such a relapse. It is absolutely necessary to resume the old diet, because no patient can stand the monotony of the oatmeal treatment for any length of time. Von Noorden mentions a number of cases in which the acidosis was cured so thoroughly that for months afterwards only very small quantities of acetone were excreted in the

urine. Such brilliant results, however, constitute exceptions. As a rule this much is attained; that all immediate danger from the acidosis is removed and the degree of acidosis remains below the danger point for weeks and months. This method has been employed in many cases of severe and very severe acidosis in von Noorden's clinic and the results have been excellent, so that we feel justified in declaring this treatment to be the best means at our disposal to-day for combating severe degrees of acidosis and for averting impending diabetic coma. The method is better than the milk cure that von Noorden himself formerly recommended in incipient coma and it is better than the potato cure of Mossé.

The Administration of Alkalies.—The second means that we possess for combating acidosis is to disintoxicate the poisonous acids and to prevent their accumulation in the blood. Both these objects can be accomplished by the abundant administration of alkalies. Although the favorable effect of alkalies in diabetes mellitus has been appreciated for a long time (Carlsbad, Neuenahr, Vichy, etc.) the great importance of really large doses of alkali was first emphasized by Stadelmann, who recommended alkali therapy particularly in the treatment of the diabetic acidosis that he discovered. Alkali therapy is intended to meet two different indications, as follows: first, the administration of fixed alkali protects the bases of the organism proper (sodium, potassium, calcium, magnesium, etc.) It does this by combining with a large quantity of

pathological acids that are circulating in the blood and tissues, particularly with oxybutyric acid. It is true that the greater number of affinities of this acid are saturated with the ammonia radicals that are liberated from the disintegration of the proteid molecules and that are prevented from forming urea by forming solid combinations with oxybutyric acid. The amount of ammonia, however, that is liberated from the proteids is not sufficient to satisfy all the acid affinities, and as a result the excess of free acid combines with some of the fixed bases of the body, so that the organism is in this way deprived of necessary earthy alkalies (Van-Ackeren, D. Gerhardt). This reduction of the alkalies of the body is in a certain sense synonymous with acidosis. The alkalies that are administered medicinally combine with the acids and in this way protect the alkali of the organism proper, so that in this sense they act as disintoxicants. The second effect of the alkali is essentially a natural sequence of the first. It is known that oxybutyric acid combined with sodium is much more readily excreted through the kidneys than the free acid, so that in this sense the alkali bears the acid with it and rids the body of the poison. In nearly every case of diabetes in which the oxybutyric acid and the other acetone bodies are regularly determined one will find that the administration of alkalies leads to an increase in the oxybutyric secretion during the first few days, while at the same time the excretion of acetone frequently decreases. Under these circumstances this cannot be considered an unfavorable but

on the contrary, a welcome sign. The most important period for alkali therapy is not during the beginning of coma or during pronounced coma, but early, during the period of slight acidosis. Physicians in general, unfortunately, do not consider this fact sufficiently. It is a good plan to give at least 15 grm. of sodium bicarbonate a day in every case of diabetes with a positive ferric chloride reaction. A portion of this sodium bicarbonate may be replaced by sodium citrate, particularly in cases that have a tendency to constipation. We usually give 5 grm. of citrate of soda early in the morning dissolved in a quarter of a litre of warm or cold water and in addition have the patient dissolve 10 grm. of sodium bicarbonate in a bottle of Fachinger or Vichy-Celestin water to be taken in the course of the day. The quantity of alkali is increased one-half or more according to the degree of acidosis. It is a very good plan to add a small quantity of calcium carbonate to the sodium salts (about 3 grm. a day). Calcium, it is true, has no specific action on the acidosis as Grube assumes. At the same time, it is a well known fact that diabetics who suffer for a long time from acidosis lose much of their body calcium, so that it is good treatment to replace this loss medicinally.

In order to determine whether the quantity of alkali is sufficient, the *urine must be frequently examined.* As soon as the reaction becomes alkaline we may consider this a certain sign that sufficient alkali is being administered. It is not necessary, however, to give so much that the urine becomes distinctly alkaline, and

the less alkali given the better, for an excess of alkali exercises an unfavorable influence on the stomach. Another excellent criterion is the amount of ammonia excreted in the urine. In severe cases of acidosis the ammonia excretion frequently amounts to 5 grm. and more *per diem*. As soon as this amount has been reduced to about 1 grm. a day, one may be sure that no more of the fixed alkali need be administered. Such examinations can, of course, only be performed in a well equipped laboratory and it is essential that the urine should reach the laboratory before it is decomposed, as otherwise a certain amount of ammonia is formed by putrefaction of the urine that has nothing whatever to do with metabolic changes going on in the organism.

The continued administration of fixed alkalies in acidosis that was introduced into practice by Stadelmann and is now recommended very warmly by Lépine, Naunyn, and von Noorden, is unquestionably an excellent means to combat the dangers of acid intoxication and to postpone coma for a long time.

Treatment of Diabetic Coma.—Alkali therapy has, of course, also been tried in coma itself. In this condition it is necessary to work quickly, and for this reason Naunyn has advised administering alkalies intravenously 35 to 40 grm. of carbonate of soda (not bicarbonate) are dissolved in a litre of water. With care the whole litre can be injected at once. If necessary the infusion is to be repeated. It is dangerous to inject such strong solutions of soda subcutaneously, for gan-

grene almost invariably results. Infusion into the blood stream, however, is remarkably well borne. We have repeatedly seen patients who were unconscious regain consciousness while the infusion was being performed. After the infusion of alkalies, the internal administration by mouth is the most valuable means at our disposal, and it is often possible to administer from 80 to 120 grm. of carbonate of soda a day. According to the reports published by Naunyn and by A. Magnus-Levy and observations by von Noorden it is occasionally possible to overcome coma in this way and to restore the patient to a fairly comfortable condition. Unfortunately, such cases are the exception, and as a rule the favorable results, if they are obtained at all, are in the majority of cases transitory and of very short duration. Within a few hours or half a day fate usually claims its victim.