years of age, to be fifty-two and a half fluidounces (1,552·6 c. c.), the average quantity per hour being two and one-tenth fluidounces (62 c. c.). The extremes were thirty-five ounces and eighty-one ounces (1,035 and 2,395 c. c.). The average quantity may be assumed to be about fifty-one fluidounces (1,500 c. c.). The normal range of variation is between thirty and sixty ounces (about 900 and 1,775 c. c.). The conditions which lead to a diminution in the quantity of urine usually are more efficient in their operation than those which tend to an increase; and the range below the normal standard is rather wider than it is above. More urine usually is secreted during the day than at night. The quantity of water discharged by the kidneys in the twenty-four hours is a little greater in the female than in the male; but in the female the specific gravity is lower, and the quantity of solid constituents is relatively and absolutely less (Becquerel).

The specific gravity of the urine should be estimated in connection with the absolute quantity in the twenty-four hours. Those who assume that the daily quantity is about fifty-one ounces (1,500 c. c.), give the ordinary specific gravity of the mixed urine of the twenty-four hours as about 1020. The specific gravity is liable to the same variations as the proportion of water, and the density is increased as the water is diminished. The ordinary range of variation in specific gravity is between 1015 and 1025; but without positively indicating any pathological condition, it may be as low as 1005 or as high as 1030.

The reaction of the urine is acid in the carnivora and alkaline in the herbivora. In the human subject it usually is acid at the moment of its discharge from the bladder; although at certain times of the day it may be neutral or feebly alkaline, the reaction depending upon the character of the food. The acidity may be measured by neutralizing the urine with an alkali in a solution that has previously been graduated with a solution of oxalic acid of known strength; and the degree of acidity is usually expressed by calling it equivalent to so many grains of crystallized oxalic acid.

As the result of a large number of observations made by Vogel and under his direction, the total quantity of acid in the urine of the twenty-four hours in a healthy adult male is equal to between thirty and sixty grains (2 and 4 grammes) of oxalic acid. The hourly quantity in these observations was equal, in round numbers, to between one and a half and three grains (0·1 and 0·2 gramme) of acid. The proportion of acid was found to be very variable in the same person at different times of the day. The urine contains no free acid, but its acidity under an animal or a mixed diet depends upon the presence of acid salts, of which the principal one is acid sodium phosphate, with possibly a little acid calcium phosphate.

Composition of the Urine.—Regarding the excrementitious constituents of the urine as a measure, to a certain extent, of the general process of dissimilation, it is more important to recognize the quantities of these products discharged in a definite time than to learn simply their proportions in the urine; and in the following table of composition of the urine, the absolute

quantities of its different constituents, excreted in twenty-four hours, have been given when practicable.

COMPOSITION OF THE HUMAN URINE.

Water (in 24 hours, 27 to 50 fluidounces, 800 to 1,480 c. c.—Becquerel)		967·47	to	940·36
Urea (in 24 hours, 355 to 463 grains, 23 to 30 grammes—Robin)		15·00	"	23·00
Uric acid, accidental, or traces				
Sodium urate, neutral and acid; Ammonium urate, neutral and acid (in small quantity); Potassium urate; Calcium urate; Magnesium urate	(In 24 hours, 6 to 9 grs., 0·39 to 0·58 gramme, of uric acid—Becquerel—or 9 to 14 grs., 0·58 to 0·9 gramme, of urates, estimated as neutral urate of soda)	1·00	"	1·60
Sodium hippurate; Potassium hippurate; Calcium hippurate	(In 24 hours, about 7·5 grs., 0·486 gramme, of hippuric acid—Thudichum—equivalent to about 8·7 grs., 0·566 gramme, of sodium hippurate)	1·00	"	1·40
Sodium lactate; Potassium lactate; Calcium lactate	(Daily quantity not estimated)	1·50	"	2·60
Creatine; Creatinine	(In 24 hours, about 11·5 grains, 0·745 gramme, of both—Thudichum)	1·60	"	3·00
Calcium oxalate (daily quantity not estimated)		traces	"	1·10
Xanthine		not estimated.		
Margarine, oleine and other fatty matters		0·10	to	0·20
Sodium chloride (in 24 hours, about 154 grains, 10 grammes—Robin)		3·00	"	8·00
Potassium chloride		traces.		
Ammonium chloride		1·50	to	2·20
Sodium sulphate; Potassium sulphate; Calcium sulphate (traces)	(In 24 hours, 23 to 38 grains, 1·5 to 2·5 grammes, of sulphuric acid—Thudichum. About equal parts of sodium sulphate and potassium sulphate—Robin—equivalent to 22·5 to 37·5 grains, 1·45 to 2·43 grammes of each)	3·00	"	7·00
Sodium phosphate, neutral; Sodium phosphate, acid	(Daily quantity not estimated)	2·50	"	4·30
Magnesium phosphate (in 24 hours, 7·7 to 11·8 grains, 0·5 to 0·768 gramme—Neubauer)		0·50	"	1·00
Calcium phosphate, acid; Calcium phosphate, basic	(In 24 hours, 4·7 to 5·7 grains, 0·307 to 0·372 gramme—Neubauer)	0·20	"	1·30
Ammonio-magnesian phosphate (daily quantity not estimated)		1·50	"	2·40
(Daily excretion of phosphoric acid, about 56 grains, 3·629 grammes—Thudichum.)				
Silicic acid		0·03	"	0·04
Urochrome; Mucus from the bladder		0·10	"	0·50
		1,000·00		1,000·00

Proportion of solid constituents, 32·63 to 59·89 parts per 1,000.

Gases of the Urine. (Parts per 1,000, in volume.)

Oxygen in solution	0·90	to	1·00
Nitrogen in solution	7·00	"	10·00
Carbon dioxide in solution	·45	"	50·00

Urea.—As regards quantity, and probably as a measure of the activity of the general process of disassimilation, urea—$CO(NH_2)_2$—is the most important of the urinary constituents. Regarding the daily excretion of urea as a measure of the physiological wear of certain tissues, its consideration would come properly under the head of nutrition, in connection with other substances known to be the results of disassimilation; but it is convenient to treat of its general physiological properties and some of its variations in common with other excrementitious principles separated by the kidneys, in connection with the composition of the urine.

The formula for urea, showing the presence of a large proportion of nitrogen, would lead to the supposition that this substance is one of the products of the wear of the nitrogenized constituents of the body. It is found, under normal conditions, in the urine, the lymph and chyle, the blood, the sweat, the vitreous humor, and a trace in the saliva. Its presence has been demonstrated, also, in the substance of the healthy liver in both carnivorous and herbivorous animals; and it has been shown that it exists in minute quantity in the muscular juice (Zalesky). Under pathological conditions, urea finds its way into various other fluids, such as the secretion from the stomach, the serous fluids etc.

Urea is one of the few organic substances that have been produced artificially. In 1828, Wöhler obtained urea by adding ammonium sulphate to a solution of potassium cyanate. The products of this combination are potassium sulphate, with cyanic acid and ammonium in a form to constitute urea. Ammonium cyanate is isomeric with urea, and the change is effected by a re-arrangement of its elements. It has long been known that urea is readily convertible into ammonium carbonate; and ammonium carbonate, when heated in sealed tubes to the temperature at which urea begins to decompose, is converted into urea (Kolbe).

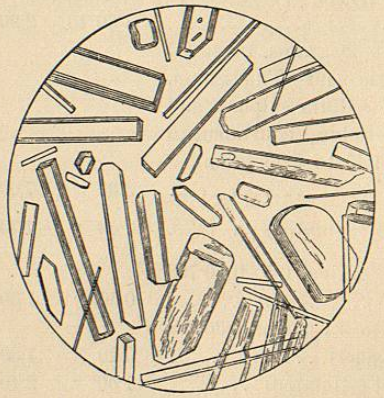

FIG. 119.—*Urea crystallized from an aqueous solution* (Funke).

Urea may readily be extracted from the urine, by processes fully described in works upon physiological chemistry; and its proportion may now easily be estimated by the various methods of volumetric analysis. It is not so easy, however, to separate it from the blood or from the substance of any of the tissues, on account of the difficulty in getting rid of other organic matters and the readiness with which it undergoes decomposition.

When perfectly pure, urea crystallizes in the form of long, four-sided, colorless and transparent prisms, which are without odor, neutral, and in taste resemble saltpetre. These crystals are very soluble in water and in alcohol, but they are entirely insoluble in ether. In its behavior with reagents,

urea acts as a base, combining readily with certain acids, particularly nitric and oxalic. It also forms combinations with certain salts, such as mercuric oxide, sodium chloride etc. It exists in the economy in a state of watery solution, with perhaps a small portion modified by the presence of sodium chloride.

Origin of Urea.—It is now universally admitted by physiologists that urea is not formed in the kidneys but pre-exists in the blood. It finds its way into the blood, in part directly from the tissues, and in part from the lymph, which contains a greater proportion of urea than is found in the blood itself. The quantity of urea in the blood is kept down by the eliminating action of the kidneys. Although a great part of the lymph is probably derived from the blood, it is not probable that the blood gives to the lymph all of the urea contained in the latter fluid; and it must be assumed that a part of the urea of the lymph passes from the tissues into the lymph-spaces and canals, although a certain quantity may be produced by the lymphatic glands.

As an outcome of many contradictory experiments and opinions on the subject, it must now be considered as proved that the liver produces urea in large quantity. If defibrinated blood be passed several times through a perfectly fresh liver, it gains urea. This observation, which was first made by Cyon, in 1870, has been repeatedly confirmed. In certain cases of structural disease of the liver, the excretion of urea is much diminished, and this substance may disappear from the urine. A number of cases illustrating this fact has been reported by Brouardel.

Assuming that urea is the most abundant and important of the nitrogenized excrementitious products—which is fully justified by physiological facts—it is difficult to avoid the conclusion that this substance represents, to a great extent, the disassimilation of the nitrogenized parts of the tissues, and necessarily the physiological wear of the muscular substance. The fact that urea exists in very minute quantity in the muscles—and some chemists state that it is absent—is probably due to its constant removal by the blood and lymph.

Uric acid, creatine, creatinine, xanthine, hypoxanthine, leucine, tyrosine and some other analogous substances are to be regarded as formations antecedent to urea, urea being the final and perfect excrementitious product.

It is convenient, in this connection, to consider the principal conditions which influence the formation and elimination of urea, or in order to compare this substance with certain constituents of food, the elimination of excrementitious nitrogen from the body.

Influence of Ingesta upon the Composition of the Urine and upon the Elimination of Nitrogen.—Water and other liquid ingesta usually increase the proportion of water in the urine and diminish its specific gravity. This is so marked after the ingestion of large quantities of liquids, that the urine passed under these conditions is sometimes spoken of by physiologists as the urina potus; but when an excess of water has been taken for purposes of experiment, the diet being carefully regulated, the absolute quantity of solid matters excreted is considerably increased. This is particularly marked as regards urea, but it is noticeable in the sulphates and phosphates, though not to any great extent in the chlorides. The results of experiments upon this point seem to show that water taken in excess increases the activity of disassimilation.

The ordinary meals increase the solid constituents of the urine, the most constant and uniform increase being in the proportion of urea. This, however, depends to a great extent upon the kind of food taken. The increase is usually noted during the first hour after a meal, and it attains its maximum at the third or fourth hour. The inorganic matters are increased as well as the excrementitious substances proper. The urine passed after food, has been called urina cibi, under the idea that it is to be distinguished from the urine supposed to be derived exclusively from disassimilation of the tissues, which is called the urina sanguinis.

It is an important question, to determine the influence of different kinds of food upon the composition of the urine, particularly the comparative effects of a nitrogenized and a non-nitrogenized diet. Lehmann has made a number of observations upon this point, and his results have been confirmed by many other physiologists. Without discussing fully all of these observations, it is sufficient to state that the ingestion of an excess of nitrogenized food always produced a great increase in the proportion of the nitrogenized constituents of the urine, particularly the urea. On a non-nitrogenized diet, the proportion of urea was found to be diminished more than one-half. The general results of the experiments of Lehmann are embodied in the following quotation:

"My experiments show that the amount of urea which is excreted is extremely dependent on the nature of the food which has been previously taken. On a purely animal diet, or on food very rich in nitrogen, there were often two-fifths more urea excreted than on a mixed diet; while, on a mixed diet, there was almost one-third more than on a purely vegetable diet; while, finally, on a non-nitrogenous diet, the amount of urea was less than half the quantity excreted during an ordinary mixed diet."

The influence of food is not absolutely confined to the period when any particular kind of food is taken, but is continued for many hours after a return to the ordinary diet.

With regard to the influence of food upon the inorganic constituents of the urine, it may be stated in general terms that the ingestion of mineral substances increases their proportion in the excretions.

There are certain articles which, when taken into the system, the diet being regular, seem to retard the process of disassimilation; or at least they diminish, in a marked manner, the quantity of matters excreted, particularly urea. Alcohol has a very decided influence of this kind. Its action may be modified by the presence of salts and other matters in the different alcoholic beverages, but in nearly all direct experiments, alcohol either taken under normal conditions of diet, when the diet is deficient or when it is in excess, diminishes the excretion of urea. The same may be stated in general terms of tea and coffee.

Influence of Muscular Exercise upon the Elimination of Nitrogen.—In all observations with regard to the influence of muscular exercise upon the elimination of nitrogen, account should be taken of the influence of diet; and those observations are most valuable which have given the proportion of nitrogen eliminated to the nitrogen of food. The observations of Fick and Wislicenus (1866) showed a diminution in the elimination of nitrogen during work; but during the time of the muscular work, no nitrogenized food was taken. The same conditions obtained in certain of the observations of Parkes. In a series of observations made in 1870 (Flint), on a person who walked 317½ miles (about 510 kilometres) in five consecutive days, the diet was normal, and the proportionate quantity of nitrogen was calculated for three periods of five days each, with the following results:

For the five days before the walk, with an average exercise of about eight miles (13 kilometres) daily, the nitrogen eliminated was 92·82 parts for 100 parts of nitrogen ingested. For the five days of the walk, for every hundred parts of nitrogen ingested, there were discharged 153·99 parts. For the five days after the walk, when there was hardly any exercise, for every hundred parts of nitrogen ingested, there were discharged 84·63 parts. During the walk, the nitrogen excreted was in direct ratio to the amount of work; and the excess of nitrogen eliminated, over the nitrogen of food, almost exactly corresponded with a calculation of the nitrogen of the muscular tissue consumed, as estimated from the loss of weight of the body. In 1876, a similar series of observations was made upon the same person by Pavy. In these observations, the subject of the experiment walked 450 miles (724·21 kilometres) in six consecutive days. During this period, the proportionate elimination of nitrogen was increased, but not to the extent observed in 1870. Similar results, although the experiments were made on a less extended scale, were obtained by North, in 1878. These results are opposed to the views of many physiologists, since the experiments of Fick and Wislicenus, who regard the elimination of nitrogen under ordinary conditions as dependent mainly upon the diet and not upon the muscular work performed. The observations of Voit, indeed, are favorable to this view.

Notwithstanding the results obtained by Fick and Wislicenus, Frankland, Haughton, Voit and others, the fact remains that excessively severe and prolonged muscular work increases the elimination of nitrogen over and above the quantity to be accounted for by the nitrogenized food taken. Actual observations (Flint, Pavy and others) are conclusive as regards this simple fact; but it is well known that muscular exercise largely increases the elimination of carbon dioxide and the consumption of oxygen. In exercise so violent as to produce dyspnœa, the distress in breathing is probably due to the impossibility of supplying by the lungs sufficient oxygen to meet the increased demand on the part of the muscular system, and the possible amount of muscular work is thereby limited.

The observations and conclusions of Oppenheim (1880) go far to harmonize the results obtained by different experimenters. Oppenheim concludes that muscular work, when not carried to the extent of producing shortness of breath or when moderate and extending over a considerable length of time, does not increase the elimination of urea; but that even less work, when violent and attended with shortness of breath, increases the discharge of urea. According to this view, moderate work draws upon the oxygen supplied to the body and at once largely increases the elimination of carbon dioxide; but the less active processes which result in the production of urea are not so promptly affected. Violent muscular work, however, or work which is excessively prolonged, consumes those parts of the tissues the destruction of which is represented by the discharge of urea. This view, if accepted, harmonizes the apparently contradictory experiments upon the influence of muscular work on the elimination of nitrogen.

The daily quantity of urea excreted is subject to very great variations. It is given in the table as 355 to 463 grains (23 to 30 grammes). This is less than the estimates frequently given; but when the quantity has been very large, it has generally depended upon an unusual amount of nitrogenized food, or the weight of the body has been above the average. Parkes has given the results of twenty-five different series of observations upon this point. The lowest estimate was 286·1 grains (18·24 grammes), and the highest, 688·4 grains (44·61 grammes).

Uric Acid and its Compounds.—Uric acid ($C_5H_4N_4O_3$) seldom if ever exists in a free state in normal urine. It is very insoluble, requiring fourteen to fifteen thousand times its volume of cold water or eighteen to nineteen hundred parts of boiling water for its solution. Its presence uncombined in the urine must be regarded as a pathological condition.

In normal urine, uric acid is combined with sodium, ammonium, potassium, calcium and magnesium. Of these combinations, the sodium urate

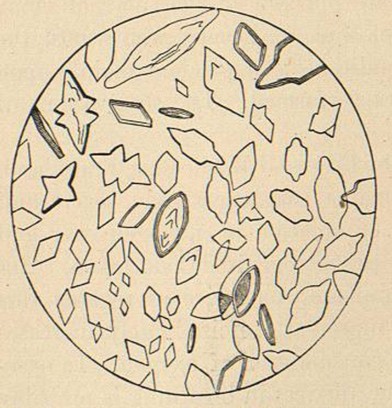

FIG. 120.—*Crystals of uric acid, obtained partly by the solution and subsequent precipitation of chemically pure acid, and partly by decomposition of the urates by nitric or acetic acid* (Funke).

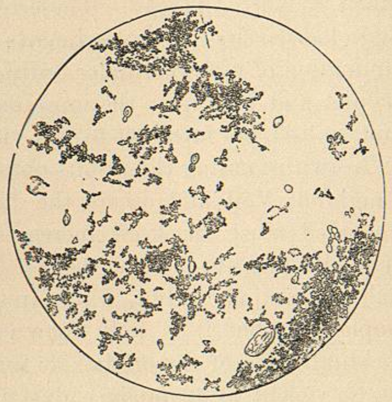

FIG. 121.—*Sodium urate* (Funke).

and ammonium urate are by far the most important, and they constitute the great proportion of the urates, potassium, calcium and magnesium urates existing only in minute traces. Sodium urate is very much more abundant than ammonium urate. The union of uric acid with the bases is very feeble.

If from any cause the urine become excessively acid after its emission, a deposit of uric acid is likely to occur. The addition of a very small quantity of almost any acid is sufficient to decompose the urates, when the uric acid appears, after a few hours, in a crystalline form.

Uric acid, probably in combination with bases, was found in the substance of the liver in large quantity by Cloetta (1858), and his observations have been confirmed by recent authorities. The urates also exist in the blood in very small quantity and pass ready-formed into the urine. The fact that the urates exist in the liver has led to the opinion that this organ is the principal seat of the formation of uric acid (Meissner). However this may be, uric acid certainly is not formed in the kidneys, but is simply separated by these organs from the blood. Meissner did not succeed in finding uric acid in the muscular tissue, although the specimens were taken from animals in which he had found large quantities in the liver. The urates, particularly sodium urate, are products of disassimilation of the nitrogenized constituents of the body.

The daily excretion of uric acid, given in the table, is six to nine grains (0·39 to 0·58 gramme), the equivalent of nine to fourteen grains (0·58 to 0·9 gramme) of urates estimated as neutral sodium urate. Like urea, the proportion of the urates in the urine is subject to certain physiological variations.

Hippuric Acid, Hippurates and Lactates.—The compounds of hippuric acid ($C_9H_9NO_3$), which are so abundant in the urine of the herbivora, are now known to be constant constituents of the human urine. Hippuric acid is always to be found in the urine of children, but it is sometimes absent temporarily in the adult. The hippurates have been detected in the blood of the ox by Verdeil and Dolfuss, and they have since been found in the blood of the human subject. There can be scarcely any doubt that they pass, ready-formed, from the blood into the urine. As to the exact mode of origin of the hippurates, there is even less information than with regard to the origin of the other urinary constituents already considered. Experiments have shown that the proportion of hippuric acid in the urine is greatest after taking vegetable food; but it is found after a purely animal diet, and probably it also exists during fasting. The daily excretion of hippuric acid is about 7·5 grains (0·486 gramme), which is equivalent to about 8·7 grains (0·566 gramme) of sodium hippurate.

Hippuric acid itself, unlike uric acid, is soluble in water and in a mixture of hydrochloric acid. It requires six hundred parts of cold water for its solution, and a much smaller proportion of warm water. Under pathological conditions it is sometimes found free in solution in the urine.

Sodium, potassium and calcium lactates exist in considerable quantity in the normal urine. They are undoubtedly derived immediately from the blood, passing ready-formed into the urine, where they exist in simple watery solution. According to Robin, the lactates are formed in the muscles, in the substance of which they can readily be detected. Physiologists have little positive information with regard to the precise mode of formation of these salts. It is probable, however, that the lactic acid is the result of transformation of glucose. The lactic acid contained in the lactates extracted from the muscular substance is not identical with the acid resulting from the transformation of the sugars. The former have been called sarcolactates, and they contain one equivalent of water less than the ordinary lactates. The compounds of lactic acid in the urine are in the form of sarcolactates (Robin).

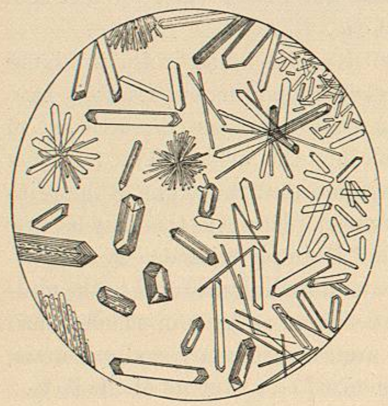

FIG. 122.—*Crystals of hippuric acid* (Funke).

Creatine and Creatinine.—Creatine ($C_4H_9N_3O_2$) and creatinine ($C_4H_7N_3O$) are probably identical in their relations to the general process of disassimilation, for one is easily converted into the other, out of the body, by very simple chemical means; and there is every reason to suppose that in the organism, they are the products of physiological wear of the same tissue or tissues. These substances have been found in the urine, blood, muscular tissue and brain. Scherer has demonstrated the presence of creatine in the amniotic fluid. By certain chemical manipulations, both creatine and creatinine may be converted into urea. Verdeil and Marcet have found both creatine and creatinine in the blood; and these substances are now regarded as excrementitious matters, taken from the tissues by the blood, to be eliminated by the kidneys.

Creatine has a bitter taste, is quite soluble in cold water (one part in seventy-five), and is much more soluble in hot water, from which it separates in

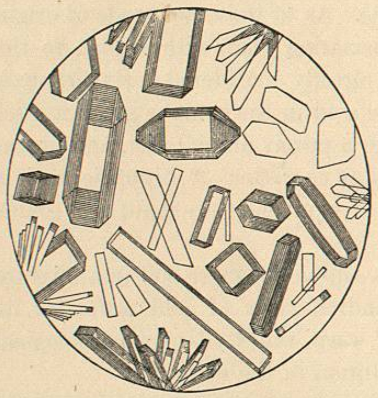

FIG. 123.—*Creatine, extracted from the muscular tissue, and crystallized from a hot, watery solution* (Funke).

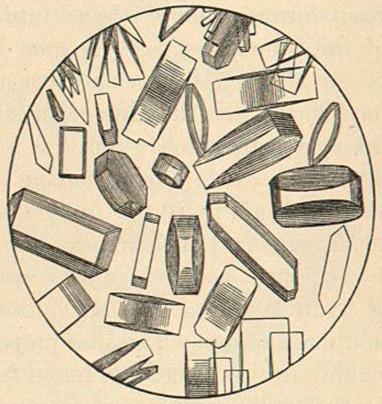

FIG. 124.—*Creatinine, formed from creatine by digestion with hydrochloric acid, and crystallized from a hot, watery solution* (Funke).

a crystalline form on cooling. It is slightly soluble in alcohol and is insoluble in ether. A watery solution of creatine is neutral. It does not readily form combinations as a base; but it has lately been made to form crystalline compounds with some of the strong mineral acids, nitric, hydrochloric and

sulphuric. When boiled for a long time with barium hydrate, it is changed into urea and sarcosine. When boiled with the strong acids, creatine loses an atom of water and is converted into creatinine. This change takes place very readily in decomposing urine, which contains neither urea nor creatine, but a large quantity of creatinine, when far advanced in putrefaction.

Creatinine is more soluble than creatine, and its watery solution has a strongly alkaline reaction. It is dissolved by eleven parts of cold water and is even more soluble in boiling water. It is slightly soluble in ether and is dissolved by one hundred parts of alcohol. This substance is one of the most powerful of the organic bases, readily forming crystalline combinations with a number of acids. According to Thudichum, creatine is the original excrementitious substance produced in the muscular substance, and creatinine is formed in the blood by a transformation of a portion of the creatine, somewhere between the muscles and the kidneys; "for, in the muscle, creatine has by far the preponderance over creatinine; in the urine, creatinine over creatine." The fact that creatine has been found in the brain would lead to the supposition that it is also one of the products of disassimilation of the nervous tissue.

The average daily excretion of creatine and creatinine was estimated by Thudichum at about 11·5 grains (0·745 gramme). Of this he estimated that 4·5 grains (0·292 gramme) consisted of creatine, and 7 grains (0·453 gramme) of creatinine.

Calcium Oxalate.—Calcium oxalate (oxalic acid, $C_2H_2O_4$) is not constantly present in normal human urine, although it may exist in certain quantity

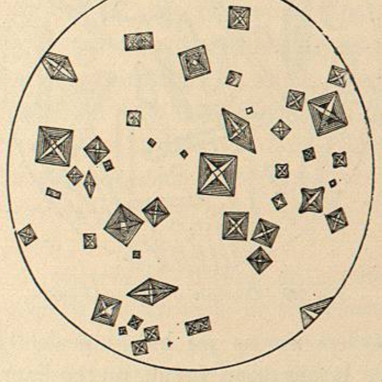

FIG. 125.—*Crystals of calcium oxalate, deposited from the normal human urine, on the addition of ammonium oxalate to the urine* (Funke).

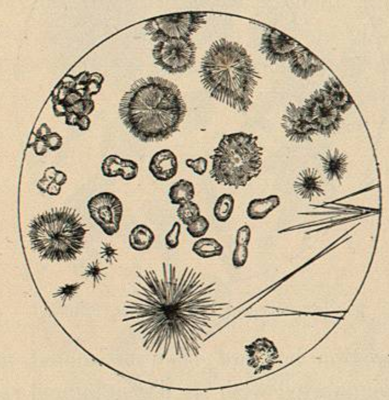

FIG. 126.—*Crystals of leucine* (Funke).

without indicating any pathological condition. It is exceedingly insoluble, and the appearance of its crystals, which are commonly in the form of small, regular octahedra, is quite characteristic. According to Neubauer, a small quantity may be retained in solution by the acid sodium phosphate in the urine. Calcium oxalate may find its way out of the system by the kidneys,