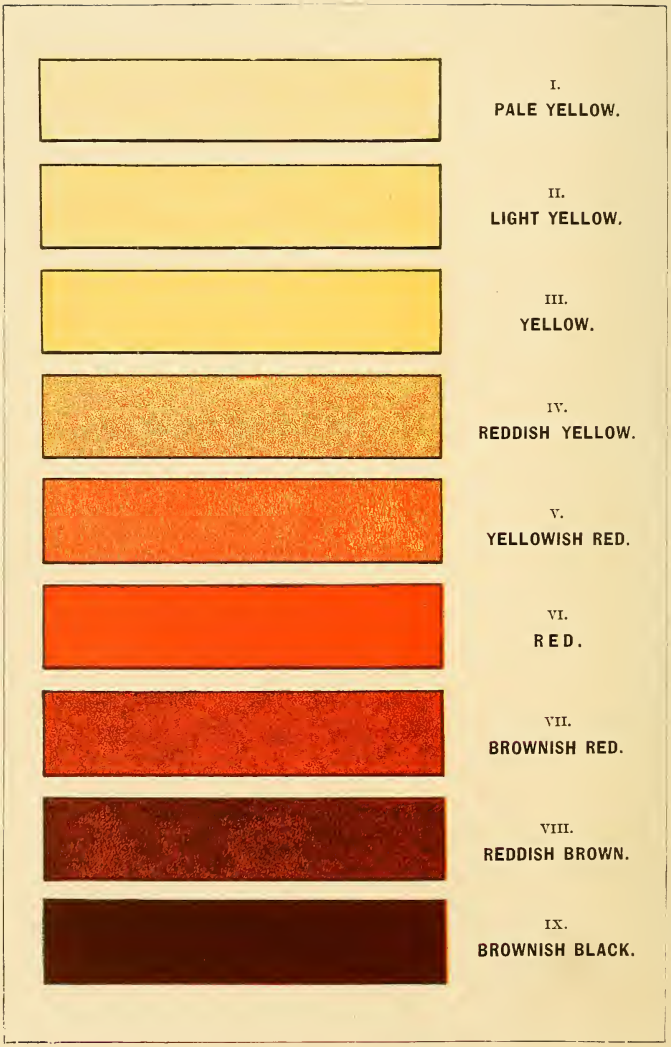

Scale of Urinary Colors, according to Vogel.

CLINICAL

EXAMINATION OF THE URINE

AND

URINARY DIAGNOSIS

A Clinical Guide for the Use of Practitioners and Students of Medicine and Surgery

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ILLUSTRATED

Second Edition, Thoroughly Revised

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TO

Edward Stickney Wood, A.M., M.D.,

PROFESSOR OF CHEMISTRY, HARVARD UNIVERSITY MEDICAL SCHOOL,

AS A SLIGHT TOKEN OF HIGHEST ESTEEM AS
A TEACHER AND FRIEND,
THIS VOLUME
IS RESPECTFULLY DEDICATED BY

THE AUTHOR.

PREFACE TO THE SECOND EDITION.

In revising this work for the second edition a special effort has been directed toward making the text complete and bringing it thoroughly up to date. Such typographical errors as have come to my notice have been corrected. Important changes have been made in Part I, especially in connection with the determinations of Urea, Uric Acid, and Total Nitrogen; and the subjects of Cryoscopy and β-Oxybutyric Acid have been given a place. Only minor changes have been made in Part II.

I am indebted to those who reviewed the first edition of the work for their suggestions, many of which have been adopted, and for their kind words of approval.

J. B. O.

262 Fifth Ave., New York City.

PREFACE.

THE design of this work is to present in as concise a manner as possible the chemistry of the urine and its relation to physiologic processes; the most approved working methods, both qualitative and quantitative; the diagnosis of diseases and disturbances of the kidneys and urinary passages.

Since most of the books on the urine at the present time are devoted almost exclusively to urinary chemistry, and since a knowledge of urinary diagnosis is obtainable only by an extended search through various works on medicine, surgery, pathology, and chemistry, I have long felt the need of a treatise which takes up in detail the subject of urinary diagnosis and the application of information furnished by careful chemic and microscopic examination of the urine.

The work naturally falls into two parts.

In Part I chemic and microscopic methods are described in detail, and numerous illustrations, many of which are original, have been introduced, thus enabling the student and practitioner who has not had special training in urinary analysis to obtain accurate results.

In Part II special attention has been paid to diagnosis, which includes our present knowledge of the character of the urine, the diagnosis and differential diagnosis of disturbances and diseases of the kidneys and urinary passages, whether they be local or general, medical or surgical; a brief enumeration of the prominent clinical symptoms of each disease; and, finally, the peculiarities of the urine in certain general diseases of the body.

My chief object, therefore, in presenting this work is to furnish the student and practitioner with a more complete clinical guide to urinary diagnosis than I have heretofore met with in a single volume.

No attempt has been made to incorporate in this volume more than a limited number of references to the literature

on the various urinary subjects that have been considered. Those references given are, for the most part, to subjects that are still under discussion, or to those that are comparatively new to medical literature.

Numerous books and original monographs have been consulted, and the views of standard authorities have been freely quoted in this work. I have endeavored in all cases to give full credit to the various writers throughout the text. If in any instances I have been remiss, I take this opportunity of thanking those who have unwittingly aided me by their researches and writings.

In conclusion, I wish to express my sincerest thanks to Dr. Edward S. Wood for the many valuable suggestions he has given me in the production of this volume.

J. Bergen Ogden.

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URINARY ANALYSIS.

INTRODUCTION.

The **urine** is an aqueous solution of organic and inorganic substances excreted and secreted by glands called the kidneys. Assuming that the reader is acquainted with the gross and minute structure of the kidneys, it remains for us to consider some of the physiologic processes which are concerned in the production of the urine. The very close relation that exists between the blood-vessels and the uriniferous tubules suggests at once the fact that the fluid called urine is the product of nature's effort to remove from the body, by way of the blood, those substances which are no longer useful to the tissues of the body; in other words, the urine is essentially a solution of waste-products of the body.

Having carefully studied the minute structure of the kidneys, we find that, unlike other secreting organs, they consist of two parts, so distinct in structure that it seems almost impossible to resist the conclusion that their functions are different, and that the mechanism by which the urine is secreted is of a double kind. The uriniferous tubules, on the one hand, with their characteristic epithelium, appear to be merely secreting structures; while, on the other hand, the Malpighian capsules with their glomeruli are structures with insignificant epithelium, strongly suggesting that their function is rather one of the nature of a filter than of a secreting structure. Such is the theory of Bowman, since he first pointed out that certain constituents of the urine only are put forth by the uriniferous tubules, which act in a manner similar to other secreting glands, and that the other constituents, including water and various soluble and diffusible salts from the blood, are apparently filtered out by the glomeruli. It is very evident from the vascular arrangement in the kidney that the

capacity of the kidney for work is closely dependent on the flow of blood through it, and this appears to be controlled largely by the vasomotor and vasodilator nerves, which are supplied by the anterior roots of the eleventh, twelfth, and thirteenth dorsal nerves.

The theory of Ludwig, based on the varying degrees of blood pressure in the glomeruli, and the elimination of certain constituents of the blood by diffusion or osmosis, can hardly be considered tenable in the light of recent physiologic research. In this theory Ludwig did not consider the importance of the renal epithelium in the secretion of urine, as has been well demonstrated by the experiments of Heidenhain, who found that by injecting a solution of sodium indigo-sulphate into the blood of an animal not only the urine became blue, but the epithelial cells lining the convoluted tubules and the looped tubes of Henle were also colored blue, while there was not the slightest trace of blue in the Malpighian bodies. By first dividing the spinal cord of an animal and then injecting the indigo solution, he also demonstrated the fact that the renal epithelium has distinct eliminative power. He found the following: That no urine reached the bladder, and the epithelium lining the convoluted tubules as well as those of Henle was stained blue the same as before; that when the animal was killed, a sufficient period after the injection, the epithelium was found to be free from coloring-matter, and the indigo compound had passed into the lumen of the tubules, where, in the absence of water from the glomeruli, it had crystallized. It often happens in some diseases of the kidneys in which the renal tubules become stripped of their epithelium that the urea and other products of the metabolism are no longer so thoroughly removed from the body, but remain in the blood, and frequently cause the symptom known as uremia, often when the watery constituent is eliminated in abundance.

It is, therefore, fair to conclude that the renal epithelial cells are normally actively engaged in the process of secretion, and that the water and some of the soluble salts of the urine are secreted largely by the glomeruli, the function of which is regulated chiefly by the varying degrees of blood pressure.

Too much can not be said regarding the importance of an accurate examination of the urine,—both chemic and

microscopic,—for it is by this means only that the condition of the kidneys—whether healthy or diseased—and their capability for work can be definitely determined. Furthermore, by the correct interpretation of the results of modern methods of urinary analysis, the variations in the body metabolism—nutrition and waste—can also be determined, and such information is often of the greatest importance to the physician in judging of the diagnosis and prognosis of disease. While it is impossible to diagnosticate *all* diseases from an examination of the urine, it is, nevertheless, a fact that an extensive disease, whether in the kidneys or not, can not exist in the human organism without showing its effect in the urine. This is more especially true in connection with diseases and disturbances of the kidneys, when any deviation in the urine from the normal furnishes us with the only reliable data concerning the nature of the diseased process.

It is, therefore, essential that the practitioner and student of medicine should become perfectly familiar with those features of the urine that are characteristic of certain diseased conditions; and also to become acquainted with those alterations of the urine found in various functional disturbances of the body, such as derangements of gastric and intestinal digestion, etc.

Nomenclature.—The student of medicine is frequently confused by the complicated nomenclature of the diseases of the kidneys. He finds that the various diseased conditions of these organs have received a variety of names, and that the terms employed indicate a number of pathologic conditions. This is partly due to the fact that a given cause does not always produce the same anatomic lesions in the kidneys, and partly to the fact that a marked lack of uniformity exists between the terms used by the pathologist and those used by the clinician in the description of any given kidney disease. What is certainly needed are more numerous and more thorough clinical observations, and, in every instance possible, a careful study of these observations in connection with the pathologic findings.

As Councilman [1] has said: "For the present, the classification of the diffuse lesions of the kidney must be founded on the character of the anatomical lesions. A classification

[1] "American Journal of the Medical Sciences," July, 1897.

on an etiological basis is the most scientific and the simplest, but we know little or nothing of the etiology of these diseases. Various forms of disease in other organs, particularly of the heart, are often found associated with them. Bacteriological investigation has shown in many cases the presence of certain organisms in the kidney. In most cases the bacteria are found in some other lesions and in the blood, and their presence in the kidney is but a part of a general septicemia. Moreover, the same condition in the kidney may be associated with a variety of organisms, and the same organism may be associated with widely different anatomical lesions."

The nomenclature which the author has adopted in this work is calculated to be abreast with recent pathologic investigation. The term *chronic parenchymatous nephritis*, which was introduced by Virchow (1852), has been replaced by the term *subacute glomerular nephritis*. This change is based upon the fact that the lesion which was formerly thought to be confined to the epithelial constituents of the kidney has recently been found to involve chiefly the glomeruli; also because the disease is subacute rather than chronic in duration.

In the use of the word *nephritis* it must be understood that the lesions referred to are not necessarily inflammatory; while inflammatory exudation in some form is frequently present, it is safe to say that the majority of lesions of the kidneys are not inflammatory.

We shall frequently refer to *diffuse* lesions of the kidney, such as acute diffuse nephritis and chronic diffuse nephritis. By the term *diffuse* we do not mean that all parts of the kidney are equally affected. It has been demonstrated, by the study of degenerations and the effect of poisons, that in some instances the most marked changes are in the convoluted tubules, while in others they are in the loops of Henle or in the collecting tubules. All parts of the kidney are equally exposed to the action of chemic irritants, but all may not be equally susceptible. Likewise, in glomerular lesions of the kidney the accompanying degenerative lesions in the renal epithelium may be in part or wholly secondary to the lesions of the glomeruli. In other words, in diffuse lesions of the kidney various parts of the organ may be primarily or secondarily affected, but usually not all parts are affected to the same extent.

CHAPTER I.

CONSTITUENTS OF NORMAL URINE.

The complexity of the urine eliminated under normal conditions is well shown by the following classification of Hoppe-Seyler:

1. Urea and allied substances: Uric acid, allantoin, oxalic acid, xanthin, guanin, kreatinin, and thio- (sulpho-) cyanic acid.

2. Fatty and other nonnitrogenous substances: Fatty acids of the series $C_nH_{2n}O_2$; oxalic, lactic, glycerophosphoric acids; minute quantities of certain carbohydrates (?).

3. Aromatic substances: The ethereal sulphates of phenol, kresol, pyrocatechin, indoxyl, and skatoxyl; hippuric acid; aromatic oxyacids.

4. Other organic substances: Pigments; ferments, especially pepsin; mucous and humous substances; kynurenic acid.

5. Inorganic salts: Chlorides of sodium and potassium; potassium sulphate; sodium, calcium, and magnesium phosphates; silicic acid; ammonia compounds, and calcium carbonate.

6. Gases: Nitrogen and carbonic acid.

Quantitative Composition of Normal Urine.—A number of estimations of the constituents of normal urine have been made, but the following table by Parkes gives the most accurate determination thus far known:

AMOUNTS OF URINARY CONSTITUENTS ELIMINATED IN TWENTY-FOUR HOURS (PARKES).

Constituents.	By an Average Man Weighing Sixty-six Kilograms.	Per Kilogram of Body-weight.
Water	1500.00 grams.	23.000 grams.
Total solids	72.00 "	1.100 "
Urea	33.18 "	0.500 "
Uric acid	0.55 "	0.008 "
Hippuric acid	0.40 "	0.006 "

AMOUNTS OF URINARY CONSTITUENTS ELIMINATED IN TWENTY-FOUR HOURS (PARKES).—(*Continued.*)

Constituents.	By an Average Man Weighing Sixty-six Kilograms.	Per Kilogram of Body-weight.
Creatinin	0.91 grams.	0.014 grams.
Pigment and other organic substances	10.00 "	0.151 "
Sulphuric acid	2.01 "	0.030 "
Phosphoric acid	3.16 "	0.048 "
Chlorine	7–8.00 "	0.126 "
Ammonia	0.77 "	. .
Potassium	2.50 "	. .
Sodium	11.09 "	. .
Calcium	0.26 "	. .
Magnesium	0.21 "	. .

Yvon and Berlioz [1] have carefully studied the urines of both male and female, and have constructed the following comparative table, which includes the amounts of some of the more important urinary solids, excepting chlorides:

	Male.		Female.	
Quantity (per diem)	1360	c.c.	1100	c.c.
Specific gravity	1022	grams	1021	grams
Urea (per liter)	21.5	"	19.0	"
" (per diem)	25.6	"	20.5	"
Uric acid (per liter)	0.5	"	0.55	"
" " (per diem)	0.6	"	0.57	"
Phosphoric acid (per liter)	2.5	"	2.4	"
" " (per diem)	3.2	"	2.6	"

Collection of Urine for Analysis.—The whole quantity of urine for twenty-four hours should, in all cases, be collected, thoroughly mixed, and carefully measured. If the entire secretion for twenty-four hours can not be conveniently submitted for analysis, a sample (from four to eight ounces) of the *mixed* urine, together with a statement of the quantity eliminated in twenty-four hours, will suffice.

A four or five pint bottle, *perfectly clean*, is perhaps the most convenient receptacle for the urine during its collection. The bottle should be well corked after each addition of the urine, and should stand in a cool place. The urine should never be collected or allowed to stand in an open or, above all, in an unclean vessel. Every effort should be made to avoid the introduction of particles of dust, fecal matter, expectorated matter, and the like, all of which seriously interfere with the subsequent analysis of the urine.

[1] "Lancet," vol. II, 1888, p. 629.

It should be borne in mind that the urine begins to undergo the process of decomposition within a few hours after it has been voided, although the changes are usually very slight and unimportant, providing the urine is kept cool. In order, however, to guard against decomposition of the urine during its collection, it is advisable to put into the bottle *one ounce of a cold saturated aqueous solution of boric acid* (about four per cent.), or *two or three drops of formalin* (not more[1]); stopper tightly, and then add the urine immediately after each micturition. The ounce of boric acid solution is to be deducted from the total quantity of urine when it is measured.

A convenient time to begin to save the urine is at 7 A. M. At that hour, or such other time as may be decided upon, the bladder should be emptied, and the urine thrown away; then all the urine voided in the subsequent twenty-four hours, including the amount of urine in the bladder at 7 A. M. the next day, will represent the total quantity for twenty-four hours. It is often important to collect the *day* and *night* urine separately; in such cases the urine voided between 7 A. M. and 7 P. M. is to be placed in one bottle, and that voided between 7 P. M. and 7 A. M. in another bottle, carefully labeling each.

For the *qualitative examination* a single specimen of urine, the product of one micturition, may be collected. Since there is a marked variation in the urine at different times of day, a specimen should be taken at a time when the urine is most likely to contain the largest proportion of morbid elements—*i. e.*, about midday or between three and four hours after a meal. For the purpose of comparison such a sample should, however, always be accompanied by another specimen collected in the morning on rising—*i. e.*, at a time when the urine contains the smallest proportion of abnormal elements. As previously indicated, the urine should always be poured into a *perfectly* clean bottle, and should be submitted for examination in a perfectly fresh condition,—that is, before decomposition has begun,—since the morphologic elements, such as casts, epithelium, etc., in a urine that has decomposed may dissolve or become so altered that they are beyond recognition.

[1] When more than two or three drops of formalin are added to from one pint to one quart of urine, a peculiar crystalline (?) precipitate is apt to be thrown down; this compound is supposed to consist of formalin and urea.

PHYSICAL PROPERTIES OF THE URINE.

Quantity.—For a healthy adult the average quantity of urine in twenty-four hours is 1500 c.c., or about 50 fluid-ounces. The normal variation is between 1200 and 1600 c.c., according to the size, habits, and sex of the individual—for example, a female of average size usually passes less urine in twenty-hours than an averaged-size male. Furthermore, a small adult, male or female, may not eliminate more than 1200 c.c., and yet be in a state of perfect health. The habits of the person have, perhaps, the greatest influence on the twenty-four-hour quantity in health; the habitual ingestion of considerable quantities of liquids, liberal eating, and the like, may cause the quantity to reach 1600 c.c., or even more. On the other hand, exercise, free perspiration, the ingestion of very little liquid, may result in the elimination of a small quantity of urine, even below 1200 c.c.

The quantity of urine in health varies considerably with the time of day, the largest amount being passed in the afternoon, the least at night, and the mean quantity in the forenoon.

The **total quantity** of urine for twenty-four hours should be accurately measured in every case in which the urine is to be examined, and it is frequently necessary, particularly in disease of the kidneys, to measure the urine every day for a period of one, two, or three weeks, in order to ascertain the average daily quantity. Upon the total quantity depend all quantitative determinations, and, therefore, intelligent inferences as to the capability of the kidneys for work.

Diminished Quantity.—A diminished quantity of urine in twenty-four hours—that is, less than 1500 c.c.—has the following causes: (1) Small quantity of liquid taken; (2) free perspiration; (3) fever; (4) diarrhea; (5) vomiting, and the following renal disturbances and diseases: (6) most cases of active hyperemia; (7) passive hyperemia; (8) first and second stages of acute diffuse nephritis; (9) subacute glomerular nephritis; (10) toward death in all diseases.

Increased Quantity.—The causes of an increased quantity of urine in twenty-four hours are as follows: (1) Large quantity of liquid taken; (2) diuretic treatment; (3) nervous excitement and some diseases of the nervous system (frequently in hysteria, and temporarily in cerebral

hemorrhage); (4) diabetes mellitus; (5) diabetes insipidus; (6) convalescence from acute diseases in general, and the following disturbances and diseases of the kidneys: (7) convalescence from a severe active hyperemia; (8) convalescence from an acute diffuse nephritis; (9) chronic interstitial nephritis; (10) chronic diffuse nephritis; (11) amyloid infiltration.

Oliguria is the term applied to those cases in which the quantity of urine is very small, typically seen during the acute stage of an acute disease, also in those chronic diseases that are attended with extensive dropsy.

Anuria is applied to cases in which there is no urine, or when only an exceedingly small quantity is passed—in other words, complete, or almost complete, *suppression of urine*. This condition is most commonly seen shortly before death, particularly in extensive disease of the kidneys. Total, or nearly total, suppression may last several days—from five to ten.

Polyuria is a term signifying the excretion of a large quantity of urine without any reference to the quantity of total solids in twenty-four hours. **Hydruria** is a term signifying the excretion of a large amount of urine—in other words, a polyuria—with either a normal quantity or a diminution in the total solids for twenty-four hours: for example, in marked cases of chronic interstitial nephritis, the solids are notably diminished.

Obstructive suppression occurs when there is a partial or complete obstruction to the outflow of urine through the *ureters*, and is sometimes found to be due to the presence of impacted calculi in both ureters; also to the pressure of a new growth, and occasionally by valves or twists of the ureters. In a case reported by Farlow[1] obstruction was caused by a new growth of the uterine appendages, and almost complete obstruction lasted for twelve days.

Retention of urine is the result of an obstruction to the outflow of urine through the *urethra*, as by a tight urethral stricture, the presence of a calculus in the urethra, or by some mechanical obstruction in the region of the neck of the bladder.

Color. — 1. The color of the urine under **normal conditions** is straw or amber yellow. This, however,

[1] J. W. Farlow, "Boston Medical and Surgical Journal," CXX, p. 333.

varies considerably even within the range of perfect health. The color may be said to vary with the dilution or concentration of the urine. Thus, a very dilute urine has a *pale* color and may be almost colorless, containing a relatively small amount of coloring-matter, and in health is usually the result of copious drinking. On the other hand, a concentrated urine usually has a *high* color, contains a relative excess of the normal coloring-matter, and is seen when too little water is taken, also after free perspiration and vigorous exercise. It is evident, therefore, that in health the color may range from a very pale or watery color through the yellows to a high or deep red. For practical purposes the color may be termed *pale*, *normal*, and *high*, according to circumstances.

Vogel has constructed a scale of colors of the urine from nature. (See Frontispiece.) These colors are expressed as (1) pale yellow; (2) light yellow; (3) yellow; (4) reddish-yellow; (5) yellowish-red; (6) red; (7) brownish-red; (8) reddish-brown; (9) brownish-black. Vogel classifies these colors into groups of three; the first three being yellow, the second three being red, and the last three brown or black. In applying the chart the urine should first be filtered if not already perfectly transparent. It should then be poured into a glass vessel at least three or four inches in diameter, and examined by transmitted light. This color chart is of considerable value as a means for comparison.

2. (*a*) Under **pathologic conditions** there is a greater variation than in health, the color being due either to an increase or diminution of the normal pigments, or to the addition of one or more pathologic coloring-matters. Very *pale* urines are usually attended with an increased quantity of urine, as in chronic interstitial nephritis, chronic diffuse nephritis, amyloid infiltration, well-advanced convalescence from acute nephritis, diabetes mellitus, and diabetes insipidus. On the contrary, the urine may have a pale color with a *diminished* quantity of urine, as in the inactive stage of subacute glomerular nephritis, and in certain chronic affections elsewhere in the body, particularly those accompanied by marked diminution in the normal solids in the urine.

The urine may have a *normal* color in certain pathologic conditions, particularly in active hyperemia of the kidneys,

frequently in the early stage of chronic interstitial nephritis, and rarely in subacute glomerular nephritis. Occasionally, in diabetes mellitus when the quantity of urine is increased to three or four liters, the color is normal, the result of an *absolute* increase of the coloring-matters.

Urines having a *high* color are almost invariably seen in the early stage of acute disease, also usually in active and passive hyperemia of the kidneys, active stage of subacute glomerular nephritis, and in certain diseases elsewhere in the body, notably liver diseases, acute articular rheumatism, and frequently in cases of chronic rheumatism and chronic gout.

From the foregoing it is seen that, either in health or disease, the urine may be *pale*, *normal*, or *highly colored;* consequently, as far as the color *alone* is concerned, only negative inferences can be deduced concerning the existing pathologic condition.

(*b*) A *dark* or *smoky* urine should always be recognized, for it invariably indicates the presence of an abnormal pigment. Great care should be taken not to confound a dark color with a high color. This abnormal pigment is most commonly found to be decomposed blood pigment (methemoglobin or hematin), although it is frequently seen after *carbolic acid* has been taken, and occasionally after its use as an external application. It is also occasionally seen after the use of *phenol* compounds, especially certain drugs, such as salol (when taken in large doses), guaiacol, etc. A urine after the ingestion of phenol is usually normal in color when passed, but on standing exposed to the air soon becomes dark, and may, if allowed to stand a still longer time, become almost black—the result of the decomposition product of the phenol (hydrochinone). A urine containing bile pigment in the form of bilirubin often has a dark color; when such a urine is shaken, the foam will be found to have a decided yellow or greenish-yellow color, and as the urine stands exposed to the air, it soon takes on a greenish, and if much bile is present a marked green, color. The presence in the urine of an abnormal pigment called *melanin* may cause a dark urine; the freshly passed urine usually has a normal color, but on standing exposed to the air it gradually grows darker from above downward, due to the slow oxidation of the chromogen,—melanogen,—which results in the pigment

melanin. *Alkapton*,[1] which has a strong affinity for oxygen, produces a dark-colored urine. The urine is usually normal, or high in color, when passed, but on standing exposed to the air rapidly absorbs oxygen, and a dark color results.

(*c*) A *black* urine is generally produced by unusually large amounts of those substances which cause a dark or smoky urine, particularly methemoglobin, melanin, and alcapton.

(*d*) A *bloody* urine indicates the presence of normal blood and its pigment, oxyhemoglobin. A urine which has a slightly bloody tint should always be distinguished from one having a high color.

(*e*) A *blue* urine is of very rare occurrence. It is due to the presence of free indigo, a result of the decomposition of the indoxyl, which, in all such instances, is present in enormous quantity. Blue urine has been seen in cholera and rarely in typhus fever. When methylene-blue is taken into the stomach, it is absorbed and eliminated in the urine, to which it gives a marked blue or green color.

(*f*) Urines having a *greenish tint* are occasionally seen, particularly after the use of an abundant quantity of milk, also in the inactive stage of a subacute glomerular nephritis, chronic diffuse nephritis, amyloid infiltration, and in some diabetic urines with a high percentage of sugar. As previously mentioned, a urine containing bile may, after the bilirubin has become oxidized, have a marked green color.

(*g*) The urine frequently has an abnormal color after the ingestion of certain *vegetable substances*, such as santonin, which imparts a yellow color, and rhubarb and senna, which cause a brown or reddish color.

The following table of Halliburton[2] shows the nature and origin of the chief variations in tint:

Color.	Cause of Color.	Pathologic Condition.
Nearly colorless.	Dilution or diminution of normal pigments.	Various nervous conditions, hydruria, diabetes insipidus, granular kidney.
Dark yellow to brown-red.	Increase of normal or occurrence of pathologic pigments.	Acute febrile diseases.
Milky.	Fat globules.	Chyluria.
	Pus corpuscles.	Purulent disease in urinary tract.

[1] For further information concerning alkapton see Neubauer u. Vogel, "Analyse des Harns," Bd. I, 1898, S. 243, 245; A. E. Garrod, "Lancet," Nov. 30, 1901.

[2] "Chemical Physiology," 1841, p. 712.

Color.	Cause of Color.	Pathologic Condition.
Orange.	Excreted drugs, *e. g.*,	Santonin, chrysophanic acid.
Red or reddish.	Unchanged hemoglobin.	Hemorrhage or hemoglobinuria.
	Pigments in food (logwood, madder, bilberries, fuchsin).	
Brown to brown-black.	Hematin.	Small hemorrhages.
	Methemoglobin.	Methemoglobinuria.
	Melanin.	Melanotic sarcoma.
	Hydrochinone and catechol.	Carbolic acid poisoning.
Greenish-yellow, greenish-brown, approaching black.	Bile pigments.	Jaundice.
Dirty green or blue.	A dark blue scum on surface with a blue deposit, due to excess of indigo-forming substances.	Cholera, typhus; seen especially when the urine is putrefying.
Brown-yellow to red-brown, becomes blood-red on addition of alkalies.	Substances introduced into the organism with senna, rhubarb, and chelidonium.	

Transparency.—Freshly passed normal urine is generally a perfectly transparent fluid; as far as can be determined by inspection, it is free from solid suspended matter. After such a urine has stood a short time (one-half to four hours), however, a light flocculent cloud, consisting of mucus, cells, etc., will be found to occupy the center of the column of urine, and if the urine be not highly concentrated, it usually settles to the bottom of the urine glass. This flocculent cloud is generally not sufficient to render the urine turbid. A perfectly normal, freshly passed urine, may, however, be turbid and have a milky appearance, due to a precipitation of earthy phosphates. Such a urine is frequently seen after a hearty meal, especially following the ingestion of vegetable food, and is the result of the elimination of the alkaline salts of the food,—alkaline carbonates, —which render the urine neutral or alkaline, and precipitate the earthy phosphates; it is perfectly physiologic, and usually of short duration, lasting only two to three hours, when the urine again becomes clear and transparent. A urine turbid from phosphates may be temporarily seen after every meal; but, on the other hand, in some individuals the after-meal urine is rarely, if ever, turbid from this cause. Any urine which is permanently turbid at the time it is voided may safely be considered pathologic.

The total twenty-four-hour urine should in all cases be perfectly clear and transparent. A clear, freshly passed normal urine may, after it becomes cool, and especially if allowed to stand in a cool or cold place, become turbid by the separation of *amorphous urates*, which soon settle to the bottom of the glass and form an abundant, usually pink, sediment. This deposit of urates is most often seen in highly concentrated, although perfectly normal, urines. It may, however, be seen in the urines of disease, as in respiratory and circulatory diseases, acute febrile conditions, and also in the active stage of subacute glomerular nephritis. A deposit of amorphous urates is readily dissolved upon the application of heat.

Bacteria frequently cause a marked turbidity in urines, and especially albuminous urines which have stood some time exposed to the air. The urine furnishes a favorable medium for the growth of bacteria, and often within twelve hours from the time the urine was passed it will be rendered very turbid. Such urines do not settle well, if at all, probably owing to the constant motion of the bacteria. Furthermore, bacteria can not be removed by filtration through ordinary filter-paper, the filtrate being usually as turbid as the unfiltered urine.

A urine which has undergone *alkaline decomposition* is generally rendered turbid by both bacteria and earthy phosphates; such permanently alkaline urines should be distinguished from those temporarily alkaline (after-meal urines); the former being ammoniacal, while the latter are alkaline from fixed alkalies (absence of ammonia).

A urine containing a large amount of *pus* is invariably turbid from the pus in suspension. Purulent urines also usually contain bacteria, which are either present when the urine is passed or grow very rapidly when the urine is allowed to stand exposed to the air.

Chyle in the urine causes a milky turbidity, due to the presence of very finely divided fat. Such a urine is of rare occurrence. (See Chyluria.)

Odor.—Normal urine usually has a pleasant, aromatic odor, due, it is believed, to the presence of extremely small quantities of volatile acids—phenylic, taurylic, damaluric, and damolic acids. This aromatic odor is most marked in urines which are concentrated. The so-called "urinous odor" is due to the products of decomposition, and is a putrescent, repulsive odor, in which ammonia is plainly dis-

tinguishable; all urines, if allowed to decompose, have a urinous odor. An ammoniacal or urinous odor is only important when it is present at the time the urine is passed, thus showing that the urine has decomposed inside the body. When a urine containing a large amount of albumin or a large quantity of pus decomposes, it may evolve the odor of sulphuretted hydrogen, which is formed from the sulphur in the albuminous matter. The H_2S in ammoniacal urine combines with the ammonium to form ammonium sulphide, hence the combined odor of sulphuretted hydrogen and ammonium.

A strong odor of sulphuretted hydrogen to the urine may accompany the evacuation of an abscess, located in the region of the intestine, into the urinary tract; a purulent urine from this cause usually has also a distinct fecal odor. When urines containing cystin decompose, H_2S is evolved, formed from the sulphur in the cystin.

The urine frequently has a peculiar odor after the ingestion of certain vegetable substances and certain drugs; thus, it has a characteristic odor after eating asparagus, and an odor of violets following the inhalation of the vapor of oil of turpentine, or following its absorption from the skin or digestive tract. The absorption of terebene gives to the urine the same odor of violets. The urine has a peculiar odor after the use of copaiba, sandalwood oil, cubebs, tolu, etc.

The odor of the freshly passed urine is of very little clinical importance, excepting in those instances in which it is ammoniacal or evolves the odor of sulphuretted hydrogen.

Reaction.—The reaction of the normal, twenty-four-hour, mixed urine is always acid. This acidity is due to acid sodium phosphate (monosodic acid phosphate, NaH_2PO_4). It is believed that the monosodic acid phosphate of the urine is partly derived from a chemic combination taking place between the disodic acid phosphate (Na_2HPO_4, neutral or alkaline in reaction) in the blood, and uric acid, also in the blood, according to the following equation:

$$Na_2HPO_4 + H_2C_5H_2N_4O_3 = NaH_2PO_4 + NaHC_5H_2N_4O_3.$$

It was formerly supposed that traces of uric and hippuric acids contributed to the acidity of the urine, but such is probably not the case, as has been shown by the experi-

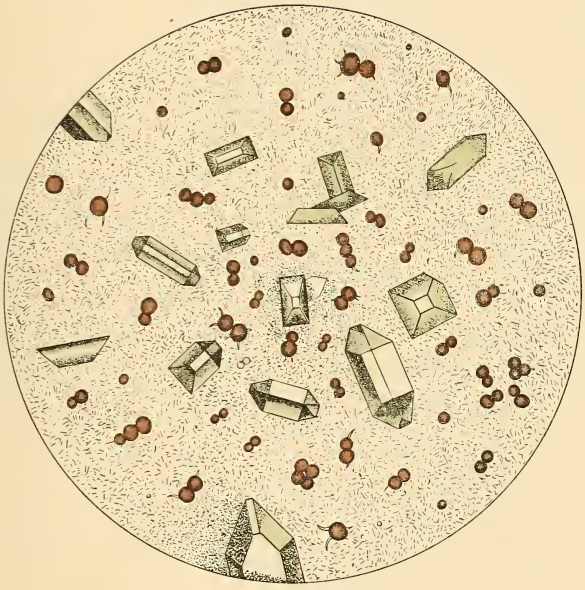
ments of Voit, Huppert, Brücke, and others, who found that both uric and hippuric acids existed in combination, the former as a urate and the latter as a hippurate.

The degree of acidity varies considerably at the different hours of the day, and particularly with the length of time before or after taking food. Usually, a specimen of urine passed at any time of day is acid, excepting after a meal, when it may be temporarily neutral or alkaline from fixed alkalies—alkaline carbonates—which are derived from the salts ingested with the food. This temporary change in the reaction is sometimes called the *alkaline tide,* beginning with a gradual diminution of the acidity, then becoming neutral or alkaline, reaching its height in from two to four hours, and finally becoming acid again. This is a physiologic condition occurring in individuals who are perfectly healthy. Such a urine is generally turbid from the deposit of earthy phosphates; the addition of a few drops of acetic acid to the urine will readily cause the turbidity to disappear entirely. The urine may be highly acid, especially after a fast,—for instance, before breakfast,—when it is usually found to be concentrated, having a high specific gravity and high color. Under normal conditions the freshly passed urine may be *faintly* acid, *normally* acid, or *strongly* acid, and in a general way it may be said that, with the exception of the after-meal urine, the degree of acidity depends largely upon the concentration—that is, if dilute, it is faintly acid, and if highly concentrated, strongly acid.

A urine that is acid when passed, upon standing exposed to the air for from six to twelve hours, often becomes more acid; this phenomenon has been termed *acid fermentation.* This increased acidity has been ascribed by Sherer to the presence of lactic and acetic acids, formed by the decomposition of the coloring-matters of the urine; the decomposing element being mucus, which acts as a ferment. This explanation has not been satisfactorily proved, however, while the increased acidity is by no means constant. A urine that has undergone this so-called acid fermentation is usually higher in color than when it was passed, and is very likely to contain crystals of acid urates or uric acid. If such a urine is allowed to stand a longer time, it begins to lose its acidity and finally becomes alkaline.

The alkalinity of the urine is due either to fixed alkalies, —sodium or potassium carbonates,—as has already been

Plate 2



Sediment of Alkaline Fermentation (after Hofmann and Ultzmann).

shown, or to the product of alkaline decomposition—ammonium carbonate formed from the decomposition of the urea. When the urea is acted upon by the *urea ferment*, it takes up two equivalents of water, and results in ammonium carbonate. Thus :

$$CH_4N_2O + 2H_2O = (NH_4)_2CO_3.$$

Such a urine has an ammoniacal or "urinous" odor, giving off free ammonia, in contradistinction to one alkaline from fixed alkalies in which no ammonia is evolved. A urine that has undergone alkaline decomposition is usually very turbid, partly from the large number of bacteria present, and partly from the deposit of amorphous phosphates of calcium and magnesium, and crystalline elements—notably ammonio-magnesium phosphate (triple phosphate), and frequently ammonium urate. (See Plate 2.) If the urine is allowed to stand undisturbed, its surface may be covered with a film, composed of bacteria and a vegetable growth, in which crystals of ammonio-magnesium phosphate and ammonium urate are often entangled. Although this alkaline decomposition is most often seen after the urine has been allowed to stand in the air (natural decomposition), it may be found to have taken place inside the body, particularly in certain chronic inflammatory processes in the bladder, into which the urea ferment has gained access ; the freshly passed urine then has a strong ammoniacal odor and alkaline reaction.

Normal urine may have an amphoteric reaction,—*i. e.*, the same urine may change blue litmus paper red, and red litmus paper blue,—because of the simultaneous presence in the urine of variable proportions of acid and neutral salts.

Causes of Diminished Acidity.—1. After a full meal, and particularly following the ingestion of a vegetable diet. In vegetarians, as in herbivora, the food contains an excess of alkaline salts with vegetable acids, such as tartaric, malic, citric, succinic, etc. These acids are converted to carbonates, which, passing into the urine, give it a neutral or alkaline reaction.

2. Following the discharge of the gastric juice from the stomach, as by vomiting or through a gastric fistula.

3. After the administration of considerable quantities of alkaline carbonates, alkaline phosphates, or caustic alkalies.

4. Decomposition of the urine (alkaline fermentation), the urea being converted into ammonium carbonate.

Causes of Increased Acidity.—1. Exclusive meat diet.

2. After hot baths and free perspiration.

3. Excessive muscular exercise with free perspiration.

4. Internal administration of acids, such as benzoic or boric acids.

5. The presence of free fatty acids resulting from pathologic conditions.

Specific Gravity.—The specific gravity of normal urine is 1021 for an average amount of 1500 c.c. in the twenty-four hours. This means that, taking distilled water at 15.5° C. (60° F.) as 1, each cubic centimeter of the urine weighs 1.021 grams ; or taking distilled water as 1000, each cubic centimeter of the urine weighs 1021 grams. The specific gravity gives the *relative* proportion of solid matter in the urine ; then, by knowing the total twenty-four-hour quantity of urine, an approximate idea of the *absolute* solids is obtained by multiplying the last two figures of the specific gravity by 2.33. (See p. 40.) Under normal conditions the specific gravity may vary between 1018 and 1025, such a variation being dependent chiefly upon the total twenty-four-hour amount of urine, the quantity and character of the food ingested, and the rapidity of tissue waste. Thus, a urine dilute from taking a large quantity of liquid may have a specific gravity of 1018, or as low as 1012 ; and, on the other hand, a concentrated urine following copious perspiration may have a specific gravity of 1025, or as high as 1030, and be passed by a perfectly healthy individual. Such variations from the normal are usually temporary ; if permanent, they are usually pathologic. Nitrogenous food, such as meat, increases the solid matter in the urine, and hence raises the specific gravity to a greater or less degree.

Under pathologic conditions there is a marked variation in the specific gravity, particularly in diseases of the kidneys, but also frequently in diseases in other parts of the body ; for example, in chronic interstitial nephritis and in diabetes insipidus the specific gravity may be as low as 1001 or 1002 ; and, again, in diabetes mellitus it may go as high as 1050. In most diseases of the kidney there is a tendency toward a low specific gravity, although it may be normal or even high. If a normal or pale colored

urine has a specific gravity of 1030 or more, the presence of sugar is strongly suggested; but, on the other hand, sugar may be present with a low specific gravity (as low as 1010); hence the importance of testing *every* specimen of urine for sugar, regardless of the specific gravity.

In albuminous urines, especially those containing one-eighth of one per cent. or more, the specific gravity is always more or less affected by the albumin in solution—that is, it is raised higher than it would be if only normal urinary constituents were present.

The specific gravity of the urine is also influenced by certain drugs: for example, following the administration of large doses of potassium acetate, the specific gravity may be 1020, the total twenty-four-hour quantity increased to 2000 c.c. or more, and the normal urinary constituents not increased. In such a case it is the presence of the increased amount of the potassium salts that affects the specific gravity.

The **urinometer** is undoubtedly the most convenient means of determining the specific gravity of the urine. This instrument is less accurate than the balance (Westphal or Mohr) and pycnometer, although for practical purposes it is sufficiently accurate if it is properly constructed. Every urinometer should be carefully tested with distilled water at 60° F. (15.5° C.), in which it should read 0 or 1000. A large number of urinometers are on the market, some of which vary several points from the standard, but those constructed by E. R. Squibb & Sons, of Brooklyn, New York, are among the most accurate. (Fig. 1.) They are very carefully standardized at 77° F. (25° C.),—a temperature much more usual than 60° F. (15.5° C.),—and with each urinometer a thermometer is furnished for temperature corrections. In ordinary work the use of the thermometer is unnecessary, since the variations by changes in temperature are usually only slight (a variation in the reading of four is the maximum error which can occur at any temperature at which urine is likely to be tested—Tyson).

A urinometer-glass should be used whenever the specific gravity is to be taken. Such a glass is usually supplied with each urinometer, but the one used by the author (Fig. 2) is strongly recommended.[1] This urinometer-glass has the

[1] Manufactured by Richard Briggs Co., 287 Washington St., Boston.

advantage of having a wide foot, perfectly parallel sides, and a well-formed lip, not usually found in the ordinary urinometer-glass. The glass made by E. R. Squibb & Sons has the added advantage of being fluted on the sides.

In case the specimen of urine is too small for the specific gravity to be taken in the urinometer-glass a sufficiently large test-tube may be used, but such a tube should not be too small in relation to the urinometer; nor should the latter be allowed to impinge against one side of the glass, lest, in consequence of the capillary attraction between the

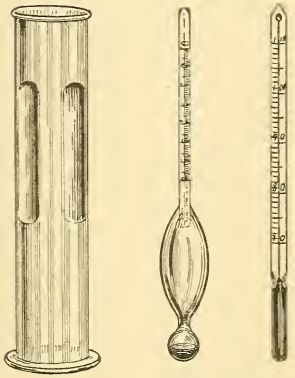


Fig. 1.—Squibb's urinometer.

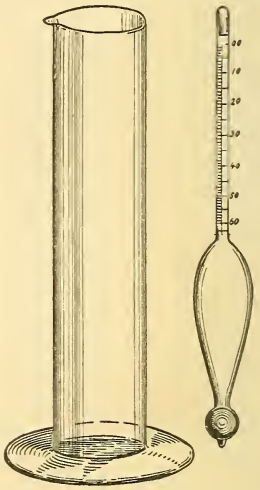


Fig. 2.—Urinometer and urinometer-glass (slightly smaller than one-half actual size).

tube and the urinometer, the latter should not sink to the proper level. The urinometer should be introduced into the tube containing the urine, allowed to find its proper level, and the reading taken; the urinometer should then be forced down into the urine, allowed to rise until it again reaches its proper level, and a second reading taken. The two readings should be exactly the same. Any discrepancy in the readings shows that in either one or the other observation the urinometer impinged against one side of the tube, from which it is readily freed by moving it gently from side to side.

Method of Taking Specific Gravity by the Urinometer.—Fill the urinometer-glass three-fourths full of urine; introduce the urinometer, pushing it down into the urine so that it just touches the bottom of the urinometer-glass, then release it and wait until it finds the correct level; when it comes to a rest, the scale is read off through the fluid from below upward, the last mark seen below the surface (at the meniscus) being the correct specific gravity. The reading should *not* be taken from above the surface of the fluid, since the capillary attraction of the fluid on the shaft of the urinometer causes an error of from one to two graduations on the scale.

If the quantity of urine is too small to fill sufficiently the cylinder, it may be diluted with enough distilled water to fill the cylinder to the required height, noting the volume added. From the specific gravity of this mixture may be calculated that of the urine. Thus, suppose it is necessary to add four times as much water as urine to enable us to use the urinometer—that is, to make five volumes—and the specific gravity of the mixed fluid is 1004, then that of the urine will be $1000 + (4 \times 5) = 1020$. Although the principle of this method is correct,—and the results must be if the data are,—the urinometers in use are not usually so finely graduated that absolute accuracy in reading is secured, while any error in reading is multiplied by the number of volumes used. Hence, it is desirable to use this method as rarely as possible, especially with urine of low specific gravity.

Solids.—The term "solids," as ordinarily applied, refers to the normal constituents of the urine present in solution, such as urea, chlorides, uric acid, phosphates, sulphates, ethereal sulphates, and various other constituents present in smaller quantities.

"Relative" and "Absolute" Solids.—The term *relative solids* applies to the proportion of solid matter to that of the water which contains it: for example, the relative quantity of urea is normally *two per cent.*—that is, two parts of urea in one hundred parts of urine. The *absolute solids* are the solids contained in the total twenty-four-hour urine, calculated in grams or grains: for example, the absolute quantity of urea is normally thirty-three grams—that is, the total quantity of urea in twenty-four hours.

The specific gravity of the urine affords a general idea of

the total solids present, but that in itself is not sufficient. It is therefore necessary, first, to obtain the *relative* proportion of the most important constituents,—as urea, chlorides, phosphates, sulphates, uric acid, etc.,—and, second, to determine the *absolute* quantities of these solids, before inferences can be deduced therefrom. Observations concerning the solids of the urine should be made upon a sample of the mixed twenty-four-hour secretion, and not on the urine of a single micturition.

Under normal conditions the total solids amount to from seventy to seventy-three grams in twenty-four hours, of which urea constitutes nearly one-half, the chlorides about one-fifth, and the phosphates about one-twenty-fifth. The absolute quantity of urea, being the most abundant solid of the urine, is of the greatest importance in judging of the capability of the kidneys for work, and also the extent of tissue metabolism in both health and disease. The absolute quantities of chlorine and phosphoric acid are also important in some cases in completing the picture of the urine.

The actual quantity of solids in the urine, particularly the total quantities of each of the most important constituents, having been ascertained, in order to make valuable deductions therefrom in health or disease it is necessary to take into consideration the weight, age, habits, diet, surroundings, and the nature of the disease in each individual case before deciding as to the extent of the increase or diminution of the solids for a given individual. For example, on an average mixed diet, a large adult male normally excretes a larger quantity of solids than a small adult male (the average for a person of 66 kilograms being from 66 to 75 grams, of which urea equals from 35 to 40 grams); and a large adult female, a larger quantity than a small adult female (the average for a person of 55 kilograms being from 60 to 70 grams, of which urea equals from 25 to 35 grams). In persons between fifty and seventy years of age the total solids fall materially in health. In healthy children, although the total solids are far below the average for an adult, they are larger in proportion to the height, age, and weight than in the adult. Much depends also on the diet—that is, a person ingesting an abundance of nitrogenous food will excrete larger quantities of solids, especially urea. On the other hand, when a

meager diet, or one consisting chiefly of milk, is taken, the solids are usually diminished.

In most chronic diseased conditions the solids are more or less diminished, whether the disease be in the kidneys or in some other organ or organs of the body, and particularly when the patient is not capable of taking or assimilating a mixed diet. The total solids are notably diminished in advanced chronic diseases of the kidney, in which the functions of these organs are greatly interfered with on account of the diseased epithelium lining the renal tubules. A marked reduction of the solids in renal disease often indicates a tendency to uremia, although this dangerous complication may arise when the solids are normal or only slightly diminished. In the early stages of acute fevers the solids may, for a short period, be normal or increased, but usually at the expense of the tissues (increased metabolism), whereas, later, they are markedly diminished. During the convalescence, however, they usually reach the normal, or are increased. In diabetes mellitus and insipidus the total solids (aside from the sugar in the former disease) are generally increased.

Determination of Total Solids.—The total solids of the urine may be determined in the following ways :

1. Take five cubic centimeters of the mixed twenty-four-hour urine in a previously dried and weighed platinum or porcelain dish. Evaporate it in a vacuum over sulphuric acid. After twenty-four hours remove this sulphuric acid and replace by fresh acid ; exhaust again, and weigh after another twenty-four hours. Deduct the weight of the dish, and the remainder gives the solids in five cubic centimeters of urine. From this the solids in the whole volume of urine are readily calculated. This method is one of the most accurate for the determination of the solids of the urine.

2. A quicker method is to evaporate to dryness over a water-bath a given quantity of urine—say twenty-five cubic centimeters—in a previously dried and weighed porcelain dish. Dry the residue by placing the dish in an oven at 110° C. (230° F.) for a few hours ; cool and weigh. This should be repeated several times until no further loss of weight occurs from drying. Subtract the weight of the dish, and the remainder will represent the solids in twenty-five cubic centimeters of the urine. This method, however, is not

very accurate, as some of the compounds in the urine are decomposed at a temperature of 110° C. (230° F.).

3. To Determine the Solids in the Twenty-four-hour Urine by Means of the Specific Gravity.—Knowing the quantity of urine passed in twenty-four hours and its specific gravity, an *approximate* estimation of the total quantity of solid matter may be readily obtained by multiplying the last two figures of the specific gravity by the arbitrary coefficient of Haeser, 2.33. This will give the approximate number of grams of solids in 1000 c.c. of the urine. For example, suppose the twenty-four-hour urine to be 1350 c.c., and the specific gravity to be 1024, then

$$24 \times 2.33 = 55.92 \text{ grams in } 1000 \text{ c.c.}$$

Since the total quantity of urine in twenty-four hours is 1350 c.c., it will contain

$$1000 : 1350 :: 55.92 : x, = \frac{55.92 \times 1350}{1000} = 75.49 \text{ grams}$$

in twenty-four hours. This result indicates that a trifle more than the average normal quantity of solids has been excreted.

While this method of arriving at the quantity of solids is not sufficiently accurate for scientific purposes, it is often of considerable value for clinical purposes. It should be borne in mind, however, that if the urine contains solid matter other than the normal constituents, the solids obtained by this method will often be found to be very high. For example, in case of diabetes mellitus they will be found to be above the normal, due to the presence of the sugar; highly albuminous urines may have increased total solids, due to the quantity of albumin present. So also, after the use of certain drugs, such as the potassium salts,—viz., acetate, citrate, bitartrate, etc.,—the solids will be considerably above the normal, because of the presence of these salts.

CHAPTER II.

ORGANIC CONSTITUENTS OF NORMAL URINE.

UREA.

CH_4N_2O.

Urea is the chief organic constituent of the urine. It is isomeric with ammonium cyanate, from which it was first prepared synthetically by Wöhler. It may also be prepared by the action of ammonia on carbonyl chloride, by hydration of cyanamide, and from ammonium carbonate.

Urea is readily soluble in alcohol and water, but insoluble in ether. It is odorless, has a salty taste, and its solution has a neutral reaction. Urea crystallizes in colorless four- or six-sided prisms with oblique ends, or, when rapidly crystallized, in delicate, white, silky needles. When treated with nitric acid, nitrate of urea—CON_2H_4,HNO_3—is formed, which crystallizes in octahedral, hexagonal, or lozenge-shaped plates. These plates are usually arranged in strata, although occasionally seen singly (Fig. 3), and are less soluble in water than urea crystals. With oxalic acid urea unites to form oxalate of urea,—$(CON_2H_4)_2$, $H_2C_2O_4 + H_2O$, —which is in the form of flat or prismatic crystals.

Other compounds of urea with acids have also been described; thus, phosphate of urea, CON_2H_4, H_3PO_4, was said by Lehmann [1] to occur in small quantities in urine; a compound of urea with uronitrotoluolic acid—with the formula $C_{14}H_{19}N_3O_{10}$—was found by Jaffé [2] in dogs' urine after the administration of orthonitrotoluol; the greater part of the urea in urine is, however, free.

Urea also forms compounds with salts, the most important being with mercuric nitrate. With this substance it forms a white precipitate having the formula $CON_2H_4 . Hg(NO_3)_2 . 3HgO$. This compound is important, as Liebig's

[1] "Chemische Centralblatt," 1866, S. 1119.
[2] "Zeitschrift für physiologische Chemie," II, 50.

volumetric process for the estimation of urea is based on its formation.

There is also a crystalline compound of urea with sodium chloride, $CON_2H_4 . NaCl + H_2O$, which may be obtained by evaporating to dryness a solution of these two substances, such as occurs, for instance, in ordinary urine.

Urea may be decomposed in various ways :

1. When heated to from 150° to 170° C., it melts and gives off ammonia ; the substance which remains is termed biuret.[1]

$$\underset{\text{Urea.}}{2CON_2H_4} - NH_3 = \underset{\text{Biuret.}}{C_2O_2N_3H_5}.$$

Biuret with caustic potash and copper sulphate gives a

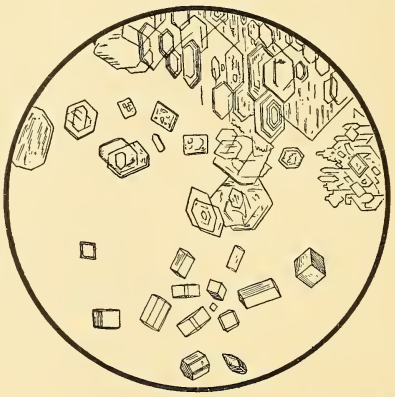


Fig. 3.—Crystals of nitrate of urea (upper half) and oxalate of urea (lower half) (after Funke).

characteristic rose-red solution. When biuret is heated, it gives off ammonia, and cyanuric acid is left—

$$\underset{\text{Biuret.}}{3C_2O_2N_3H_5} - 3NH_3 = \underset{\text{Cyanuric acid.}}{2C_3H_3N_3O_3}.$$

Cyanuric acid gives a violet solution with caustic potash and copper sulphate.

2. By means of an organized ferment, the torula, or micrococcus ureæ (which grows readily in stale urine), urea takes up water, and is converted into ammonium carbonate— $CON_2H_4 + 2H_2O = (NH_4)_2CO_3$.

[1] "Poggendorf's Annalen," LXXIV, 67.

3. By means of nitrous acid urea is broken up into carbonic acid, water, and nitrogen—$CON_2H_4 + N_2O_3 = CO_2 + 2H_2O + 2N_2$.

4. Chlorine water causes a somewhat similar decomposition—$CON_2H_4 + H_2O + 3Cl_2 = CO_2 + N_2 + 6HCl$.

5. Hypochlorite or hypobromite of soda decomposes urea in the following way: $CON_2H_4 + 3NaOBr = CO_2 + N_2 + 2H_2O + 3NaBr$. This reaction is important, as upon it is based one of the best methods of estimating the quantity of urea in urine. (See p. 50.)

Since urea is the chief organic constituent of the urine, it is a fair index of the excretion of nitrogenous matter from the body. Not all of the nitrogen, however, is excreted as urea, as very small amounts of it go out as uric acid, xanthin, hypoxanthin, sarkin, kreatinin, allantoin, etc.

Much discussion has arisen in the past in relation to the formation of urea—especially where it is formed and from what it is formed. As first pointed out by Meissner,[1] urea is probably formed chiefly in the liver. This view has been confirmed by the more recent experiments of Brouardel,[2] Roster,[3] Schroeder,[4] and Minkowski.[5] It is also probable that the spleen and lymphatic and secreting glands participate in the formation of urea. The urea passes into the blood, and is carried to the kidneys, where it is excreted. Contrary to the early belief, urea is not formed in the kidneys, or, if at all, only in minute quantities, as was first demonstrated by Prévost and Dumas,[5] who found that the formation of urea continued, accumulating in the blood and tissues, even after the complete extirpation of the kidneys. Similarly, in extensive disease of the kidneys in which there is almost complete suppression of urine, urea continues to be formed and collects in the organism. Furthermore, in support of this view we find that in extensive degenerative changes in the liver, as in acute yellow atrophy, the formation of urea is greatly diminished. On the other hand, in those diseases of the liver in which the activity of the liver-cells is greatly increased, as in diabetes mellitus, the urea formation is increased.

[1] "Zeit. f. rat. Med.," N. F., XXXI, 234.
[2] "Archiv de physiol. norm. et pathol.," [2] III, 373, 551.
[3] Quoted by Hoppe-Seyler, "Physiol. Chem.," S. 807.
[4] "Ludwig's Festschrift," 1887, S. 89.
[5] "Ann. de Chim. et de Physiol.," XXIII, 90.

The quantity of urea eliminated in twenty-four hours varies considerably, the chief cause of variation being the amount of proteid food ingested, together with the rapidity of tissue metabolism in health or disease. In a man who is in a state of equilibrium, and on an ordinary mixed diet, the quantity of urea excreted daily is between 25 and 40 grams, the average being about 33 grams (500 grains). On a diet poor in nitrogenous matter it may fall to from 15 to 20 grams ; and, on the other hand, on a diet rich in nitrogen it may rise to from 60 to 80 grams per diem. The percentage of urea varies considerably ; it may be roughly said that the average relative quantity in health is two per cent. ; but the percentage usually varies with the concentration of the urine.

Women excrete rather less urea than men ; children less, absolutely, than adults, but more in proportion to their weight. Uhle gives the following table, which represents the quantity of urea excreted in twenty-four hours *per kilogram of body-weight* at different ages :

From 3–6 years, ...	about 1	gram.
" 8–11 "	" 0.8	"
" 13–16 "	" 0.4–0.6	"
Adults, ...	" 0.37–0.6	"

From this it is seen that, per kilogram weight, children up to eleven years of age excrete about twice the quantity of urea that adults do, and after eleven years practically the same as adults.

An Increased Quantity of Urea.—(a) **In health** the absolute quantity of urea may be increased by (1) a hearty mixed diet. (2) Strenuous exercise causing increased metabolism ; and it is for this reason that the quantity of urea is greater during the day than during the night : the average proportion of the day to the night urea being as three is to two. (3) By the ingestion of ammonium compounds, particularly ammonium chloride, it having been found that practically nine-tenths of the nitrogen in the ammonium chloride is eliminated as urea. (4) By the ingestion of large quantities of water, the metabolism being increased thereby, especially when an abundance of water is taken for a short time. If this ingestion is continued for a long time, the metabolism is diminished, and hence there is a diminution in the urea. (5) Following hot baths the urea may be increased.

(b) **In disease** the absolute quantity of urea is increased (1) in the early stages of acute febrile diseases, the increase being due largely to the increased metabolism of the tissues, which, together with the ingestion of very little food, results in emaciation. One notable exception to this, however, is in acute diseases associated with increasing dropsy, as in acute nephritis; also those accompanied by exudations into other parts of the body, as in cholera; and other acute intestinal diseases in which there is marked diarrhea. (2) During the convalescence from acute diseases associated with dropsy the urea may be increased during the time that the dropsical fluid is being reabsorbed. Such an increase, however, is usually only temporary, and after all of the dropsical fluid has been absorbed the urea falls below the normal, as is the rule in convalescence from other acute diseases. (3) In intermittent fever the urea is increased before the patient has a chill, but diminished afterward. (4) In diabetes insipidus the urea is much increased absolutely (may go as high as 130 grams), the twenty-four-hour quantity of urine being very large, but the specific gravity very low. (5) In diabetes mellitus, on account of the increased metabolism, the total urea is usually above the normal. (6) In chronic interstitial nephritis, although the absolute quantity of urea is usually diminished, it may, in rare instances, be absolutely increased. This has been occasionally observed in children by the writer, where, at the autopsy, the disease was found to exist to a marked degree. (7) In chronic gout the urea may be increased to fifty or sixty grams in twenty-four hours.

A Diminished Quantity of Urea.—(a) **In health** the urea is diminished absolutely (1) whenever very little nitrogenous food is taken—seen especially in vegetarians; also in those instances in which the individual takes very little food of any kind. (2) Sometimes, following very free perspiration, the urea is diminished absolutely on account of the elimination of a certain amount of this substance by the sweat-glands. (3) In many instances of normal pregnancy the total urea is diminished. This is explained on the ground that the nitrogenous elements ingested go to nourish the fetus. The average amount of urea in normal pregnancy is about twenty grams in twenty-four hours. (4) Following the administration of small doses of quinine

(Oppenheim) the urea is low, although not markedly diminished. (5) The long-continued ingestion of excessive quantities of water results in more or less reduction in the total quantity of urea.

(b) **In disease** the urea is generally diminished, the extent of the diminution being usually dependent upon, first, the degree of diminished metabolism, and, second, the capability of the kidneys to excrete the urea. (1) In most diseases of the kidneys—especially the advanced chronic forms, such as chronic interstitial, chronic diffuse, and subacute glomerular nephritis—the urea is usually markedly diminished. In amyloid infiltration it may be normal or diminished, but usually not so much diminished as in chronic interstitial nephritis, since in the former disease the infiltration takes place about the blood-vessels, and consequently does not interfere with the secreting structure of the kidney until very late. On the other hand, in chronic interstitial nephritis the secreting portion of the kidney is affected much earlier in the disease. Not infrequently a determination of the absolute amount of urea is of considerable aid in the differential diagnosis of these two forms of Bright's disease. In the first two stages of acute nephritis the urea, absolutely, is much below the normal, especially in the first stage or at the time when the dropsy is increasing. (2) In the functional disturbances of the kidneys—active and passive hyperemias—the urea is frequently diminished, the extent of the diminution being largely dependent upon the cause of the disturbance. (3) In acute febrile diseases following the acme of the disease the quantity of urea is low, and likewise during the convalescence from these diseases, since the nitrogenous elements go to build up the tissues. (4) In all diseases attended with extensive dropsy the urea is diminished up to the time the effusion begins to be reabsorbed, when it gradually increases. (5) Shortly before death from any cause the urea is usually markedly diminished (five to six grams in twenty-four hours), more especially in chronic kidney diseases. In those cases in which the degeneration of the renal tissue is very extensive and the kidneys are not capable of excreting the urea, the elimination may take place through other glands, notably the sweat-glands. In such instances the skin, especially in the axillæ and groins, has been found to be covered with a coating of crystallized urea. (6) Extensive vomiting, and (7) marked

cases of diarrhea cause a diminution in the amount of the urea eliminated; this is particularly true in connection with extensive renal disease, a portion of the urea being eliminated by these channels. (8) In all degenerative changes in the liver there is very low urea, probably the result of the greatly reduced metabolism of the liver.

Detection.—The presence of urea may be detected in the following ways:

1. Place a drop of the urine on a watch-glass or glass slide, add one drop of pure nitric acid (the yellow nitric acid should be avoided), and allow the mixture to evaporate spontaneously in the air. If urea be present, crystals of nitrate of urea will be seen when examined with the microscope.

2. To a drop of the urine add a drop of a saturated solution of oxalic acid. If urea be present, crystals of oxalate of urea form, which, under the microscope, appear in the form of rhombic plates, or short, thick, rhombic prisms.

3. To the urine add an equal volume of sodium hypobromite or hypochlorite, and if urea be present, the evolution of nitrogen gas takes place.

4. Place a few crystals of urea in a test-tube, and heat to melting; then add a few drops of sodium or potassium hydrate and a drop or two of a dilute solution of sulphate of copper. The biuret reaction occurs, which consists of a violet or a rose-red color.

5. To a crystal of urea about the size of the head of a pin add one drop of a moderately concentrated solution of furfurol, and then a drop of concentrated hydrochloric acid, and heat. A play of colors results: a yellow, green, blue, violet, and, finally, in the course of a few minutes, a purple-violet (furfurol reaction of Schiff[1]).

Quantitative Determination of Urea. — Various methods have been suggested for the quantitative determination of urea. Of these, the three following are most suitable: (*a*) The mercuric nitrate or Liebig's method; (*b*) the hypobromite or hypochlorite method; (*c*) Mörner-Sjöqvist method.

(a) **Liebig's Method.**—If albumin be present, it must first be removed by coagulation (heat). The combination between urea and mercuric oxide, which is $(CON_2H_4)_2Hg(NO_3)_2 \cdot 3HgO$,

[1] "Berichte d. Chem. Gesellsch.," x, 773, 1887.

results in a white precipitate, insoluble in water and weak alkaline solutions. It is, therefore, necessary to prepare a standard solution of mercury, and to have an indicator by which to detect the point when all the urea has entered into combination with the mercury, and the latter slightly predominates. This indicator is sodium carbonate, which gives a yellow color with the excess of mercury, owing to the formation of hydrated mercuric oxide.

Theoretically, 100 parts of urea should require 720 parts of mercuric oxide; but practically, 772 of the latter are necessary to remove all the urea, and at the same time show the yellow color with alkali; consequently, the solution of mercuric nitrate must be of empiric strength in order to give accurate results.

The following solutions must be prepared:

1. Standard Mercuric Nitrate Solution: Dissolve 77.2 grams of red oxide of mercury (weighed after it has been dried over a water-bath), or 71.5 grams of the metal itself, in dilute nitric acid. Expel the excess of acid by evaporating the liquid to a syrupy consistence. Make up to 1000 c.c. with distilled water, adding the water gradually. This solution is of such strength that 19 c.c. will precipitate 10 c.c. of a 2 per cent. urea solution. Add 52.6 c.c. of water to the liter of the mercuric nitrate solution, and shake well; then 20 c.c. (instead of 19) = 10 c.c. 2 per cent. urea solution—*i. e.*, 1 c.c. = 0.01 of urea.

2. Baryta Mixture: This is a mixture of two volumes of solution of barium hydrate with one of solution of barium nitrate, both saturated in the cold.

Analysis.—Take 40 c.c. urine; add to this 20 c.c. of baryta mixture, and filter off the precipitate of baryta salts (phosphates and sulphates); take 15 c.c. of the filtrate (this corresponds to 10 c.c. of urine) in a beaker. Run into it the mercuric nitrate solution from a burette, until, on mixing a drop of the mixture with a drop of a saturated solution of sodium carbonate on a white tile, a pale lemon color appears. Then read from the burette the amount used, and calculate from this the percentage of urea.

Corrections.—This method approaches accuracy only when the quantity of urea present is about 2 per cent., which is about the normal percentage of urea in urine. The chlorine in the urine must also be estimated, and the quantity of urea indicated reduced by the subtraction of 1 gram of urea for every 1.3 grams of sodium chloride found. If the urine contains less than 2 per cent. of urea, 0.1 c.c. of mercuric nitrate solution must be deducted for every 4 c.c. used; if more than 2 per cent. of urea, a second titration must be performed with the urine diluted with half as much water as has been needed of the mercurial solution above 20 c.c. Suppose, then, 28 c.c.

have been used in the first titration, the excess is 8 c.c.; therefore 4 c.c. of water must be added to the urine before the second titration is made. When ammonium carbonate is present, first estimate the urea in one portion of urine, and the ammonia by titration with normal sulphuric acid in another; 0.017 gram of ammonia = 0.030 of urea. The equivalent of ammonia in terms of urea must be added to the urea found in the first portion of urine.

Modifications.—Rautenberg and Pflüger have devised modifications of Liebig's original method. Rautenberg's method consists in maintaining the urea solution neutral throughout by successive additions of calcium carbonate. Pflüger's method is as follows: A 2 per cent. solution of urea is prepared; 10 c.c. of this are placed in a beaker, and 20 c.c. of the mercuric nitrate solution are run into it in a continuous stream; the mixture is then brought under a burette containing normal sodium carbonate, and this is added with constant agitation until a permanent yellow color appears. The volume so used is noted as that necessary to neutralize the acidity produced by 20 c.c. of the mercurial solution in the presence of urea. A plate of glass is then laid on a black cloth, and some drops of a strong solution of sodium bicarbonate (free from carbonate) are placed upon it at convenient distances. The mercurial solution is added to the urine in such volume as is judged appropriate, and from time to time a drop of the white mixture is placed beside the bicarbonate, so as to touch but not mix completely. A point is at last reached when the white gives place to yellow; both drops are then quickly mixed with a glass rod, and the color disappears; further addition of mercury is then made to the urine until a drop mixed with the bicarbonate remains permanently yellow. Now is the time to neutralize by the addition of the normal sodium carbonate to near the volume found necessary in the preliminary experiment. If this is quickly done, a few tenths of a cubic centimeter of mercuric nitrate will be found sufficient to complete the reaction. If, however, much time has been lost, it may happen that, notwithstanding the mixture is distinctly acid, it gives, even after the addition of sodium carbonate, a permanent yellow, although no more mercuric nitrate be added. Under those circumstances the analysis must be repeated, taking the first titration as a guide to the quantities that are necessary. Pflüger's correction for concentration of urea is different from Liebig's, and is as follows:

V^1 = volume of urea solution + volume of sodium carbonate solution + volume of any other fluid free from urea that may be added.

V^2 = volume of mercuric nitrate solution used.

C = correction = $-(V^1 - V^2) \times 0.08$.

This formula holds good for cases in which the total mixture is less than three times the volume of mercuric nitrate solution used; with more concentrated solutions the formula gives results too high.

Liebig's method is by far the most accurate for the quantitative determination of urea, but it is too long and complicated for clinical purposes.

(b) **The Hypobromite or Hypochlorite Method.**—The principle upon which this method is based is that urea, when brought in contact with sodium hypobromite or sodium hypochlorite, is decomposed into nitrogen, carbon dioxide, and water. Thus:

$$CH_4N_2O + 3NaOBr = 3NaBr + CO_2 + N_2 + 2H_2O,$$

the volume of nitrogen disengaged being the measure of the urea. The carbon dioxide set free immediately combines with the excess of sodic hydrate in the hypobromite mixture used, and forms sodium carbonate, which remains in solution.

All quantitative determinations by this method are dependent upon the fact that one cubic centimeter of nitrogen gas at the standard temperature and pressure is equivalent to 0.0027 gram of urea; or, on the other hand, that one gram of urea at 0° C. furnishes 370 c.c. of nitrogen.

Various forms of apparatus for the application of this process have been devised, among which are those of Hüfner, Gerrard, Dupré, W. H. Greene, Charles A. Doremus, E. R. Squibb, and others. In the use of these various forms only approximate results are obtained, but the one devised by E. R. Squibb is by far the most satisfactory for clinical purposes.

Squibb's Apparatus[1] (Fig. 4).—This apparatus consists of two two-ounce bottles, *a* and *b*, each being supplied with a double-bored rubber stopper and connected by means of a rubber tube, *c*; a 2 c.c. pipette that is closed at its upper end by a nipple; a 30 c.c. graduate, *g*, into which a rubber tube, *d*, extends from bottle *b*; and a small glass plug, *e*.

Reagents.—Among the reagents that may be used for decom-

[1] This apparatus can be purchased of E. R. Squibb & Sons, Brooklyn, N. Y., or of Messrs. Eimer & Amend, 205–211 Third Avenue, New York City, at a moderate cost.

posing the urea in urine by this apparatus, the following are the most convenient and the best:

1. The Solution of Chlorinated Soda of the United States Pharmacopeia of 1840 to 1870 inclusive, but the solution of the U. S. P. of 1880 must be avoided, as it will not answer the purpose. If this solution of 1870 is not accessible when this apparatus is to be used, it may be extemporaneously made by the following formula and process from the chlorinated lime

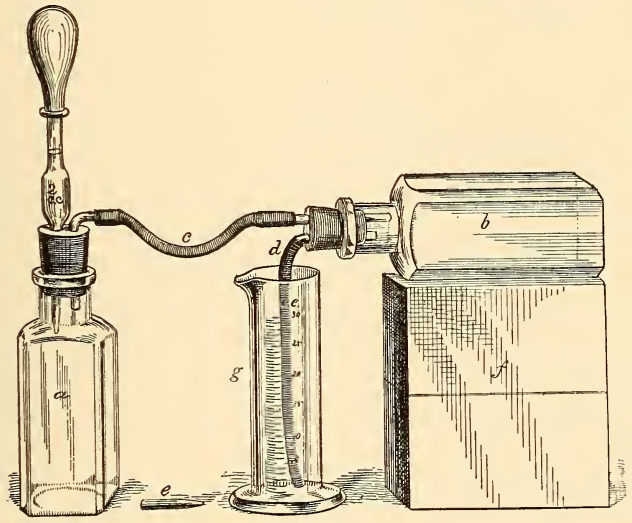


Fig. 4.—Squibb's urea apparatus, for the approximate estimation of urea in urine.

supplied with the apparatus, or from any other source. Fifteen or twenty cubic centimeters of this solution are sufficient for each assay.

2. Extemporaneous Solution of Chlorinated Soda: Take of chlorinated lime (chloride of lime or bleaching powder) 20 grams, or 318 grains; and sodium carbonate (common washing soda, or "sal soda"), 40 grams, or 636 grains. Shake the chlorinated lime in a bottle with 45 c.c. or 1½ fluidounces of water until thoroughly disintegrated. Allow the mixture to settle for a minute or two, and pour the thin portion upon a paper filter in a funnel, filtering into a bottle of about 100 c.c. capacity. Shake the thick residue remaining in the bottle with 30 c.c. or 1 fluidounce more water, and when the first portion on the filter has drained through, pour the whole of the second portion on the filter and allow this to drain through. Then dissolve the sodium carbonate in 30 c.c., or 1

fluidounce, of hot water, and add this solution to the filtrate in the first bottle. Shake the solutions well, and if the mixture gelatinizes, warm the bottle and shake until it liquefies, and then pour it upon a new filter-paper, filtering off the clear solution into a bottle marked at 100 c.c. When the filtrate has drained through, pour water into the filter until the filtrate reaches the 100 c.c. mark on the bottle. This solution is about equivalent to that of the U. S. P. of 1870 for this assay, and when recently made, 10 c.c. of it are sufficient for each assay, but when old or made from old chlorinated lime, 15 c.c. are a safer quantity.

3. Solution of Chlorinated Lime: Take of chlorinated lime ("chloride of lime") 40 grams, or 617 grains; water, a sufficient quantity. Shake the chlorinated lime well with 120 c.c., or 4 fluidounces, of water, and after the mixture has settled for a minute or two pour off the thinner portion on to a filter-paper, and filter into a bottle marked at 200 c.c., or 6⅔ fluidounces. Add 80 c.c. more water to the thick residue of the chlorinated lime, again shake well, and pour the whole upon the filter after the first portion has nearly all drained through. When the second portion has drained through, pour water on the residue in the filter until the filtrate reaches the 200 c.c. mark on the bottle. Then cork the bottle and shake it, label it, and date the label.

For the decomposition of urea this solution is the best of all reagents yet tried. It is very efficient when a month old, but how much longer it will retain its efficiency is not known. Its reaction with the urea is very prompt, and is divided into two stages of very active reaction, which are usually from one to three minutes apart. Then the end reaction is fairly sharp. The whole time of shaking is usually not over six minutes, and a warm bath is not needed. Even when made from 18 per cent. chlorinated lime, 10 c.c. of this solution are quite sufficient for an assay, and, therefore, the foregoing formula yields enough for 20 assays; the bottle of chlorinated lime supplied with the apparatus contains about enough to make solution for 40 assays before it will need replenishing.

4. Solution of Sodium Hypobromite: This, as applied by the improved process of Dr. Charles Rice, is kept in two separate solutions, which are mixed shortly before using them.

(*a*) The solution of caustic soda is made by dissolving 100 grams of caustic soda in 250 c.c. of water, the resulting solution measuring about 284 c.c.

(*b*) The solution of bromine is made by carefully weighing each of the following ingredients:

Bromine	1 part.
Potassium bromide	1 "
Water	8 parts.

Dissolve the potassium bromide in the water and add it to the bromine; shake until the bromine is dissolved, when the solution is ready for use.

For the assay the bromine and the soda solutions are taken in equal measures, and are mixed near the time of using. While 2.5 c.c. of each solution with 5 c.c. of water, or 3.5 c.c. of each solution with 3 c.c. of water, are sufficient for an assay, it is better to take 5 c.c. of each solution for safety, and not dilute with water. The reaction is very prompt, and the end reaction is fairly definite and sharp, and there is no perceptible double reaction with an interval between them, as in the chlorinated lime solution, unless there is a larger dilution.

Process.—1. Provide a vessel containing enough water to immerse bottle *a*, the water being at room-temperature,—or about 18° C. (64.4° F.),—to be used as a cold bath.

2. Put one end of the short rubber tube *d* on the bent glass tube of the stopper of the bottle *b*, and slip it on the glass tube just so far that when the bottle *b* is laid on its side on its support, the free end of the rubber tube will just clear the bottom of the measuring jar, as shown in the cut.

3. Fill the bottle *b* with water at room-temperature, and put the stopper firmly in place, allowing the displaced water to escape through the tubes. Then, taking the bottle in the right hand with the forefinger over the end of the straight glass tube of the stopper, incline the bottle toward the bent glass tube, and relax the pressure of the forefinger on the end of the straight tube so that water enough may escape to completely fill the rubber tube *d*. Then with the left hand put the little glass stopper *e* in the free end of *d* and lay bottle *b*, thus filled, on its support; this requirement may be fulfilled by the lid of the box.

4. Next, put one end of the long piece of rubber tubing (*c*) on the bent glass tube of the stopper of the bottle *a*.

5. Measure out in the graduate the quantity of the reagent to be used, and having poured it into bottle *a*, rinse out the graduate-glass.

6. Dip the stopper of bottle *a* into water, and put it loosely in its place.

7. Dip the mouth of the rubber bulb of the pipette in water for lubrication, and put the bulb on the pipette nearly as far as it will go. Compress the large part of the bulb upon the pipette, and having dipped the point in the urine, relax the compression entirely. The expansion of the bulb will cause the urine to rise and fill—or nearly fill—the body of the pipette. Then, taking the body of the pipette between the left thumb and fingers while the point is still immersed in the urine, with the right thumb and forefinger applied to the rubber ring at the mouth of

the bulb, screw the bulb upward on the pipette so that the urine may slowly rise to the mark until the lower limb of the meniscus lies just above the mark. Now, when the point of the pipette is raised out of the urine, the meniscus will fall a little, and lie exactly on the mark. Then screw the bulb a little higher, so that a very little air may enter the point of the pipette, to prevent loss of the measured urine.

8. Pass the lower end of the charged pipette through the vacant hole in the stopper of bottle *a*, and then screw the stopper into its place by holding the stopper firmly, and turning the bottle upon it.

9. Then put the free end of the long rubber tube *c* on the end of the straight glass tube of the stopper of bottle *b*, thus connecting *a* and *b*.

10. Next, take out the little glass stopper *e* from the free end of the short rubber tube *d*, and allow the few drops of water that will flow to escape, seeing that the flow ceases completely.

11. Then put the empty measuring jar in its place under the tube *d*, to receive the displaced water of the process, when the preparation for the process will be complete.

12. Take the bottle *a* by the neck, between the right thumb and forefinger, and take the upper part of the pipette with the left thumb and fingers, in readiness to compress the rubber bulb, shaking the lower part of the bottle from side to side, and not up and down. During this gentle shaking compress the bulb, so as to force all the urine out of the pipette into the bottle with the reagent. Active effervescence will soon commence, and while it is active relax the compression of the bulb gradually and completely. If this be properly done, no liquid—or but a drop or two—will get into the rubber tube to be carried over into bottle *b*. Continue the shaking as long as bubbles of gas pass over into bottle *b*. If chlorinated soda solution be used as the reagent and without a warm bath, the shaking will require from twenty to thirty minutes; but with the warm bath, not more than from six to eight minutes.

13. Bottle *a* is then immersed in the cold bath, at about 18° C. (64.4° F.), for about four minutes. During this immersion the contraction in bottle *a* will draw water from bottle *b* into *a* and from the measuring jar back into bottle *b*, and when there is no longer any change in the measuring jar, the contraction is finished.

14. The bottles are removed and set aside to be prepared for a new assay; and the contents of the measuring jar are carefully read off to half a cubic centimeter, and the quantity thus obtained is noted and referred to the first column of the urea table. There the proportion of urea present is found calculated in percentage, and in grams and grains for various

TABLE OF APPROXIMATE PROPORTIONS OF UREA IN URINE, FOR CLINICAL USE.

One cubic centimeter of nitrogen gas at 0° C. (32° F.) equals 0.0027 gram of urea.

Assumed room-temperature for measurements, 18° C. (64.4° F.).

Rate of expansion, 0.003663 times the volume for each 1° C. Correction applied for 18° C. (64.4° F.) is $0.003663 \times 18 = 0.0659$ subtracted for each 1 c.c. as read off from the measuring jar, and the percentage is calculated from the corrected reading.

Thirty cubic centimeters are assumed as equal to one fluidounce, but in converting any considerable quantities from one measure to the other 29.52 c.c. should be taken as one fluidounce.

In converting measures to weights, and in using measures and weights together, an assumed specific gravity for abnormal urine is taken—namely, 1025 at 25° C. (77° F.); and 30 c.c. of urine of such specific gravity weigh 30.75 grams, and one fluidounce weighs 467.4 grains.

Four hundred and seventy-three cubic centimeters are assumed as equal to one pint, or sixteen fluidounces, and when these measures are used for urine, they are assumed as weighing 484.83 grams (1025×473) and 7478.4 grains (467.4×16) respectively.

The seventh and eighth columns must not be taken as having any definite relation to, or bearing upon, the assay, excepting when the total twenty-four-hour excretion amounts to just 1181 c.c., or 40 fluidounces, or very near to this measure, as the calculations are based upon this arbitrary quantity.

Reading of the Measuring Jar in c.c. (Corrected.)	Percentage of Urea.	Urea Contained in 30 c.c., or 1 Fluidounce, of Urine.		Urea Contained in 473 c.c., or 1 Pint, of Urine.		Urea Contained in 1181 c.c., or 40 Fluidounces, of Urine.		Limits Consistent with Ordinary Health in Adults. (Probable.)
		In Grams.	In Grains.	In Grams.	In Grains.	In Grams.	In Grains.	
4 c.c.	0.50	0.1538	2.34	2.425	37.44	6.055	93.60	. . .
5 "	0.63	0.1937	2.94	3.054	47.04	7.625	117.60	. . .
6 "	0.76	0.2337	3.55	3.685	56.80	9.200	142.00	. . .
7 "	0.88	0.2706	4.11	4.267	65.76	10.653	164.40	. . .
8 "	1.01	0.3106	4.72	4.897	75.52	12.227	188.80	. . .
9 "	1.13	0.3475	5.28	5.479	84.48	13.680	211.20	. . .
10 "	1.26	0.3875	5.89	6.110	94.24	15.255	235.60	. . .
11 "	1.39	0.4274	6.50	6.739	104.00	16.825	260.00	. . .
12 "	1.51	0.4643	7.06	7.321	112.96	18.278	282.40	. . .
13 "	1.64	0.5043	7.67	7.951	122.72	19.853	306.80	Lowest.
14 "	1.77	0.5443	8.27	8.582	132.32	21.427	330.80	. . .
15 "	1.89	0.5812	8.83	9.164	141.28	22.880	353.20	. . .
16 "	2.02	0.6212	9.44	9.794	151.04	24.455	377.60	. . .
17 "	2.14	0.6581	10.00	10.376	160.00	25.907	400.00	. . .
18 "	2.27	0.6980	10.61	11.005	169.76	27.478	424.40	. . .
19 "	2.40	0.7380	11.22	11.636	179.52	29.053	448.80	. . .
20 "	2.52	0.7749	11.78	12.218	188.48	30.505	471.20	Normal.
21 "	2.65	0.8149	12.39	12.849	198.24	32.080	495.60	. . .
22 "	2.77	0.8518	12.95	13.430	207.20	33.533	518.00	. . .
23 "	2.90	0.8918	13.55	14.061	216.80	35.107	542.00	. . .
24 "	3.03	0.9317	14.16	14.690	226.56	36.678	566.40	. . .
25 "	3.15	0.9686	14.72	15.272	235.52	38.131	588.80	. . .
26 "	3.28	1.0086	15.33	15.903	245.28	39.706	613.20	. . .
27 "	3.40	1.0455	15.89	16.484	254.24	41.158	635.60	Highest.

measures of urine. For example, if the graduate-glass contains 16 c.c. of displaced water, from the urea table it will be found that the urine contains 2.02 per cent. of urea, or 0.6212 grams in 30 c.c. of urine. (*a*) If the twenty-four-hour quantity of urine be 1500 c.c., then calculating from the percentage $\frac{1500 \times 2.02}{100} = 30.30$ grams, which represents the *approximate* number of grams of urea in twenty-four hours. (*b*) Or, calculating from the third column in the table, $\frac{0.6212 \times 1500}{30} = 31.06$ grams, which represents the *accurate* number of grams of urea in twenty-four hours.

Joslin [1] has recently pointed out that in severe cases of diabetes mellitus the amount of urea obtained by the use of Squibb's apparatus for urea (Hypobromite Method) is invariably too high; that either the acetone, β-oxybutyric acid or ammonia present in the urine has an action similar to urea. He recommends the use of Braunstein's method [2] in such cases.

Doremus Ureometer.—The apparatus as represented in figure 5 was devised by Dr. Charles A. Doremus, of New York. It is much used for rapid clinical purposes, and consists of a bulb with an upright graduated tube, and a small nipple-pipette to hold one cubic centimeter of urine. The tube is so graduated that each of the small divisions represents 0.001 gram of urea. The bulb is filled with the sodium hypobromite solution, and the apparatus inclined sufficiently to fill the upright graduated tube, and then water is added to fill the remainder of the tube and lower part of the bulb. The pipette is filled with urine to the one cubic centimeter mark, and the point carefully introduced into the bend as far as it will go, holding the graduated tube perpendicularly. The nipple is then slowly compressed to expel all of the urine, care being taken not to force air into the tube after the urine has been expelled. The pipette is then withdrawn, and after the evolution of gas is complete the number of cubic centimeters of nitrogen gas is read off, and the result multiplied by 100 in order to obtain the percentage of urea. Two forms of this apparatus are obtainable—one graduated to read fractions of a gram per cubic centimeter of urine, and the other graduated to read the number of grains of urea per fluidounce of urine.

[1] "Journal of Medical Research," vol. VI, Nov., 1901.
[2] "Hoppe-Seyler's Zeitschr. f. physiol. Chemie," 1900, XXXI.

The *Doremus ureometer as modified by Professor J. D. Hinds* (Fig. 6) has many advantages over the original form of apparatus. This instrument consists of a bulb with an upright graduated tube (*a*), the same as the original; near the lower portion of this tube is a horizontal glass connec-

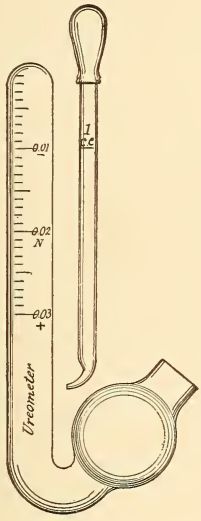


Fig. 5.—Doremus ureometer.

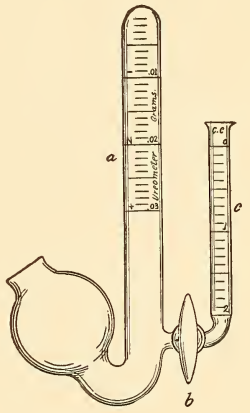


Fig. 6.—Hinds' modification of the Doremus ureometer.

tion, which is provided with a ground glass stop-cock (*b*), and which supports another upright graduated tube (*c*) with a capacity of two cubic centimeters. The bulb and upright tube (*a*) are filled with the sodium hypobromite solution in precisely the same manner as previously described. The upright tube (*c*) is then filled to the zero mark with the urine to be tested. The stop-cock (*b*) is then turned, and exactly one cubic centimeter of the urine allowed to enter tube *a* with the reagent. As soon as the evolution of nitrogen gas is complete, the number of cubic centimeters of the gas is read off, and the result multiplied by 100 in order to obtain the percentage of urea.

This form of apparatus [1] gives more exact results than the

[1] This instrument, as well as the original Doremus ureometer, can be obtained at a moderate cost from Messrs. Eimer & Amend, 205 to 211 Third Ave., New York City.

original form, since the one cubic centimeter of urine required for the test is delivered with greater accuracy, and no nitrogen gas is lost by its escape from the bulb.

(c) **Mörner-Sjöqvist Method.**—By the use of this method all of the nitrogenous constituents of the urine, except the urea and ammonia, are precipitated by means of alcohol and ether after the addition of a solution of barium chloride and barium hydrate; and finally the urea is determined in the concentrated filtrate, after driving off the ammonia, by Kjeldahl's Nitrogen Method.

Process.—Place 5 c.c. of the urine in a flask; add 5 c.c. of a saturated solution of barium chloride which contains 5 per cent. of barium hydrate; to this add 100 c.c. of a mixture of two parts of alcohol (97 per cent.) and one part of ether and allow it to stand in the closed flask for twelve hours. The precipitate is then filtered off and washed with alcohol and ether. The alcohol and ether are removed from the filtrate by distillation at about 55° C. When the fluid has become concentrated to about 25 c.c. add a little water and some calcined magnesia. Continue the evaporation down to 10 or 15 c.c., or until the vapors are no longer alkaline in reaction. Transfer the liquid to a flask by the aid of a little water, treat with a few drops of concentrated H_2SO_4, and further concentrate on the water-bath. In this concentrated liquid the total nitrogen is determined according to the method of Kjeldahl. (See below.)

The quantitative estimation of urea should be accompanied by a determination of the total nitrogen in the diet, feces, and urine, in order to be able to draw intelligent inferences regarding excretion.

KJELDAHL'S TOTAL NITROGEN DETERMINATION.

This method consists in converting all the nitrogen of organic compounds into ammonia by the use of concentrated sulphuric acid and heat. The ammonia is distilled over and collected in standard sulphuric acid.

Process.—Take exactly 5 c.c. of the filtered urine; place in a long-necked Kjeldahl digestion flask, add a drop of metallic mercury, and then treat with from 10 to 20 c.c. of strong sulphuric acid. Adjust the flask obliquely over a gas-flame, and heat gently until the vigorous action has ceased; then gradually

increase the heat until the mixture boils. After boiling for about fifteen minutes, add 10 grams of potassium sulphate and continue the boiling until the contents of the flask are clear and colorless. On cooling, wash the contents of the flask into a spacious distilling flask, thoroughly rinsing the digestion flask with water. Place some zinc shavings in the distilling flask to prevent bumping, and then add an excess of a 30 to 40 per cent. solution of caustic soda which is free from nitrates and which has previously been treated with 30 to 40 c.c. of a 4 per cent. solution of potassium sulphide. Quickly connect the flask with the condenser tube, and distil off all the ammonia, which is collected in a measured amount (not less than 25 c.c.) of $\frac{N}{5}$ sulphuric acid. In order to prevent loss of ammonia, the end of the exit tube should be below the surface of the standard acid; a bulb blown on the exit tube will prevent the regurgitation of the acid.

When the distillation is completed, the standard acid solution that has been used is titrated with $\frac{N}{5}$ caustic soda, using litmus, cochineal, methyl-orange, rosolic acid, or lacmoid as an indicator. Each cubic centimeter of the $\frac{N}{5}$ sulphuric acid corresponds to 2.8 milligrams of nitrogen.

It is, of course, essential that the reagents employed should be practically free from nitrogen, but it is desirable to make a blank experiment from time to time in order to ascertain the correction to be made for the unavoidable traces of nitrogen that may be present.

The use of mercury or its oxide hastens the destruction of the organic matter, and therefore shortens the time of digestion, which is rarely more than one hour. Potassium sulphide is used to remove all mercury from the solution, and thus prevent the formation of mercuro-ammonium compounds, which are not completely decomposed by the caustic soda. The addition of the zinc gives rise to the evolution of hydrogen and prevents violent bumping.

URIC ACID.

$C_5H_4N_4O_3$.

Uric acid ($H_2\bar{U}$, expressed also $\bar{U}$) is, in mammals, next to urea, the medium by which the largest quantity of nitrogen is excreted from the body. It is, however, in birds and reptiles the principal nitrogenous constituent of the urine.

Until recently, the theory of the formation of uric acid was that it was a product of the metabolism of the nitrogenous material ingested, and that it represented an inter-

mediate product between the nitrogenous substances and the final product, urea. The researches of Horbaczewski,[1] Hopkins and Hope,[2] Jerome,[3] and others tend to show that uric acid has an entirely different origin. It is now believed that uric acid is at least partly derived from the nucleins that form a constituent of all cell-nuclei, and which are taken into the body as food. The nucleins are capable of being split up into an albumin and nucleic acid, and it is thought that the uric acid is formed in the body from the nucleic acid through the oxidation of the xanthin or alloxur groups contained in a molecule of nucleic acid. It has been demonstrated that the ingestion of food that is rich in nucleins results in the formation and elimination of a much larger quantity of uric acid than the ingestion of an equal amount of food that is poor in nucleins. The chief evidence, however, in favor of the view that nucleins play a rôle as precursors of uric acid is based upon the results of thymus feeding. The experiments of Hopkins and Hope, however, show that extracts of the thymus gland may be prepared which contain only traces of nucleins and nucleic acid, but which, when ingested, produce the characteristically large excretion of uric acid. It, therefore, appears that some more soluble constituent of the diet acts either as a direct precursor, or as a factor in the formation of uric acid.

Our knowledge of this subject is yet too meager to warrant the conclusion that this new theory fully explains the formation of uric acid, but there can be no doubt that the nucleins (nucleic acid) play an important part in its formation.

When uric acid is referred to as a constituent of normal urine, it is never to its free state that allusion is made, but to its combinations chiefly with potassium, sodium, and ammonium, and also with calcium and magnesium; such combinations being usually known as mixed urates.

Under ordinary conditions uric acid exists in the urine in the form of urates. Since uric acid is dibasic,—that is, has two replaceable atoms of hydrogen,—two forms of salts exist—*i. e.*, acid urates of potassium, sodium, and ammonium, in which only one atom of the hydrogen is replaced

[1] "Monatsh. f. Chem.," S. 624, 1889. [2] "Journ. of Physiol.," XXIII, p. 271.
[3] "Journ of Physiol.," XXII, p. 146.

by the positive elements or radicles ; and normal (neutral) salts of the same substances, in which both atoms of hydrogen are replaced. According to Neubauer and Vogel, there are two forms of acid urates—monacid urates (biurate), and triacid urates (quadriurate or tetraurate). The normal salts are readily soluble in water at 70° F., but the acid urates are only feebly soluble, while uric acid itself is almost insoluble in water. Hence, the precipitation of the acid urates or uric acid often occurs when the urine cools, or is allowed to stand in a cold place. A urine containing a deposit of acid urates (amorphous urates) is usually more or less concentrated, and always contains a relative excess of the acid urates. If a strong acid be added to a urine that contains a relative excess of urates, they are precipitated on account of the feeble solubility of the acid urates and the almost insoluble uric acid. Also, if the urine contains an excess of normal urates, they are partially decomposed by the acid, which chemically unites with the excess of the base to form acid urates, hence their precipitation. Thus, in the nitric-acid test for albumin (performed according to instructions given on p. 124) a white zone of acid urates is frequently seen above the zone of albumin (Fig. 15), or above where the zone of albumin would be if present. It should be borne in mind that a zone of urates may be present when albumin is absent.

Pure uric acid is soluble in 16,000 parts of cold water and in 1600 parts of boiling water ; impure uric acid is more readily soluble in water than the pure. Its cold solutions do not show an acid reaction with litmus paper. Uric acid is insoluble in alcohol and ether, but dissolves in warm glycerin, from which, on cooling, it separates in crystalline form. It is insoluble in strong mineral acids, but is soluble in alkaline hydrates as well as in alkaline carbonates, phosphates, lactates, and acetates. It is more soluble in solutions of urea than in water (Rüdel).

On boiling, uric acid reduces alkaline solutions of copper ; before reduction occurs, however, a white precipitate, consisting of cuprous urate, is formed.

When uric acid is artificially decomposed, an interesting series of products results, the most important of which is urea. Whether similar changes take place in the body is still a matter of doubt.

The following is a list of the principal changes which may be brought about by various reagents:

1. When uric acid is reduced with weak sodium amalgam, two substances—xanthin ($C_5H_4N_4O_2$) and hypoxanthin or sarkin ($C_5H_4N_4O$)—may be obtained. Their formulas differ from that of uric acid in containing one or two atoms less oxygen respectively than that substance.

2. When uric acid is heated in a closed tube with hydrochloric acid, it is decomposed into glycocoll, carbonic acid, and ammonia:

$$C_5H_4N_4O_3 + 5H_2O = C_2H_5NO_2 + 3CO_2 + 3NH_3.$$

3. By the action of cold, concentrated nitric acid or lead dioxide, uric acid takes up water and oxygen, forming alloxan and urea:

$$\underset{\text{Uric acid.}}{2C_5H_4N_4O_3} + 2H_2O + O_2 = \underset{\text{Alloxan.}}{2C_4H_2N_2O_4} + \underset{\text{Urea.}}{2CON_2H_4}.$$

$$\underset{\text{Alloxan.}}{2C_4H_2N_2O_4} + O_2 = \underset{\text{Parabanic acid.}}{2C_3H_2N_2O_3} + 2CO_2.$$

$$C_3H_2N_2O_3 + H_2O = \underset{\text{Oxaluric acid.}}{C_3H_4N_2O_4}. \quad \text{By boiling} =$$

$$C_3H_4N_2O_4 + H_2O = \underset{\text{Oxalic acid.}}{H_2C_2O_4} + \underset{\text{Urea.}}{CH_4N_2O}.$$

Alloxan, when boiled with a strong alkali, takes up water and is decomposed, forming mesoxalic acid and urea:

$$\underset{\text{Alloxan.}}{2C_4H_2N_2O_4} + 4H_2O = \underset{\text{Mesoxalic acid.}}{2C_3H_2O_5} + \underset{\text{Urea.}}{2CON_2H_4}.$$

On oxidation, mesoxalic acid forms oxalic and carbonic acids:

$$2C_3H_2O_5 + O_2 = 2C_2H_2O_4 + 2CO_2.$$

Thus, it is seen that in three steps the ultimate products of uric acid are urea, oxalic acid, and carbonic acid.

4. There is another way in which the same three ultimate products are obtained, but the intermediate step in the process is not the formation of alloxan, but of another somewhat similar substance called allantoin. This process is interesting, as allantoin is in fetal life one of the products of nitrogenous metabolism, and it is thus possible that some sort of change, such as can be produced artificially, occurs in embryonic life.

Uric acid when oxidized with potassium permanganate (care

being taken that the temperature does not rise) takes up water and oxygen, forming allantoin and carbonic acid:

$$\underset{\text{Uric acid.}}{2C_5H_4N_4O_3} + 2H_2O + O_2 = \underset{\text{Allantoin.}}{2C_4H_6N_4O_3} + 2CO_2.$$

The allantoin crystallizes out in about twenty-four hours. By subjecting allantoin to the action of baryta water, hydrolysis and oxidation again take place, and urea and oxalic acid are formed:

$$\underset{\text{Allantoin.}}{2C_4H_6N_4O_3} + 4H_2O + O_2 = \underset{\text{Urea.}}{4CON_2H_4} + \underset{\text{Oxalic acid.}}{2C_2H_2O_4}.$$

5. The following decompositions are interesting, as the murexide test is the chief characteristic test for uric acid.

By oxidation with nitric acid, alloxan and urea are formed:

$$2C_5H_4N_4O_3 + 2H_2O + O_2 = 2C_4H_2N_2O_4 + 2CON_2H_4.$$

By heating or by electrolysis, alloxan splits into alloxantin, parabanic acid, and carbonic acid:

$$\underset{\text{Alloxan.}}{3C_4H_2N_2O_4} = \underset{\text{Alloxantin.}}{C_8H_4N_4O_7} + \underset{\text{Parabanic acid.}}{C_3H_2N_2O_3} + CO_2;$$

and on treating alloxantin with ammonia the purple color due to murexide or purpurate of ammonia appears:

$$\underset{\text{Alloxantin.}}{C_8H_4N_4O_7} + 2NH_3 = \underset{\text{Murexide.}}{C_8H_8N_6O_6} + H_2O.$$

Since uric acid exists in combination as urates, it is not ordinarily found in a free state. It may, however, be deposited in the urine in crystalline form, either while in the body or after the urine has been voided. It may then be seen as a deposit of minute reddish crystals, or, more rarely, as reddish sand or gravel.

Uric acid crystallizes in the form of yellow or yellowish-red crystals of a variety of shapes—rhombic and rectangular prisms, whetstone-, barrel-, wedge-, club-, diamond-shaped, and as rosettes. (Plate 3.) The diamond-shaped crystals usually either have a very faint yellow tint or are, not infrequently, perfectly colorless.

Crystals of uric acid and those of its salt,—ammonium urate,—together with those of hippuric acid and leucin, constitute the only crystalline sediments of the urine colored yellow or yellowish-red.

There are certain conditions of the body in which, as a result of overfeeding and consequent sedentary habits, and in some cases from hereditary influences, the oxidation

changes in the body are lessened, and uric and oxalic acids are formed in greater proportion to urea than under normal conditions.

Where is Uric Acid Formed?—Two different views upon this subject have been advanced : (1) That it is formed in the tissues, especially in the liver and spleen, and merely excreted by the kidneys ; (2) that the kidneys not only excrete, but also constitute the seat of formation of, uric acid. The former view (1) is most generally held, and is supported by the following facts : (*a*) Under normal conditions uric acid is found in traces in the blood. (*b*) After extirpation of the kidneys it continues to be formed. (*c*) The secretion

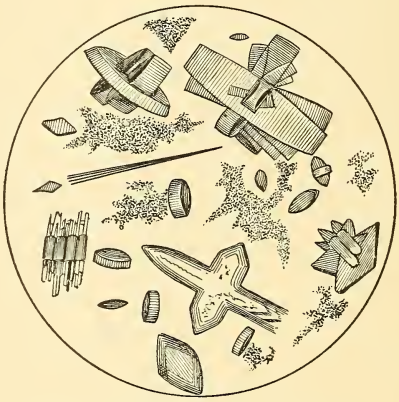


Fig. 7.—Uric acid and urates (Funke).

of uric acid is greatest during the period of digestion—that is, at a time when the liver and spleen are most active. (*d*) In gout and in anemic conditions,[1] where the excretion of uric acid is diminished, it accumulates in the blood and tissues.

The chief advocate of the second view (2) is Garrod, who bases his conclusions on the fact of the small amount of uric acid in the blood of reptiles, and also on the fact that he was unable to find a larger quantity of uric acid in the liver and spleen of birds than in those organs in mammals.

Horbaczewski[2] claims that uric acid is formed as a result of the disintegration of the tissues containing nuclein,

[1] Von Jaksch, "Deutsche med. Wochenschr.," 1890, No. 23.

[2] "Monatsh. f. Chemie," Bd. XII, 232, 1891.

PLATE 3

URIC-ACID CRYSTALS; NORMAL COLOR (AFTER PEYER).

especially the leucocytes; that the amount of uric acid excreted increases when the number of leucocytes in the blood is increased. He also claims that this is the explanation of the large amount of uric acid in the urine of children, especially the new-born, the small amount in hunger, and the larger quantity following the ingestion of a meat diet.

The investigations of Schröder[1] and Minkowski[2] justify the conclusion that uric acid is formed chiefly in the liver, where it appears as a result of the synthesis of ammonia and lactic acid, which, after the removal of the liver, and also in extensive degenerative changes of this organ (cirrhosis, acute yellow atrophy, etc.), appear in the urine in equivalent quantities. Further, that small quantities of uric acid following extirpation of the liver are formed from xanthin and similar substances.

The quantity of uric acid eliminated in twenty-four hours under normal conditions ranges between 0.2 and 1 gram, the average being about 0.5 gram. According to Neubauer and Vogel,[3] the twenty-four-hour quantity may, normally, go as high as 1.25 grams. In rare instances, especially in disease, the total quantity of uric acid may exceed this figure. The proportion of uric acid to urea is normally about as 1 : 45.

The quantity of uric acid in the urine is not necessarily excessive when a deposit of uric acid crystals takes place in the urine upon cooling. As a matter of fact, such a deposit may, and very often does, occur when the quantity of uric acid is both relatively and absolutely diminished. The separation of uric acid crystals from the urine is usually dependent upon one of three conditions:

1. A high degree of concentration of the urine, too little water being present to keep the uric acid in solution.

2. Marked acidity of the urine, the salts of uric acid being deprived of a part of the alkali; the larger the proportion of alkali combined with the uric acid, the more soluble it becomes.

3. A high percentage of uric acid. Any condition that results in an increased formation of uric acid in the body causes its increase in the blood, and hence an increased amount in the urine, with, usually, a resulting deposition of the crystals.

When urine habitually contains a deposit of uric acid, an

[1] "Ludwig's Festschrift," 1887, S. 89. [2] *Loc. cit.*

[3] "Analyse des Harns," Bd. 1, 1898, S. 312.

alkali or some substance with which the uric acid will combine should be administered, in order to prevent an irritation or inflammation of the urinary tract by the crystals.

In the consideration which follows the writer refers to the uric acid in solution (as urates) and not to a deposit of uric acid crystals.

Clinical Significance.—Uric acid is absolutely increased (1) by an abundant nucleo-proteid diet, especially when combined with a limited amount of outdoor exercise: in other words, increased metabolism together with limited oxidation. (2) In most of the acute diseases. (3) In acute diseases of the lung, as in pneumonia, or by any disease that interferes with respiration, as hydrothorax and pneumothorax, also by the upward pressure of abdominal tumors, marked ascites, etc. (4) In chronic heart disease or in any condition that interferes with the circulation. (5) In liver disease. (6) In disease of the spleen. (7) In various forms of anemia, especially splenic leukemia, in which case the proportion of uric acid to urea may be as high as 1 : 15, or even more. (8) In gout *following* the paroxysm. (9) In diabetes mellitus.[1] (10) Following the administration of nuclein.[2]

Uric acid is absolutely diminished (1) by a diet low in nucleo-proteids. (2) By the habitual ingestion of large quantities of water (long-continued use). (3) In most forms of advanced disease of the kidneys. (4) In gout *during* the paroxysm. (5) Following the administration of large doses of quinine. (6) In most of the general chronic diseases.

Detection.—1. The Murexide Test.—A small portion of urinary sediment is evaporated to dryness on a porcelain plate or capsule, and a drop or two of nitric acid is added to dissolve it. The mixture is then stirred thoroughly with a glass rod, and carefully evaporated to dryness over a spirit or a small Bunsen flame. When dry and cool, add one or two drops of ammonic hydrate, and if uric acid or urates are present, a beautiful purple-red color promptly appears, gradually diffusing itself over the bottom of the plate or capsule as the ammonia spreads.

[1] The question as to whether uric acid is actually increased in diabetes mellitus has given rise to much controversy. It is probable that the increase, if any, is not marked.

[2] "Monatsh. f. Chemie," Bd. XII, 234, 1891.

2. Strongly acidulate the urine with concentrated hydrochloric acid, and allow the mixture to stand from eighteen to twenty-four hours. Usually, a deposit of uric acid crystals appears.

3. Uric acid may be detected in the urine and other fluids, when traces of the acid or of urates are present, by a method suggested by Garrod. A small portion of the suspected fluid is treated on a watch-glass with a few drops of glacial acetic acid. A few filaments of tow or very thin silk are placed in the mixture, and the whole is set aside under a bell-jar in a warm place for from twenty-four to forty-eight hours. Gradually, crystals of uric acid separate and are deposited upon the filaments. Their character may be readily recognized by microscopic examination.

4. When a solution of uric acid or of a urate is boiled with an alkaline solution of copper (Fehling's solution), a yellowish-red or reddish precipitate of suboxide of copper occurs.

Quantitative Determination of Uric Acid.—Heintz's Method.—Take 200 c.c. of *filtered* urine that is free from albumin, and add 10 c.c. of concentrated hydrochloric acid. Let this stand for twenty-four hours in a cool place, then collect the separated uric acid crystals on a previously dried and weighed filter-paper, and wash once or twice with cold distilled water. Dry the filter-paper holding the uric acid crystals at about 100° C.; cool and weigh. By subtracting the weight of the filter-paper, the result will be the weight of the uric acid in 200 c.c. of urine.

This process can be considered only approximate, and should not be relied upon for accurate results. It frequently happens that urines containing uric acid do not give a precipitate by this method; it then becomes necessary to employ other longer and, probably, more accurate methods.

Salkowski-Ludwig Method.[1]—Of the several gravimetric methods which have been suggested, this is perhaps the most reliable. It consists in separating the uric acid from the urine by means of magnesia mixture and silver nitrate, and weighing the uric acid obtained from the silver precipitate.

[1] Salkowski, "Virchow's Archiv," Bd. LII, 1871, S. 58; "Pflüger's Archiv," Bd. V, 1872, S. 210. E. Ludwig, "Wiener med. Jahrbuch," 1884, S. 597; "Zeitschr. f. analyt. Chemie," 24, 1885, S. 637.

Process.—Place from 100 to 200 c.c. of the filtered urine, freed from albumin (see p. 131), in a beaker. In another beaker mix 10 to 20 c.c. of an ammoniacal solution of silver[1] with 10 to 20 c.c. of magnesia mixture (see foot-note, p. 109), and add ammonia, and also, when necessary, some ammonium chloride, until the mixture is clear. Add this mixture to the urine, stir thoroughly, and allow to stand for half an hour. Collect the precipitate on a filter paper, wash with ammoniacal water, and then return the precipitate to the same beaker by means of a glass rod and a wash-bottle, without destroying the filter. Next heat 10 to 20 c.c. of the sodium sulphide solution,[2] which has been previously diluted with water, and allow it to flow through the filter that has already been used, into the beaker containing the silver precipitate, and wash with boiling water; then heat the contents of the beaker over a water-bath for a few minutes, constantly stirring. Cool, filter into a porcelain dish, wash with boiling water, acidulate the filtrate with hydrochloric acid, evaporate to about 15 c.c., add a little more hydrochloric acid, and finally allow it to stand (preferably in an ice-chest) for from eighteen to twenty-four hours. Collect the crystallized uric acid on a previously dried and weighed filter paper; wash with a small amount of water, then with alcohol, ether, and carbon disulphide; dry in an oven at 100° to 110° C., and weigh.

Corrections and Precautions.—(1) For each 10 c.c. of watery filtrate add 0.00048 gram to the final quantity of uric acid obtained. (2) A portion of the uric acid may be decomposed if heated too long or too vigorously with the sodium sulphide solution.

Hopkin's Method.—In this process the uric acid and all of the urates are precipitated by saturating the urine with ammonium chloride, which converts all into ammonium urate. This is then filtered out, and the uric acid separated by the action of hydrochloric acid. The final estimation is then made by titrating with a standard solution of potassium permanganate, which Hopkins has found to be more accurate than weighing. Exceedingly

[1] Silver nitrate 26 grams, distilled water ad. 1 liter; add sufficient ammonic hydrate to completely redissolve the precipitate produced by the first addition of the ammonia.

[2] Caustic soda (free from nitric and nitrous acids) 10 grams, distilled water 1 liter. Completely saturate one-half of this solution with sulphuretted hydrogen, and then add it to the other half.

accurate results are claimed for this process, and it has the advantage of being conducted with ease and comparative rapidity.

The following solution is required: *A twentieth-normal solution of potassium permanganate.* This solution is prepared by dissolving 1.577 grams of pure crystals of potassium permanganate in about 900 c.c. of distilled water. A portion of this solution is then placed in a burette and titrated against a decinormal solution of oxalic acid as follows: Take 10 c.c. of the decinormal oxalic acid solution in a beaker, add some dilute sulphuric acid, and heat this mixture to 60° C. To this hot mixture add the solution of potassium permanganate until a faint but permanent pink color is produced. Note the number of cubic centimeters of the permanganate solution used, and then dilute the remainder so that 20 c.c. of it will exactly correspond to 10 c.c. of the decinormal solution of oxalic acid.

Each cubic centimeter of the twentieth-normal solution of potassium permanganate corresponds to 0.00375 gram of uric acid.

The permanganate solution will usually retain its strength for several weeks, but it should always be restandardized by titration with oxalic acid before it is used.

The process, as applied to all urines, normal and pathologic, is as follows:

1. *In Normal Urine without Deposit.*—(*a*) To 100 c.c. of the urine is added ammonium chloride until practically saturated; about 35 grams are necessary. When a small quantity of the chloride remains undissolved, even after brisk stirring at intervals of a few minutes, saturation is nearly complete. As the temperature of the urine again rises, from the depression due to the process of solution, any residual crystals will, for the most part, dissolve; but there is no necessity for adding more.

(*b*) After having stood for two hours or longer,—better with occasional agitation to promote subsidence,—the precipitate produced is filtered through a thin filter-paper, and washed three or four times with a saturated solution of ammonium chloride. The filtrate should remain perfectly clear.

(*c*) With a jet of hot distilled water the urate, which will be somewhat pigmented, is now washed off the filter

into a small beaker, and heated just to boiling with an excess of hydrochloric acid. It is then allowed to stand, in order that the uric acid may separate completely. Two hours are sufficient if the liquid be cooled. The acid is then filtered off and washed with cold distilled water. The filtrate should be measured *before* the washing is begun, and one milligram added to the final result for each 15 c.c. of liquid present. This need never be more than from 20 to 30 c.c.

(*d*) The acid is now again washed off the filter with hot water, sodium carbonate is added, it is warmed until dissolved, and the solution then made up to 100 c.c. Being transferred to a flask of sufficient capacity, it is mixed with 20 c.c. of concentrated pure sulphuric acid, and immediately titrated with the twentieth-normal potassium permanganate solution. The latter should be added slowly toward the end of the reaction, the close of which is marked by the first approach of a pink color, which is permanent for an appreciable interval. The flask should be agitated throughout the titration.

Since each cubic centimeter of the potassium permanganate solution is equal to 0.00375 gram of uric acid, the number of cubic centimeters of permanganate solution multiplied by 0.00375, plus the correction of one milligram for each 15 c.c. of liquid present, will give the amount of uric acid in the 100 c.c. of urine used. From this the quantity of uric acid in the twenty-four-hour urine can be readily calculated.

2. Acid Urines Containing Cystin.—The author recommends the addition of a small amount of ammonic hydrate; heat and filter. The ammonium chloride may be added while the urine is still warm.

3. Alkaline Urines with an Abundant Deposit of Phosphates.—Filter off the phosphates after complete precipitation by heat. The ammonium urate separates more rapidly in alkaline than in acid urine. The only objection to adding ammonic hydrate in all cases is its tendency to precipitate the phosphates.

4. Albuminous Urines.—Albumin does not interfere with the accurate determination of uric acid by this method, but requires a little longer digestion with an excess of hydrochloric acid, in order to form the soluble acid-albumin.

5. Highly Pigmented Urine.—The pigment should be removed from the urate precipitate by treating thoroughly with alcohol, and after acidulation the filtrate is gradually heated to boiling and then digested for some time on a water-bath. The separated crystals are then thoroughly washed.

In a urine containing *bile* the biliary pigment may come down in considerable quantity ; but despite this, the ultimate error is small.

Folin's Method.[1]—This process depends upon the precipitation of uric acid as ammonium urate, by means of ammonium sulphate, and is conducted as follows :

Process.—To 100 c.c. of filtered urine add 10 grams of ammonium sulphate ; allow it to stand two hours, filter, and wash the urate precipitate with a ten per cent. solution of ammonium sulphate until it is free from chlorine. Dissolve the entire urate precipitate in hot distilled water, add to this solution 15 c.c. of concentrated sulphuric acid, and then titrate, while hot, with a twentieth-normal solution of potassium permanganate, each cubic centimeter of which corresponds to 0.00375 gram of uric acid. Read off the number of cubic centimeters of permanganate solution used, multiply by 0.00375, and to the result add one milligram for correction. This equals the amount of uric acid in 100 c.c. of urine. From this calculate the quantity for twenty-four hours.

According to Hofmeister,[2] neither albumin nor globulin are precipitated by a ten per cent. solution of ammonium sulphate.

Quantitative Estimation of Uric Acid by the Centrifuge.—The following method, devised by Dr. R. Harvey Cook,[3] promises excellent results and has the advantages of being rapid and quite accurate. It is based, chemically, on the method of Haycraft, in that the uric acid is precipitated as urate of silver.

The following apparatus are necessary : a centrifuge, four graduated tubes of a capacity of 15 c.c. each, and a pipette holding one cubic centimeter.

Process.—Place 10 c.c. of urine in the graduated tubes, add to this from 0.5 to 1 gram of crystals of sodium car-

[1] "Zeitschr. f. physiol. Chemie," Bd. XXIV, 3, S. 224.
[2] "Archiv f. exp. Pathol. u. Pharm.," Bd. XXV, 247, 1888.
[3] "Medical Record," March 12, 1898, p. 373.

bonate, and 1 or 2 c.c. of ammonium hydrate. Shake until the sodium carbonate is dissolved; this precipitates the earthy phosphates. Separate this precipitate in the centrifuge, and decant all of the supernatant clear urine into another graduated tube. To the clear urine, now free from phosphates, add 2 c.c. of ammonic hydrate and 2 c.c. of an ammoniacal solution of silver nitrate made by dissolving 5 grams of silver nitrate in 100 c.c. of distilled water, and adding ammonic hydrate until the solution becomes clear.

The addition of the silver solution causes the uric acid to be precipitated as the urate of silver—a translucent, slimy substance. Separate this precipitate in the centrifuge, pour off the supernatant urine, and add to the precipitate an excess of ammonic hydrate—at least 5 c.c.—and mix thoroughly. By this last step any of the chlorides that may have been precipitated are redissolved, leaving only pure urate of silver. Lastly, centrifugalize again until the silver urate precipitate has fallen as low as it will go.

Each $\frac{1}{10}$ of a cubic centimeter as marked on the graduated tube is equivalent to 0.001176 gram of uric acid in 10 c.c. of urine. For example: if 0.5 be the lowest reading obtainable, then $5 \times 0.001176 = 0.00588$ gram of uric acid in 10 c.c. of urine. In order to obtain the percentage, multiply this result by 10; if the twenty-four-hour quantity of urine be known, the total uric acid can be easily calculated.

XANTHIN BASES.

A number of xanthin bases have been found in urine: Xanthin, $C_5H_4N_4O_2$; Heteroxanthin, $C_6H_6N_4O_2$; Paraxanthin, $C_7H_8N_4O_2$; Guanin, $C_5H_5N_5O$; Hypoxanthin (sarkin), $C_5H_4N_4O$; Adenin, $C_5H_5N_5$; Episarkin, $C_4H_6N_3O$; Carnin, $C_7H_8N_4O_3$; Epiguanin, $C_{10}H_{13}N_9O_2$; and, finally, an unknown base discovered by Krüger.

The xanthin bases have also been called nuclein bases (Kossel) and alloxur bases (Kossel and Krüger). The alloxur bases, together with uric acid, have been given the names alloxur bodies (Kossel and Krüger) and purin bodies (E. Fischer).

Krüger and Salomon [1] have recently made an extensive study of the alloxur bases. From 10,000 liters of urine they obtained

[1] "Zeitschr. f. physiol. Chemie," Bd. xxvi, 1898, S. 350.

the following: Xanthin, 10.11 gm.; heteroxanthin, 22.345 gm.; l-methylxanthin, 31.285 gm.; paraxanthin, 15.31 gm.; hypoxanthin, 8.50 gm.; adenin, 3.54 gm.; and epiguanin, 3.4 gm. The bases adenin, hypoxanthin, and xanthin, due to the breaking down of nuclein, occur in smaller quantities than the homologues of xanthin which are probably derived from the theobromin, caffein, and theophyllin introduced into the system by the use of tea and coffee, paraxanthin being obtained from caffein, heteroxanthin from theobromin, and l-methylxanthin from theophyllin.

A brief consideration of the most important of the xanthin bases follows.[1]

Xanthin ($C_5H_4N_4O_2$).—When pure xanthin is dissolved in a weak alkali with the aid of heat, strongly diluted

Fig. 8.—Xanthin crystals (after the drawings of Horbaczewski, as represented in Neubauer and Vogel).

(1 : 2000), and then saturated with acetic acid, it crystallizes in macroscopic, colorless, glistening, rhombic plates, arranged in groups. (Fig. 8.) Xanthin, which is separated from its concentrated aqueous solution by boiling, is amorphous, but on standing soon collects in flakes, films, or crusts.

Xanthin is soluble in 13,000 to 14,000 parts of cold water, and in 1300 to 1400 parts of hot water; it is difficultly soluble in dilute alcohol and dilute acids, but much more soluble in ammonic hydrate than in water. On cooling, xanthin separates from its warm saturated solution

[1] For details see Neubauer and Vogel, Bd. 1, 1898, S. 331.

in ten per cent. ammonia in the form of fine needles of xanthin-ammonium. If xanthin be dissolved in very weak sodic hydrate, on standing small crystals of xanthin-sodium, $C_5H_3NaN_4O_2 . H_2O$, separate. A solution of xanthin in ammonia gives, with an ammoniacal solution of zinc chloride, a white precipitate which is soluble in an excess of ammonia. Xanthin in crystalline form contains one molecule of water of crystallization; when amorphous, it is water-free. If xanthin is heated in a closed tube, it sublimes without melting, and results in a decomposition with the evolution of hydrocyanic acid.

Xanthin is a constituent of normal urine, but is present only in traces. Krüger and Salomon [1] found a maximum of only 13 grams in 10,000 liters of normal human urine. Stadthagen was able to isolate from the twenty-four-hour quantity of urine of a healthy individual on a mixed diet 0.032 and 0.025 gram.

Xanthin contains one atom less of oxygen than uric acid, to which it is closely allied. It has rarely been encountered as a constituent of the urinary sediment. It has been found as a constituent of a very rare form of calculus, and in those cases reported, was always observed in children.

Xanthin is increased in leukemia (as high as 0.028 gram in 100 c.c.); Stadthagen found 0.07 gram in the twenty-four-hour urine as an average of seven determinations. Pouchet[2] found it in unusual quantities in fever, and particularly in affections of the nervous system—pachymeningitis cervicalis hypertrophica and tabes dorsalis.

Detection.—(1) When a solution of xanthin in a fixed alkali is added to sodium or calcium hypochlorite, nitrogen gas is evolved and the solution becomes green, changing to a brown and finally to a yellow. (2) When xanthin is heated to 200° C. with fuming hydrochloric acid, it is decomposed into glycocoll, ammonia, carbonic acid, and formic acid. (3) When evaporated to dryness with nitric acid, a yellow residue remains, which becomes violet on the addition of potassium hydrate, the violet color increasing upon the application of heat. (See *Murexide Test for Uric Acid.*)

Heteroxanthin ($C_5H_3N_4O_2 . CH_3$). — Heteroxanthin, when pure, crystallizes from its hot aqueous solution in

[1] "Zeitschr. f. physiol. Chemie," Bd. xxi, 169, 1895.

[2] "Thesis," Paris, 1880.

glossy needles about a half centimeter in length, also in thorn-like spheres, and in thick columns which have a fan-like arrangement. It is soluble in 1592 parts of water at 18° C., in 109 parts of boiling water, and is sparingly soluble in absolute alcohol. When pure, it is insoluble in ether and chloroform; but when impure, it is sparingly soluble in chloroform. It is readily soluble in ammonia and other alkalies. Heteroxanthin combines with sodium to form a double salt, prepared by the addition of sodic hydrate to its concentrated solution.

Heteroxanthin is a constituent of normal urine, but is present only in minute quantities. Salomon found only 1 gram in 1000 liters; Krüger and Salomon isolated 7.5 gram from 10,000 liters of normal human urine.

Clinically, it is increased in leukemia, in phosphorus-poisoning, and following the ingestion of theobromin and caffein.

Detection.—Heteroxanthin does not respond to the tests for xanthin. It gives an intense reaction with hydrochloric acid and a trace of potassium chlorate; the red residue changes to a violet on the addition of potassium hydrate (Weidel's test).

Hypoxanthin ($C_5H_4N_4O$).—Hypoxanthin, also termed sarkin, is present in normal urine, but only in minute quantities. Pure hypoxanthin does not crystallize in the form of needles, but always appears on the bottom and sides of the glass or on the surface of the fluid in the form of a film, as oval kernels with sharp angles. Like xanthin and heteroxanthin, when heated in a closed tube it sublimes and evolves hydrocyanic acid. It is soluble in 300 parts of cold water and in 78 parts of hot water, also in 900 parts of hot alcohol. It is more readily soluble in ammonia than in water. It is not precipitated by saturating its solution with ammonium chloride. Hypoxanthin is precipitated from its solution in alkalies by carbonic acid. It combines with the salts of sodium, zinc, and calcium to form double salts.

Hypoxanthin has been found in the normal urine of man by Salomon, Salkowski, and others. It is most abundant after a hearty meat diet (in dogs). It appears to be in larger quantities in the urine of leukemia than in that of health (Stadthagen isolated an average quantity of 0.009 gram—as high as 0.027 gram—from leukemic urine), also

in diseases of the liver and kidneys (Thudichum), and in fever and diseases of the central nervous system (Pouchet).

Detection.—When hypoxanthin is treated with zinc and dilute hydrochloric acid, and then sodic hydrate is added, a red or reddish-brown color appears, the result of the absorption of oxygen from the air. Hypoxanthin does not give a green color with sodic hydrate and calcium hypochlorite as does xanthin.

Paraxanthin ($C_5H_2N_4O_2(CH_3)_2$).—Paraxanthin is isomeric with theobromin and theophyllin. It crystallizes in colorless, glossy, six-sided plates. It is difficultly soluble in cold water, but dissolves much more readily in hot water, its solutions having a neutral reaction. It is insoluble in alcohol and ether. It combines with sodium to form a double salt, which has much the same general properties as the compound of sodium with heteroxanthin.

Paraxanthin has been detected in the urine of man by Thudichum and Salomon. Like the other bases of this group, it was found in unusual quantities in leukemic urines. Comparatively little is known of the clinical significance of this substance.

Detection.—Paraxanthin gives Weidel's test, but does not respond to the tests for xanthin.

The *isolation of the xanthin bases* [1] is accomplished in four ways: (1) Precipitation with ammoniacal solution of silver nitrate; (2) with copper suboxide; (3) with phosphotungstic acid; (4) with cupric acetate.

NUCLEIC ACID.

This acid has been found by Mörner in very small quantities in the urine. It appears, however, in large amounts in combination with albumin as nucleo-albumin. (See p. 142.) The nucleic acids are compounds of phosphoric acid, xanthin bases, and a nitrogen-free substance. Some of these compounds have been recognized as pentose and hexose. The amount of phosphorus in the nucleic acids varies, but may reach as high as 9 or 10 per cent. They are amorphous, have an acid reaction, are soluble in ammonia, in alkaline hydrates, or in distilled water holding a small amount of alkali, and are precipitated from their

[1] See Neubauer and Vogel, "Analyse des Harns," Bd. 1, 1898, S. 362.

solutions by a small amount of hydrochloric acid, but not by acetic acid. They are, however, precipitated by an excess of glacial acetic acid. They are completely precipitated by alcohol in the presence of hydrochloric acid. According to Kutscher, nuclein is precipitated from a neutral solution of the salts of nucleic acid by an aqueous solution of albumose. Noll [1] has recently succeeded in forming levulinic acid from nucleic acid by heating with thirty per cent. sulphuric acid for two hours.

Nucleic acid is not precipitated by the reagents used for the precipitation of proteids, and does not give the color reactions of proteids. When some of the nucleic acids are boiled with dilute mineral acids, a substance (carbohydrate) is produced which reduces alkaline solutions of cupric oxide.

The **detection** of the nucleic acids depends upon the isolation of their chief constituents—phosphoric acid and xanthin bases.

ALLANTOIN.

$C_4H_6N_4O_3$.

This substance has been found in the urine of infants within the first eight days after birth, in new-born calves (Wöhler), and in the urine of man (Ziegler and Hermann).

Allantoin, when pure, crystallizes in large monoclinic prisms with hexagonal bases, often arranged in star-like groups; when impure, in warty and granular particles. It has a neutral reaction, is difficultly soluble in cold water (160 parts), more readily in hot water (30 parts), very soluble in alkaline hydrates, and, according to Salkowski, more readily soluble in a solution of piperazin than in water. It is insoluble in alcohol and ether. It combines with acids and bases to form salts. The compounds with silver oxide and mercuric oxide are particularly serviceable for the detection of allantoin.

When a freshly prepared solution of allantoin in sodic or potassic hydrate is supersaturated with acetic acid, it is immediately precipitated. It then contains allantoic acid.

Allantoin is obtainable from uric acid by oxidation with potassium permanganate:

$$\underset{\text{Uric acid.}}{2C_5H_4N_4O_3} + 2H_2O + O_2 = \underset{\text{Allantoin.}}{2C_4H_6N_4O_3} + 2CO_2.$$

[1] "Zeitschr. f. physiol. Chemie," Bd. XXV, S. 430.

Allantoin is decomposed by heating with hydrochloric acid into allanturic acid and urea :

$$\underset{\text{Allantoin.}}{C_4H_6N_4O_3} + H_2O = \underset{\text{Allanturic acid.}}{C_3H_4N_2O_3} + \underset{\text{Urea.}}{CH_4N_2O}.$$

When allantoin is boiled with an alkali or baryta water, it furnishes first, as in the decomposition with acids, allanturic acid and urea ; but the allanturic acid is further decomposed into hydantoic and parabanic acids :

$$2\underset{\substack{\text{Allanturic}\\\text{acid.}}}{C_3H_4N_2O_3} = \underset{\substack{\text{Hydantoic}\\\text{acid.}}}{C_3H_6N_2O_3} + \underset{\substack{\text{Parabanic}\\\text{acid.}}}{C_3H_2N_2O_3}.$$

and the parabanic acid is finally decomposed into oxalic acid and urea :

$$C_3H_2N_2O_3 + 2H_2O = \underset{\substack{\text{Oxalic}\\\text{acid.}}}{C_2H_2O_4} + \underset{\text{Urea.}}{CH_4N_2O}.$$

Allantoin reduces Fehling's solution on boiling. It is not precipitated by lead acetate or phosphotungstic acid, and does not give the murexide reaction.

Allantoin is present in normal urine in mere traces, except directly after birth. It has been found to be increased by a meat diet, and by the administration of tannic acid. Pouchet found allantoin considerably increased in the urine of a case of diabetes insipidus and in a case of hysteria with convulsions.

Detection.—In order to detect allantoin, it must first be separated from the urine. The following method of G. Meissner [1] best serves this purpose : Precipitate the urine with baryta water, exactly neutralize the filtrate with sulphuric acid, filter at once, and evaporate to beginning crystallization. The fluid, while still warm, is treated with sufficient alcohol to completely precipitate (this precipitate should be saved). The alcoholic solution is then decanted from the precipitate or filtered off, and completely precipitated with ether. Both precipitates, especially the one obtained with the ether, contain the allantoin together with other substances. The precipitates are then extracted with a little cold water or with hot alcohol, the allantoin remaining undissolved. Characteristic crystals of allantoin are then obtained by recrystallizing the residue from hot water.

[1] "Zeitschr. f. rat. Med.," [3] Bd. XXIV, 104, u. Bd. XXXI, 297.

KREATIN AND KREATININ.

$C_4H_9N_3O_2$—$C_4H_7N_3O$.

These two substances are constituents of normal urine. They differ chemically in that kreatinin contains one molecule less of H_2O than kreatin, as seen by the foregoing formulæ. Kreatin, which is constantly present in muscle tissue, is in all probability the antecedent of kreatinin, so that two sources of this substance must be recognized—*i. e.*, the muscle tissue of the body and the muscle tissue taken as food. Kreatin is more abundant in alkaline urine than kreatinin, while in a strongly acid urine the reverse is the case. Since the urine is generally acid, kreatinin is the pre-

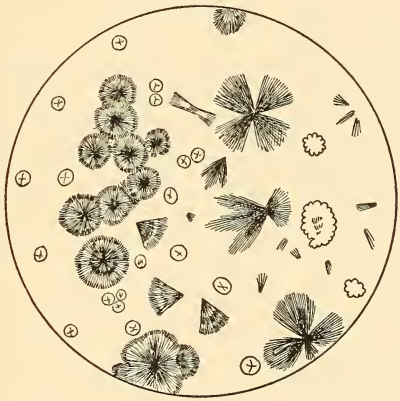


Fig. 9.—Crystals of kreatinin-zinc chloride (Salkowski).

dominating constituent of normal urine, and will be further considered.

Kreatinin crystallizes without water of crystallization in colorless, glistening prisms of the monoclinic system ; sometimes these crystals, when found lying on their sides, appear in the form of whet-stones. Kreatinin is readily soluble in hot water and quite soluble in cold water ; it is very soluble in hot alcohol, but more difficultly so in cold alcohol and ether. It reduces alkaline solutions of copper (Fehling's solution) upon boiling. It forms salts with the acids, and double salts with some of the salts of the heavy metals. Among these may be mentioned kreatinin chloride or

hydrochlorate, which is easily soluble in water and crystallizes in the form of transparent prisms or rhombic plates. One of the most important of the double salts is the compound of kreatinin with zinc chloride $(C_4H_7N_3O)_2 . ZnCl_2$, produced by treating an aqueous or alcoholic solution of kreatinin with zinc chloride. If the kreatinin is pure, the compound crystallizes in the form of fine needles grouped together in rosettes or sheaves. (Fig. 9.) Kreatinin-zinc chloride is very slightly soluble in water and insoluble in alcohol.

Kreatinin is a constituent of normal human urine. According to the determinations of Neubauer, a healthy man on a well-mixed diet eliminates from 0.6 to 1.3 grams of kreatinin in twenty-four hours. As indicated, the quantity of kreatinin appears to vary according to the disintegration of muscle tissue in the body and the amount of meat ingested with the food.

Clinically, it is excreted in increased quantity in acute diseases, such as typhoid fever, pneumonia, etc. It is diminished in hunger, in convalescence from acute diseases, in advanced degeneration of the kidneys, and in wasting diseases.

Detection of Kreatinin.—1. *Weyl's Test.*—To a few cubic centimeters of the urine add a few drops of a very dilute solution of sodium nitroprusside, and render alkaline with sodic hydrate. If kreatinin be present, the mixture assumes a ruby-red color, which disappears in a few minutes and is replaced by an intense yellow color, which, on warming with glacial acetic acid, gives rise to a green color. The presence of albumin and sugar does not interfere with the reaction.

2. To a solution of kreatinin add a small quantity of an aqueous solution of picric acid, and then a few drops of dilute sodic or potassic hydrate. An intense red color appears. This red color is apparent (only less intense) when kreatinin is present in the proportion of 1 : 5000 (Jaffé).

3. When a solution of kreatinin is acidulated with nitric acid and treated with phosphomolybdic acid, a yellow, crystalline precipitate is produced, which is soluble in hot nitric acid.

4. The double compound of kreatinin and zinc chloride shows, microscopically, characteristic crystals. (Fig. 9.) This test is used for the quantitative estimation of kreatinin.[1]

[1] See Neubauer and Vogel, "Analyse des Harns," Bd. 1, 1898, S. 396.

THE AROMATIC SUBSTANCES IN URINE.

The aromatic substances that occur in urine belong to four classes :

1. Hippuric acid, and similar aromatic compounds of glycocoll.
2. Combinations of glycuronic acid with aromatic substances. (See p. 171.)
3. Aromatic oxyacids.
4. Ethereal sulphates.

Hippuric Acid ($C_9H_9NO_3$).—Hippuric acid is a constituent of the urine of man in both health and disease. The twenty-four-hour quantity of urine contains between 0.1 and 1 gram It is very abundant in the urine of herbivora,

Fig. 10.—Hippuric acid crystals.

and in man the quantity varies largely according to the amount of vegetable food ingested. It is absent from the urine of carnivora.

Hippuric acid crystallizes either in the form of fine needles or four-sided prisms and pillars, the ends of which terminate in two or four planes. (Fig. 10.) At times these resemble the crystals of ammonio-magnesium phosphate, with which they should not be confounded. Typically, the crystals of hippuric acid are in the form of vertical rhombic prisms.

Hippuric acid is soluble in 600 parts of water at 0° C., and much more soluble in hot water and alcohol. Its solutions have a strongly acid reaction. It combines with bases to form salts. Its compounds with the alkalies and alkaline earths are soluble in water and alcohol, but the silver, copper, and lead salts are difficultly soluble in water. Strong acids precipitate the hippuric acid from its salts, and it

reappears in crystalline form. When hippuric acid is boiled with an alkaline hydrate or with mineral acids, it takes up a molecule of water and is decomposed into benzoic acid and glycocoll:

$$\underset{\text{Hippuric acid.}}{C_6H_5 . CO — HN . CH_2 . COOH} + H_2O =$$

$$\underset{\text{Benzoic acid.}}{C_6H_5 . COOH} + \underset{\text{Glycocoll.}}{H_2N . CH_2 . COOH}.$$

This same decomposition takes place during the alkaline fermentation of the urine, especially of urine containing albumin, the hippuric acid being acted upon by the micrococcus ureæ. No hippuric acid, therefore, is found in decomposing urine, benzoic acid taking its place. Hippuric acid reduces alkaline solutions of cupric oxide (Fehling's solution) on boiling.

The experiments of Meissner and Shepard, and of Schmiedeberg and Bunge show that hippuric acid is probably formed by the union of benzoic acid and glycocoll, and that this union takes place in the kidneys, as they failed to find that the synthesis occurred after the removal of the kidneys.

As previously indicated, the amount of hippuric acid in the urine of man is dependent chiefly upon the character and quantity of food ingested, being *increased* by a vegetable diet, especially by certain fruits, as prunes, mulberries, cranberries, blueberries, or by any substance containing the benzoic acid radicle. It is increased by the administration of benzoic acid, cinnamic acid, oil of bitter almonds, salicylic acid, toluol, etc.; also in acute febrile diseases, hepatic diseases, diabetes mellitus, and cholera. It is *diminished* by an exclusive meat diet, although generally it does not disappear entirely from the urine upon such a diet. It is an interesting fact that, in accordance with Bunge's experiments on dogs, the elimination of hippuric acid appears to be wholly suspended in cases of acute and chronic parenchymatous nephritis, following the ingestion of benzoic acid, which reappears in the urine unchanged.

Detection.—When urine containing hippuric acid or one of its salts is evaporated to dryness with concentrated nitric acid, and the residue is heated in a test-tube, the odor of bitter almonds is noticed, due to the formation of nitrobenzol (benzoic acid gives the same result).

Hippuric acid may be separated from urine containing an excess of it by evaporating the urine to one-fourth of its volume and acidulating with hydrochloric acid. In a few hours characteristic crystals of hippuric acid will be found in the deposit, when examined microscopically.

Quantitative Estimation.—*Method.*—From 500 to 1000 c.c. of fresh urine are evaporated to a syrupy consistence on a water-bath, care being taken to keep the urine neutral by the addition of sodium carbonate. The residue is extracted with cold alcohol (ninety to ninety-five per cent.), taking a quantity about half as great as that of urine employed, and setting aside the mixture for twenty-four hours. The alcoholic filtrate, which contains the salts of hippuric acid, is then freed from alcohol by distillation. The remaining solution is strongly acidulated with acetic acid, in order to liberate the lactic acid, and extracted with at least five times its own volume of alcoholic ether (one part of alcohol to nine parts of ether). From the combined extracts the ether is distilled off and the remaining solution evaporated on a water-bath. The resinous residue is boiled with water, set aside to cool, and filtered through a well-moistened filter. The hippuric acid, which is easily soluble in boiling water, is thus separated from constituents that are soluble in alcohol and ether. The filtrate is rendered alkaline with a little milk of lime, any excess of calcium hydrate being removed by passing carbon dioxide through the mixture. This mixture is then brought to the boiling-point and filtered. Any impurities present are removed by shaking with ether. The calcium salts remaining in solution are decomposed by means of an acid, and the solution is again extracted with ether. The remaining solution is evaporated to a few cubic centimeters, when the hippuric acid will separate on standing. The crystals are dried on plates of plaster-of-Paris; they are then shaken with benzol or petroleum ether to remove any benzoic acid, and finally weighed. These crystals may be shown to be hippuric acid by their microscopic appearance, their solubility in alcohol, and their behavior when evaporated with concentrated nitric acid, as previously indicated.

Aromatic Oxyacids.—Two of these, hydroparacumaric acid and paraoxyphenyl-acetic acid, are found in the urine in small quantities in combination with potassium. They apparently are derived from the decomposition that takes

place in proteids in the intestine; tryosin is probably an intermediate product (Baumann):

$$\underset{\text{Tyrosin.}}{C_9H_{11}NO_3} + H_2 = \underset{\substack{\text{Hydropara-}\\\text{cumaric acid.}}}{C_9H_{10}O_3} + NH_3.$$

$$\underset{\substack{\text{Hydropara-}\\\text{cumaric acid.}}}{C_9H_{10}O_3} = \underset{\substack{\text{Paraethyl}\\\text{phenol.}}}{C_8H_{10}O} + CO_2.$$

$$\underset{\substack{\text{Paraethyl}\\\text{phenol.}}}{C_8H_{10}O} + O_3 = \underset{\substack{\text{Paraoxy-}\\\text{phenyl-acetic}\\\text{acid.}}}{C_8H_8O_3} + H_2O.$$

Ethereal Sulphates.—A few of the products of decomposition are of especial interest because of their behavior within the body, and because after their absorption they appear in the urine in the form of ethereal or conjugate sulphates of sodium and potassium. A few, such as the oxy-acids, pass unchanged into the urine; others, such as phenols, are changed into ethereal sulphates by synthesis, and are eliminated by the urine. Still others, such as indol and skatol, are converted into ethereal sulphates only after oxidation. The quantities of these bodies in the urine vary largely with the extent of the putrefaction that is constantly taking place in the intestine.

The earliest information bearing upon this subject was furnished in 1851 by Städeler, who found that on distilling the urine of oxen and of men with dilute sulphuric acid, he obtained in the distillate small amounts of phenol. It was not, however, until 1875 that Baumann discovered that phenol existed in an ethereal combination with sulphuric acid. He also determined the presence of other ethereal sulphates, all of which were found to be compounds of the radicle HSO_3.

The ethereal sulphates appear to have one or both of two origins: (1) From the aromatic substances in the food; hence their greater abundance in the urine of herbivora. (2) From the intestine as a result of putrefaction. They are absorbed from the intestine, pass into the blood, and are eliminated in the urine in combination with potassium and sodium as ethereal sulphates.

A large number of determinations have been made relative to the proportion of the ethereal sulphates to the ordinary (alkaline) sulphates in the urine of man, and the normal proportion may be stated as about 1 : 10.

In disease, whenever the putrefaction in the intestine or in other parts of the body is increased, the proportion of ethereal sulphates rises. The investigations of G. Hoppe-Seyler are noteworthy, his results being summarized as follows:

1. Deficient absorption of the normal products of digestion, such as occurs in peritonitis and tubercular disease of the intestine, leads to an increase of the ethereal sulphates in the urine, because the products of digestion undergo putrefactive changes, and the putrefactive products are absorbed.
2. Diseases of the stomach, in which the food lies in the stomach a long time and undergoes fermentative changes, always lead to an increase of the ethereal sulphates in the urine.
3. Simple constipation and typhoid fever do not produce this result.
4. Putrefactive processes outside the alimentary canal, putrid cystitis, putrid abscesses, putrid peritonitis, etc., have the same result as putrefactive processes within the intestine. The amount of the ethereal sulphates is, moreover, in all cases proportional to the degree of the putrefaction, and is increased by the retention and diminished by the discharge of putrid matter.

It has been conclusively shown by these and other observations that the best criterion of the occurrence and amount of putrefaction in the body is the relation of the ethereal sulphates to the total sulphates.[1]

Indoxyl-potassium Sulphate ($C_8H_6NO \cdot SO_2 \cdot OK$), *Indoxyl—Indican (?)*—This substance is formed from indol, —C_8H_7N,—which is a product of the putrefaction of albuminous substances in the intestine. The indol is then absorbed from the intestine and enters the blood, where it becomes oxidized to indoxyl,—C_8H_6NO,—which immediately combines with potassium (and to a slight extent with sodium) sulphate to form indoxyl-potassium sulphate, in which form it is eliminated in the urine.

By the oxidation of indoxyl-potassium sulphate indigo-blue is formed:

$$2C_8H_6NKSO_4 + O_2 = 2C_8H_5NO + 2HK \cdot SO_4.$$

Indoxyl-potassium sulphate. — Indigo-blue. — Potassium hydrate sulphate.

Indigo-red, which has the same elementary composition as indigo-blue, is also one of the products of the oxidation of indoxyl sulphate.

Indoxyl is a constituent of normal human urine, as a

[1] For quantitative determination of ethereal sulphates, see p. 115.

result of the natural intestinal putrefaction. It is absent from the urine of the new-born.

Under ordinary conditions indoxyl does not contribute to the color of freshly passed urine. It may, however, become partially oxidized in the body, especially in disease, or oxidation may take place outside of the body during the ammoniacal decomposition of the urine, when it probably furnishes some color to the urine. In rare instances the indoxyl sulphate is completely oxidized within the body, and a blue color is imparted to the urine, due to the deposit of indigo-blue. Furthermore, indigo calculi have been found in the urinary tract following the long-continued separation of indigo from the urine, but such instances are of very rare occurrence.

The quantity of indoxyl separated from the urine as indigo-blue has been found to be between 0.005 and 0.025 gram in the twenty-four-hour secretion of a healthy individual on a mixed diet (Neubauer and Vogel). The largest quantities excreted in health are observed after a liberal ingestion of a meat diet, particularly the so-called red meats, while the smallest quantities have been found during the ingestion of a milk diet.

Clinical Significance.—The clinical importance of indoxyl rests chiefly upon its *increased* elimination, its diminution having little or no importance. *Indoxyl is increased:* (1) In all cases of increased intestinal putrefaction, especially that taking place in the small intestine. Thus, in diarrhea it is increased, whereas in dysentery (disease of the large intestine) no such increase takes place. It is increased in typhoid fever and in cholera, also in some forms of Bright's disease, notably chronic diffuse, chronic interstitial, and subacute glomerular nephritis. Simon has observed an increase in cases in which the gastric juices contained an abnormally small amount of free hydrochloric acid or in which it was absent entirely, notably carcinoma of the stomach, and he believes that it is possible to form a fairly accurate idea of the amount of free hydrochloric acid in the stomach by examining the urine for indoxyl. There are exceptions to this, however, to explain which he grants is impossible at the present time. Indoxyl is also increased in acute, subacute, and chronic gastritis of whatever origin ; in acute peritonitis (marked increase), cancer of the mesentery, appendicitis, diseases of the liver and pancreas, especially

those accompanied by an acute peritonitis; in Addison's disease, lead colic, and, in short, in any disease of the abdominal viscera accompanied by an increase in the intestinal putrefaction. It is also increased in acute diseases elsewhere in the body, as in pneumonia, pleurisy, meningitis, acute articular rheumatism, etc.

(2) The indoxyl is increased by any condition that prevents the passage of fecal matter through the *small* intestine, as in intussusception, twists, new growths, and the like. In diseases of the *large* intestine an increase of indoxyl is *never* seen; thus, the tests for indoxyl in the urine are of decided value in the differential diagnosis. In simple, uncomplicated constipation the indoxyl is not increased.

(3) An increase in the indoxyl is also seen when albuminous putrefaction takes place in other parts of the body, as in cases of empyema, putrid bronchitis, gangrene of the lungs, advanced phthisis, etc.

There can be no doubt of the clinical significance of the test for indoxyl in the urine, for points of decided importance, not only in diagnosis, but also in prognosis and treatment, can thus be gained.

Detection.—(1) The following color reaction depends upon the decomposition and oxidation of the indoxyl-sulphate of potassium by means of hydrochloric acid, the oxidation being accelerated by the use of nitric acid. The color that results usually consists of a mixture of indigo-blue and indigo-red (amethyst).

Take 15 c.c. of strong hydrochloric acid (C. P.) in a wine-glass, add one or two drops of strong nitric acid (C. P.), stir, then add thirty drops of the urine to be tested, and stir immediately. An amethyst color soon makes its appearance, reaching its greatest intensity in from five to twenty minutes. The amount of color obtained at the point of greatest intensity furnishes some data as to the amount of indoxyl present. If *normal*, a distinct but not intense amethyst color appears; if *increased*, the color is decided and often very deep; and if *diminished*, there will be but very little color, and rarely an entire absence of color.

The reaction can also be obtained by using hydrochloric acid alone, but has the disadvantage of requiring a longer time for the greatest color to appear. It is, therefore, advisable to add one or two drops of nitric acid in order to hasten oxidation, care being taken not to add more, or the

oxidation will be so rapid that the amethyst color can not be seen, only a yellow color resulting.[1]

The thirty drops of urine added should always be uniform in size, and such as are obtained when the urine is dropped from the lip of a urinometer-glass. (Fig. 2.) It is, therefore, advisable to have a pipette for the performance of the test, made by dropping thirty drops of urine into a wine-glass, then drawing it up into the pipette, and indicating the level of the urine by means of a scratch on the glass.

In urine containing potassium iodide the test for indoxyl can not be satisfactorily applied, particularly if hydrochloric acid containing free hydrochloric-acid gas be used, or if nitric acid be added to the hydrochloric acid. This is because of the oxidizing action of the iodine that is set free. Under such circumstances a yellow color immediately results; in other words, the oxidation is so rapid that the amethyst color can not be seen.

(2) Take about 10 c.c. of the urine in a test-tube, add an equal volume of hydrochloric acid and a few drops of a freshly prepared saturated solution of sodium hypochlorite, calcium hypochlorite, or common saltpeter, and then 1 or 2 c.c. of chloroform. The mixture is thoroughly agitated and set aside. The indigo that has been set free is taken up by the chloroform, coloring this to a greater or less extent, the degree of increase as compared with the normal being determined by the intensity of color.

Albumin does not interfere with these two tests. Bile pigment, which interferes with the reaction, may be removed by the addition of a solution of basic acetate of lead, carefully avoiding an excess. Urines presenting a very dark color may be freed from the greater part of their coloring-matter in the same manner. If potassium iodide be present, the chloroform will be colored more or less of a carmine, owing to the liberation of free iodine.

Skatoxyl-potassium Sulphate ($C_9H_8NO \cdot SO_2K$).—This substance is formed from skatol, which, like indol, is a product of the putrefaction of proteids in the intestine. Some of it is absorbed by the blood, where it combines with potassium sulphate, in which form it is eliminated in

[1] If hydrochloric acid containing much free hydrochloric-acid gas be used for the test, nitric acid should not be added, since the oxidation is effected by the free gas present.

the urine as a colorless compound, and when it is oxidized, it yields a red color.

Skatoxyl-potassium sulphate is a constituent of normal urine, but is usually present in smaller quantities than the indoxyl sulphate.

Clinically, this substance is of little interest except in connection with indoxyl, and since both the skatoxyl and indoxyl sulphates are, clinically, considered as one, it is not necessary here to enter into the consideration of its properties or modes of detection further than to state that the indigo-red oxidation products obtained in the tests for indoxyl are probably partly due to the presence of skatoxyl-potassium sulphate.

Phenol-potassium Sulphate ($C_6H_5O\,SO_3\,.\,K$).—Phenol, C_6H_6O, is one of the products of intestinal putrefaction. The production of phenol probably takes place lower down in the small intestine than indol, but higher up in the intestine than skatol. It is absorbed from the intestine, and, entering the blood, combines with potassium sulphate to form the ethereal or conjugate sulphate, phenol-potassium sulphate. According to Baumann, some of the sulphate comes from tyrosine, which passes through the stages of parakresol and paraoxybenzoic acid before conversion into the phenol salt. This substance is the form in which all of the phenol or carbolic acid of the body exists. It is a constituent of normal urine, and is present in amounts varying between 0.017 and 0.5 gram—an average of about 0.03 gram—for twenty-four hours. Phenol sulphuric acid is abundant in the urine of herbivora.

A urine rich in indoxyl usually contains an excess of phenol, but one rich in phenol does not always contain an excess of indoxyl. In those cases in which an increased elimination of ethereal sulphates is due to albuminous putrefaction in other parts of the body than the intestine, as in empyema, pulmonary gangrene, putrid bronchitis, etc., an increased elimination of phenol alone may be noted, the amount of indoxyl being about normal.

Clinical Significance.—The use internally or externally of large amounts of carbolic acid, lysol, salol, and other phenol compounds results in an increase in the amount of phenol sulphate and a corresponding diminution in the ordinary sulphates, the latter being taken up by the excess of phenol in the blood. Two substances, pyrocatechin and

hydrochinon, are formed as a result of the splitting up of carbolic acid. Urines containing these substances, although usually normal in color when voided, become smoky, dark brown, or black on standing exposed to the air. This dark color is often more pronounced after alkaline decomposition begins, and is, in all probability, due to the oxidation products of hydrochinon.

The phenol sulphate is increased in those conditions that cause increased putrefaction in the lower part of the small intestine and upper portion of the large intestine. In other words, most of the conditions that cause an increase in the indoxyl sulphate also cause an increase in the phenol sulphate. Its increase is especially marked in peritonitis, pyemia, and in phosphorus-poisoning.

Detection.—Distil the urine with sufficient sulphuric acid to make a five per cent. mixture. (1) To a portion of the distillate add bromine water, which gives a yellow precipitate of tribromphenol. (2) To another portion add Millon's reagent, and heat. A beautiful red color results. (3) Saturate still another portion of the distillate with sodic carbonate in the cold, and shake with ether in order to remove salicylic acid and other substances that give a ferric chloride reaction. Evaporate the ether, and to an aqueous solution of the residue add ferric chloride, which gives a deep violet color.

Determination.—The following procedure may be applied for the determination of phenol in urine: Take 500 to 1000 c.c. of the urine, treat with sufficient sulphuric acid to represent five per cent. of the mixture, and distil as long as a specimen of the distillate is rendered cloudy by bromine water (1 : 30), the specimens used for this purpose being carefully preserved. The total quantity of the filtered distillate, together with the specimens that have been set aside, is now treated with bromine water, shaking the mixture after each addition of the reagent until a permanent yellow color results. After two or three days the precipitate of tribromphenol that forms is collected on a filter that has been previously dried and weighed, washed with water containing a trace of bromine, and then dried over sulphuric acid and weighed. One hundred parts of tribromphenol correspond to 28.4 parts of phenol.

The urine contains small quantities of two other ethereal sulphates: *i. e.*, *kresol-potassium sulphate* and *katechol-potas-*

sium sulphate. These have practically the same significance as those already considered, so that only mere mention here is necessary. For a detailed consideration of these substances see Neubauer and Vogel, "Analyse des Harns," Bd. 1, 1898, S. 156 and 158.

URINARY COLORING-MATTERS.

Urobilin ($C_{32}H_{40}N_4O_7$).—Normal urobilin was first isolated from the urine by Jaffé (1868). Although this substance has for a long time been considered the chief coloring-matter of the urine, it probably contributes very little to the color of the freshly passed urine of a healthy individual. Normal urobilin is present in the urine chiefly as a chromogen,—urobilinogen,—and it is not until this chromogen is decomposed that its color is set free. In many pathologic conditions, on the other hand, there appears to be a larger amount of free urobilin than normally, and to this MacMunn has given the name "pathological urobilin." This can be artificially prepared from normal urobilin by the action of reducing agents.

Normal urobilin is amorphous and not deliquescent. Its color varies according to the method of isolation: that precipitated by means of ammonium sulphate is brown; that precipitated upon the addition of an acid to its alkaline solution is red; and that obtained by the evaporation of its alcoholic solution is reddish-brown. It is readily soluble in alcohol and chloroform, also in ether, acids, and ammonic hydrate. It is very sparingly soluble in water. Neutral salts increase its solubility in water, but by saturating its solution with some of these salts it is more or less completely precipitated. It combines with alkalies to form salts, and is precipitated from solutions of these salts upon the addition of acids.

When an acid solution of normal urobilin is examined with the spectroscope, it shows a broad absorption band to the right of *E*, the left border of which reaches nearly to *b*, while the right border incloses *F*. In alkaline solution it shows a less broad absorption band between *E* and *F*, inclosing *b*. (Fig. 11.)

The **origin of urobilin** has been the subject of much discussion. Two theories have been advanced: (1) That urobilin is formed from the bilirubin which enters the in-

testine with the bile, is there acted upon by the nascent hydrogen resulting from fermentation, a reduction product being formed which is absorbed and eliminated by the kidneys ; (2) that urobilin is formed rather as the result of oxidation processes by means of the nascent oxygen in the intestine, or elsewhere in the body, than by a process of reduction. This theory was originally advanced by MacMunn, who based his view chiefly on the fact that by the action of hydrogen peroxide on acid hematin he was able to prepare an artificial product which showed the same spectroscopic appearances as normal urobilin. Hoppe-Seyler had previously prepared an artificial urobilin from hemoglobin, and also from hematin, by the action of tin

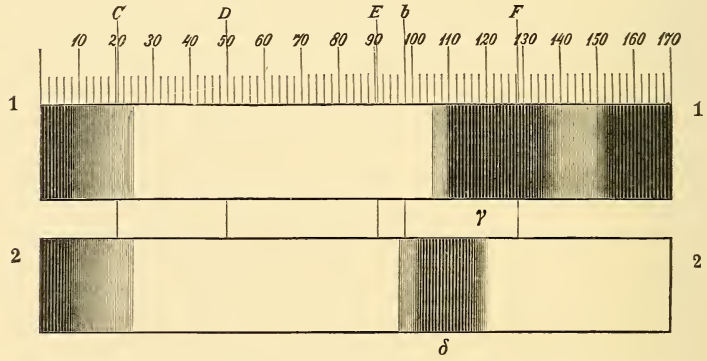


Fig. 11.—1, Acid urobilin; 2, alkaline urobilin (after Neubauer and Vogel).

and hydrochloric acid. Whether stercobilin and urobilin are to be looked upon as products of reduction or oxidation must, therefore, still be regarded as unsettled. The most important point to notice, however, is that urobilin may originate either from bile pigment or from blood pigment. It has been conclusively proved that the bile pigment is formed from hemoglobin ; and that in nearly all diseases of the liver accompanied by jaundice, urobilin is largely increased in the urine. Furthermore, that those conditions which are attended with a destruction of the blood-corpuscles are accompanied by an increased amount of urobilin in the urine. It is, therefore, safe to infer that the amount of urobilin in the urine is a measure of the destruction of the hemoglobin, or blood pigment.

The average quantity of urobilin in the twenty-four-hour urine, under normal conditions, is 123 milligrams; in disease the quantity may reach 800 milligrams. The excretion of urobilin is greater in the tropical than in the temperate climates (Lawson).

Clinical Significance.—Urobilin is *increased* in acute infectious diseases, such as scarlet fever, pneumonia, erysipelas, malaria, typhoid fever (moderately increased); also in acute sepsis, lymphangitis, acute articular rheumatism, appendicitis, atrophic cirrhosis and carcinoma of the liver, catarrhal icterus, lead colic, and pernicious anemia. It is also increased in cases of poisoning by potassium chlorate, antipyrin, antifebrin, and pyridin. On the other hand, it is nearly absent from the urine in phosphorus-poisoning.

Detection.[1]—Urobilin is best detected by means of the spectroscope: (1) Take from 10 to 20 c.c. of the urine, acidulate with a few drops of hydrochloric acid, and shake with from 6 to 10 c.c. of amyl alcohol. On spectroscopic examination the clear amyl-alcohol solution of urobilin shows a characteristic absorption band of acid urobilin. (Fig. 11.) (2) If to a small portion of this amyl-alcohol solution be added a few drops of a clear solution of 1 gram of zinc chloride in 100 c.c. of alcohol that has been rendered strongly alkaline with ammonia, a beautiful green fluorescence appears. This solution shows the spectrum of alkaline urobilin. (Fig. 11.)

For the isolation of urobilin the reader is referred to more extensive works on urinary analysis.

Urochrome.—This substance is the chief coloring-matter of normal and pathologic urine, and imparts a yellow, orange, and even a brownish color to the urine. According to Garrod,[2] a urate sediment always contains some urochrome,

[1] An old test, and one frequently applied for the detection and approximate estimation of urobilin, is the so-called **urophaein test** (*Heller*): Take about seven cubic centimeters of concentrated sulphuric acid in a wine-glass, and add twice the quantity of urine, which is poured into the acid from a height of about four inches. A garnet-red color appears which, if *normal* in amount, is so intense that only a little light can be seen through the mixture. If *increased*, the mixture is opaque, and if *diminished*, it is transparent. This test is most unsatisfactory, as normal coloring-matters other than urobilin are set free by the acid. This test is also modified by the presence of abnormal constituents, such as bile, sugar, etc. The test, therefore, is of very little, if of any, importance for the detection or approximate determination of urobilin in urine.

[2] "Journ. of Physiol.," XVII, 441, 1895.

either alone or with uroerythrin and other coloring-matters. The name *urochrome* was first applied in 1864 by Thudichum, who then considered it the chief coloring-matter of the urine. Urochrome is thought by some to consist of impure urobilin. It probably does contain some urobilin, but that it is an independent substance has been satisfactorily demonstrated by Thudichum, Garrod, and others.

Urochrome contains nitrogen, but is free from iron. Its solutions have an amphoteric reaction. In a dry state it is amorphous, and has a brown color. It is odorless in the cold, but when heated over the water-bath it has a faint odor of urine. It is very readily soluble in water and alcohol; only sparingly soluble in acetic ether, amyl alcohol, and acetone; and is insoluble in ether, chloroform, and benzol. Its solution, on the addition of an acid, shows only a diffused absorption of the spectrum at the violet end. According to Thudichum, the acid alcoholic solution shows a faint, narrow absorption band between *F* and *G*, its left edge bordering on *F*. The neutral and alkaline solutions do not show absorption bands. It is precipitated by phosphotungstic and phosphomolybdic acids, acetate of lead, silver nitrate, mercuric acetate, and also by saturating its solution with ammonium sulphate.

When uric acid is precipitated from a solution that has been treated with urochrome, the crystals are of a yellow or even brown color, and of the whetstone shape, the same as when they crystallize from the urine spontaneously. When uric acid is precipitated by an acid from a solution containing urochrome, the crystals are colored brown, the same as when they are precipitated from the urine by an acid.

Detection.—Urochrome is recognized by the fact that it is precipitated from its solutions by ammonium sulphate, and that when it is decomposed by acids, it furnishes a brown or black substance. It is also distinguished by its color and spectrum.

Urochrome is isolated, according to Garrod, by saturating the urine with ammonium sulphate, and extracting the precipitate with absolute alcohol. According to Thudichum, it is best isolated by first precipitating the urine with a mixture of barium hydrate and acetate, and then treating the filtrate with lead acetate and ammonia.[1]

[1] See Neubauer and Vogel, "Analyse des Harns," Bd. 1, 1898, S. 508.

Uroerythrin.—This substance is a constituent of normal urine, and is usually present only in small quantities. It has been termed *rosacic acid* by Prout, and *purpurin* by Golding Bird.

Uroerythrin is free from iron, and when isolated, is amorphous and of a brick-red color. It is soluble in amyl alcohol, slightly soluble in acetic ether and absolute alcohol, and very difficultly soluble in water. Its solution in alcohol soon decomposes. It is also decomposed by both oxidizing and reducing agents. Uroerythrin does not occur in the urine as a chromogen. When a urine is saturated with ammonium sulphate or chloride, uroerythrin is precipitated with the ammonium urate. Its solutions are not fluorescent. It is extracted from a reddish urate sediment by boiling alcohol.

Uroerythrin in dilute solutions shows two ill-defined ab-

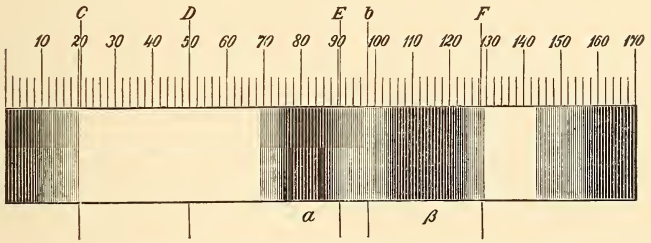


Fig. 12.—Spectrum of uroerythrin (after Neubauer and Vogel).

sorption bands, one with its left border midway between *D* and *E*, its right border inclosing *E* (*D* 70 *E*—*E* 13 *F*), and the other band with its left border to the right of *b*, and its right border inclosing *F* (*E* 44 *F*—*F* 9 *G*). (Fig. 12.) The right band is somewhat darker than the left, the light space between the two being rather ill defined.

Uroerythrin, for the most part, exists in the urine in chemic combination with uric acid. It not only gives a yellow, or yellowish-red, color to uric acid crystals, but also colors a urate sediment pink or brick-red.

Clinically, uroerythrin is increased in acute febrile diseases, such as pneumonia, influenza, typhoid fever, malaria, acute articular rheumatism, etc.; in diseases of the liver, especially those in which there is a disturbance in the circulation; in cirrhosis of the liver following the excessive use

of alcohol; and in chronic diseases of the heart and lungs. An increase of uroerythrin is usually accompanied by an increase of urobilin.

Detection.—A deposit of amorphous urates having a pink or reddish color shows the presence of uroerythrin. On the addition of an alkaline hydrate its solution is immediately colored dark green. An amyl-alcohol solution of uroerythrin, obtained by shaking the urine with amyl alcohol, shows the characteristic absorption bands. It is isolated by saturating the urine with ammonium chloride.

Urorosein.—Urorosein does not occur in the urine as such, but as a chromogen, which, upon the addition of mineral acids, is gradually broken up, a rose-red color resulting. According to Robin, this substance is present in very small amounts in every normal urine, and in much larger quantities in certain diseased conditions.

Urorosein dissolves in water with a resulting red color; also in dilute mineral and many of the organic acids; in alcohol and amyl alcohol. It is extracted from its aqueous solution by amyl alcohol, but not by ether, chloroform, benzol, or carbon disulphide. Its alcoholic solution shows a sharp and narrow absorption band between *D* and *E* (*D* 48 *E*). Ammonia, hydrates of the fixed alkalies, and alkaline carbonates immediately decolorize the red solution.

The chromogen, according to Robin, crystallizes in colorless transparent needles when its concentrated alcoholic solution is precipitated with ether. These crystals are readily soluble in alcohol and water, but not in ether or chloroform. It is incompletely precipitated by lead acetate.

Clinically, urorosein is increased in the urine in diseases of the lungs (tuberculosis), pernicious anemia, and in cases of marked chlorosis. It is also increased in diabetes mellitus, osteomalacia, typhoid fever, carcinoma of any of the abdominal viscera, appendicitis, nephritis, and especially in diseases of the stomach. It is increased by vegetable food.

Detection.—(1) To 10 c.c. of the urine add 15 drops of concentrated hydrochloric acid, and if the urine be rich in urorosein, a rose-red color appears in the cold in about ten minutes; the color appears more quickly when the mixture is heated to 70° C. (Robin). (2) Take from 50 to 100 c.c. of the urine and add from 5 to 10 c.c. of 25 per cent. sulphuric acid. A reddish or rose-red color appears

in a few minutes. If this colored mixture is then shaken with amyl alcohol, the coloring-matter is removed (Nencki and Sieber).

The spectroscopic examination of the amyl-alcohol extract is indispensable for the *certain* detection of urorosein.

OTHER ORGANIC CONSTITUENTS OF THE URINE.

A number of organic constituents, in addition to those already described, may occur in small quantities in the urine. We may divide these into the following groups :

1. Nonnitrogenous acids : oxalic, lactic, and succinic acids.
2. Fatty acids.
3. Glycerophosphoric acid (?).
4. Carbohydrates : dextrose (see p. 147) and animal gum.
5. Ferments : pepsin, trypsin.
6. Mucin.

Oxalic Acid ($C_2H_2O_4$).—Oxalic acid is usually, and perhaps always, a constituent of the urine in health, but is present in very small amounts (as high as 0.02 gram in twenty-four hours). Under pathologic conditions it appears in increased quantities in diabetes mellitus, organic diseases of the liver, and, indeed, in all conditions in which the oxidizing power of the system is decidedly interfered with, as in various diseases of the heart and lungs.

Oxalic acid crystallizes with two molecules of H_2O in colorless, rhombic prisms, which are readily soluble in water and alcohol.

The greater part of the oxalic acid taken into or formed in the body exists in the form of a salt of calcium—calcium oxalate.

Calcium Oxalate.—This salt crystallizes in two different forms according to the number of molecules of water it contains—*i. e.*, crystals belonging to the monoclinic system —C_2CaO_4, H_2O (small plates)—and those belonging to the tetragonal system—$C_2CaO_4,3H_2O$ (octahedra, etc.). The monoclinic crystals are seen when the salt rapidly separates from a concentrated solution ; the amorphous precipitate of calcium oxalate apparently has the same chemic composition. The tetragonal crystals are seen when the salt slowly separates from dilute acid solutions.

For a further consideration of this subject see page 219

Lactic Acid ($C_3H_6O_3$) is not a constituent of normal urine. Liebig was unable to detect the slightest trace of it in 41, 42, and 56 liters of healthy urine. It does not appear in the urine after the administration of sodium lactate (Nencki and Sieber). It has been found in the urine in combination with bases in cases of acute yellow atrophy and marked cirrhosis of the liver, trichinosis, phosphorus-poisoning, and after severe muscular exertion. According to Colasanti and Moscatelli, it occurs in the urine as sarcolactic acid.

Sarcolactic acid consists of a colorless, odorless, syrupy fluid, soluble in water, alcohol, and ether; it is nonvolatile. The free acid rotates the plane of polarized light slightly toward the right, while solutions of its salts rotate the plane slightly toward the left (Wislicenus). Lactic acid is monobasic; it combines with bases to form salts, of which zinc lactate is the most important. Nearly all of its salts are soluble.

For the detection of lactic acid see Neubauer and Vogel, "Analyse des Harns," Bd. I, 1898, S. 183.

Succinic Acid ($C_4H_6O_4$) has been occasionally found in the urine. Under ordinary conditions it probably exists in the urine chiefly in combination with sodium—sodium succinate. Succinic acid has been found in the urine especially after the ingestion of asparagus and asparagin. Baumann failed to find it after the ingestion of sodium succinate.

Fatty Acids.—These consist of acetic, butyric, formic, and propionic acids. They are apparently free in the urine, and present only in mere traces (0.008 gram per diem). They can be increased to 0.9–1.5 gram by treating the urine with oxidizing agents (v. Jaksch [1]). The amount of fatty acids also increases during the period of the ammoniacal fermentation (Salkowski [2]). In certain febrile conditions they are increased to 0.6 gram, and in certain liver diseases may go as high as one gram per diem. This condition is called *lipaciduria* by v. Jaksch.

Ferments.—*Pepsin.*—Several observers (Brücke, Sahli, Leo, and others) have found pepsin in the urine. The following is an abstract of Leo's [3] work on the subject: "Small pieces of fibrin soaked in the urine absorb the pepsin, and on removing them to 0.1 per cent. hydrochloric acid, they are rapidly digested. Control experiments with fibrin not previously soaked in urine gave negative results. The morning urine was found to be richest in pepsin."

Neumeister and Stadelmann have both shown that the ferment in the urine is true pepsin.

[1] "Zeitschr. f. physiol. Chem.," X, 536. [2] *Ibid.*, XIII, 264.
[3] "Pflüger's Archiv," XXXVII, 223, and XXXIX, 246.

Trypsin.—This ferment is probably absent from normal urine, although Sahli claims to have found it.

Mucin.—Much discussion has arisen as to whether the substance that is nearly always present in very minute quantities in the urine is mucin or really nucleo-albumin. It is considered by some observers to be the chief constituent of the mucus derived from the muciparous glands of the urinary tract below the kidneys. Further, that it occurs in normal urine as a viscid, slimy substance, which is precipitated by the vegetable acids, especially acetic acid; also by alcohol; that it is free from phosphorus, and, when boiled with dilute acids, yields a substance that reduces alkaline solutions. More recent observers consider it to be nucleo-albumin, and at the present time this theory is most tenable. (See p. 142.) The question, however, is unsettled, and needs further investigation.

CHAPTER III.

INORGANIC CONSTITUENTS OF NORMAL URINE.

The principal inorganic constituents of the urine are the chlorides, phosphates, and sulphates, which are in combination with sodium, potassium, ammonium, calcium, and magnesium; also traces of carbonates of the alkalies. There are also traces of iron, fluorine, and silicic acid, as well as free gases, including carbonic acid, nitrogen, and oxygen.

The combined quantities of these various substances amount to between nine and twenty-five grams in twenty-four hours.

CHLORIDES.

Chlorine exists in the urine chiefly as sodium chloride, although small amounts are in combination with potassium and ammonium. The chlorides, next to urea, constitute the chief solid constituent of the urine. They are derived from the food,—that is, the sodium chloride ingested with the food,—and under normal conditions practically all of this salt ingested is eliminated in the urine in an equivalent amount.

The quantity of sodium chloride in the twenty-four-hour urine is normally between 10 and 20 grams, and, calculated as chlorine, amounts to between 8 and 12 grams. A person ingesting food unusually rich in sodium chloride may eliminate more than 20 grams (NaCl), and the quantity may even reach 40 or 50 grams in the twenty-four hours. On the other hand, if the amount of nourishment is diminished, a decrease in the elimination of the chlorides is observed. If this is carried to the point of starvation, the chlorides almost entirely disappear from the urine, the traces remaining being derived from the tissues and fluids of the body. The latter retain tenaciously a certain amount of sodium

chloride, and if, following a period of starvation, food containing sodium chloride is again taken, not all appears in the urine, but a portion is retained in the body until the original equilibrium is restored. A similar retention may be observed for a few days following the ingestion of large quantities of water, which, under ordinary conditions, causes an increased elimination of chlorides.

An *increased* quantity of chlorine is due to an abundance of NaCl in the food, and is of no clinical importance. In diabetes insipidus, however, the increase of chlorine, which may reach thirty grams or more, is obtained at the expense of the body-fluids, and is, therefore, associated with marked emaciation. A *diminution* in the quantity of chlorine is in many instances of the greatest clinical importance. Such a diminution is often the result of disease, and not dependent entirely on a diminished quantity of salt ingested, although a low diet, naturally, has some effect on the quantity of chlorine eliminated.

Clinical Significance.—The chlorides are *diminished* in the acute stage of all acute diseases, and especially those associated with a serous exudation or transudation (dropsy), vomiting, or diarrhea. One of the most important examples of this is pneumonia, in the acute stage of which, on account of the serous exudation, the chlorine is very low or may even be entirely absent from the urine. As soon as convalescence commences and the serous exudation begins to be absorbed, the chlorine reappears or gradually increases until it may, in a few days, exceed the normal temporarily. The test for chlorides is, therefore, of definite clinical value in determining the progress of the pneumonic process. The quantity of chlorine in the urine is very important in the differential diagnosis between acute meningitis and typhoid fever, the former being attended with a serous exudation, and hence a *marked* diminution in the chlorides, while in the latter they are only moderately diminished. The chlorine is markedly diminished or absent in cholera, pyemia, and puerperal fever, and also much diminished in acute articular rheumatism.

In the convalescent stage of most acute diseases the chlorine gradually rises to normal, but is dependent chiefly on the appetite.

The chlorides are diminished in all chronic diseases, more particularly in those attended with dropsy, when they may

be absent from the urine. In the chronic diseases without exudation or transudation the diminution in the amount of chlorine is in proportion to the amount of sodium chloride taken with the food—in other words, the quantity of chlorine may be looked upon as a measure of the appetite. If at any time during the course of a chronic disease accompanied by dropsy the fluid be absorbed, the quantity of chlorine in the urine slowly rises to near the normal, but only rarely does it exceed the normal, since the absorption of the serous fluid is usually very gradual.

Detection.—The following test, which depends upon the precipitation of the chlorine by nitrate of silver, can be readily applied for the detection and approximate estimation of chlorides in the urine :

Take one-half of a wine-glass of urine, underlie with a third as much concentrated nitric acid in the same manner as in the nitric acid test for albumin. (See p. 124.) Then add one drop of a solution of silver nitrate,—one part of silver nitrate and eight parts of water,—and if chlorides be present, a precipitate of silver chloride is formed. If the relative proportion of chlorides is normal or increased, a solid compact ball of silver chloride is obtained, which falls to the surface of the nitric acid. If the relative proportion is diminished, however, instead of forming a solid ball the silver chloride precipitate spreads out or becomes diffused to a greater or less extent through the layer of urine.

This same test can also be applied by adding to one-half of a wine-glass of urine one or two drops of concentrated nitric acid, stirring the mixture, and adding one drop of the solution of silver nitrate (prepared as directed). If the resulting precipitate quickly falls to the bottom of the glass in a solid, flaky mass and does not tend to diffuse through the urine, the chlorides are normal or increased ; if diffused, they are diminished.

If the urine contains more than a *trace* of albumin, it must be removed by heat before the test is applied, for the following reasons : (1) The precipitate or ball of silver chloride can not be distinctly seen because of the cloud of precipitated albumin ; (2) the silver and albumin combine to form the albuminate of silver, thus modifying the inferences to be deduced from the test.

Quantitative Tests.—(a) **Mohr's Method.**—Precipitation by silver nitrate.

The following solutions are necessary:

1. Standard Silver Nitrate Solution: Dissolve 29.075 grams of fused silver nitrate in distilled water, and make the whole quantity up to exactly one liter (1000 c.c.). One cubic centimeter of this solution is equivalent to 0.01 gram of sodium chloride, or 0.006065 gram of chlorine.

2. A solution of neutral potassium chromate, made by dissolving one part of the chlorine-free salt in five parts of water.

Process.—Take 10 c.c. of urine; dilute with 50 c.c. of distilled water; add to this 8 or 10 drops of potassium chromate solution. Drop into this mixture from a burette the standard nitrate of silver solution. The chlorine combines with the silver to form silver chloride—a white precipitate. When all the chlorine is precipitated, silver chromate (red in color) forms, but not while any chloride remains in solution. The silver nitrate solution must, therefore, be added until a pink tinge appears. Read off the quantity of standard solution of silver used, subtract 1 c. c. for correction (see below), and calculate therefrom the quantity of chlorine, or sodium chloride, in the 10 c.c. of urine tested. From this deduce the percentage, or the total number of grams in the twenty-four-hour urine. For example, suppose that, after deducting 1 c.c. for correction, exactly 10.5 c.c. of the standard silver nitrate solution were used. Since 1 c.c. of this solution is equivalent to 0.006065 gram of chlorine, $10.5 \times 0.006065 = 0.0636825$ gram, or the amount of chlorine in the 10 c.c. of urine used.

Precautions and Corrections.—If the urine contains albumin, it must be removed by means of heat and acetic acid.

Alkaline urines should be rendered acid, preferably with acetic acid, previous to the titration.

The phosphate of silver is not precipitated in this test, as the silver salts of hydrochloric, chromic, and phosphoric acids are precipitated in the following order: chloride, chromate, and, finally, the phosphate.

A highly colored urine may give rise to difficulty in detecting the pink tinge of the chromate of silver. This is overcome by diluting the urine to a greater extent than in the directions given. It is not always necessary to dilute a pale-colored urine to the extent previously stated, the addition of 20 to 30 c.c. of water often being sufficient.

One cubic centimeter should always be subtracted from the total number of cubic centimeters of silver nitrate solution used, as the urine contains small quantities of certain compounds more easily precipitable than the chromate of silver. To obviate this error, *Sutton has advised the following modification of Mohr's test:* Take 10 c.c. of urine in a thin porcelain dish, and add 1 gram of pure ammonium nitrate. The whole is then evaporated to dryness, and gently heated over a small flame to low redness until all vapors are dissipated and the residue becomes white. It is then dissolved in a small quantity of water, and the carbonates produced by combustion of the organic matter neutralized by dilute acetic acid. A few grains of pure carbonate of calcium are added to remove all free acid, and then one or two drops of a solution of potassium chromate. The mixture is then titrated with decinormal silver solution (16.966 grams of silver nitrate to the liter) until the pink color appears. Since each cubic centimeter of the silver solution represents 0.005837 gram of sodium chloride, the quantity of sodium chloride, or chlorine, can be readily calculated.

The results obtained by direct titration of the urine with a standard solution of silver nitrate can not be considered absolutely accurate, since uric acid, xanthin bases, sulphocyanides, sulphites, coloring-matters, etc., are precipitated with the silver chloride before the end-reaction appears. To obviate such errors, Neubauer and Salkowski have advised the following process :

Neubauer-Salkowski Method.—The necessary solutions are to be prepared according to the directions given under Mohr's method.

Take 10 c.c. of urine in a small platinum or porcelain crucible ; add one gram of sodic carbonate that is free from chlorine, and 1 or 2 grams of chlorine-free potassium nitrate, and evaporate to dryness at 100° C. Heat over a free flame—at first gently, later strongly—until the molten mass is perfectly white. Dissolve the white residue in distilled water, and transfer the solution to a small flask. To this alkaline solution add dilute nitric acid, drop by drop, until faintly acid, and then neutralize again with chlorine-free sodic carbonate. Add a few drops of the solution of potassium chromate to the mixture, and allow the standard solution of silver nitrate to flow from a burette into the mixture in the flask, until the first appearance of a permanent pink

tinge (end-reaction). Read the number of cubic centimeters of standard solution of silver used, and calculate therefrom the quantity of chlorine or sodium chloride in the 10 c.c. of urine tested.

Volhard and Falck Method.—This method depends upon the action of soluble sulphocyanides with solutions of silver and ferric salts. Soluble sulphocyanides produce in silver solutions a white precipitate of sulphocyanide of silver, which is insoluble in dilute nitric acid. A like precipitate of sulphocyanide of silver with a solution of nitrate of silver is given by the blood-red solution of sulphocyanide of iron, and the color of the latter at last completely disappears. If, therefore, a solution of sulphocyanide of potassium be added to an acid solution of nitrate of silver to which a little ferric sulphate has been added, every drop of the sulphocyanide solution at first produces a blood-red cloud, which, however, quickly disappears on stirring, while the fluid becomes milk-white. It is not until all the silver is precipitated that the red color of the sulphocyanide of iron remains permanent and the end of the process is reached.

The following solutions are necessary :

1. *Standard solution of silver nitrate*, made according to directions given under Mohr's method. One cubic centimeter is equivalent to 0.006065 gram (6.065 milligrams) of chlorine, or 0.010 gram (10 milligrams) of sodium chloride.

2. *Solution of Ferric Oxide.*—A cold, saturated solution of crystallized ferric alum free from chlorine, or a solution of ferric sulphate that contains 50 grams of oxide of iron to the liter.

3. *Standard Solution of Potassium Sulphocyanide.*—Since potassium sulphocyanide can not be accurately weighed, because of its hygroscopic property, it is necessary to standardize by titrating with a standard solution of silver nitrate. Dissolve 10 grams of potassium sulphocyanide in a little less than a liter of distilled water, and place a portion of this in a burette. Take 10 c.c. of the standard silver solution, place in a beaker, add 5 c.c. of the iron solution, and then pure nitric acid, drop by drop, until the mixture is colorless. Then allow the sulphocyanide solution to flow in from the burette until the fluid has a permanent red color, the first appearance of which indicates the end-reaction—that is, when all of the silver is precipitated as silver sulpho-

cyanide, the next drop gives a permanent red color, due to the precipitation of the sulphocyanide of iron. If, for example, to 10 c.c. of the silver solution 9.6 c.c. of the potassium sulphocyanide solution have been used before the red color is permanent, 960 c.c. are measured off, and diluted with 40 c.c. of distilled water to make a liter. Titrate once more, in order to be sure that the strength of the two solutions—standard silver and potassium sulphocyanide solutions—is equivalent.

Process.—Take 10 c.c. of urine, add 1 or 2 grams of potassium nitrate free from chlorine, and evaporate to dryness on a water-bath. The residue is then heated over a free flame—at first gently, afterward strongly—until the carbon is completely oxidized and the residue is a white mass. Since the nitrous acid formed in this process prevents the end-reaction, the fused mass is dissolved in water, acidulated with nitric acid, and then the chlorine precipitated with an excess of the standard solution of silver. After this mixture has been warmed on a water-bath for a time to remove completely the nitrous acid, it is allowed to cool. Then 5 c.c. of the iron solution are added; and, finally, the potassium sulphocyanide solution, until the excess of the silver added is precipitated, which is known by the permanent red color of the mixture. The difference between the number of cubic centimeters of the silver and sulphocyanide solutions corresponds to the chlorine contained in the urine. If, for instance, at first 15 c.c. of the silver solution were added to 10 c.c. of urine, and 5 c.c. of the sulphocyanide solution were required to titrate back the excess, the amount of chlorine in the urine would correspond to 15 — 5 = 10 c.c. of the silver solution.

(b) **Purdy's Method, by the Electric Centrifuge.**—The percentage tubes of the Purdy electric centrifuge are filled to the 10-c.c. mark with the urine to be tested; fifteen (15) drops of nitric acid are added to prevent precipitation of the phosphates (if the specific gravity be very high, 20 to 30 drops should be added), and then the tubes are filled to the 15-c.c. mark with a strong solution of nitrate of silver (1 : 8). The tubes are next closed, and inverted several times, until the urine and the reagents are thoroughly mingled. The tubes are then placed in the centrifuge, and revolved at the rate of 1000 revolutions a minute for three successive periods of five minutes each, when the

quantity in bulk percentage may be read off from the graduated scale on the sides of the tubes. Purdy has found that the *bulk* percentage of chlorides in normal urine thus obtained ranges from 10 to 12 per cent.

By a comparison of the bulk percentages of chlorides with the volumetric determinations of the same the author has been able to obtain, from a large number of observations, a standard of percentage by *weight*. He has found that each $\frac{1}{10}$ of a c.c. of precipitate, calculated as chlorine, is equivalent to 0.123 per cent. by weight.

PHOSPHATES.

Phosphoric acid in the urine occurs in the form of two classes of phosphates :

1. Earthy Phosphates : phosphates of calcium and magnesium, the former being the more abundant.

2. Alkaline Phosphates : phosphates of sodium and potassium, the former being the more abundant.

The **earthy phosphates**, which consist of the phosphates of the alkaline earths,—calcium and magnesium,—are insoluble in water, but soluble in acids. In an *acid* urine they are in the form of acid phosphates, which are in solution. Occasionally, a crystalline deposit of acid calcium phosphate (see p. 218) having the composition $CaHPO_4 + 2H_2O$ (Hassal, Stein) separates from a faintly acid urine.

In an *alkaline* urine the acid phosphates of magnesium and calcium are converted to normal phosphates, and are precipitated as a heavy, whitish sediment, frequently termed *amorphous phosphates*. A similar phosphatic precipitate is often obtained when a faintly acid, neutral, or alkaline urine is heated, owing to the conversion of the acid phosphate to normal phosphate, which is precipitated, and the superphosphate, which remains in solution :

$$4CaHPO_4 = CaH_42PO_4 + Ca_32PO_4.$$

This phenomenon is a frequent source of error in testing for albumin in urine by heat. If, upon heating, such a precipitate appears, it may be readily distinguished from the precipitate of albumin by the addition of a few drops of acetic acid, which quickly dissolves the earthy phosphates. When a urine becomes *ammoniacal*, the phosphate of mag-

nesium combines chemically with ammonia to form the *ammonio-magnesium phosphate*, or "triple phosphate," which is in crystalline form. (See p. 217.)

The **alkaline phosphates** consist chiefly of the phosphates of sodium and potassium, which, unlike the earthy phosphates, are soluble in water and alkalies. The sodium salt—monosodic acid phosphate (the disodic acid phosphate is also sometimes present)—is much more abundant than the potassium salt, and, as previously stated, it is to this compound that the acidity of the urine is chiefly due. The alkaline phosphates form the chief bulk of the phosphates of the urine, being in excess of those combined with the alkaline earths, the proportion being between 1 ½ and 2 of the former, to 1 of the latter.

The phosphoric acid of the urine is derived partly from the food and, apparently, partly from the decomposition products of phosphorus-containing organic substances such as nuclein and lecithin.

The average quantity of phosphoric acid in the twenty-four-hour urine, calculated as phosphoric anhydride (P_2O_5), is from 2.5 to 3.5 grams. This quantity is subject to much variation in health, and on a diet rich in earthy salts may fall to only a fraction of a gram, owing to the fact that the phosphoric acid combines with the earthy salts, and is thus prevented from being absorbed.

Clinical Significance.—Under pathologic conditions the phosphoric acid is largely *increased* in the urine in extensive diseases of the bones, as rickets, osteomalacia, diffuse periostosis, etc.; in destructive diseases of the lung, as in pulmonary tuberculosis, particularly in the early stages; in extensive diseases of the nervous tissue, diseases of the brain, in chorea, etc.; in acute yellow atrophy of the liver; after sleep produced by potassium bromide, or chloral hydrate (Mendel); and it is temporarily increased after copious drafts of water.

Phosphoric acid is *diminished* in acute diseases, probably because only a small amount of food is taken; and most of the chronic diseases, excepting those previously mentioned; in all diseases of the kidney; in gout; in pregnancy, probably due to the formation of the fetal bones; and also after large doses of chalk, ether, or alcohol.

The term **phosphaturia** should be restricted to indicate a constant increase in the total quantity of phosphoric acid

in solution in the urine. The term is frequently *incorrectly* applied to urine that has, constantly, a deposit of amorphous or crystalline phosphates. Those pathologic conditions in which the urine contains an abnormally large excess of phosphates in the twenty-four-hour urine may be said to be attended with "phosphaturia."

A condition of so-called **phosphatic diabetes** has been described by a few writers, in which the urine is free from sugar, but contains a continued large excess of phosphates. The symptoms are not unlike those of diabetes: *i. e.*, large daily quantity of urine, emaciation, aching pains in the lumbar region, morbid appetite, dry, harsh skin, etc. Not infrequently this condition seems to alternate with diabetes mellitus: that is, the symptoms of diabetes continuing, the sugar disappears from the urine, and is apparently replaced by a very large excess of the phosphoric acid—as much as 10 grams. If the sugar reappears, the quantity of phosphoric acid falls to normal or even below the normal.

Detection.—1. Earthy Phosphates.—The following test serves for the detection and approximate estimation of the earthy phosphates: Take a half test-tube of filtered urine, and add sufficient ammonic hydrate to render it alkaline. Upon warming the mixture the earthy phosphates separate, and soon begin to settle at the bottom of the tube. If, after eighteen to twenty-four hours, the deposit thus formed is from ¼ to ½ of an inch deep, the relative proportion may be said to be within normal limits; if less than ¼ of an inch, diminished; and if more than ½ of an inch, increased.

2. Alkaline Phosphates.—The following test may be applied for the detection and approximate estimation of the alkaline phosphates: After having separated the earthy phosphates as directed, the mixture is filtered. Take the entire filtrate in another test-tube, and add about one finger-breadth of magnesia mixture.[1] Upon warming the mixture a white precipitate, representing the alkaline phosphates, occurs, which, if normal, settles down to between ½ and ¾ of an inch after eighteen to twenty-four hours; if less than ½ of an inch, diminished; and if more than ¾ of an inch, increased.

[1] *Magnesia Mixture.* — Magnesium sulphate, ammonic hydrate, ammonium chloride, of each, 1 part; water, 8 parts.

Determination of Total Phosphoric Acid.—The following test is based upon the facts that (1) when a solution of a phosphate acidulated with acetic acid is treated with a solution of uranium nitrate or acetate, a precipitate falls that is composed of uranium phosphate; (2) when a soluble salt of uranium is added to a solution of potassium ferrocyanide, a reddish-brown precipitate, or color, is developed.

Prepare the following solutions:

(*a*) *A Standard Solution of Uranium Nitrate or Acetate.*—Dissolve exactly 35.5 grams of pure uranium nitrate or acetate in distilled water sufficient to make 1000 c.c.; 1 c.c. of this solution corresponds to 0.005 gram of phosphoric anhydride (P_2O_5).

Oftentimes it is not safe to use these salts of uranium, since they are frequently contaminated with uranic oxides. It then becomes necessary to prepare the standard solution in the following manner:

1. Make a standard solution of sodium phosphate by dissolving 10.085 grams of the well-crystallized salt in distilled water, and dilute to a liter; 50 c.c. then contain 0.1 gram of P_2O_5.

2. To prepare the uranium acetate or nitrate solution, dissolve 20.3 grams of yellow uranic oxide in pure strong acetic acid to make the acetate, or in pure concentrated nitric acid to make the nitrate, and dilute with distilled water to nearly a liter. To determine the strength of this solution, take 50 c.c. of the standard solution of sodium phosphate in a glass evaporating dish, add 5 c.c. of the sodium acetate solution (given below), and proceed exactly as with urine (process, see below). The quantity of uranium solution used is then read off, being that which is necessary to decompose the sodium phosphate, corresponding to 0.1 gram of P_2O_5. Then calculate the amount of distilled water to be added to make 1 c.c. correspond to 0.005 gram of phosphoric anhydride.

(*b*) *Acid Solution of Sodium Acetate.*—Dissolve 100 grams of sodium acetate in 800 c.c. of distilled water; add 100 c.c. of 30 per cent. acetic acid, and finally dilute with distilled water to 1000 c.c.

(*c*) A *saturated solution of potassium ferrocyanide*, to be used as an indicator.

Process.—Take 50 c.c. of the urine in a glass evaporating dish, add 5 c.c. of the sodium acetate solution, and

heat the mixture to 80° C. over a water-bath. From a burette, run into the hot urine, drop by drop, the standard solution of uranium, as long as a precipitate forms or until a drop of the mixture, removed by means of a glass rod and placed on a porcelain plate or slab, gives a distinct brown color with a drop of the potassium ferrocyanide solution. When this point is reached, the quantity of uranium solution used from the burette is read off. The number of cubic centimeters used multiplied by 0.005 will give the quantity of phosphoric acid (calculated as phosphoric anhydride) in 50 c.c. of urine, and from this is calculated the quantity in twenty-four hours.

The reddish-brown color which takes place with the solution of potassium ferrocyanide and the mixture, first makes its appearance at the time when the uranium solution has precipitated all of the phosphoric acid, and the mixture contains free uranium.

Cochineal tincture is highly recommended by Malot and Mercier as an indicator, instead of the potassium ferrocyanide. The tincture is prepared by digesting a few grams of cochineal with a 250-c.c. mixture of one part of alcohol and three or four parts of water, in the cold. After several hours the solution is filtered and it is then ready for use. In the phosphoric acid test a few drops of this tincture are added to the urine, or phosphate solution, in the evaporating dish ; the heat is then applied, and the standard uranium solution added until a faint but distinct permanent green color appears. The green color begins to appear as soon as there is the slightest excess of uranium in the solution—in other words, as soon as the phosphoric acid has been entirely precipitated.

Quantitative Estimation of Phosphoric Acid Combined with Calcium and Magnesium (Earthy Phosphates).—Process.—Take 200 c.c. of urine, precipitate with ammonic hydrate with the aid of gentle heat, allow to stand from twelve to twenty-four hours, then filter and wash with ammonia water. The filter-paper is then pierced at the point and the precipitate washed through into a beaker with a stream of hot water, and dissolved while warm in as little acetic acid as possible. Add 5 c.c. of the sodium acetate solution, dilute to 50 c.c., and proceed as previously indicated. The difference between the total amount of phosphoric acid and that in combination with

calcium and magnesium—earthy phosphates—also represents the quantity combined with the alkalies—alkaline phosphates.

Purdy's Centrifugal Method for Total Phosphoric Acid.—Fill the percentage tubes to the 10-c.c. mark with the urine to be tested, and add magnesia mixture (formula, see p. 109) to the 15-c.c. mark. The tubes are then closed and inverted several times, until the urine and reagent are thoroughly mixed. The tubes are next placed in the centrifuge and revolved for three successive periods of five minutes each at the rate of 1000 revolutions a minute. The *volume* percentage is then read off. In *normal* urine this will be found to be in the neighborhood of 8 per cent.

The author has obtained, from a large number of observations, a standard of percentage by *weight*, by a comparison of the volume percentages with the volumetric determinations. He has found that each $\frac{1}{10}$ of a c.c. of precipitate calculated as P_2O_5 is equivalent to 0.0225 per cent. by weight.

SULPHATES.

Sulphuric acid is present in the urine in two forms—as ordinary alkaline sulphates of potassium and sodium (preformed sulphuric acid), and as ethereal sulphates [1] (conjugate sulphuric acid). The sulphates are derived partly from the food and partly from the chemic changes of proteids in the tissues. The albuminous substances taken as food contain sulphur, which becomes oxidized in the economy and results in sulphuric acid, some of which, in turn, immediately combines with a portion of the sodium and potassium to form ordinary sulphates, and a small portion to form the ethereal sulphates by pairing.

The total quantity of sulphuric acid in the twenty-four-hour amount of urine of an adult taking a mixed diet is from 1.5 to 3 grams, or an average of 2 grams. About one-tenth of the total sulphuric acid is in the form of ethereal sulphates. The quantity of sulphuric acid is subject to considerable variation, being largely dependent upon the amount of proteid food ingested.

The sulphates are never found in the urine as a deposit, owing to the fact that they are very soluble compounds.

[1] See p. 84.

Clinical Significance.—The sulphates are *increased* in acute fevers, probably due to the markedly increased metabolism. According to Bence Jones, they are especially increased in acute inflammatory diseases of the brain and spinal cord and in delirium.

The sulphates are *diminished* in all diseases, especially the chronic forms, and during the convalescent stage of acute diseases, when the metabolism and appetite are much diminished. They are notably diminished in cases of carbolic acid poisoning, or following the internal or external use of large amounts of any phenol compound, such as salol, lysol, etc; under such circumstances, however, the diminution of the ordinary sulphates is attended with a corresponding increase of the ethereal sulphates (phenol-potassium sulphate).

In general, it may be stated that the variation in the quantity of ordinary sulphates eliminated in the urine runs parallel to that of urea.

Detection.—The following test serves for both the detection and approximate estimation: Take one-half test-tube of filtered urine and add from one to two fingerbreadths of barium solution.[1] A white precipitate occurs which, if it fills one-half the concavity of the test-tube in from eighteen to twenty-four hours, may be considered normal in quantity; if less than one-half the concavity, diminished; and if more than one-half the concavity, increased.

Quantitative Determination.—1. Total Sulphuric Acid.—For the determination of the total amount of sulphuric acid (SO_3)—*i. e.*, preformed and conjugate sulphuric acid together—one of two methods is adopted: (*a*) Gravimetric method and (*b*) volumetric method.

(*a*) *Gravimetric Method.*—This method consists in weighing the precipitate of barium sulphate obtained by adding barium chloride to a known volume of urine; 100 parts of sulphate of barium correspond to 34.33 parts of sulphuric acid (SO_3).

Method (*Salkowski*).—Take 100 c.c. of urine in a beaker, and acidulate with 5 c.c. of pure hydrochloric acid. This mixture is then boiled, and chloride of barium added to the boiling fluid until no more precipitate occurs.

The precipitate is collected on a small filter of known ash, and washed with hot distilled water until no more

[1] *Barium Solution.*—Barium chloride, 4 parts; concentrated hydrochloric acid, 1 part; distilled water, 16 parts.

barium chloride occurs in the filtrate : *i. e.*, until the filtrate remains clear after the addition of a few drops of sulphuric acid. Then wash with hot alcohol and afterward with ether. Remove the filter, and place it with its contents in a platinum crucible. Heat to redness. Cool over sulphuric acid in an exsiccator ; weigh, and deduct the weight of the crucible and filter ash. The remainder is the weight of barium sulphate formed, from which the SO_3 is calculated—100 parts of barium sulphate corresponding to 34.33 parts of SO_3.

Correction.—When the experiment is carried out as above, there is a slight error from the formation of a small quantity of sulphide of barium. This may be corrected as follows : After the platinum crucible has cooled, add a few drops of pure sulphuric acid, which converts into a sulphate any sulphide present. The contents of the crucible are again heated to redness to drive off any excess of sulphuric acid, cooled and dried over sulphuric acid, and weighed.

(*b*) *Volumetric Method.*—This process is conducted by adding a standard solution of barium chloride to a given quantity of urine as long as a precipitate occurs.

The following solutions are necessary :

1. A standard solution of barium chloride made by dissolving 30.54 grams of pure crystallized barium chloride in water, and diluting to exactly one liter ; 1 cubic centimeter corresponds to 0.010 gram of SO_3.

2. An aqueous solution of potassium sulphate so made that one liter will contain 21.775 grams of the salt.

Process.—Place 50 c.c. of the urine in a flask or small beaker, and add from 5 to 10 c.c. of pure hydrochloric acid. The mixture is then boiled over a free flame for fifteen minutes, or heated on a water-bath for one hour. To the hot fluid the standard barium chloride solution is added, 1 c.c. at a time, until a precipitate fails to occur. After 5 to 8 c.c. of the standard solution have been added, filter a small portion of the mixture through a very small filter-paper, and to the filtrate add a few drops of the standard solution. If a precipitate occurs, return the whole to the flask, add more barium solution, and test as before. Continue until no more precipitate is formed on the addition of the barium chloride solution. Any excess of barium (that uncombined with sulphuric acid) is shown by placing a drop or two of the filtrate on a glass plate over a dark back-

ground, and adding a drop or two of the solution of potassium sulphate, when a decided cloudiness appears. This excess of barium must be avoided, and, therefore, in the test with potassium sulphate only the slightest cloudiness should appear, which shows that just the right amount of barium has been added; if an excess of barium is present, the entire analysis must be repeated.

The quantity of sulphuric acid is calculated from the amount of barium chloride solution used—one cubic centimeter of which corresponds to 0.010 gram of SO_3.

2. Conjugate Sulphuric Acid (Ethereal Sulphates).—*Salkowski's Method.*—One hundred cubic centimeters of clear, filtered urine are mixed with 100 c.c. of an alkaline solution of barium chloride (saturated solution of barium chloride, 1 part; and a saturated solution of barium hydrate, 2 parts, both saturated in the cold), the mixture being thoroughly stirred. After a few minutes this is filtered through a dry filter into a dry graduate up to the 100-c.c. mark. This portion, corresponding to 50 c.c. of urine, is now strongly acidulated with 10 c.c. of hydrochloric acid, boiled, kept at 100° C. on the water-bath for an hour, and then allowed to stand until the precipitate has completely settled: if possible, it should remain undisturbed for twenty-four hours. The further treatment of this precipitate (conjugate sulphates) is then carried out as in the above-described gravimetric process. (See (*a*).)

Calculations.—The molecular weight of $BaSO_4$ being 232.82; that of SO_3, 79.86; of H_2SO_4, 97.82; and of S, 32, the figure expressing the amount of H_2SO_4, SO_3, or S, corresponding to 1 gram of $BaSO_4$, is found according to the following equations:

232.82 : 79.86 : : 1 : x, and $x = 0.34301$. ∴ 1 gram of $BaSO_4 = 0.34301$ gram of SO_3.

232.82 : 97.82 : : 1 : x, and $x = 0.42015$. ∴ 1 gram of $BaSO_4 = 0.42015$ gram of H_2SO_4.

232.82 : 32 : : 1 : x, and $x = 0.13744$. ∴ 1 gram of $BaSO_4 = 0.13744$ gram of S.

To calculate results, it is only necessary to multiply the weight of $BaSO_4$ found by 0.34301, 0.42015, or 0.13744, in order to ascertain the amount of sulphuric acid contained in 50 c.c. of urine in terms of SO_3, H_2SO_4, or S, respectively. This method of calculation applies to the gravimetric esti-

mation of both the total sulphates and the combined sulphates.

To obtain the amount of preformed sulphuric acid, or that in combination with the alkalies, subtract the amount of combined SO_3 from the total amount of SO_3. The difference is the preformed SO_3.

Example: One hundred cubic centimeters of urine gave 0.5 gram of total barium sulphate. Then 0.5 multiplied by 0.34301 = 0.171 gram of total SO_3. Another 100 c.c. of the same urine gave 0.05 gram of barium sulphate from the ethereal sulphates; then 0.05 multiplied by 0.34301 = 0.017 gram of combined SO_3. The difference between the total and the combined SO_3 = 0.171 — 0.017 = 0.154 gram of SO_3 in combination with the alkalies.

CARBONATES.

A freshly passed urine of alkaline reaction generally contains small quantities of carbonates and bicarbonates of sodium, magnesium, calcium, and ammonium, all of which arise in the economy from the carbonates of the food, or from salts of malic, tartaric, lactic, succinic, and other vegetable acids ingested with the food. They are, therefore, most abundant in the urine of herbivora, whose urine is thus rendered alkaline. A urine containing carbonates is either turbid when passed, or soon becomes so on standing. The deposit, if allowed to settle, will, on examination, be found to consist of calcium carbonate mixed with phosphates.

According to Wurster and Schmidt,[1] a liter of normal human urine of a specific gravity of 1020, if acid in reaction, contains, on an average, from 40 to 50 c.c., and if neutral or alkaline, over 100 c.c. of carbonic acid, which is capable of being expelled by a current of air. The amount of carbonic acid per 100 c.c. varies between 17 c.c. (urine of low specific gravity) and 294 c.c. (urine of high specific gravity).

Carbonic acid forms neutral (normal) and acid salts. Of the alkaline carbonates, both the acid and the normal are soluble, but the acid is considerably less soluble than the normal. The normal carbonates of calcium and magnesium, on the other hand, are very slightly soluble, but the acid is

[1] "Centralbl. f. Physiologie," 1887, 421.

more soluble than the normal. The carbonate of ammonium is volatile at ordinary temperature.

For the detection and quantitative determination of carbonic acid, both free and combined, see Neubauer and Vogel, "Analyse des Harns," Bd. 1, 1898, S. 37 u. 735.

IRON.

Iron is found only in minute traces in the residue of the urine after ignition. According to Magnier, the amount of iron in a healthy man of medium weight varies between 0.003 and 0.011 gram in a liter. The coloring-matter, which is precipitated with the uric acid on the addition of concentrated hydrochloric acid, according to Kunkel, contains iron.

Detection.—The ash of the residue of urine is always used for the isolation and detection of iron. It is dissolved in a little hydrochloric acid, and the solution divided into two parts. The first part is boiled with a drop of nitric acid and treated with a solution of potassium sulphocyanide which, if ferric oxide be present, produces a red or blood-red color. If potassium ferrocyanide is added to the other half of the solution, after boiling with nitric acid and diluting, flocculi of Prussian blue separate after standing a time.

For the quantitative determination of iron and further information regarding this substance the reader is referred to Neubauer and Vogel, "Analyse des Harns," Bd. 1, 1898, S. 47 u. 750.

HYDROGEN PEROXIDE.

This substance was first detected in the urine by Schönbein.[1] The most reliable reaction that serves for its recognition depends upon the power it possesses of bleaching a dilute tincture of indigo. The urine to be tested must be perfectly fresh.

The relative unimportance of this substance in the urine forbids more than a mere mention here.[2]

[1] "Journ. f. prakt. Ch.," XCII, 168, 1864.

[2] See Neubauer and Vogel, "Analyse des Harns," 1898, S. 39.

URINARY CRYOSCOPY.

The determination of the freezing-point of urine, which was first studied and used by Bouchard in 1870, has received special attention during the past two years. It is dependent on Raoult's law—i. e.: "One molecule of any compound, when dissolved in one hundred molecules of a liquid, lowers the freezing-point of the liquid by an amount which is nearly constant."

The freezing-point of the urine is normally from —1.30° to —2.20° C. Special apparatus and a thermometer registering from $\frac{1}{100}$ to $\frac{1}{1000}$ degree are necessary for an accurate determination. The following data are required: (1) the freezing-point of the urine; (2) the percentage of sodium chloride; (3) the twenty-four-hour quantity of urine; (4) the weight of the person in kilos; and (5) the total solids of the urine calculated from the specific gravity (see page 40).

The ratio of the freezing-point of the urine to the percentage of sodium chloride sometimes furnishes information of value in the diagnosis of heart disease and chronic nephritis. The subject requires further investigation before much of practical value can be ascribed to it.

(For further information see *Archiv f. exp. Path. u. Pharmacologie*, v, 29, 5303; *Zeitschrift f. klin. Medicin*, 1900, Bd. 65, S. 1; *Physical Review*, 1893, 1896, 1897, and 1901; *Münch. med. Wochenschr.*, Oct. 30, 1900; *Philadelphia Medical Journal*, June 29, 1901.)

CHAPTER IV.

ABNORMAL CONSTITUENTS OF URINE.

PROTEIDS.

Under pathologic conditions urine may contain a number of proteids—*i. e.*, serum albumin, serum (or para-) globulin, albumose, peptone (?), hemoglobin and methemoglobin, and fibrin and fibrinogen. Egg-albumin is occasionally found, especially after the liberal ingestion of eggs as a food. Several of these proteids may be present in the urine at the same time, or, on the other hand, only a limited number present, such as albumin and globulin, albumin and hemoglobin, etc.

General Reactions of the Proteids.

A. Color tests.

1. Xanthoproteic Reaction.—Heat the solution of the proteid with concentrated nitric acid. There results a yellow color, which, on the addition of an alkaline hydrate, changes to a deep orange. If *much* proteid, except albumose and peptone, be present, a yellow precipitate is obtained at the same time; with *less* proteid, its solution merely turns yellow on boiling, and orange on the addition of an alkali; if only a *trace* is present, no yellow color is observed until after the addition of the alkali.

2. Millon's Reaction.—With Millon's reagent [1] proteids, when present in sufficient quantity, give a precipitate that turns red on heating. If only present in traces, no precipitate is observed on heating, but merely a red colorization of the solution.

3. Piotrowski's Reaction.—If a solution of the proteid be mixed with an excess of a concentrated solution of sodic hydrate, and one or two drops of a dilute solution of sulphate of copper be added, a violet color is obtained, which deepens on boiling. Albumoses and peptones give a rose-red color (*biuret reaction*); care must be taken in the addition of the cupric sulphate solution, since an excess gives a reddish-violet color

[1] See foot-note, p. 170.

somewhat similar to that obtained in the presence of other proteids.

The foregoing tests serve to detect the smallest traces of proteids.

B. General Precipitants.—Solutions of proteids are precipitated by the following reagents (peptones are exceptions in most cases):

1. Render the solution strongly acid with acetic acid, and add a few drops of a solution of potassium ferrocyanide. A precipitate shows the presence of proteids, except true peptone and some forms of albumose.

2. Render the fluid as before strongly acid with acetic acid, add an equal volume of concentrated solution of sodium sulphate, and boil. A precipitate forms if proteids, except peptone, are present. This test is particularly useful, since the reagents used do not produce any decomposition of other substances that may be present, and do not interfere with certain other tests that may be applied after the removal of the proteids by filtration.

3. Completely saturate the fluid with ammonium sulphate, having previously neutralized and then rendered *faintly* acid with acetic acid; this precipitates all proteids except peptones.

4. Alcohol, tannic acid, phosphotungstic acid, and potassio-mercuric iodide are also general precipitants, the last two being particularly useful for delicate tests.

The term "albumin," in its ordinary clinical use, includes not only serum albumin, but also serum globulin, and, in rare instances, albumose. It should be remembered that these proteids differ in many respects, and, so far as is possible, should be separately identified.

ALBUMIN.

Serum albumin is doubtless the most important proteid found in the urine. It can safely be considered an abnormal constituent when present in amounts capable of being detected by the tests that are ordinarily used. Whether or not albumin is present in minute traces in the urine in health—such traces being incapable of detection by the tests generally employed—is still a debated question. From a practical point of view this question can be disregarded.

Albuminuria is not necessarily an indication of renal disease, for albumin may be present in the urine without the slightest alteration in the renal structure. In general, the presence of albumin indicates a disturbance or disease in

some part of the genito-urinary tract, and with one exception —*i. e.*, "functional albuminuria"—is always accompanied by formed physiologic or pathologic elements in the urinary sediment.

Albumin is not capable of crystallization; it is soluble in water, in dilute saline solutions, and in saturated solutions of sodium chloride and magnesium sulphate. It is, however, precipitated by saturating with sodium or ammonium sulphate. It is coagulated by heat, usually at from 70° to 73° C., particularly in the presence of sodium chloride. It is not precipitated by ether, in which respect it differs from egg-albumin. Under ordinary conditions it does not pass through animal membranes.

Causes of Albuminuria.—In general, the causes of albumin in the urine are: (1) Changes in the kidney structure, which, on account of its abnormal state, allows the albumin to transude; (2) alterations in the blood pressure in the kidneys; (3) abnormal changes in the quality of the blood entering the kidney, thus rendering its serum albumin more diffusible; and (4) disturbances or diseases of the urinary tract below the kidneys—*i. e.*, renal pelvis, ureters, bladder, prostate gland, and urethra. Under this heading may be included, also, albuminous elements entering from the genital tract.

Clinical Importance.—1. Albuminuria due to pathologic changes—inflammatory and degenerative—in the kidneys is without doubt the most important, and often the most serious, form. These changes include the variety of diseases commonly grouped under the term of Bright's disease. Not only do we have to deal with these extensive diseases of the kidney, but also with certain disturbances of the renal function that are accompanied by the presence of albumin.

The quantity of albumin in the urine in various renal affections may vary between the *slightest possible trace* and from three to four per cent. From the quantity of albumin alone it is impossible to judge in all cases of the nature or severity of the renal changes. For instance, the grave condition—chronic interstitial nephritis—may exist with only the *slightest possible trace* of albumin in the urine. On the other hand, a simple renal congestion may, for a short time, be accompanied by from 1/8 to 1/4 of one per cent. of albumin. In certain conditions—for example, an acute

nephritis in which the diagnosis has already been established—very general information concerning the progress of the disease may be gained by examining the urine daily for albumin. Such information, however, is unsafe if not accompanied by a complete chemic and microscopic examination of the *twenty-four-hour secretion.*

2. The second form—alterations in the blood pressure in the kidneys—is a common cause of albuminuria. It is always the result of circulatory disturbances that include the renal vessels. There is usually more or less structural change in the kidneys, and, besides albuminuria, a greater or smaller number of formed pathologic elements in the sediment. There may be an increase in the arterial pressure, as in certain affections of the nervous system in which there is an interference with the vasomotor regulation of the coats of the blood-vessels; also in *sudden exposure to cold and wet*, in which case the internal organs become abnormally filled with blood; and in arteriosclerosis. On the other hand, the blood pressure may be diminished, as in certain forms of cardiac disease, which results in a back pressure in the renal veins (passive congestion), and hence albuminuria. The pressure of tumors or of the pregnant uterus on the abdominal veins will often cause albuminuria, but soon after the cause is removed the albumin disappears from the urine.

So-called "Functional or Physiologic Albuminuria."—The most marked condition in which this occurs is after prolonged muscular exertion. A study of this condition was made by Leube,[1] who found albumin in the urine in 16 per cent. of soldiers after a prolonged march; Oertels[2] found it in 3 per cent. of the cases examined.

3. This form, which causes albuminuria by changes in the quality of the blood entering the kidney, is notably seen in cases of anemia (this is perhaps partially explained by the lessened nutrition of the renal cells), and in the first stage of the convalescence from cholera. In phosphorus-poisoning and hemoglobinemia, also in carbon monoxide poisoning and after the excessive use of morphine, the blood is probably so altered as to permit the transudation of the serum albumin into the renal tubules. In some of these

[1] "Virchow's archiv," LXXII, 145; LXXIX.

[2] "Ziemssen's Handbuch der allgemein. Therapie," IV.

cases of poisoning the kidneys are simultaneously affected, so that the cause of the albuminuria may be partly explained by the renal disturbance.

4. This form of albuminuria has been variously termed *false*, *adventitious*, or *accidental*. Under this class are included a large number of urines that contain comparatively small amounts of albumin. The quantity of albumin usually depends upon the amount of blood and pus coming from the diseased area, and, therefore, may be abundant if much blood is present. In many instances, particularly when the disturbance or disease is located in the bladder or urethra, the kidney is not affected at all by the condition, the urine being normal until it reaches the affected area. On the other hand, in cases of pyelitis and prostatitis, the function of the kidneys is very apt to be secondarily disturbed by the local disease, and consequently more or less albumin of renal origin. Albumin not infrequently gets into the urine from the genital tract: in the female, from the vaginal discharge, consisting of a mixture of more or less pus, blood, and epithelium, also, occasionally, menstrual fluid; in the male, from seminal fluid. As a rule, the source of albumin in such cases may be determined by both chemic and microscopic investigation, together with the local symptoms. It is important that this variety of albuminuria be borne in mind by the student in order to avoid error.

Albuminuria of Adolescence and Cyclic Albuminuria.—These forms may, or may not, be accompanied by a renal disturbance: in other words, renal casts and cells may or may not be present in the sediment. A large proportion of these cases occurs in youths and young adults. The quantity of albumin usually varies between a *slightest possible trace* and *one-half of one per cent.*, generally averaging one-eighth of one per cent., or less. The quantity often varies as the time of day—*i. e.*, being less (or sometimes absent) at night during the hours of rest, appearing in the morning, especially upon exercising, increasing during the day, and diminishing toward evening. In some of these cases the amount of albumin is fairly constant, day and night, particularly in cases of albuminuria of adolescence. The presence of albumin may continue for weeks, months, or even years, and then finally disappear. Little can be said concerning the causes of these forms of albuminuria. There are often circulatory changes that appear

to be functional in character, and the individual is generally found to be somewhat below the standard of vigorous health. An abnormal increase in the blood pressure or changes in the quality of the blood have been suggested as the possible explanation of this form of albuminuria.

It is safe to conclude from the foregoing consideration that the presence of albumin in the urine is to be regarded merely as a "danger signal," and that when it is present, a further chemic and microscopic study of the urine is necessary before deciding as to the existing condition. Albuminuria in itself can not be considered diagnostic.

Detection of Albumin in Urine.—Nitric Acid Test.—*Always filter the urine to be tested.* This is an important step, even though the urine appears to be perfectly clear, since all urines contain a certain amount of suspended matter, which must be removed in order to detect the smallest traces of albumin.

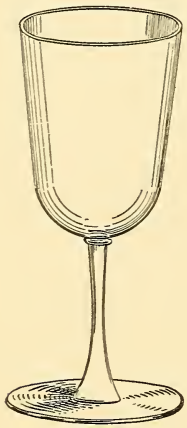


Fig. 13.—Wine-glass (one-half actual size).

Take a perfectly clear and dry wine-glass (Fig. 13),[1] and one-half fill with the filtered urine. Incline the glass so that the urine reaches nearly the edge, and then *underlie with concentrated nitric acid* (C. P.), *pouring it from the bottle as slowly as possible* (Fig. 14), until the acid equals approximately *one-third* the volume of urine used. If albumin be present, a more or less distinct white band or zone of coagulated albumin will be seen just above the junction of the acid and urine. This zone will vary in thickness according to the quantity of albumin present, the rapidity with which the acid is poured, or, in other words, the extent to which the acid and urine are mixed, and, lastly, the amount of effervescence that follows the addition of acid (decomposition of carbonate, and in case yellow nitric acid is used, the decomposition of the urea and uric acid, with effervescence).

[1] The wine-glass here represented is perhaps best suited for the satisfactory performance of the nitric acid test. It is made of clear white glass, and is free from defects. It was formerly manufactured by the Sandwich Glass Co., under the name of "Collamore Wine Glass."

Approximate Estimation of Albumin.—If in every case the proportion of urine and acid is as previously indicated, and the nitric acid is poured from the bottle as slowly as possible, much can be told concerning the approximate quantity of albumin present by the appearance of the zone obtained. It is very difficult, and, indeed, practically impossible, to give the percentage of albumin as judged from the zone, if the quantity is less than a *trace;* if more than a trace, a general idea as to the percentage can be given.

(*a*) *Slightest Possible Trace.*—This is, naturally, the smallest amount of albumin capable of being detected by ordinary tests, and can certainly be considered an entity in connection with the nitric acid test. These slightest traces, I regret to say, are often overlooked, especially by the inexperienced, because the proper means for their detection

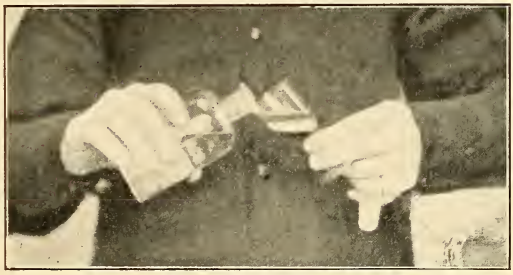


Fig. 14.—Method of performing the nitric acid test for albumin.

are not employed. It is important, first of all, that the wine-glass be perfectly clean, and, secondly, that a dark background be adjusted obliquely in front of, or a little to one side of, the glass, between the source of light and the glass, but not so placed as entirely to cut off the light. (See Fig. 15.) In this way the merest haze of albumin, which is usually a rather wide, hazy band, approximately $\frac{1}{16}$ to $\frac{1}{8}$ of an inch in width, and not a sharp and narrow band, is discernible. A clear, but usually narrow, layer of clear urine can frequently be seen between this haze or cloud of albumin and the zone of acid urates that forms higher up in the layer of urine. The slightest possible trace can not be seen without the use of a dark background.

(*b*) *Very Slight Trace.*—This is a faint zone which is best seen by using a dark background. If the wine-glass is held between the eye and the light, a very faint cloud may be seen, but the observer will often be in doubt as to the presence of albumin until a dark background is used. This zone can not be discerned as the observer looks down on to the surface of the urine: that is, the bottom of the wine-glass can be distinctly seen.

(*c*) *Slight Trace.*—This is a distinct white zone which can readily be seen from the side without a dark background. In looking through the urine from above downward, a very faint cloud can be made out, although the bottom of the wine-glass can be distinctly seen.

Fig. 15.—Method for the detection of minute quantities of albumin. Lower zone, albumin; upper zone, acid urates.

(*d*) *Trace.*—A trace of albumin is a zone which is distinctly seen without a dark background, when viewed from the side. In looking through the urine from above downward a decided cloud is seen, but this cloud is usually not so dense as to prevent one's seeing the bottom of the wine-glass.

(*e*) *Large Trace* (including $\frac{1}{10}$ of 1 per cent.).—A zone which, seen from the side, is very evident, but not granular (flocculent). When viewed from above downward, it is found to be quite dense, although not so dense as to obstruct entirely the transmission of a little light. (The

light can be cut off by placing the hand between the source of light and the glass.)

(*f*) *One-eighth of One Per Cent.*—A marked zone which is not flocculent. The bottom of the glass can not be seen, although a faint ray of light can usually be seen coming through the zone.

(*g*) *One-fourth of One Per Cent.*—A zone which is quite flocculent when viewed from the side. No light can be seen through the band in looking from above downward.

(*h*) *One-half of One Per Cent. or More.*—When the quantity of albumin reaches one-half of one per cent. or more, a dense, *very flocculent* band forms; light can not be seen through it. Above one-half of one per cent. it is difficult to estimate the approximate quantity present; a quantitative test should then be made according to the instructions given on page 131.

If the proper appliances are at hand, it is advisable to make a quantitative determination of the albumin in all cases in which the amount is a *trace* or more.

In the nitric acid test practically nothing can be determined from the width of the zone of albumin. In dealing with the smaller quantities the width of the band will depend largely on the rapidity with which the nitric acid is poured, and also upon the amount of effervescence that follows the addition of the acid. The bands will usually vary in width from about $\frac{1}{32}$ of an inch to $\frac{1}{2}$ of an inch or more. Usually in the presence of the large quantities of albumin the band is quite narrow, but exceedingly dense.

In the nitric acid test, when minute traces of albumin are present, the hazy band or cloud of albumin generally becomes more intense after the lapse of one or two minutes.

Heat Test.—The heat test for albumin depends upon the separation (coagulation) of this proteid from fluids which are *faintly* acid, preferably with acetic acid, by heating at a temperature of about 75° C.

It is essential that the urine should have a *faintly acid reaction;* for, if the urine is alkaline, the albumin is in the form of alkali albumin, which is not coagulable by heat. Again, if *too strongly acidulated*, the albumin is in the form of acid albumin, which is likewise incapable of being coagulated by heat.

1. *If the urine is acid*, take one-half test-tube of the filtered urine, add one drop (not more) of 10 per cent. acetic acid, and mix thoroughly; hold the test-tube by the lower portion,

and boil the upper one-third of acidulated urine. If a cloud forms, it consists of either albumin or earthy phosphates. Add another drop or two of acetic acid, boil again, and if the cloud remains, albumin is present; if the cloud disappears, the precipitate is phosphatic.

2. *If the urine is alkaline*, take one-half test-tube of the filtered urine, add two or three drops of 10 per cent. acetic acid, and boil the upper one-third of the urine as directed. If the urine has not yet been rendered faintly acid, a precipitate or coagulum of albumin will not appear until sufficient acetic acid has been added, drop by drop, to the hot urine, to faintly acidulate. As soon as the proper reaction has been reached, a precipitate will appear if albumin be present. As stated previously, the further addition of one or two drops of acetic acid will help to determine whether the precipitate is phosphatic or a coagulum of albumin.

It scarcely ever happens that a urine, when voided, is *too acid* for the successful application of the heat test, and even in a strongly acid urine it is often necessary to use one drop of acetic acid in order that the examiner may be satisfied of the presence or absence of albumin.

Nitric acid, which is often used for acidulation instead of acetic acid, is liable to lead to serious error in judging of the presence of albumin by the heat test. This is especially so if the albumin is present in small amount, since the addition of so strong an acid converts the albumin to acid albumin,—syntonin,—which is soluble and not coagulated by boiling. Less danger exists in the use of acetic acid (10 per cent.), providing, however, that an excess of the acid is avoided. Nitric acid should, therefore, not be used in connection with the heat test.

The approximate estimation of the quantity of albumin from the density of the coagulum of albumin by heat is not always a simple matter in the hands of most observers, since a standard for comparison can not be easily fixed. On the other hand, those who prefer to use the heat test instead of the nitric acid test for routine work can learn to estimate the approximate quantity in a general way.

The Potassium Ferrocyanide and Acetic Acid Test.—This test may be applied in two ways: *i. e.*, (*a*) by actual mixture and (*b*) by the contact method.

(*a*) To a half test-tube of urine add from three to five cubic centimeters of a solution of potassium ferrocyanide (1 : 10), and from one to three cubic centimeters of 50 per

cent. acetic acid; the reagents and urine should be thoroughly mixed. If albumin be present, a white, finely divided precipitate will appear within half a minute or a minute.

(*b*) Take a mixture of one part of 50 per cent. acetic acid and two parts of potassium ferrocyanide solution in a wine-glass, and carefully overlay with the urine to be tested. If albumin be present, a narrow, sharply defined, white zone will appear just above the junction of the two fluids. The urine to be tested must be acid in reaction in order to obtain a satisfactory test. This reagent does not precipitate peptones, alkaloids, or phosphates, but may precipitate acid urates. It has been found to react slightly with artificial solutions of nucleo-albumin.

A comparative experimental study of the three tests described convinces the writer of the following order of delicacy: (1) nitric acid test; (2) heat test; (3) potassium ferrocyanide and acetic acid test.

Other Tests for Albumin.—It has long been known that albumin is coagulated or precipitated by other agents than nitric acid, heat, and potassium ferrocyanide and acetic acid. Some of these tests have claimed much attention, and have been found to be extremely delicate, but it is safe to say that their delicacy is often at the expense of accuracy. The chief objection to many of the tests is that they precipitate other substances than albumin, and although these substances are distinguished from albumin by taking certain precautions, or by the application of other tests, the observer is either misled, and considers that albumin is present, or he is left in a confused state of mind. While, doubtless, it is desirable that we should possess tests for albumin which are very sensitive, yet extreme delicacy of reaction is of secondary consideration and not of clinical importance. Such tests should, therefore, not enter into the routine examination of the urine, thus avoiding unnecessary confusion.

Picric Acid Test.—This test has been strongly advised by Dr. George Johnson.[1] The test is applied as follows: Into a test-tube six inches long pour a four-inch column of filtered urine. Then, holding the test-tube in a slanting position, pour gently an inch of a saturated solution of picric acid (made by adding six or seven grains of picric acid to a fluidounce of boil-

[1] "Albumin and Sugar-testing," London, 1884.

ing distilled water) over the surface of the urine; the reagent thus mixing with only the upper layer of the urine. As far as the yellow color of the reagent extends, the coagulated albumin renders the liquid turbid, contrasting with the clear urine below. In order to obtain a satisfactory reaction there must be an actual mixture and not a mere surface contact. When the quantity of albumin is small and the turbidity is slight, the application of heat to the upper part of the turbid mixture increases it. This reagent also precipitates urates, peptone, albumose, vegetable alkaloids, and mucin, all of which, except mucin, are dissolved by a degree of heat much below that of the boiling-point.

The Potassio-mercuric-iodide Test.—This test was suggested by M. Charles Tanret. The reagent (double iodide of mercury and potassium, acidulated with acetic acid) is prepared as follows: Bichloride of mercury, 1.35 grams; potassium iodide, 3.32 grams; acetic acid, 20 c.c.; distilled water, sufficient to make 100 c.c. The bichloride of mercury and the potassium iodide should be dissolved separately in water, and the two solutions mixed; the acetic acid is then added, and the whole mixture made up to 100 c.c. The contact method is used, and since the reagent is heavier than the urine, the latter is carefully poured on to the surface of the reagent in a test-tube or wine-glass. If albumin be present, a white, sharply defined band appears at the junction of the two fluids. This test precipitates the same substances as picric acid, including nucleo-albumin. All of these precipitates except albumin are dissolved by gentle heat, the precipitate reappearing upon being cooled. According to Oliver, the precipitate of nucleo-albumin is not dissolved by heat if a large excess of reagent is used, the mercuric salt apparently preventing solution. This test is exceedingly delicate.

Trichloracetic Acid Test.—This test is applied by means of the contact method. The reagent is prepared by dissolving 15 grams of the crystals of trichloracetic acid in about 10 c.c. of distilled water, making a saturated solution. Delicate results are claimed for this test, but, from the fact that it precipitates mucin and nucleo-albumin, it can not be regarded as a reliable test for albumin.

Sodium Tungstate.—This test was suggested by Dr. George Oliver as a very sensitive reagent for albumin. The reagent is prepared by mixing equal parts of a saturated solution of sodium tungstate (1 : 4) and a saturated solution of citric acid. The contact method is used, and since the reagent is heavier than urine, it is best applied by the overlaying method. The reagent precipitates, in addition to albumin, acid urates, peptone, and mucin. It gives no reaction with the alkaloids, and all precipitates, except albumin and mucin, are readily dissolved by heat.

A large number of other so-called "delicate tests" have been suggested for the detection of albumin, only a few of which are worthy of mention: Acidulated brine test (Roberts), nitric-magnesium test (Roberts), phenic acid test (Millard), Heidenlang's test, Heynsius's test, acetic acid and sodium sulphate, etc.

Albumin-test Papers.—According to the suggestion of Dr. George Oliver, a number of the tests named have been prepared and used in paper form. This is accomplished by using chemically inert filter-paper, some of which is to be saturated with solutions of the albumin reagents, and some with citric acid, and then drying. The papers are then cut into slips of convenient size for testing, and may be carried about in the pocket-case for use at the bedside of the patient. In testing, the following method is followed: Into a small test-tube containing 5 c.c. of distilled water are dropped a reagent paper and one charged with citric acid. After agitation for a minute or so the test-papers are removed, and the solution is ready for testing. The urine is now added; the test may be conducted either by a mixture of the two or by the contact method, of which Dr. Oliver advises the latter.

Dr. Oliver now recommends the use of two reagents only for albumin—viz., the potassium ferrocyanide and potassio-mercuric-iodide papers. The former of these will be found trustworthy, and of very great convenience at the bedside.

The potassio-mercuric-iodide test must, in all cases, be controlled by heating, otherwise it may be misleading.

The Removal of Albumin by Heat.—If the urine to be examined contains more than a trace of albumin, it should be removed before testing for chlorides, sulphates, and sugar, since the albumin either enters into combination with the reagents or reacts with them in such a manner as to render the tests unreliable. The best method for the removal of albumin is to coagulate it by heat; this should be applied in connection with both qualitative and quantitative analyses.

1. **For Qualitative Tests.**—Take one-third of a test-tube of urine, add *one drop* of dilute acetic acid, and boil the whole mixture thoroughly. If a flocculent precipitate does not form, add at intervals, *drop by drop*, more acetic acid, heating the mixture after each addition until a distinct flocculent coagulum forms. Filter; the filtrate should be perfectly clear and practically free from albumin.

2. **For Quantitative Analysis.**—Take a definite quantity of the urine, say 50 c.c., place in a porcelain evap-

orating dish, add two or three drops of dilute acetic acid, and boil thoroughly. If a flocculent coagulum of albumin does not appear, add a few more drops of the acetic acid, drop by drop, stirring constantly and continuing the heat until such a flocculent coagulum forms. Filter,—the filtrate should be free from precipitate,—and wash once or twice with water. Allow the filtrate and wash-water to run into a graduate, and add sufficient water to make the original volume (50 c.c.). Mix the contents of the graduate thoroughly, and use for the quantitative tests.

In removing albumin by heat a flocculent coagulum should be obtained in all cases, and this is accomplished when the urine has a faintly acid reaction (preferably with acetic acid). In case a flocculent coagulum is not obtained, the filtrate will be more or less turbid, the turbidity being due to the finely divided precipitate of albumin. Such a turbid filtrate is unfit for further tests.

Quantitative Estimation of Albumin in Urine.—Expression of Quantity of Albumin Found in Urine.—In referring to the quantity of albumin found in the urine the author, in all cases, means the *quantity by weight*, and not the bulk measure; thus, if the expression "¼ of 1 per cent." be used, it is ¼ of 1 per cent. by weight that is intended. We not infrequently read that urines contain 25, 50, and even 75 per cent. of albumin. The quantity by bulk is, of course, intended, since 3 to 5 per cent. by weight is probably the maximum amount of albumin that urine can contain. Much greater care should be exercised in speaking of the quantity of albumin present, using the terms *percentage by weight* or *percentage by bulk*, according to the meaning of the writer. Attention given this matter will be the means of avoiding much confusion, particularly to students.

The term "1 per mille," or "1 p. m.," refers to the number of grams of albumin contained in 1 liter of urine; thus, the foregoing expression equals 1 gram of albumin in 1000 c. c. of urine, or $\frac{1}{10}$ of 1 per cent. by weight; 2 p. m. equals 2 grams in 1000 c. c., or $\frac{2}{10}$ of 1 per cent.; 5 p. m. equals 5 grams in 1000 c. c., or $\frac{1}{2}$ of 1 per cent., etc.

Gravimetric Process.—This process for the quantitative estimation of albumin gives accurate results, but is unsuitable for clinical purposes on account of the length of time and the apparatus required for its completion.

Take 100 c.c. of the urine, place in a beaker or glass evaporating dish, and heat on a water-bath. A two per cent. solution of acetic acid is then added, drop by drop, until, upon boiling, a flocculent precipitate of albumin separates. This is then filtered through an ash-free filter which has been previously dried and weighed. The precipitate is washed successively with water, alcohol, and ether, and dried at a temperature of 120° to 130° C. After cooling the filter is again weighed, and the difference in weight due to the precipitate represents the quantity of albumin in the 100 c.c. of urine used.

Fig. 16. — Esbach's albuminometer.

Devoto[1] recommends the following procedure: Take a definite quantity of urine, precipitate the albumin with ammonium sulphate, heat on a water-bath, and wash the precipitate with *boiling* water until the filtrate no longer becomes cloudy on standing, or upon the addition of sodium chloride. The precipitate is then washed with alcohol and ether, and the remainder of the process conducted as previously directed.

Esbach's Method.—This test is made by means of a standard graduated glass tube or albuminometer,[2] as shown in figure 16. The process is as follows: The following solution is prepared: Picric acid, 10 grams; citric acid, 20 grams; distilled water, to 1000 c.c. (1 liter). Fill the albuminometer tube with the urine to the letter U, then add the reagent to R, close the tube with the stopper, and invert several times, until the urine and the reagent are thoroughly mixed. Stand the tube in a rack for twenty-four hours, and then read off the number of grams of albumin to the liter, as will be indicated by the number on the side of the tube on a level where the albumin settles. If it is desired to know the

[1] Devoto, "Zeitschr. f. physiol. Ch.," xv, 474, 1891.

[2] Esbach's tubes are supplied by Eimer & Amend, of Third Avenue, New York, at a moderate cost.

percentage of albumin in the urine instead of the number of grams per liter, remove the decimal point one figure to the left; thus, 5 grams per liter would be 0.5 per cent. of albumin. It will be observed that Esbach's albuminometer tubes are so graduated that their highest range is 7 grams per liter—0.7 per cent. of albumin. If, therefore, the urine be highly albuminous, it should be diluted with one or two volumes of water before testing, and the product multiplied by two or three, according as the volume is doubled or trebled.

Centrifugal Method—Potassium Ferrocyanide and Acetic Acid.—Albumin can be readily precipitated by means of a mixture of potassium ferrocyanide and acetic acid, and quantitated by using the graduated tubes of a centrifugal apparatus.

Process.—Take 10 c.c. of filtered urine, add 3.5 c.c. of a solution of potassium ferrocyanide (1 : 10), and 1.5 c.c. of acetic acid (U. S. P.); close the tube with the thumb, and invert several times in order to mix thoroughly. The tubes are then placed in the centrifuge, which is revolved until the precipitate of albumin has been completely settled and the supernatant fluid is perfectly clear. The centrifuge should be run at the speed of 1000 revolutions per minute and for from three to five minutes. According to Purdy, each $\frac{1}{10}$ c.c. of precipitate represents 1 per cent. *bulk measure*, or volume per cent. of albumin.

In order to determine the percentage of albumin by *weight* in the use of the above method the writer, a few years ago, made a series of experiments which led to the following conclusion: *each* $\frac{1}{10}$ *c.c. of precipitate represents* $\frac{1}{60}$ *of 1 per cent. of albumin by weight.*

An important source of error in this test is a separation of amorphous urates that may occur when the reagent, especially the acetic acid, is added to a concentrated urine or one containing a relatively large amount of urates in solution; also when a deposit of urates is present previous to the addition of the reagent. When this exigency exists, centrifugalize the precipitate consisting of albumin and urates, decant the clear supernatant fluid, add *hot* water, which dissolves the urates, and centrifugalize again. The remaining deposit represents the amount of albumin present.

This method furnishes a very rapid, accurate, and convenient means of quantitating albumin. The most important part of the test is to *thoroughly* settle the precipitate.

GLOBULIN.

Serum globulin, also termed paraglobulin, is a proteid which is usually associated with serum albumin, and is frequently found in the urine. Globulin is insoluble in water and soluble in dilute (1 per cent.) solutions of sodium chloride. It is also soluble in dilute acids or alkalies, being changed into acid- and alkali-proteid respectively, unless the acids and alkalies are exceedingly dilute and their action is not prolonged. It is precipitated by saturating its solutions with magnesium sulphate, with sodium chloride, and by half-saturation with ammonium sulphate. Globulin can be quantitated by saturating its neutral solution with magnesium sulphate, since the other proteids are not precipitated by it. It is partially precipitated from its solution by carbonic acid gas. When its solutions are dialyzed, it is precipitated, owing to the fact that the percentage of salt is so far reduced by dilution that it is no longer sufficient to hold the globulin in solution. Its dilute saline solutions coagulate on heating to 75° C. (Halliburton).

Normal urine is free from globulin, but this proteid may be found in the urine under pathologic conditions.

Clinical Significance.—The clinical significance of the presence of globulin is much the same as that of albumin. It has been found in abundance in amyloid infiltration of the kidneys (in much larger quantities than in other forms of Bright's disease—Senator), acute nephritis, chronic cystitis, pyonephrosis,[1] following deranged digestion, and in the severe hyperemia following cantharides poisoning. Although globulin is usually present in the urine in much smaller quantities than albumin, it may equal or even exceed it in amount. It is occasionally found in the urine when albumin is absent. In severe organic disease of the kidneys and in the albuminuria that occurs in diabetes, Maguire [2] found that the proportion of albumin to globulin was as 2.5 : 1 (normal in the *blood*, 1.5 : 1).

Detection.—Saturate the urine, which has been previously neutralized and filtered, with magnesium sulphate; a white precipitate results if globulin is present.

When a few drops of the globulin-containing urine are allowed to fall into a large volume of distilled water, a tur-

[1] "Boston Medical and Surgical Journal," March 3, 1898, p. 197.

[2] "British Medical Journal," vol. II, 1886, p. 543.

bidity appears (nucleo-albumin gives a similar turbidity); when much globulin is present, the water assumes a milky opalescence.

Quantitative Estimation of Globulin.—Take 100 c.c. of the urine-containing globulin, render neutral or faintly alkaline with ammonic hydrate, and remove the precipitated phosphates by filtration; then completely saturate with magnesium sulphate; filter, and wash with a saturated solution of magnesium sulphate. The entire precipitate on the filter-paper is then dissolved in water or a weak solution of sodium chloride, and the globulin coagulated by boiling, the solution having been previously faintly acidulated with acetic acid. The coagulation must be complete. Filter through a previously dried and weighed filter-paper. The filter containing the precipitate is then dried at a temperature of 110° to 120° C., cooled, and weighed. The difference between the filter-paper and filter-paper *plus* precipitate equals the quantity of globulin in 100 c.c. of urine.

This test is probably not perfectly accurate, since small amounts of other proteids, notably some forms of albumose,[1] are precipitated by magnesium sulphate.

ALBUMOSES.

This proteid belongs to the general class of *proteoses*. The albumoses, together with another proteose,—*globulose*, —are absent from normal urine (except perhaps in the slightest traces), but are occasionally found under pathologic conditions. Up to the present time very little, if anything, is known of the clinical significance of the globuloses, so that they will not be considered here.

The *albumoses* are formed by the action of the gastric and pancreatic juices on proteid material, and appear as intermediate products between the proteid material and the final product, *peptone*.

Varieties.—According to Kühne, there are at least two albumoses—*antialbumose*, the forerunner of *antipeptone*, and *hemialbumose*, the forerunner of *hemipeptone*. Of these two forms *hemialbumose* is the more important. Kühne and Chittenden, in their earlier work,[2] at first distinguished

[1] Halliburton, "Text-book of Chem., Physiol., and Pathol.," p. 783.
[2] "Zeitschr. f. Biol.," Bd. XIX, 1883, S. 174.

between a soluble and insoluble form, but more recently they have described four closely allied, though distinct forms of albumose.[1] (1) *Protalbumose*, soluble in hot and cold water and precipitated by saturation with sodium chloride and magnesium sulphate. (2) *Heteroalbumose*, insoluble in hot and cold water, soluble in dilute (0.5 per cent.) and in more concentrated (15 per cent.) solutions of sodium chloride, but precipitated from these by saturation with the salt. It is precipitated by alcohol, when it is partly converted into (3) *dysalbumose*, which is insoluble in saline solutions. (4) *Deutero-albumose* soluble in hot and cold water, not precipitated by saturating with sodium chloride or magnesium sulphate, unless an acid be added at the same time, but is precipitated by saturating with ammonium sulphate and by nitric acid, if an excess is not added.

Clinical Significance.—Albumose was first discovered in the urine by Bence Jones [2] in a case of osteomalacia. It has since been found in this disease by Kühne [3] and others. Virchow [4] has found albumose in the bone-marrow in cases of osteomalacia; Hoppe-Seyler [5] found it in several cases of atrophy of the kidneys; Lassar [6] found it in the urine of people who had been rubbed with petroleum, and Oertel [7] in a few cases after severe exertion. Senator has found albumose in the urine in croupous pneumonia, diphtheria, tertiary syphilis, carcinoma, hemiplegia, and muscular atrophy. It has been found by a number of observers in sarcomata of the bones of the trunk, especially of the ribs and sternum. Fitz [8] has reported a case of myxedema in which albumosuria was a prominent feature.

H. Senator [9] has recently reported a case of multiple sarcomatosis of the ribs in which albumosuria was a prominent feature. His patient also suffered from chronic parenchymatous nephritis with amyloid infiltration of the kidneys,

[1] "Zeitschr. f. Biol.," Bd. XX, S. 11.
[2] "Phil. Trans. Roy. Soc.," vol. I, 1848.
[3] "Zeitschr. f. Biol.," XIX, S 209.
[4] "Virchow's Archiv," IV, S. 309.
[5] "Physiol. Chem.," S. 858.
[6] "Virchow's Archiv," LXXVII, S. 164.
[7] "Ziemssen's Handbuch d. Therapie," 1884.
[8] "American Jour. Med. Sciences," July, 1898.
[9] "Berliner klin. Wochenschr.," Feb. 20, 1899.

fibrinous pleurisy, bronchopneumonia, and gangrene in the region of the left trochanter.

The quantity of albumose found in the urine of croupous pneumonia, diphtheria, tertiary syphilis, carcinoma, muscular atrophy, after severe exertion, etc., is usually very small, it being present only in traces; in cases of sarcomata of the bones of the trunk the quantity may reach as high as ½ of 1 per cent.

Although the condition of albumosuria has been thoroughly studied by a number of able chemists and clinicians, its true clinical significance, up to the present time, is very indefinite. The fact that albumose has been so frequently found in bone diseases would suggest a possible cause of the condition.

Detection.—From a clinical point of view it is not essential to distinguish between the various forms of albumose; the following reactions suffice for its detection:

1. Take a small portion of the urine in a test-tube, and *warm gently*. A precipitate appears which is redissolved on *boiling* and reappears on cooling.

2. Acidulate the urine with acetic acid, and add a few drops of a saturated solution of sodium chloride. A precipitate is formed which disappears on heating and reappears on cooling.

3. Add a few drops of nitric acid to the urine in a test-tube. If the acid is not in excess, a precipitate is formed which disappears on boiling and reappears on cooling.

4. Add acetic acid, avoiding an excess, and then a few drops of a solution of potassium ferrocyanide (1 to 10). A precipitate is formed which disappears on boiling and reappears on cooling.

5. Completely saturate the urine (preferably, according to Kühne, at boiling temperature) with neutral ammonium sulphate. Filter and wash the precipitate with a saturated solution of ammonium sulphate. Dissolve the precipitate in water or dilute sodium chloride solution, and, if albumose be present, its solution will give the *biuret reaction*. This method separates the albumoses from the peptones, the former being precipitated, the latter remaining in solution and appearing in the filtrate from the ammonium sulphate precipitate.

PEPTONE.

Peptones are rarely, if ever, met with in the urine. They are the final products of gastric and pancreatic digestion of albuminous bodies, in so far as these final products are still true albuminous substances. When, however, the digestion (hydration) is continued, the peptones split up into simpler bodies, which are no longer proteid in character. Peptones are, furthermore, products of pathologic changes in the blood-corpuscles. They may also be produced from albumin by the continued action of acids and alkalies, and it is said, also, by the decomposing action of bacteria, as well as the long-continued operation of a temperature of 130° to 143° C.

Peptones are not coagulated by heat. They are not precipitated by nitric acid, ammonium sulphate, potassium ferrocyanide and acetic acid, but are thrown down by a mixture of picric and citric acids, tannic acid, phosphomolybdic acid, phosphotungstic acid, potassio-mercuric iodide (Tanret's reagent), mercuric chloride, and Millon's reagent. They are precipitated, but not coagulated, by alcohol. Peptone is very soluble in water, and is readily diffused through animal membranes; albumoses are only slightly diffusible.

Peptones exist in two forms: (1) *Hemipeptone*, which is obtained by the action of trypsin on hemialbumose. When purified and digested with trypsin it yields much leucin and tyrosin, and in this respect alone does it differ from antipeptone. (2) *Antipeptone* is formed as the result of digestion of antialbumose, but is not capable of yielding leucin and tyrosin when purified and subjected to the most prolonged action of the pancreatic juice. It, moreover, does not yield leucin and tyrosin when treated with sulphuric acid, and does not react with Millon's reagent. Peptone is not present in healthy blood or normal urine.

Clinical Significance.—Peptone was first described in the urine by Gerhardt.[1] Up to the publication of the very able researches of Kühne and Chittenden, most of the proteids classed as peptones were probably albumoses, or mixtures of albumoses and peptones, so that the early data concerning peptonuria are far from reliable. The proteid

[1] "Deutsch. Archiv f. klin. Med.," v, 215.

most liable to be mistaken for peptone is deutero-albumose, and it is highly probable that what has heretofore been described as urine-peptone has been chiefly, if not entirely, deutero-albumose. The author has thus far failed to meet with an instance of true peptonuria.

A number of observers have described peptonuria in a variety of pathologic conditions: Suppurative diseases, empyema, croupous pneumonia, gangrene of the lung, small-pox, erysipelas, scarlet fever, typhoid fever, tuberculosis, acute rheumatism, cancer of the gastro-intestinal tract and liver, cerebral hemorrhage, phosphorus-poisoning, typhus, etc. Naturally, the accuracy of observation in connection with some of the above-mentioned diseases is doubted, since, previous to the work of Kühne and Chittenden, nothing was known of the means of distinguishing between peptone and the albumoses.

Detection.—The accurate detection of peptone depends upon its separation from albumose, and this is accomplished as follows: The urine, first faintly acidulated with acetic acid, is completely saturated with ammonium sulphate, and filtered. The precipitate may consist of albumin, globulin, or albumose. The only proteid in the filtrate, however, is peptone, which can be detected by the *biuret* reaction, or by precipitation with tannic acid, potassio-mercuric iodide, picric acid, phosphotungstic acid, or phosphomolybdic acid. According to Kühne, in order to separate completely the albumoses from the peptones the saturation with ammonium sulphate should be conducted at the *boiling* temperature. Furthermore, a single saturation with ammonium sulphate should not be depended upon for the removal of all of the albumose, but saturation should be repeated until precipitation fails to occur.

Separation.—Chittenden recommends the following process for the separation of the peptone from the ammonium sulphate saturated solution. The fluid is concentrated somewhat, and set aside in a cool place for the crystallization of a portion of the ammonium salt. The fluid is then mixed with about one-fifth of its volume of alcohol, and allowed to stand for some time, when it separates into two layers, an upper one rich in alcohol, and a lower one rich in salts. The latter is again treated with alcohol, by which another separation of the same order is accomplished. The lighter alcoholic layers containing the peptone are united

and exposed to a low temperature until considerable of the contained salt crystallizes out. The fluid is then concentrated, and after the addition of a little water is boiled with barium carbonate until the fluid is entirely free from ammonium sulphate. Any excess of baryta in the filtrate is removed by the cautious addition of sulphuric acid, after which the concentrated fluid, reduced almost to a syrupy mass, is poured into absolute alcohol for the precipitation of the peptone.

Biuret Reaction.—Take a small portion of the fluid to be tested in a test-tube, add an excess of sodic hydrate, and then add, drop by drop, a dilute solution of copper sulphate. The characteristic reaction is the appearance of a rose-red color. Great care must be exercised in the addition of the copper solution, since an excess of it gives a reddish-violet color, which is often misleading.

The substances in the urine which give the characteristic biuret reaction are *albumoses*, *peptones*, and *urobilin*. Since more or less urobilin is present in every urine, it must be thoroughly removed before this test can be satisfactorily applied for the detection of albumoses and peptone.

METHOD OF SEPARATION AND IDENTIFICATION OF PROTEIDS.

The following table, proposed by Halliburton,[1] gives the method for separating serum albumin, serum globulin, albumoses, and peptone, should they happen to be present together in the urine. This is a very rare occurrence, but in doubtful cases it is best to test for every one in the list:

1. If the urine gives no precipitate on boiling after faintly acidulating with acetic acid, albumin and globulin are absent. If a precipitate occurs, albumin or globulin or both are present.

2. If the urine after neutralization gives no precipitate on saturation with magnesium sulphate, globulin and heteroproteose are absent. If such a precipitate occurs, one or the other is present.

3. If the urine be saturated with ammonium sulphate and filtered, and the filtrate gives no xanthoproteic or biuret reaction, peptone is absent.

4. If the urine gives no precipitate on boiling after acidulation, no precipitate with nitric acid, and no precipitate on

[1] "Text-book of Chem., Physiology, and Pathology," p. 788.

adding ammonium sulphate to saturation, peptone can be the only proteid present. Confirm this by the biuret reaction.

5. If all proteids are present, they may be separated as follows:

Saturate the urine (faintly acidified with acetic acid) with ammonium sulphate. A precipitate is produced. Filter.

(*a*) *Precipitate.*	(*b*) *Filtrate.*
Contains albumin, globulin, hetero- and deuteroproteose. Collect	Contains peptone.

the precipitate on a filter, wash it with saturated solution of ammonium sulphate, and redissolve it by adding a small quantity of water. To this solution add ten times its volume of alcohol; a precipitate is formed; collect this, and let it stand in absolute alcohol for from seven to fourteen days. Then filter off the alcohol, dry the precipitate at 40° C., extract it with water, and filter. An insoluble residue is left.

(*a*) *Residue.*	(*b*) *Extract.*
This consists of albumin and globulin coagulated by the alcohol.	This contains the proteoses in solution.

Heterocaseose is precipitated by heating the solution to 65° C., or by saturating a portion of the extract with magnesium sulphate. Deuteroproteose remains in solution.

Take another portion of urine, neutralize it, and saturate with magnesium sulphate. A precipitate is produced. Filter.

(*a*) *Precipitate.*	(*b*) *Filtrate.*
This consists of globulin and heteroproteose, which may be separated by the prolonged use of alcohol, as above.	This contains albumin, deuteroproteose, and peptone. Add alcohol as above; albumin is rendered insoluble in water in from seven to ten days. The deuteroproteose and peptone are soluble, and may then be separated by ammonium sulphate.

NUCLEO-ALBUMIN (MUCIN?)

A true nucleo-proteid, or nucleo-albumin is a combination of a nuclein with more albuminous matter.[1] This form of proteid formerly known as mucin is probably not true mucin. The presence of small quantities of nucleo-albumin in the urine occurs under normal conditions, it being a product of the secretion of the cells lining the urinary tract. This substance is probably identical with the nucleo-albumin of bile.

[1] A nuclein is a combination of some form of proteid matter with a nucleic acid (Chittenden).

Native nucleo-albumins contain approximately 1.5 per cent. of phosphorus, are amorphous, and insoluble in water, but they dissolve in weak solutions of the neutral salts. They are completely precipitated by saturating their solutions with ammonium sulphate, and only incompletely precipitated when their solutions are saturated with magnesium sulphate, or sodium chloride. They are soluble in alkaline hydrates and carbonates, and are readily precipitated from these alkaline solutions by means of strong mineral acids. They are, however, soluble in acetic acid and dilute mineral acids, and in this respect they differ from the nucleins.

When nucleo-albumin is dissolved in a solution of sodium chloride and boiled, a precipitate separates. It is precipitated by all of the reagents used for the precipitation of albuminous bodies, and gives all of the color reactions of proteid substances. When nucleo-albumin is repeatedly dissolved and precipitated, it becomes decomposed, with the separation of a portion, which is rich in phosphorus. When it is subjected to the action of pepsin-hydrochloric acid, it furnishes a proteid and insoluble nuclein. When some of the nucleo-albumins are boiled with moderately dilute mineral acids, a substance is produced which reduces an alkaline solution of cupric oxide with a resulting brown color; this reaction is considered by Mörner [1] and Hammarsten [2] to be characteristic only of mucin.

Clinical Significance.—Nucleo-albumin has been repeatedly found in increased proportion in the urine of women, in which case it is derived chiefly from the genital tract. It is also found in increased amounts in urine that has passed over the irritated mucous membrane of some portion of the urinary tract. Such a urine is usually turbid when passed, and in a short time deposits a bulky cloud, usually found to contain a small, and sometimes a large, number of leucocytes, red blood-globules, and epithelial cells. It was first found in large quantities by Müller in the urine of leukemia, and afterward by Malfutti and others in diphtheria, scarlatinal nephritis, cystitis, and after the use of pyrogallic acid, naphthol, and corrosive sublimate. It was also observed by Obermayer in the urine of a case of acute atrophy of the liver. Ott found it in abnormal quantities in the urine during high fever. Nucleo-albumin is always present in increased quantities in urine that contains bile.

[1] K. A. H. Mörner, "Skandin. Arch.," VI, 1895.
[2] Hammarsten, "Physiol. Chemie," 1895, 487.

Detection.—For the detection of nucleo-albumin the urine is treated with an excess of acetic acid, when it is rendered turbid if much of this proteid be present. In testing a concentrated urine for nucleo-albumin it is advisable to dilute it before acidulating, on account of the high proportion of salts, which retain nucleo-albumin in solution even in the presence of an excess of acetic acid. In testing for the presence of nucleo-albumin in an albuminous urine it is necessary first to remove, by boiling, the great bulk of the serum albumin, and any serum globulin present. The fluid is then filtered, and allowed to cool before testing with acetic acid.

Ott's method for the detection of nucleo-albumin is very serviceable: To the urine add an equal quantity of saturated salt solution (NaCl), and then Almén's tannin solution [1] is slowly added. If nucleo-albumin be present, even in small amounts, an abundant precipitate will fall.

Von Jaksch recommends for the precipitation of nucleo-albumin a solution of acetate of lead.

HEMOGLOBIN.

Hemoglobin is the pigment of the red blood-corpuscles. It gives the reactions of a proteid, but differs from proteids in containing iron and in being crystallizable. It belongs to the group of compound proteids, and yields as cleavage products, besides very small amounts of volatile fatty acids and other bodies, chiefly *proteid* (96 per cent.) and a coloring-matter, *hemochromogen* (4 per cent.) containing iron, which in the presence of oxygen is readily oxidized into *hematin* (Hammarsten).

Hemoglobin is found in two forms—*i. e.* (*a*), *oxyhemoglobin*, that charged with oxygen and found in arterial blood, and presenting, in dilute solutions, two absorption bands between Frauenhofer's lines *D* and *E*; and (*b*), *reduced hemoglobin*, that deprived of its oxygen and found in venous blood, and presenting a single absorption band between *D* and *E*, occupying a space about midway between the two bands of oxyhemoglobin.

For further details concerning this subject see page 232.

[1] *Almén's tannin solution* consists of: Tannin, 5 grams; 25 per cent. acetic acid, 10 c.c.; 40 to 50 per cent. methylated spirit, 250 c.c.

FIBRIN.

Fibrin is the albuminous body that separates on the so-called spontaneous coagulation of blood, lymph, and transudations, as also on the coagulation of a fibrinogen solution after the addition of blood-serum or the fibrin ferment. It is an elastic, white, stringy substance, which is insoluble in water, ether, and alcohol. It is soluble with difficulty in solutions of sodium chloride (5 to 15 per cent.), in solutions of potassium nitrate (6 per cent.), and in solutions of magnesium sulphate (5 to 10 per cent.). The substance that goes into solution when fibrin is dissolved in saline solutions is undoubtedly a proteid of the globulin class. It is coagulated by heat, precipitated from its solutions by saturating them with magnesium sulphate, and also by dialyzing away the salt from such solutions. The temperature of coagulation is 60° to 75° C. in a sodium chloride solution, and 73° to 75° C. in a magnesium sulphate solution. Weak hydrochloric acid (0.2 per cent.) causes fibrin to swell up into a transparent jelly. Fibrin is slowly dissolved by the strong acids, with the formation of acid albumin or syntonin, and albumoses. Fibrin is readily digested by pepsin in the presence of hydrochloric acid (0.2 per cent.), and by the pancreatic juice, with the resulting formation of albumoses and peptone. Fibrinogen, which has also been found to have the properties characteristic of globulin, is the fibrin-precursor in blood plasma.

Clinical Significance.—Fibrin most commonly appears in the urine as an accompaniment of blood, whether the blood comes from the kidneys or some other part of the urinary tract. Usually, if there is an extensive hemorrhage into the urinary tract, fibrin is abundant, and, on the other hand, if only little blood is present, the quantity of fibrin is small. But fibrin may be present in the urine when blood-corpuscles are absent; thus, the so-called *coagulable urine*, which, upon standing some time, forms the fibrinous coagula. The extent of coagulation depends upon the quantity of fibrin present; sometimes only a sticky sediment forms in the bottom of the sediment-glass; more rarely, the urine is converted into a gelatinous mass.

Detection.—Fibrin is insoluble in water; it is also insoluble in sodic hydrate, in which respect it differs from albuminous substances. If washed, fibrin is dissolved in a solu-

tion of sodic carbonate (one per cent.) with the aid of gentle heat, and its solution gives the xanthoproteic and Millon's reaction for proteids. It is readily digested by artificial gastric juice.

Fibrin should not be mistaken for the grayish, *ropy* mass that usually forms in purulent, alkaline urines, alkaline from the ammonia and ammonium carbonate resulting from the decomposition of the urea. (See p. 239.)

CHAPTER V.

CARBOHYDRATES.

The carbohydrates, which are either normally or abnormally present in urine, resemble one another in a few of their chemic characteristics. All are hydrocarbons containing five or six atoms of C, or a multiple thereof; excepting inosite, all have a strong rotary power over polarized light, are soluble in water, and have a neutral reaction.

Normal urine under physiologic conditions contains a small amount of carbohydrates, among which are animal gum and also grape-sugar, but in amounts which can not be recognized by the ordinary sugar reactions. The glucoside—mucin—increases the proportion of carbohydrates in the urine.

Glucose, pentose, lactose, levulose, cane sugar, inosite, glycogen, and the like are not infrequently found abnormally in amounts sufficient to respond to certain chemic tests, and under such circumstances they are of pathologic interest. The most important of these, from a clinical point of view, is glucose.

GLUCOSE.

$C_6H_{12}O_6$.

(Diabetic Sugar, Dextrose, Grape-sugar.)

Careful chemic examinations have shown it to be highly probable that normal urine contains traces of sugar.[1] Under pathologic conditions glucose is present either temporarily—glycosuria—or permanently—diabetes mellitus. (See Diabetes Mellitus, p. 370.)

Glucose crystallizes in colorless, transparent prisms, which collect in bundles or in hard, tenacious crusts. It is soluble in its own weight of water, slightly soluble in cold

[1] Neubauer and Vogel, "Analyse des Harns," Bd. 1, 1898, S. 62.

alcohol, more readily in hot alcohol, and insoluble in ether. Animal charcoal extracts it from its solutions (Bence Jones [1] and Seegen[2]). Solutions of glucose turn the rays of polarized light to the right (dextrose), and, according to the last accurate determinations of Tollens,[3] the specific rotation of the aqueous solution was found to be + 52.5°. In alkaline solutions it reduces the salts of copper, bismuth, mercury, and silver; in the copper tests the cupric oxide is reduced to cuprous oxide (suboxide of copper). Glucose forms an osazone with phenylhydrazin,—phenylglucosazone (Plate 4), which crystallizes in highly characteristic groups of yellow needles.

Isolation.—Grape-sugar may be separated from the urine in a number of ways, but the most practical method is that advised by Salkowski.[4]

Salkowski's Method.—Take 20 c.c. of urine and add 10 c.c. of a 1.6 normal solution of copper sulphate (with 199.52 grams of copper sulphate to the liter), and 17.6 c.c. of normal sodic hydrate. After twenty to thirty minutes, dilute with 100 c.c. water, and filter. When the fluid has passed through, the filter-paper is immediately placed on bibulous paper and entirely freed from the rest of the fluid. The precipitate is then dissolved in 50 c.c. of dilute hydrochloric acid (1 of hydrochloric acid, specific gravity 1120, to 10 of water), the copper removed by sulphuretted hydrogen, the filtrate exactly neutralized with sodic carbonate, and evaporated to 20 c.c. This fluid is then to be tested for sugar, either qualitatively or quantitatively. Salkowski claims that 0.5 per cent. of sugar can be detected in urine in this way. Einhorn has detected as little as 0.05 per cent. of sugar by this method.

Detection of Sugar in Urine.—The **copper tests,** which depend upon the power that grape-sugar possesses in alkaline solution of reducing the oxide of copper to lower oxides, are perhaps more commonly used than all others for the detection of sugar in the urine. It is safe to say that they are the most convenient and rapid of all tests that are capable of being applied by the student and practitioner of medicine.

[1] "Lancet," I, 1861, No. 3.

[2] "Pflüger's Archiv," V, 375, 1872.

[3] "Berichte der chem. Gesellsch.," XVII, 2234, 1884.

[4] "Zeitschr. f. physiol. Ch.," III, 96, 1879.

The oldest of the copper tests is Trommer's, in which the hydrate of copper is set free at the time of its application by an excess of sodic or potassic hydrate.

Trommer's Test.—1. Take a third of a test-tube of urine, render alkaline with sodic or potassic hydrate. To this mixture then add, drop by drop, a weak solution (five per cent.) of sulphate of copper, shaking the mixture after each addition, until a deep-blue solution is obtained, or until the cupric hydrate, which forms as the copper is added, fails to dissolve. The upper one-half of the mixture is then boiled, and if sugar be present, a yellow precipitate of suboxide of copper soon forms.

2. A second similarly prepared mixture of these ingredients may be made and set aside for from six to twenty-four hours without the addition of heat. If sugar be present, a similar precipitate of cuprous oxide will take place. If the reaction, with heat, is at all doubtful, it is important that this control-test should be made, since, as Neubauer has pointed out, most of the organic substances that reduce copper do so only when heated or after prolonged boiling.

Fehling's Test.—This test is performed by the use of Fehling's solution, which is prepared according to the *original formula*, as follows: Pure crystallized cupric sulphate, 34.639 grams; a solution of caustic soda,—specific gravity 1120,—about 500 c.c.; chemically pure crystallized neutral sodic tartrate, 173 grams. Prepare by dissolving the sulphate of copper in 100 c.c. of distilled water; next dissolve the neutral sodic tartrate in the solution of caustic soda, and add the copper solution, little by little; finally, bring the whole volume to 1000 c.c. (1 liter) with distilled water. Ten cubic centimeters of this solution require 50 milligrams of sugar to completely reduce it.

It is a well-known fact that Fehling's solution prepared in the manner described soon decomposes on standing, and therefore becomes unfit for use. Furthermore, it has been found (Soxhlet) that the solution as previously given is too concentrated to obtain a delicate reaction. *The following modification of Fehling's solution is therefore recommended for the purpose of obtaining a permanent solution, and one which also furnishes a rapid and yet delicate reaction.* The solution is divided into two parts—viz., copper solution (A) and alkaline tartrate solution (B).

A.	Cupric sulphate	34.639	grams.
	Distilled water . . . . . ad	1000	c.c.
B.	Sodio-potassium tartrate (Rochelle salt) .	173	grams.
	Sodic hydrate (specific gravity 1120)[1] . .	500	c.c.
	Distilled water . . . . . ad	1000	"

These solutions—A and B—are to be kept in separate bottles and in a dark place. Equal parts of the two solutions produce diluted Fehling's solution. It will be seen that the combined volume of the two solutions amounts to 2000 c.c., or one-half the strength of the solution of the original formula. Therefore, 20 c.c. of the combined mixture (10 c.c. of each) require 50 milligrams of sugar to completely reduce it.

Process.—*Qualitative Test.*—Take equal parts of the two solutions—A and B, about one fingerbreadth of each—in a test-tube, and boil. If the Fehling's solution remains clear on boiling, then add 20 to 30 drops of the suspected urine which is free from albumin. *Do not boil after the addition of the urine.* If much sugar be present, a yellow or red precipitate of suboxide of copper readily appears. In case the quantity of sugar in the urine is less than 1 per cent. the reduction will not appear until after several minutes—five to thirty. If a reduction does not take place in thirty minutes, it is advisable to let the test stand for from eighteen to twenty-four hours, since traces of sugar show evidence of a reduction of the copper only after several hours, when a small amount of the suboxide will be found in the bottom of the test-tube. Less time is required for the test if the urine is gently heated previous to its being added to the boiling Fehling's solution. The nonappearance of a suboxide precipitate shows that the urine is free from sugar.

In the hands of the author Fehling's test, performed in the manner previously indicated, is one of the most delicate and reliable tests available for routine work. The phenylhydrazin test is more delicate than Fehling's, but is less suitable for routine examinations on account of the length of time required for the performance of the test. (See p. 152.)

If the two solutions, which constitute Fehling's solution, are kept in separate bottles and mixed at the time they are

[1] Sodic hydrate, having a specific gravity of 1120, is prepared as follows: Caustic soda, 52.727 grams; distilled water, sufficient to make 500 c.c.

to be used, there need be no fear that the solutions will decompose, even after keeping them several months.

Professor Haines, of Chicago, has advised a modification of Fehling's solution,[1] and claims that the solution prepared according to his formula is stable, and, although kept on hand indefinitely, it may always be depended upon to be in good order for testing.

Haines' Test (*Simplified Formula*).—Take pure copper sulphate, 30 grains ; distilled water, ½ of an ounce ; make a perfect solution, and add pure glycerin, ½ of an ounce ; mix thoroughly, and add 5 ounces of liquor potassæ. In testing with this solution take about 1 dram and gently boil it in an ordinary test-tube. Next add 6 to 8 drops (not more) of the suspected urine, and again gently boil. If sugar be present, a copious yellow or yellowish-red precipitate separates ; if no such precipitate appears, sugar is absent.

On account of the decomposition of Fehling's solution on standing, Schmiedeburg has suggested the substitution of 15 grams of pure *mannite* for the neutral sodic tartrate of Fehling's solution. The mannite should first be dissolved in 100 c.c. of distilled water, then 500 grams of the solution of caustic soda, specific gravity 1140, should be added, and the solution completed according to the original formula for Fehling's solution.

With the same end in view 173 grams of pure glycerin have likewise been substituted for the neutral sodic tartrate of Fehling's solution.

When the proper precautions are observed, reliable results may be expected with Fehling's solution, with saccharine urine which contains about $\frac{2}{10}$ of 1 per cent. of sugar.

Precautions and Errors.—These are applicable to all copper tests :

1. If the urine contains more than a *trace* of albumin, it must be removed, as it interferes with the reduction of the oxide of copper.

2. When the mixture of urine and reagent is allowed to stand several hours without boiling, a considerable quantity of sugar is necessary before a satisfactory reaction occurs.

3. The mixed urine and reagent should never be heated or boiled, since, as already stated, there are often organic substances other than sugar in the urine, which have, in the

[1] Purdy, "Practical Urinalysis," p. 103.

presence of heat, a reducing action on an alkaline solution of cupric oxide. These substances are uric acid, urates, kreatinin, hippuric acid, mucin, hypoxanthin, glycuronic acid, alkapton, alkaloids, arsenic, and carbolic acid. Uric acid is the chief source of error, and should always be borne in mind in the use of the copper tests.

4. The flocculent precipitate of earthy phosphates that is thrown down by the alkaline hydrate should not be mistaken for the suboxide of copper. Such a precipitate is either colorless or of a greenish hue.

5. Decolorization of the reagent by the urine should not be mistaken for a reduction of the copper. There must be an actual yellow or red precipitate. Any highly acid normal or pathologic urine may have a decolorizing action on the copper reagent.

6. Too strong a solution of copper should not be used, since, in the presence of heat, a yellow or greenish-yellow color is often produced. This color may not appear until the mixture has cooled.

Phenylhydrazin Test.—The phenylhydrazin test for sugar is applied as follows: To 50 c.c. of the suspected urine add 1 or 2 grams of hydrochlorate of phenylhydrazin, 2 grams of sodium acetate, and heat on a water-bath for one hour; or add 10 to 20 drops of pure phenylhydrazin and an equal number of drops of 50 per cent. acetic acid, and heat as before. On cooling, if not before, *phenylglucosazone* separates out as a crystalline or amorphous precipitate. If upon microscopic examination the precipitate is found to be amorphous, it is dissolved in hot alcohol, and the solution diluted with water, and boiled to expel the alcohol, whereupon the compound is obtained in the characteristic form of yellow needles. It is claimed that by this method it is possible to obtain the crystals from a urine that contains only 0.15 gram of sugar per liter, or 0.015 per cent. (Williamson).

Williamson has modified the phenylhydrazin test for sugar, as described in the work on urinary analysis by Hoffmann and Ultzmann, and has found it very useful.

Williamson's Test.[1]—"A test-tube of ordinary size is filled for about *half an inch* with hydrochlorate of phenylhydrazin (in powder); then acetate of soda in powder (or

[1] Williamson, "Diabetes Mellitus and its Treatment," 1898, p. 25.

small crystals) is added for another *half-inch*. The test-tube is then half filled with urine, and boiled over a spirit-lamp. In performing the test I have not attempted to dissolve the salts by shaking the tube, but have simply applied the flame of the lamp to the bottom of the tube, and the powders have soon passed into solution. After the urine has reached the boiling-point I have always continued to boil for about *two minutes*. The tube is then left in the test-stand, and examined again some time afterward."

If sugar be present, a yellowish deposit forms at the bottom of the tube, and on microscopic examination it is seen to consist chiefly of beautiful needle-shaped crystals of a bright sulphur-yellow color. If no sugar is present, only brownish amorphous globules or yellow scales are found in the deposit. By performing the test in this simple manner Williamson has never obtained any crystals of phenylglucosazone in normal urine.

Much discussion has arisen concerning the proper method of performing this test for sugar. According to Hirschl,[1] if a mixture be left on a water-bath for a shorter time than one hour, a glycuronic acid compound (melting-point, 150° C.) is formed, which is liable to be mistaken for phenylglucosazone. On the other hand, it has been pointed out by a number of observers that if the mixture be kept on a water-bath for as long a period as one hour, a small deposit of the crystals may be obtained in many normal urines. These crystals are frequently of a doubtful nature, even after they have been dissolved in hot alcohol and recrystallized.

According to Fischer, the reaction which takes place between phenylhydrazin and glucose is represented by the following equation:

$$C_6H_{12}O_6 + 2C_6H_5 . N_2H_3 = C_{18}H_{22}N_4O_4 + 2H_2O + 2H.$$

A great advantage of the phenylhydrazin test for sugar is that it gives no reaction with uric acid, kreatinin, hippuric acid, pyrocatechin, etc., while with Fehling's test, as ordinarily applied (boiling the urine and Fehling's solution together), these substances are often a source of fallacy.

Phenylglucosazone ($C_{18}H_{22}N_4O_4$) crystallizes in bright, fine, yellow needles (see Plate 4), which are arranged singly or in stellate groups. They are almost insoluble in water,

[1] "Zeitschr. f. physiol. Ch.," XIV, 377.

but dissolve in boiling alcohol, and melt at 204° to 205° C.

Fermentation Test.—The fermentation test is an excellent and reliable one for the detection of sugar (glucose) in all cases in which the urine contains more than ½ of 1 per cent. of sugar. The test depends upon the fermentation of the sugar by means of yeast, yielding alcohol, carbon dioxide, and various other less important substances, with a resulting decrease in the specific gravity. The following equation represents the reaction which takes place:

$$C_6H_{12}O_6 = 2C_2H_6O + 2CO_2.$$

The most convenient method of applying this test is as follows: Take a test-tube, preferably one of large diameter, introduce into it a piece of compressed yeast about the size of a pea, and fill the test-tube to the top with the urine to be tested. Stopper tightly with a rubber cork having a single perforation, through which a glass tube is passed so that it reaches nearly to the bottom of the test-tube. Above the cork the glass tube is bent at right angles to the perpendicular of the test-tube, and some four inches from this bend the tube is again given a right-angled bend downward. A receptacle is then placed under the end of the glass tube.

If sugar is present, evidences of fermentation will present themselves, generally within twelve hours, by the formation of carbon dioxide which rises to the surface of the urine, but, being held in by the cork, forces the urine out through the bent glass tube into the receptacle at the end of the tube. Sufficient carbonic acid gas is usually obtained from highly saccharine urines to force out all of the urine in the test-tube. The test should be subjected to a temperature of 80° to 90° F.

This test can not be relied upon if less than ½ per cent. of sugar is present, since a small quantity of carbon dioxide is likely to be absorbed by the urine (water will absorb an equal volume of carbonic acid gas).

In the performance of this test it should be borne in mind that some specimens of yeast spontaneously evolve gas, and it is, therefore, best to perform with each urine tested a control experiment with yeast mixed with water instead of urine, in order to judge of the amount of gas in the yeast itself.

Plate 4

Crystals of Phenylglucosazone (after von Jaksch).

The chief disadvantage of the fermentation test is that it requires several hours for its completion, and it is therefore not practical for routine work.

Bismuth Tests.—These tests depend upon the power that sugar (glucose) possesses of reducing the salts of bismuth, with a resulting black precipitate of metallic bismuth.

(*a*) *Böttger's Test.*—Take one-fourth of a test-tube of the suspected urine, add an equal volume of potassic hydrate (liquor potassæ, U. S. P.), or a solution of sodic carbonate (1 part of crystals to 3 parts of distilled water), mix, and add a small amount of subnitrate of bismuth. Shake, and boil the whole mixture, and if sugar be present, a black precipitate appears, which clings to the sides of the test-tube. A gray, instead of a black, precipitate is obtained if the quantity of sugar is small, in which case a smaller amount of bismuth should be used in making the test. According to Tyson, this gray precipitate, said to be characteristic of small quantities of glucose, sometimes presents itself when no sugar is present.

The urine to be tested should be free from albumin and other substances containing sulphur, since traces of sulphur combine with the bismuth salts to form bismuth sulphide, which is likely to be mistaken for metallic bismuth. To obviate this difficulty, Brücke has suggested the following :

(*b*) *Brücke's Modification of Böttger's Test.*—Frohn's reagent [1] is recommended for the removal of the sulphur compounds in the following way : Pour into a test-tube a certain quantity of water, say 10 c.c., and fill another tube to the same level with the suspected urine. To the first add a drop of Frohn's reagent, which will cause a precipitate. Then add, drop by drop, concentrated hydrochloric acid until the precipitate is redissolved. In this way the approximate quantity to be added to the suspected urine is ascertained. Acidulate the urine in the other test-tube with the same quantity of hydrochloric acid ; treat it with the reagent until precipitation is complete, and filter. The filtrate, which should not be rendered turbid on the further addition of hydrochloric acid or the reagent, is thoroughly boiled with an excess of sodic or potassic

[1] Frohn's reagent : 1.5 grams of freshly precipitated bismuth subnitrate are mixed with 20 grams of water, and heated to boiling ; then 7 grams of potassium iodide and 20 drops of concentrated hydrochloric acid are added.

hydrate, as in Böttger's test. If a gray or black precipitate or color is formed, sugar is present. Brücke claims that this test will detect 0.4 per cent. of glucose in water.

(*c*) *Nylander's Test.*—Almén's fluid is used. It consists of 4 grams of Rochelle salt (sodio-potassic tartrate), dissolved in 100 c.c. of a 10 per cent. solution of caustic soda. The fluid is warmed, and 2 grams of subnitrate of bismuth are added. One volume of this fluid is added to 10 volumes of urine, and the mixture heated. In a few minutes (three to five) it will become black if sugar be present. The reaction will indicate the presence of at least 0.1 per cent. of sugar. This test is not applicable to albuminous urines, and the reaction occurs in the presence of melanin or melanogen, or when the fluid is rich in reducing substances other than sugar.

Methylene-blue Test.—Methylene-blue is decolorized by glucose in a warm alkaline solution. In performing the test the diabetic or suspected urine is diluted (1 part to 9 of water). Of this diluted urine 2 c.c. are mixed with 6 c.c. of a 1 : 3000 solution of methylene-blue, and 2 c.c. of potassic hydrate are then added. The mixture is boiled for one or two minutes, when the blue color disappears if sugar be present. Care must be taken that the fluid is shaken as little as possible, since the blue color returns easily, owing to the action of the oxygen in the air. It is important to dilute the urine, as all *undiluted* urine discharges the blue color; but normal urine diluted 1 : 9 of water does not decolorize methylene-blue.

Williamson has found that a distinct reaction is obtainable by this method when diabetic urine is diluted until the percentage of sugar is only 0.07, but when further diluted, until it is 0.014, no reaction is obtained. Urines rich in urates give a doubtful reaction when diluted 1 : 9. Since urine often contains reducing substances other than sugar, Fröhlich [1] recommends that it be treated first with 5 c.c. of a concentrated solution of lead acetate, and with 5 c.c. of a solution of basic acetate of lead; then take an equal quantity of the filtrate and a concentrated solution of methylene-blue (1 : 300), add potassic hydrate, and boil, as previously indicated. This test is not so satisfactory as the phenylhydrazin or the Fehling test.

[1] "Centralbl. f. inn. Med.," 1898, No. 4.

Numerous other tests have been suggested for the detection of sugar in urine. The following may be mentioned: Diazobenzolsulphonic acid (Penzoldt), picric acid (Johnson), sodium or potassium hydrate and heat (Moore), acetate of lead and ammonia (Rubner), alpha-naphthol and thymol (Molisch), and indigo-carmine (Mülder). Most of the above-named tests are greatly inferior to those that have been described.

Quantitative Determination of Sugar in Urine.—A quantitative determination of the sugar should be made in all cases in which it has been detected. It is only by a knowledge of the quantity of sugar present that a diagnosis of the condition can be made, the severity of the disease ascertained, and the results of treatment judged. The twenty-four-hour quantity of urine should be accurately kept, and while it is being collected, put in a cool place to prevent fermentation. The entire secretion for the twenty-four hours should then be thoroughly mixed and measured, and a sample of this taken for the determination. The urine obtained at a single micturition should not be used for the quantitative test, for the reason that there is considerable variation in the quantity of sugar eliminated: according to the time of day, and the length of time after a meal.

The total quantity in grams should in every instance be calculated. A knowledge of the percentage of sugar alone is never sufficient, for the percentage in itself means little if the total quantity is not determined. In routine work the percentage is usually obtained, but only for the sake of convenience in figuring the total number of grams of sugar.

Fehling's Test.—This is one of the most practical quantitative tests for sugar in urine, and is conducted by the titration method, using the *modified Fehling's solution*, the formula of which is given on page 150.

The process depends upon the fact that the blue color disappears, and that the copper is completely precipitated from a definite quantity of Fehling's solution by a given amount of grape-sugar; thus, every 20 c.c. of the modified Fehling's solution used require 50 milligrams of sugar to completely reduce it.

Necessary Apparatus (Fig. 17).—A Florence flask of 250 c.c. capacity; a common retort-stand with a burette-holder attachment, and with a piece of copper- or iron-wire

gauze that is large enough to cover one of the rings of the stand (a tripod, the top of which is covered with copper-wire gauze, may be conveniently used); a 25- or 50-c.c. burette, which is graduated to tenths of a cubic centimeter; a 10-c.c. pipette; a 100-c.c. glass-stoppered graduate; and a Bunsen burner or a large spirit-lamp.

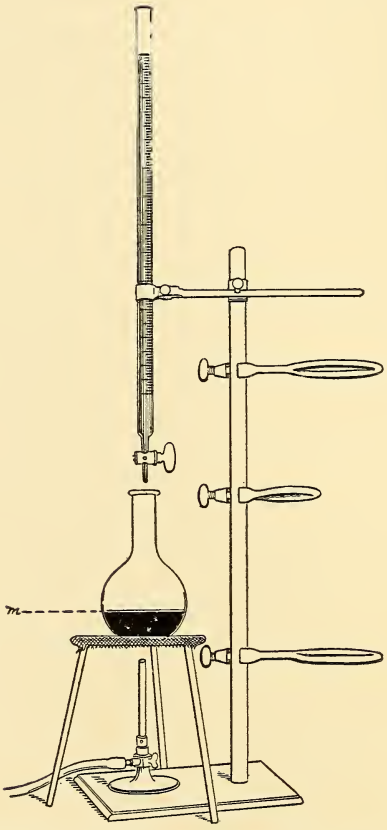


Fig. 17.—Apparatus for the quantitative estimation of sugar: *m*, Meniscus.

The analysis should be conducted as follows: First take the specific gravity of the urine to be tested, then test for albumin,—preferably by the nitric acid test,—and if *more than a trace* be present, remove it according to the directions given on page 131.

If the specific gravity of the urine is *more* than 1030, dilute it 1 : 10 with distilled water (urine, 1 ; water, 9) ; if *less* than 1030, dilute it 1 : 5 (urine, 1 ; water, 4). Mix thoroughly, and pour the diluted urine into the burette, filling it to the zero mark, care being taken to expel all air from below the stop-cock. Next take 10 c.c. of *each* of the solutions A and B by means of the 10-c.c. pipette, and place in the 250-c.c. flask. Add 60 c.c. of distilled water, making the entire volume amount to 80 c.c. Place the flask on the wire gauze, and boil the mixture. After the diluted Fehling's solution has boiled for a short time,—say for two or three minutes,—and it is found that the solution does not show evidences of reduction, the diluted urine is added, *drop by drop*, from the burette into the Fehling's solution, which is kept boiling. When, on removing the flame, after a series of observations, it is found that the meniscus has lost its blue color and has become colorless,[1] the reaction is complete.

The *meniscus* (Fig. 17, *m*), which is seen as a clear line (blue at first and later colorless), is best detected by placing the flask between the eye and the light. As the eye is raised and lowered, this clear line will be seen just beneath the surface of the fluid.

The blue color having disappeared from the mixture, the number of cubic centimeters of diluted urine employed is read off. Since it takes just 50 milligrams (0.050 gram) of sugar to completely reduce the cupric oxide in the 20 c.c. of Fehling's solution used, the percentage of sugar in the urine may be readily calculated, and from the per cent., the number of grams of sugar eliminated in twenty-four hours.

Example: If 15 c.c. of *diluted* urine were necessary to complete the test, and the urine was originally diluted 1 : 10, then $15 \div 10 = 1.5$ c.c. of *undiluted* urine. Since 1.5 c.c. of undiluted urine reduced the copper, and 50 milligrams of sugar accomplish the same end, then 1.5 c.c. of urine must contain 50 milligrams of sugar. The percentage is obtained according to the following proportion :

$$1.5 : 0.050 :: 100 : x$$
$$x = 3.33 \text{ per cent.}$$

[1] When the test solution is allowed to stand for a short time after the test has been completed, it again becomes blue, due to the reoxidation by the oxygen from the air. This should not be mistaken for an incomplete reduction.

Suppose the total quantity of urine in twenty-four hours amounted to 2000 c.c., then $\frac{3.33 \times 2000}{100} = 66.6$ grams,[1] the quantity of sugar in twenty-four hours.

Precautions: 1. The urine should be added to the boiling Fehling's solution, drop by drop, in order to obtain a suboxide precipitate that will settle in a very short time. If a considerable quantity of the urine is added at a time, the precipitate will not settle well, and the meniscus can not be distinctly seen.

2. A yellow color to the meniscus or to the body of the solution, besides that produced by the suboxide precipitate, indicates that too much of the saccharine urine has been added, and that the end reaction has passed. A new titration is then necessary.

3. The Fehling's solution should be kept at the boiling temperature, except during the time required for observing the meniscus. As soon as the solution cools, reoxidization of the copper begins, and consequently the blue color reappears.

Purdy's Method.—The following modification of Fehling's method is advised by Dr. Purdy, who claims that by the use of his solution various defects of Fehling's method are overcome:

Take of pure cupric sulphate, 4.752 grams; potassium hydroxide, 23.5 grams; strong ammonia (U. S. P.—specific gravity 0.9) 350 c.c.; glycerine (C.P.), 38 c.c.; distilled water, to make 1000 c.c.

Prepare by dissolving the cupric sulphate and glycerine in 200 c.c. of distilled water with the aid of gentle heat. In another 200 c.c. of distilled water dissolve the potassium hydrate, mix the two solutions, and, when cool, add the ammonia. Finally, with distilled water bring the volume of the whole to exactly 1000 c.c. Thirty-five cubic centimeters of this solution are reduced, upon boiling, by exactly 2 centigrams (0.02 gram) of grape-sugar.

Proceed by accurately measuring 35 c.c. of the solution into the flask, dilute with about two volumes of distilled

[1] Since this method of figuring is based on the supposition that 1 c.c. is equal to 1 gram, the same as distilled water, it can not rightly be applied to urine, 1 c.c. of which weighs more than 1 c.c. of distilled water; therefore, the figures 66.6 represent only the approximate quantity of sugar. Accurate figures may be obtained by correcting for the difference between the specific gravity of the urine tested and that of distilled water.

water, and bring the whole thoroughly to the boiling-point. Fill the burette to the zero mark with the urine to be tested, and *slowly discharge* the urine into the *boiling* test solution, drop by drop, until the blue color begins to fade; then, still more slowly, three to five seconds elapsing after each drop, until the blue color completely disappears and the test solution is left perfectly *colorless and transparent.* The number of cubic centimeters required to discharge the blue color in 35 c.c. of the test solution contains exactly 2 centigrams (0.02 gram) of sugar.

If 35 c.c. of the test solution are reduced by 2 c.c. of urine, then 2 : 0.02 :: 100 : x, and x = 1 per cent. of sugar; reduced by 1 c.c., 2 per cent.; reduced by ¾ of a cubic centimeter, 3 per cent.; reduced by ½ of a cubic centimeter, 4 per cent.; reduced by ¼ of a cubic centimeter, 8 per cent.

If absolute accuracy of results is desired, it is better to dilute the urine to be tested with 2 volumes of distilled water, and divide the product by 3; especially if the percentage of sugar is high.

The advantages claimed by Purdy for this test are (1) its perfect end-reaction; (2) the stability of the solution; (3) its rapidity of application, only requiring about five minutes, and (4) its accuracy.

Fermentation Test.—The fermentation test for sugar can not be considered an *accurate* quantitative test, although it may be used with advantage for determining the *approximate quantity* of sugar present. The method suggested by Roberts is as follows: Four ounces of the saccharine urine are placed in a twelve-ounce bottle, and a piece of compressed yeast is added. The bottle is then stoppered with a nicked cork to permit the escape of the carbonic acid gas, and set aside in a warm place to ferment. Beside it is placed a tightly corked four-ounce bottle filled with the same urine, but without any yeast. In from eighteen to twenty-four hours fermentation will have ceased. The fermented urine is then decanted into a urinometer-glass, and the specific gravity taken. The specific gravity of the unfermented urine in the other bottle is taken at the same time, and the *loss of density* ascertained. Roberts has shown that every degree in the specific gravity lost in fermentation corresponds approximately to *one grain of sugar per fluidounce.* Thus, if before fermentation the

specific gravity was 1040 and after fermentation it is 1020, it will have contained 20 grains of sugar to the fluidounce of urine. The two portions of urine in the bottles should be subjected to exactly the same temperature.

The percentage of sugar may be roughly ascertained by multiplying the number of degrees lost in the specific gravity by the arbitrary coefficient 0.23.

In the hands of the writer the fermentation test yields results which are in the neighborhood of one-half per cent. below those obtained by using Fehling's solution. A decided objection to this method is that it requires from eighteen to twenty-four hours for the completion of the analysis.

Einhorn has devised a fermentation apparatus that gives only approximate results. Two specially constructed and graduated tubes are used, one of which is filled with a mixture of the suspected urine and a small quantity of yeast, and the other with a mixture of normal urine and yeast, as a control. The tubes are then set aside at a temperature of from 30°–34° C. (86°–93° F.), and left until fermentation has ceased. The percentage of sugar is then read off from the column of carbon dioxide present. If the second tube also shows a small amount of gas, the figure corresponding to the amount is deducted from the reading in the first tube.

By Polarization.—Glucose, or grape-sugar, rotates the plane of polarized light toward the right, and upon this fact a quantitative test for that substance is based. Although a quantitative determination of grape-sugar by this method is theoretically accurate, when applied to urine it is open to fallacy, since the urine is apt to contain other substances such as lævulose, β-oxybutyric acid, etc., which rotate the plane of polarized light in the opposite direction. As pointed out by v. Jaksch, Hoppe-Seyler, and others, it is advisable to apply the test both before and after fermentation, and the difference in the results will represent the quantity of grape-sugar in solution.

A large variety of polariscopes have been constructed for this purpose, among the best of which are those of Soleil, Laurent, Lippich, Ultzmann, Misterlich, v. Fleischl, and Schmidt & Haensch. In recent years the use of the half-shadow polariscope has rendered this quantitative test

more reliable, on account of the accuracy with which the extent of rotation is determined.

The polariscope manufactured by Schmidt & Haensch, of Berlin, is one of the best.[1] It is a half-shadow instrument, being so made that gas or petroleum light can be used instead of a sodium light. It determines direct percentages of sugar, and is not only accurate, but its operation is quick and simple.

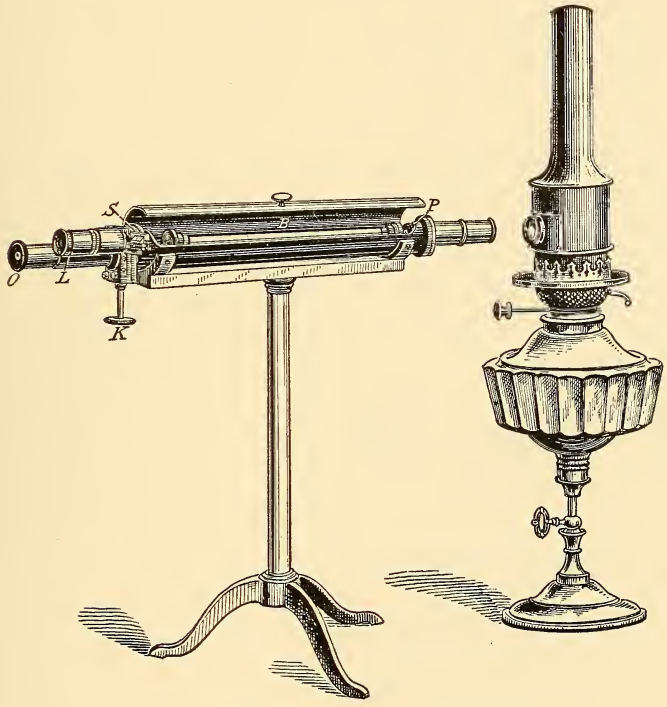


Fig. 18.—The Schmidt & Haensch polariscope.

In the Schmidt & Haensch apparatus, as represented in figure 18, *O* is the ocular; *S*, the ivory scale with vernier; *L*, the ocular by means of which the scale is read; *K*, the screw-head by which the quartz wedge is moved; *B*, the glass tube for holding the suspected fluid; and *P*, the receptacle for the glass tube.

[1] This instrument can be obtained of Messrs. Eimer & Amend, 205–211 Third Avenue, New York city.

The source of light is a well-constructed lamp, with a flat burner, for either gas or petroleum; a special lamp can be constructed so as to use electric light. The lamp should be removed about 30 cm. from the apparatus, and so adjusted that the illuminating lens in the chimney of the lamp shall be exactly central to the optical axis of the apparatus. In looking through the instrument a clear circular field should be seen, with a sharp perpendicular line between the two halves of the field. If the field is not perfectly distinct, the ocular (*O*) should be drawn out until the perpendicular line and the circular outline of the field are sharply defined. This adjustment should be made without the glass tube—that is, the receptacle should be empty and its cover closed.

The delicate scale (*F*), on which are found numbers corresponding to the principal lines, is read through the ocular (*L*). The zero point on the vernier (*S*) should be made to correspond exactly with that on the scale (*F*) by means of the adjustment-screw (*K*). When the zero point on the vernier is opposite that on the scale, the two halves of the field of the apparatus should exactly correspond—that is, they should be equally lighted. (See *b*, Fig. 19.) If, however, the two halves of the field should not receive an equal amount of light, they should be made to correspond exactly by the use of the adjustment-screw (*K*). The vernier (*S*) is then moved to the side corresponding by means of a micrometer-screw, until its zero point is opposite that on the scale (*F*).

Fig. 19.

Having adjusted the apparatus, the glass tube is then filled with the suspected urine, and placed in the receptacle. The two halves of the field, which are then found to receive an *unequal* amount of light, are made to correspond by means of the adjustment-screw (*K*), and the rotation to the right or to the left read on the scale. The result is the percentage of sugar in the fluid. Every interval on the scale corresponds to ½ per cent., and between these intervals are lines which are equivalent to $\frac{1}{10}$ per cent.

Example.—If the scale is moved toward the left, the number of scale intervals that have been passed is reckoned from the zero point on the vernier. Suppose that the

number of scale-intervals passed is 7, and that the zero point of the vernier stands between 7 and 8 and at the mark corresponding to 0.3 per cent., then

$$7 \text{ half per cent.} = 3.5 + 0.3 = 3.8 \text{ per cent.}$$

A similar reading is made when the scale is moved toward the right. In order to read direct percentages of sugar on the scale the 200-mm. tube should always be used. If it should be necessary, on account of the turbidity of the urine, to use the 100- or 50-mm. tubes, the reading in every instance should be multiplied by either 2 (100-mm. tube) or 4 (50-mm. tube).

Grape-sugar rotates the plane of polarized light toward the right; albumin rotates toward the left. Consequently, in a urine containing both albumin and sugar the degree of rotation to the right or to the left will depend upon the predominance of one or the other of these substances.

Precautions.—The urine must be clear; if it is turbid, it should be filtered as rapidly as possible through a plaited filter of soft filter-paper. If the urine is then so highly colored that when the long glass observation tube (200 mm.) is used the line of separation between the two halves of the field can not be distinctly seen, the shorter glass observation tube (100 or 50 mm.) should be used. If the field is still indistinct, the urine should be shaken in a flask with pure, dry, animal charcoal, or decolorized by adding to the urine one-tenth of its volume of basic acetate of lead, and then filtered. In the latter instance the results obtained by polarization must be multiplied by $\frac{11}{10}$, on account of the dilution.

The temperature of the urine must be from 15° to 20° C. If the urine is free from albumin, the percentage of sugar is obtained directly by the use of the 200-mm. tube, in the manner mentioned. If, on the other hand, the urine contains albumin, a second polarization is necessary after the removal of the albumin. The albumin is removed as follows: Take 100 c.c. of the urine in an evaporating dish, and place on a water-bath. Add acetic acid, drop by drop, continuing the heat until a flocculent precipitate appears. Filter as quickly as possible, cool, and add sufficient distilled water to the filtrate to make 100 c.c. The result of the second polarization will represent the exact percentage of sugar.

LACTOSE.

(MILK-SUGAR.)

Lactose, $C_{12}H_{22}O_{11}$, is not infrequently found in small amounts in the urine of women (the maximum being about one per cent.) near the end of gestation, but more especially in nursing women in whom the flow of milk has become impeded, as in cases of mastitis. Lactose is also frequently seen in the urine of women who have weaned their children. Its presence may continue for from three to four days, and even a week, particularly in those in whom the secretion of milk is copious. Whereas lactose, when present, is an abnormal constituent of the urine, its presence can not be considered of pathologic significance. Its chief importance lies in the fact that it should, in all cases, be distinguished from glucose.

Lactose crystallizes in colorless, four-sided prisms, with acuminated ends, bounded by four angles. The specific rotary power of lactose is + 52.5°, and is independent of the concentration in solutions that contain up to 56 per cent. at ordinary temperatures. It reduces the salts of copper upon boiling in alkaline solution, but more feebly than grape-sugar. It does not undergo alcoholic fermentation with yeast; is quite soluble in cold, and freely soluble in hot, water; insoluble in alcohol and ether. It is precipitated by acetate of lead and ammonia (Brücke).

Isolation.—According to F. Hofmeister, the following process serves for the isolation of milk-sugar: Since evaporation of the urine is liable to decompose the lactose, it is directly precipitated by a solution of acetate of lead and ammonia, and the precipitate is washed. The filtrate and wash-water should again be precipitated with lead acetate and ammonia, and the process repeated until the filtrate shows no more rotation. The washed precipitate is then suspended in cold water, and decomposed with sulphureted hydrogen. The solution is freed from the greater part of the hydrochloric acid by shaking with silver oxide, and from the remainder of the HCl by neutralizing the filtrate. The solution is once more treated with H_2S, and the mixture evaporated after the addition of barium carbonate. Before the residue becomes syrupy it should be treated with a sufficient amount of 90 per cent. alcohol to produce a flocculent, rapidly settling precipitate. The filtrate, placed

in a desiccator, yields crystals of lactose, which should be washed with dilute alcohol, then recrystallized from water after decolorizing with animal charcoal, and finally freed from adhering substances by boiling with 60 to 70 per cent. alcohol. These crystals are then subjected to the tests for lactose, including that with Barfoed's reagent.

Detection.—If the urine reduces Fehling's solution feebly, does not ferment with yeast, and rotates the polarized light strongly to the right, lactose is probably present, especially if the urine is that of a pregnant or nursing woman. A confirmatory test may be made by using the phenylhydrazin test, which, in the presence of lactose, forms an osazone. Phenyl-lactosazone crystallizes in the form of yellow needles, which are usually aggregated in clusters, and melts at 200° C., with the evolution of gas. Lactose, unlike glucose, does not reduce Barfoed's reagent,[1] but this test can not be applied to urine, since Barfoed's reagent is reduced to a slight extent by normal urine.

The certain detection of lactose is secured only by isolating it from the urine.

LEVULOSE.

(Fruit Sugar.)

Levulose, $C_6H_{12}O_6$, is only rarely found to be a constituent of the urine. When present, it is usually found associated with grape-sugar, and is rarely, if ever, found alone. In such instances it usually happens that considerably more sugar is found in diabetic urine by titration than by polarization, thus showing the presence of a substance that rotates to the left. The diminution in the optical activity of the urine is not necessarily caused by a sugar that rotates to the left, but may be produced in the absence of albuminous substances (albumin, globulin, albumose, and peptone) by other bodies, especially β-oxybutyric acid, glycuronic acid, cystin, and other compounds.

It is characterized by being noncrystallizable when impure (although it crystallizes in long, wavy needles when pure), and by turning the plane of polarized light to

[1] Barfoed's Reagent: Dissolve one part of cupric acetate in 15 parts of water; to 200 c.c. of this solution add 5 c.c. of acetic acid containing 38 per cent. of glacial acetic acid ("Journ. f. prakt. Chem." [2], Bd. VI (1872), S. 344).

the left instead of to the right. Its rotary power diminishes as the temperature rises, while that of grape-sugar is independent of the temperature. Levulose reduces the salts of copper, although much more feebly than grape-sugar.

There is no sure process known for the isolation of levulose.

Detection.—Levulose is best detected by means of the polariscope, since it rotates the plane of polarized light to the left. It yields with phenylhydrazin an osazone (phenyl-levulosazone) that crystallizes in yellow needles whose melting-point is 150° C., while those formed from grape-sugar have a melting-point of 204° C.

If the left-handed rotation is caused by substances other than levulose, by subjecting the urine to alcoholic fermentation the left-handed rotation disappears if due to this form of sugar, and persists if caused by other bodies.

LAIOSE.

(Leo's Sugar.)

Laiose, $C_6H_{12}O_6$, was first discovered by Leo,[1] who found it in the urine of 3 out of 21 severe cases of diabetes mellitus. These urines gave 1.2 to 1.8 per cent. more sugar by titration than by polarization. This sugar could not be isolated from 20 liters of normal urine.

Laiose is closely allied to levulose in that it rotates the plane of polarized light to the left, reduces alkaline solutions of the cupric salts, and combines with phenylhydrazin. It is not fermentable and does not have a sweet taste. The neutral pale-yellow syrup does not crystallize if kept for a year. It is readily soluble in water, moderately in methyl alcohol, sparingly in ethyl alcohol, and insoluble in ether and chloroform. It is completely precipitated by basic acetate of lead and ammonia.

Isolation.—The urine is precipitated with basic acetate of lead, and the filtrate with ammonia. The second precipitate contains the laiose together with the dextrose. The precipitate is washed and decomposed with sulphuretted hydrogen. Since the filtered fluid becomes dark by evaporating in the air, Leo concentrated it by distilling in a vacuum, and finally drying over sulphuric acid. The syrupy residue is then dissolved in methyl alcohol, and the grape-sugar that has dissolved with it is

[1] Hans Leo, "Virchow's Archiv," CVII, 108, 1887.

precipitated by a solution of baryta in methyl alcohol, sufficient to give a strongly alkaline reaction. It is quickly filtered, and the filtrate allowed to stand over sulphuric acid to remove the ammonia, by which procedure, besides the baric carbonate, the remainder of the barium compound of sugar is precipitated. Carbonic acid gas is passed through the filtrate to remove the excess of baryta, and the methyl alcohol is distilled off in a vacuum, the residue dissolved in water, and the baryta in solution precipitated by sulphuric acid.

Detection.—Urines that do not contain any more sugar by titration than by polarization need not be tested for this form of sugar. If the isolated substance is a reducing body, it is probably laiose.

SUBSTANCES ALLIED TO SUGAR.

INOSITE.

(Muscle Sugar.)

Inosite, $C_6H_{12}O_6 + 2H_2O$, is a rare constituent of the urine. It has occasionally been found in small quantity in diabetes mellitus, as an accompaniment of grape-sugar; in the last stages of certain forms of chronic disease, particularly subacute glomerular and chronic diffuse nephritis; and also after the ingestion of large quantities of water (Külz). It has also been found in phthisis, syphilis, and typhus fever.

According to Neubauer and Vogel, inosite is not a sugar; but from the experiments of Maquenne [1] it should be grouped among the compounds of the fat series, mannite.

Inosite forms in cauliflower groups of crystals, and, at times, in single crystals that are three or four lines in length. It has a sweet taste, dissolves in 7.5 volumes of cold water at 17° to 20° C., readily in hot water, and is slightly soluble in alcohol. It is very soluble in dilute or concentrated acetic acid, and crystallizes more readily from these solutions than from water (Maquenne). It is insoluble in absolute alcohol and in ether. Its solutions are optically inactive, and it does not combine with phenylhydrazin, and is not fermentable by yeast; it, however, undergoes lactic- and butyric-acid fermentation. Inosite does not reduce the cupric salts when boiled in the presence of an alkaline

[1] "Bull. de la Soc. Chim." [2], XLVII, 290; XLVIII, 58, 1887; "Comptes Rendus," CIV, 225, 297, and 1719.

hydrate, but not infrequently gives a greenish precipitate, which redissolves on cooling.

Isolation.—The urine to be tested for inosite, after any albumin present has been removed, is first concentrated to one-fourth of its bulk, then completely precipitated with a solution of neutral acetate of lead, avoiding an excess, or with baryta water, filtered, and the warmed filtrate treated with subacetate of lead as long as any precipitate occurs. After twelve hours the subacetate precipitate that contains the inosite, together with lead oxide, is collected on a filter-paper, and after washing is suspended in water and decomposed with sulphureted hydrogen. After standing a while a little uric acid first separates from the filtrate; the fluid is filtered from it, then concentrated as much as possible, and while boiling treated with three or four times its volume of alcohol. If a heavy precipitate results that rapidly settles, the hot alcoholic solution is simply poured off, but if a flocculent nonadhesive precipitate occurs, the hot solution is filtered through a heated funnel and allowed to cool. If, after twenty-four hours, groups of inosite crystals have deposited, they are filtered and washed with a little cold alcohol. In this case it is advisable to dissolve the precipitate once more in as little boiling water as possible, and precipitate it a second time with three or four volumes of alcohol in order to avoid any loss of the inosite. If, however, no crystals of inosite have separated, ether is gradually added to the clear, cold, alcoholic filtrate until a milky cloudiness results on shaking thoroughly, and it is then allowed to stand twenty-four hours. Almost all of the inosite present is separated in the form of shining, pearly leaflets if too small an amount of ether has not been used (an excess does no harm). The separated inosite is recognized by the reactions 1 and 2, given below.

Detection.—The urine should be free from albumin. The following tests (1 and 2) depend upon the action of concentrated nitric acid which oxidizes inosite to rhodizonic acid. The carbohydrates do not give these reactions.

1. If a fluid containing inosite is evaporated in a porcelain dish to a few drops, and a small drop of Millon's reagent [1] is then added, a yellow precipitate is soon formed.

[1] Millon's Reagent: Dissolve one part of metallic mercury in two parts of ordinary nitric acid, evaporate to one-half volume, and add 1½ parts of water. After twenty-four hours the clear supernatant fluid is decanted from the basic salt.

If this is spread out as much as possible on the edge of the dish and again gently warmed, there remains, as soon as the fluid is all evaporated, first a yellowish residue, which soon becomes red providing too much of the reagent has not been added. The color disappears on cooling, but reappears upon the application of gentle heat. Starch, lactose, mannite, glycogen, uric acid, urea, taurin, and cystin do not give this red color; albumin is colored red, and therefore, if present, must be previously separated.

2. Evaporate the fluid containing inosite with concentrated nitric acid nearly to dryness, on a platinum dish, moisten the residue with a few drops of ammonic hydrate and a solution of calcium chloride. Then evaporate the mixture to dryness, and there appears a vivid rose-red color, which, according to Scherer,[1] appears with even one milligram of inosite.

GLYCURONIC ACID.

Glycuronic acid, $C_6H_{10}O_7$, is sometimes found in the urine, and is, above all, most likely to be mistaken for sugar. It probably occurs normally in very small amounts in the urine as *combined glycuronic acid*, coupled with potassium sulphate. It may appear in the urine in much larger quantities, particularly after the administration of chloral, butyl-chloral, chloroform, turpentine, camphor, morphine, naphthalene, curare, and nitrobenzol, when it also exists in combination. After the administration of chloral it appears as urochloralic acid; after camphor, as campho-glycuronic acid; after turpentine, as turpen-glycuronic acid; after naphthalene, as naphthol-glycuronic acid, etc. It is said to occur in considerable quantities in the urine of apparently healthy people who have not a diabetic history.

Glycuronic acid, when pure, is not crystalline, but is obtained only as a syrup. It dissolves in alcohol, is readily soluble in water, but insoluble in ether. Glycuronic acid itself is dextrorotatory, but when in *combination*, turns the plane of polarized light to the left. It is converted into saccharic acid by the action of bromine, and seems to occupy an intermediate position between this acid and gluconic acid, $C_6H_{12}O_7$, obtained by the oxidation of glucose or cane sugar with chlorine or bromine. It reduces the salts of copper, bismuth, silver, and mercury, and does not undergo alcoholic fermentation with yeast. It gives a crystalline compound with phenylhydrazin.

[1] "Ann. d. Chem. u. Pharm.," LXXXI, 375.

Isolation.—Glycuronic acid is best isolated from the urine by the method of Schmiedeberg and Meyer,[1] as follows:

Take a large quantity of urine and decolorize by means of animal charcoal. Then evaporate it to a syrup, and treat with a large quantity of damp barium hydrate, heating for some time over a water-bath. Extract with absolute alcohol, which leaves glycuronic acid and various other substances undissolved; mix the residue with water and filter. Add more baryta to the filtrate, again filter, and evaporate the filtrate to a small volume over a water-bath. An amorphous barium precipitate separates, which is washed with water, and then decomposed by sulphuric acid. The barium sulphate is then filtered off, the filtrate evaporated down and dried in a vacuum, when crystals of the anhydride will be obtained.

Detection.—If the urine reduces the salts of copper, and does not undergo alcoholic fermentation with yeast, and is dextrorotatory, glycuronic acid is probably present.

CANE SUGAR.

(SACCHAROSE.)

Cane sugar, $C_{12}H_{22}O_{11}$, is a very uncommon constituent of the urine. It has been found after the ingestion of large quantities of cane-sugar, but only in rare instances, and, therefore, is of no practical importance from a clinical standpoint. It occasionally appears in the urine from extraneous sources, particularly when the urine is transported in a bottle that is not clean or has contained simple syrup. It is sometimes added to the urine by the insane, or those persons who are disposed to deceive the physician or chemist.

Cane sugar, when pure, does not reduce the salts of copper, but, on account of the fact that the commercial article contains traces of glucose as an impurity, a reduction of the cupric oxide may follow the test. It crystallizes in prismatic form, and its aqueous solutions rotate the polarized light strongly to the right, + 73.8. When boiled with dilute hydrochloric or sulphuric acids, it undergoes the process of "*inversion*"—that is. it takes up a molecule of water and is converted into dextrose and levulose, according to the following equation:

$$C_{12}H_{22}O_{11} + H_2O = \underset{\text{Dextrose.}}{C_6H_{12}O_6} + \underset{\text{Levulose.}}{C_6H_{12}O_6}.$$

On account of the strong rotation of levulose the solution now rotates to the left instead of to the right; hence the term *inversion.*

[1] "Zeitschr. f. physiol. Ch.," III, 422, 1879.

Detection.—Traces of cane sugar may be overlooked in the ordinary analysis of the urine. When present in larger quantities, the specific gravity is usually very high, even though the normal solids are not increased; any glucose present is usually found to be in small quantities. The dextrorotatory polarization, which, after inversion, becomes levulorotatory, indicates the presence of cane sugar.

PENTOSES.

Pentoses ($C_5H_{10}O_5$) were first found by Salkowski and Jastrowitz,[1] in the urine of persons addicted to the use of morphine. They were later found by Külz and Vogel [2] in the urine of those suffering from diabetes mellitus.

They are nonfermentable, and on heating with dilute mineral acids yield furfurol, but no levulinic acid. They form osazones with phenylhydrazin (melting-point 159° C.), are dextrorotatory, and reduce alkaline solution of copper.

Pentoses are present in vegetable food. They seem to be absorbed by man, and utilized at least in part (Hammarsten). There are two important pentoses—*i. e.*, arabinose and xylose.

Arabinose (pectin sugar) is dextrorotatory, α (D) = +104° to 105°. Its osazone melts at 157° to 158° C., and 10 c.c. of Fehling's solution are reduced by 43 milligrams of arabinose (Hammarsten).

Xylose (wood sugar) is only feebly dextrorotatory, α (D) = +18.1°. Its osazone melts at 159° to 160° C.

Detection.—Pentoses are detected (1) by their reducing action on alkaline solutions of copper; (2) by being nonfermentable; (3) by the melting-point of their osazones; (4) by their spectroscopic appearance—*i. e.*, two absorption bands between D and E. It should be borne in mind that glycuronic acid has the same spectrum as the pentoses. In a mixture of pentoses and glycuronic acid the separation is made, according to Külz and Vogel,[3] by extracting the osazones of these two substances with water at 60° C., which dissolves the pentosazone; filter while hot, and allow to cool. The pentosazone separates upon cooling.

ACETONE.

Acetone is a volatile compound frequently found in large amounts in the urine under certain diseased conditions. According to v. Jaksch, de Boeck, and A. Slosse, normal

[1] E. Salkowski u. M. Jastrowitz, "Centralbl. f. d. med. Wissensch.," 1892; Salkowski, "Berliner klin. Wochenschr.," 1895.

[2] E. Külz u. J. Vogel, "Zeitschr. f. Biologie," 22, 1895.

[3] *Ibid.*

urine contains traces of acetone (0.1 gram in twenty-four hours—"physiological acetonuria"). Le Noble claims, however, that this body is only found in the urine of healthy persons after the use of alcohol and food rich in proteid matter.

Acetone, C_3H_6O, is the typical member of the group known as ketones, and may be prepared artificially by the dry distillation of calcium or barium acetate. It may be obtained in considerable quantities by distillation of the urine or the blood of certain diabetic individuals. The peculiar fruity, sweet odor frequently noticed in the breath and in the urine of diabetic subjects is due to acetone. It is a volatile, colorless liquid, of a specific gravity of 0.792, boiling at 56.5° C., soluble in water, and characterized by an ethereal or fruity odor. The principal source of acetone is the decomposition of the proteids of the body as well as those taken as food (v. Jaksch). Some writers believe, on the contrary, that it is the decomposition of the fats, and not the proteids, which constitutes the chief source of acetone.

Clinical Significance.—The condition of acetonuria is divided by v. Jaksch, according to *cause*, into: (1) Febrile acetonuria (scarlet fever, typhoid fever, pneumonia, measles, smallpox, etc.); (2) diabetic acetonuria; (3) acetonuria accompanying certain forms of cancer independent of inanition; (4) acetonuria of starvation, seen especially in cases of gastric ulcer and following the use of rectal feeding; (5) the production of acetone in psychoses; (6) acetonuria as an expression of autointoxication; (7) acetonuria in derangements of digestion; (8) acetonuria in chloroform narcosis. The most common of these forms is febrile acetonuria. It is seen in children as well as in adults, and does not belong to any particular fever. In diabetes the appearance of acetone in the urine indicates an advanced stage of the disease. The ingestion of an abundance of nitrogenous food tends to the production of acetonuria. Thus it is that the urine of diabetics often contains a larger amount of acetone after eliminating starches and sugars from the diet, and restricting it chiefly to nitrogenous substances. Acetonuria existing alone (autointoxication with acetone) tends to a favorable termination. Of greater importance are those cases in which much acetone is found as an accompaniment of grave symptoms of cerebral irritation.

Detection.—Legal's Test.—This is a rough test, but is of service on account of being easy of application.

One-fourth of a test-tube of urine is treated with a few drops of a freshly prepared and somewhat concentrated solution of sodium nitroprusside, a few drops of acetic acid are added to prevent the reaction with kreatinin, and the mixture is then rendered alkaline with ammonic or sodic hydrate. The mixture gradually develops a red color, which increases to a deep purple-red color. In the absence of acetone the red or purple-red tint does not form.

For purposes of greater accuracy it is necessary to distil the urine (500 to 1000 c.c.), after the addition of a little phosphoric acid (1 gram per liter), to prevent the evolution of gases; the first 10 to 30 c.c. of the distillate are used for the following tests:

Lieben's Test.—A few cubic centimeters of the distillate are treated with several drops of a dilute solution of iodo-potassic iodide and sodic hydrate. In the presence even of traces of acetone, a precipitation of iodoform in crystalline form occurs, which may be readily recognized by its odor.

Quantitative Estimation of Acetone.—The method of Messinger, as modified by Huppert, is best adapted to the estimation of acetone in urine, and is based upon the observation of Lieben, that acetone gives rise to the formation of iodoform when treated with iodine in an alkaline solution. If, then, a solution of acetone be treated with a known amount of iodine, the quantity present is determined by retitrating the iodine that was not used in the formation of iodoform.

Solutions Required.—(1) Acetic acid (50 per cent. solution); (2) sulphuric acid (12 per cent. solution); (3) sodic hydrate solution (50 per cent.); (4) a decinormal solution of iodine; (5) a decinormal solution of sodium thiosulphate.

Process.—One hundred cubic centimeters of urine, or less if much acetone be present as determined by Legal's test, are treated with 2 c.c. of the acetic acid solution, and distilled until seven-eighths of the total amount has passed over. The distillate is received in a retort that is connected with a bulb apparatus filled with water. As soon as seven-eighths of the urine has distilled over, a small amount of the distillate of the remainder is tested for acetone by Lieben's method. Should a positive reaction be obtained, it will be necessary either to repeat the entire process with less urine, diluted to about 200 c.c., or to add about 100 c.c. of water to the residue and to

distil until all the acetone has been driven over. The distillate is then treated with 1 c.c. of the sulphuric acid, and redistilled. The addition of the acetic acid and of the sulphuric acid, respectively, serves the purpose of holding back the phenol and the ammonia. Should the first distillate contain nitrous acid, which may be recognized by the addition of a little starch-paste containing a trace of potassium iodide, when the solution will turn blue, this is removed by adding a little urea. The second distillate is received in a bottle provided with a well-ground glass stopper, and holding about one liter. To prevent the escape of acetone, the glass stopper is replaced by a doubly perforated cork, through which two glass tubes pass, one to the distilling apparatus, the other to the bulb apparatus. The distillate is then treated with a carefully measured quantity of the decinormal solution of iodine—about 10 c.c. for each 100 c.c. of urine used—and sodic hydrate solution, which should be added drop by drop until the blue color has disappeared and the iodoform separates out. To this end a slight excess of the solution must be added. Should ammonia be present, a blackish cloud will be observed at the zone of contact of the sodic hydrate and the iodine solution, and it will be necessary to repeat the entire process. The bottle is closed and shaken for about one minute. The solution is then acidulated with concentrated hydrochloric acid, when the mixture assumes a brown color if iodine be present in excess. If this does not occur, more of the iodine solution must be added, and the process repeated until an excess is present. The excess is then retitrated with the thiosulphate solution until the solution presents a faint yellow color. A few cubic centimeters of starch solution are then added, and the titration continued until the last trace of blue has disappeared. The number of cubic centimeters employed in the titration is finally deducted from the total amount of the iodine solution added, and the result multiplied by 0.967. The figure thus obtained will then indicate, in terms of milligrams, the amount of acetone contained in the 100 c.c. of urine, as 1 c.c. of the thiosulphate solution is equivalent to 1 c.c. of the iodine solution, or to 0.967 milligrams of acetone.

DIACETIC ACID.

Diacetic acid, also termed aceto-acetic or ethyl-diacetic acid, $C_6H_{10}O_3$, sometimes appears in the urine. Its presence must always be regarded as abnormal. Urine containing diacetic acid is always rich in acetone, for which diacetic acid is often mistaken. These two bodies exist in the urine independently, although by the action of alkalies

diacetic acid is readily converted to acetone, alcohol, and CO_2, as shown by the following:

$$\underset{\text{Diacetic acid.}}{C_6H_{10}O_3} + H_2O = \underset{\text{Acetone.}}{C_3H_6O} + \underset{\text{Alcohol.}}{C_2H_6O} + CO_2.$$

Whether a similar decomposition takes place in the blood remains still an open question.

Diacetic acid is a colorless liquid, which gives a characteristic Bordeaux-red color with a solution of ferric chloride. But this color with ferric chloride may be produced by the presence of other substances in the urine, such as salicylic acid, carbolic acid, antipyrin, thallin (Legal and Hammarsten); also acetic and formic acids, sulpho- (thio-) cyanates, and β-hydroxybutyric acid. Diacetic acid is distinguished from these substances by the fact that, if the urine be previously boiled, diacetic acid does not give the ferric chloride reaction, while the other substances continue to give the Bordeaux-red color as before. Furthermore, that salicylic acid, carbolic acid, etc., are not extracted from the urine by ether, whereas diacetic acid is soluble in ether.

Clinical Significance.—As already mentioned, the presence of diacetic acid in the urine (diaceturia) is always pathologic, and should in general be considered a serious symptom. Diacetic acid is frequently found in the urine in diabetes mellitus, in fevers, and also idiopathically as a form of autointoxication (diacetemia). It is of common occurrence in the urine of children as a concomitant of fever (v. Jaksch), and is then generally devoid of serious importance; but in children or adults suffering from diabetes it is a symptom of grave import. Diaceturia is most common in the advanced stages of diabetes mellitus, and particularly in children and persons under the age of thirty. The occurrence of this symptom may be looked upon as a very probable forerunner of diabetic coma and rapid death. The author's experience has led him to make an unfavorable prognosis in all cases of diabetes mellitus (under thirty years of age) in which the urine contains diacetic acid.

The form of autointoxication of which diaceturia is the chief index is usually rapidly fatal, being accompanied by such symptoms as vomiting, dyspnea, jactitation, and coma, without evidence of any other pathologic process.

Detection.—The process suggested by v. Jaksch is most reliable, and is as follows: To the urine a fairly concen-

trated solution of perchloride of iron is cautiously added, and if a phosphatic precipitate forms, this is removed by filtration, and more of the perchloride of iron solution supplied. If the Bordeaux-red color appears, one portion of the urine is boiled, while another portion is treated with sulphuric acid and extracted with ether. If now the urine that has been boiled gives no reaction with the perchloride of iron solution, while the ethereal extract shows a claret-red color with the iron solution, diacetic acid is probably present, particularly if, at the same time (on testing the urine directly and its distillate), it is found to be rich in acetone.

The urine to be tested should be perfectly fresh, for the reason that in a urine that has begun to decompose the diacetic acid takes up a molecule of water and splits into acetone, alcohol, and carbon dioxide.

β-OXYBUTYRIC ACID.

($C_4H_8O_3$.)

β-oxybutyric acid not infrequently appears in the urine as an accompaniment of diacetic acid and acetone. It forms with aqueous vapor an odorless, colorless, transparent, non-volatile syrup, which rotates the plane of polarized light toward the left. It is monobasic, and its salts are readily soluble in water; it is only moderately soluble in absolute alcohol, and is precipitated from its solutions by ether. It gives no reaction with a solution of ferric chloride. It is easily convertible into acetone and diacetic acid by oxidizing agents.

Although β-oxybutyric acid is usually found as an accompaniment of acetone and diacetic acid, the presence of the two last-named substances does not necessarily indicate the presence of β-oxybutyric acid.

Clinical Significance.—β-oxybutyric acid is met with in large amounts in the urine of those suffering from the severe forms of diabetes mellitus; in small amounts in scurvy, scarlet fever, and measles (Minkowski, E. Külz), but not in other febrile diseases (Minkowski). It has also been found in the urine of starving insane patients, in that of cancer patients dying from coma (Klemperer, Lorenz), and in individuals living on an exclusive meat and fat diet. β-oxybutyric acid is of greatest importance in severe cases of

diabetes mellitus, in which it is probably the cause of the acid intoxication which usually precedes and accompanies diabetic coma. According to Herter,[1] the persistent excretion of more than 25 grams of β-oxybutyric acid indicates impending coma.

Isolation.—The isolation of β-oxybutyric acid is rather difficult, but the process advised by Magnus-Levy[2] may be used.

Process.—Take 400 c.c. of the urine, add 15 or 20 grams of ammonium sulphate, and evaporate to about 80 c.c. Filter, and treat an aliquot portion of the filtrate corresponding to 250 c.c. of the urine with dilute sulphuric acid which has been previously saturated with ammonium sulphate. Shake this acid mixture for about fifteen minutes with 400 c.c. of ether; make at least eighteen extractions, and employ 400 c.c. of ether for each extraction. Wash the ether used for each extraction with 25 c.c. of water, and finally unite the ethereal extracts and distil. The β-oxybutyric acid, together with hippuric acid, volatile fatty acids, and an unidentified acid-equivalent, is contained in the clear dark brown liquid that remains. This fluid is then examined by means of the polariscope.

BILE.

Of the constituents of bile, the biliary pigments and acids chiefly concern us here. Another constituent of bile —viz., cholesterin—has never yet been found in the urine in jaundice, but has been met with in considerable quantities in other connections.

BILIARY PIGMENTS.

A urine containing more than a minute trace of bile is always abnormally colored. The chief unaltered biliary pigment is *bilirubin*, which is an intermediate product in the body between hemoglobin and urobilin. (See p. 92.) When bilirubin (orange-yellow) becomes oxidized, either by exposure to the air or by reagents, the first and most important oxidation product is *biliverdin* (green); then follow the less important products, *bilicyanin* (blue), *bilifuscin*, *biliprasin*, and finally *choletelin* (*?*). Bilirubin is in the urine in a free state; but in biliary calculi,

[1] "Journ. Exper. Med.," Nov., 1901, p. 617.

[2] Magnus-Levy, "Centralbl. f. innere Med.," Bd. XLV, S. 390.

in which it is often present in abundance, it exists as a calcium compound—*bilirubin calcium.*

The color of a bile-containing urine is either greenish-yellow, yellowish-brown, deep brown, greenish-brown, or, on standing exposed to the air, may be nearly pure green. On shaking the urine it gives a persistent greenish-yellow or yellow froth or foam. Furthermore, if a piece of filter-paper or linen be moistened with such urine, it retains a permanent yellow color on drying. A jaundiced urine almost invariably contains an excess of urobilin and indoxyl. A urine from which the bile has recently disappeared is usually highly colored, due to the large excess of urobilin.

A bile-containing urine is always albuminous. The chief proteid appears to be nucleo-albumin, which is usually accompanied by traces of serum albumin. In this connection it is noteworthy that the nitric acid test for albumin can not be satisfactorily used for the detection of slight traces, on account of the amount of coloring-matter set free by the acid, thus obscuring a faint zone of albumin. For this reason, therefore, in a urine containing much bile, the heat test for albumin is preferable. The sediment usually contains a large number of renal epithelial cells, which are more or less colored by the bile pigment. Not infrequently, they have attached to their surfaces stellate clusters of bilirubin crystals, which have a yellowish-brown color; also small, irregular, brown, bilirubin granules. (See p. 226.) The sediment also contains renal casts and abnormal blood globules, free and adherent to casts, the result of the irritation of the kidneys by the bile. If more than a mere trace of bile pigment be present in the urine, the organized elements of the sediment are invariably stained yellow or yellowish-brown.

Clinical Significance.—Bile pigments occur in the urine in every case of jaundice—in other words, in every case in which there is an obstruction to the outflow of bile from the bile-ducts (*hepatogenous icterus*). Thus they are found in a variety of pathologic conditions of the liver, of which the most common are catarrhal jaundice, obstruction in the common bile-duct by biliary calculi, cancer, and cirrhosis of the liver. They may also appear in the urine in cases of destruction of the red blood globules, as in severe infectious conditions, phosphorus-poisoning, etc. (*hematogenous icterus*). Bile pigments often make their appearance in the

urine before there is much coloration of the conjunctivæ, or any yellow color in the skin.

Detection.—Marechalt's Test.—Take about one finger-breadth of an alcoholic solution of iodine (not too strong) in a test-tube, and underlie with urine by allowing it to flow down the side of the inclined test-tube from a pipette placed above the level of the iodine. If biliary pigments are present, a green color appears just below the point of contact of the two fluids, and remains for some time, even for twenty-four hours. In this test the possibility of confounding with indoxyl is said to be excluded.

Gmelin's Test.—This test is performed in two ways :

1. A quantity of urine is placed in a wine-glass, and a small quantity of concentrated nitric acid is allowed to flow carefully down the side of the wine-glass to underlie the urine, as described in the nitric acid test for albumin. If biliary coloring-matters are present, at the point of union between the urine and the acid a play of colors will very soon appear, which, if typical, should be green, blue, violet, red, and yellow or yellowish-green, in the order named. Often, however, one or more colors are wanting. The green is most constant, the *first green* being indispensable to prove the presence of bile ; but violet, shading into red and yellow, is also very constantly seen. The other colors may be produced by other coloring-matters, especially indoxyl.

2. The test can also be applied by placing a drop of the suspected urine on a porcelain plate, and allowing a drop of the fuming nitric acid, which has been placed adjacent, to gradually mingle with the urine. The same play of color occurs.

Another method consists in precipitating the urine with a small amount of *milk of lime*. A small portion of this precipitate is then treated with a drop of concentrated nitric acid, and if bile pigments are present, a play of colors, like that seen in Gmelin's test, occurs.

The two tests for biliary pigments just described are quite satisfactory, providing the urine contains a large amount of bile, but they are far from conclusive when the urine contains minute traces of biliary pigments. Various other tests for bile pigments have been advised, but all possess greater shortcomings than Marechalt's or Gmelin's tests, and many of them are valueless. In the hands of the writer Marechalt's test is the most serviceable of all tests, especially

when applied in the manner previously outlined. It is to be said, however, that a normal urine often reacts with iodine so as to suggest a trace of bile when it is evident that no bile pigments are present. It is certain that this subject needs further investigation in order to be able to demonstrate satisfactorily the presence of traces of bile pigments in urine.

BILIARY ACIDS.

Any interference with the discharge of bile from the liver or common bile-duct results in the passage of the bile constituents into the blood and their elimination by the urine (*hepatogenous icterus*). But bile pigments may also pass into the urine under other circumstances, especially when there is destruction of the red blood-corpuscles through poisoning by ether, chloroform, arseniureted hydrogen, phosphorus, and in grave infectious diseases. In this second form of icterus the blood coloring-matter appears to be transformed into bile pigment elsewhere than in the liver, possibly in the blood, and thus it is that we have the so-called *hematogenous* icterus. Only the bile pigments appear in the urine in these cases, while in hepatogenous icterus the urine contains the bile pigments and bile acids at the same time (Leyden). This arbitrary distinction, however, can not be fully maintained in all cases. It is certainly true that the presence of more than mere traces of bile acids in the urine indicates the existence of hepatogenous jaundice, but cases of absorption icterus undoubtedly occur in which no bile acids can be detected in the urine.

According to Dragendorf, Vogel, and Oliver, traces of bile acids occur in normal urine, but Hoppe-Seyler and Udránszky both hold the opposite view. This question must be considered unsettled until confirmatory evidence bearing upon one or the other view is at hand.

All bile acids can be conveniently divided into two groups —the *glycocholic* and the *taurocholic acid* groups. The glycocholic acids contain nitrogen, but are free from sulphur, and can be split, with the addition of water, into glycocoll and an acid free from nitrogen—cholic acid. The taurocholic acids contain nitrogen and sulphur, and are split, with the addition of water, into taurin, which contains sulphur and cholalic acid. The existence of different glycocholic and taurocholic acids depends on the fact that there

are several cholalic acids. These two groups of acids exist in the urine chiefly as salts of sodium.

Clinical Significance.—As already intimated, bile acids are most commonly found in the urine in cases of obstructive jaundice—that is, in the *hepatogenous* form, and not generally present in the *hematogenous* form of icterus. This very general rule, however, is subject to much variation, and, therefore, the determination of the presence of bile acids can not be considered especially diagnostic of the existence of hepatogenous jaundice. They are present in the urine of hepatic congestion, cirrhosis, and hepatic tumors ; also in carcinoma and severe acute bilious attacks. They have also been found in anemia, hemoglobinuria, scurvy, and splenic leukemia. They are much less common in the urine in amyloid infiltration of the liver.

Tests for bile acids are not usually made in the routine analysis of urine. In fact, for purposes of diagnosis, the detection of bile pigments is generally sufficient. It is impossible to apply satisfactorily the ordinary test—Pettenkofer's —for bile acids directly to the urine ; they must, therefore, be isolated.

Isolation.—The simplest method of obtaining the biliary acids is the one suggested by Dr. Tyson,[1] and is as follows : " Six or eight ounces (180 to 240 c.c.) of the suspected urine are evaporated to dryness over a water-bath. The residue thus obtained is treated with an excess of absolute alcohol, filtered, and the filtrate treated with an excess of ether (12 to 24 times its bulk), by which the bile acids, if present, are precipitated. These are then removed by filtration, and redissolved in distilled water. The solution is then decolorized by passing through animal charcoal, and the resulting colorless fluid subjected to Pettenkofer's test."

According to Hoppe-Seyler, the bile acids can be separated from the urine in the following manner: Render the urine alkaline with ammonic hydrate, and precipitate directly with basic acetate of lead ; wash the precipitate with water, dry by gentle heat, heat several times with absolute alcohol, and filter while hot. To the alcoholic solution of lead salts of the bile acids add a few drops of sodic hydrate and evaporate to dryness. Extract the residue with absolute alcohol by the aid of heat ; evapo-

[1] " Philadelphia Medical Times," July 5, 1873.

rate the solution to a small volume, and shake with an excess of ether, whereby the biliary salts are separated as an amorphous precipitate. Filter, dissolve the precipitate in distilled water, and apply Pettenkofer's test.

Dragendorff has shown that the bile acids can be extracted from urine that has been acidulated with hydrochloric acid by shaking with chloroform.

If *ox bile* be added to urine, Pettenkofer's reaction can generally be demonstrated without separating the bile salts as just indicated, providing, however, the color of the urine used is normal or pale, and not high.

Detection.—Pettenkofer's Test for Bile Acids.—The test, as usually applied, is as follows:

Process.—Bile, which may be considerably diluted, or a dilute solution of bile salts or acids, is mixed in a porcelain dish with a few drops of a 10 per cent. solution of cane sugar. Concentrated sulphuric acid is then added to the mixture, with constant stirring, to an extent not exceeding two-thirds of its volume, the addition of the acid being so regulated that the temperature of the mixture is not allowed to rise above 70° C. A brilliant cherry-red changing to a reddish-purple color soon makes its appearance. On standing for some time the color becomes darker and assumes more of a blue tint. The reaction may also be obtained by the addition of first the acid and then the sugar solution. The success of the test depends upon keeping the temperature of the mixture below 70° C. (a cold water-bath may be used), and the avoidance of any excess of sugar, which, by being charred by the acid, gives a brown color and masks the typical purple. To avoid this, Drechsel recommends the use of phosphoric acid (5 of the glacial acid to 1 of water) instead of sulphuric acid. In this case the solution must be heated by immersion in boiling water.

According to Schenk,[1] if the typical purple solution is diluted with alcohol, it shows with the spectroscope a characteristic absorption spectrum, consisting of two absorption bands, one between D and E, bordering on E, and a second between E and F, adjoining F.

Pettenkofer's reaction depends upon the presence of cholalic (or cholic) acid, a constituent of the bile acids; also

[1] "Jahresber. f. Thier-Ch.," II, 232.

upon the formation of *furfurol* (also known as furfuraldehyde) which results from the action of the sulphuric acid upon the sugar, the characteristic color arising from the interaction of the furfurol with the cholalic acid.

This test is far from satisfactory when applied directly to the urine, even when the bile acids are present in considerable amount, since, on the one hand, urinary pigments and other substances are charred by the sulphuric acid, thus interfering with the brilliancy of the reaction; and, secondly, if the urine contains proteids, cholesterin, amyl alcohol, and various other substances, a purple color is produced which closely resembles that due to bile acids.

Oliver's Peptone Test.—This test is based on the physiologic fact that, when the products of gastric digestion, peptone and parapeptone, which pass from the stomach in an acid medium, meet with the bile in the duodenum, they are precipitated. So, too, albuminous urine, or urine charged with peptone, is precipitated by a solution of bile salts,—sodium glycocholate or taurocholate. Thus an acid solution of peptone is recommended and is prepared as follows:

Pulverized peptone (Savary and Moore), 30 grains; salicylic acid, 4 grains; acetic acid, 30 minims; and distilled water up to 8 fluidounces. Filter until a clear filtrate is obtained.

Process.—To 60 minims of this test solution add 20 minims of perfectly clear urine which has been previously rendered normally acid if alkaline, and which has been reduced to a specific gravity of 1008. If the proportion of bile salts be normal or subnormal, no immediate reaction occurs, but in a short time a mere tinge of milkiness appears. If in excess, a distinct turbidity promptly appears, becoming more intense in a minute or two, the degree of opacity being directly proportionate to the amount of bile acids present. On agitation the opalescence diminishes, and may finally disappear, but is restored on adding more of the test solution.

Approximate Quantitative Test.—This is based upon a permanent standard of opacity provided by mixing equal proportions of the test solution and normal urine reduced to the specific gravity of 1008. To 60 minims of the test solution add the suspected urine diluted to a specific gravity of 1008, usually 10 to 20 minims at a time, allowing a minute to elapse after each addition, until the opacity induced is exactly equal to or slightly exceeds that of the standard, the tubes being held to the light, shaded by a dark background. If 50 or 60 minims bring up the opacity to that of the standard, the proportion of bile salts does not exceed the normal. Any smaller quantity

required indicates an excess, while the smaller the amount needed, the larger the proportion of bile salts present.

OLIVER'S STANDARD TABLE.

Urine. Minims.		Drops.		Percentage of Increase over the Normal Standard.
1	or	2	=	6000
2	or	4	=	3000
3	or	6	=	2000
4	or	8	=	1500
5	or	10	=	1200
10	or	20	=	600
15	or	30	=	400
20	or	40	=	300
25	or	50	=	240
30	or	60	=	100
35	or	70	=	83
40	or	80	=	66
45	or	90	=	50

This test, according to Dr. Oliver, is so delicate that one part of bile salts can readily be detected in 18,000 to 20,000 parts of a solution of sodium chloride. An increase over 700 per cent. beyond the normal is rarely encountered. Oliver has yet to find anything that interferes with this test for bile acids in the urine.

Dr. Oliver has also devised a *peptone test-paper* that he considers permanent, reliable, and convenient for use.

EHRLICH'S DIAZO REACTION.

This reaction was first described by Ehrlich [1] in 1882. It depends upon the peculiar color produced in the urine (and more particularly in the foam) by the action of diazo-benzol-sulphonic acid upon certain unknown substances in the presence of an excess of ammonic hydrate.

The following solutions are necessary for the reaction:

Solution A.

Sulphanilic acid (saturated aqueous solution)	200 c.c.
Hydrochloric acid (concentrated)	10 "

Solution B.

Sodium nitrite	1 "
Distilled water	200 "

These solutions (*A* and *B*) are to be kept separate, in well-stoppered bottles, and preferably in a dark place. It is necessary to have the sodium nitrite solution as fresh as possible, and, since it decomposes in the course of a few

[1] "Zeitschr. f. klin. Med.," IV, 285–288.

weeks, it is advisable to keep only a small quantity of it on hand.

Method of Applying Test.—Take in a test-tube a mixture of 40 parts of solution *A* and 1 part of solution *B;* add an equal volume of urine; shake the whole mixture thoroughly, and allow an excess of ammonic hydrate to run slowly down the side of the tube. If the diazo reaction be present, the foam will be colored pink, and that portion which is acted upon by the ammonic hydrate will have a crimson color. When the test-tube is inverted, the entire column of liquid in the tube will be found to have a crimson color, while the foam still remains pink.

Ehrlich found that this reaction was almost constantly present in the urine of typhoid fever. He also obtained the reaction in the urine of a variety of other diseases, mostly acute febrile diseases, but in these its occurrence was not constant. He, therefore, called attention to the value of the diazo reaction as an aid in the diagnosis of typhoid fever.

Since the discovery of this peculiar reaction in the urine considerable discussion has arisen as to its clinical value in connection with the diagnosis of typhoid. It is safe to say that the reaction, as ordinarily applied, has met with much disfavor, owing partly to the fact that it is frequently obtained in the urines of a number of other diseases, such as pulmonary phthisis, pneumonia, pleurisy, scarlet fever, diphtheria, measles, erysipelas, acute miliary tuberculosis, syphilis, carcinoma, puerperal septicemia and other septic conditions, acute and chronic rheumatism, etc., and partly on account of the failure of some observers to follow the methods laid down by Ehrlich.

Dr. Charles L. Greene, of St. Paul, Minn., who has made a very careful study [1] of this subject, has found that much more satisfactory results are obtained by modifying the proportions of solutions *A* and *B*. He, therefore, recommends the use of a *test solution*, which shall consist of 100 parts of solution *A* and 1 part of solution *B*, instead of 40 parts of *A* and 1 part of *B* as ordinarily used. In a study of 315 cases representing many of the common forms of disease he obtained by means of this modified test solution characteristic reactions

[1] "Medical Record," Nov. 14, 1896.

in only five diseases: *i. e.*, typhoid fever, 95 per cent.; pneumonia, 9 per cent.; carcinoma, 50 per cent.; pulmonary phthisis, 12.5 per cent.; and septicemia, 75 per cent. He firmly believes that all cases of severe typhoid will show a diazo reaction if the test is properly applied during the height of the disease—that is, between the tenth and eighteenth days.

Von Jaksch,[1] on the other hand, believes that the so-called diazo reaction is always due to the presence of acetone, and he considers the reaction rather an uncertain test for acetone than a test for anything else.

The author can recommend Greene's modified *test solution*, since by its use positive reactions are obtained in a much smaller number of diseases than by the use of the original Ehrlich solution. However, he can not agree with Greene as to its diagnostic value in typhoid, owing to the fact that in some cases of this disease, especially the milder forms, no characteristic reactions can be obtained at any time during the disease. It is certain that many of the urines that show this reaction contain acetone, but further investigation is necessary to prove that the so-called diazo reaction is directly or indirectly due to acetone.

VARIOUS METALLIC AND NONMETALLIC SUBSTANCES.

Various metallic substances, notably lead, arsenic, and mercury, are eliminated in the urine, and, when suspected, should be carefully sought for.

Arsenic may be absorbed in either small or large amounts, and is quite readily eliminated in the urine without the aid of drugs. It is, to a slight degree, cumulative—that is, sufficient arsenic may be absorbed in three or four days' time to require from sixty to ninety days for its complete elimination.

Lead is usually absorbed in very small quantities, and the cause of its very slow elimination from the body is probably its accumulation in the system as a fixed constituent of the tissues. The natural channel of elimination is by way of the kidneys, and in order that it should become a constituent of the urine it must first be converted into a

[1] Von Jaksch, "Clinical Diagnosis," 1897, p. 375.

soluble salt of lead. This is best effected by giving potassium iodide, which combines with the lead, forming iodide of lead, and is eliminated by the kidneys. Even after giving potassium iodide, and under the most favorable conditions, only minute traces of lead are eliminated in twenty-four hours. Therefore, a large quantity of urine is required for the analysis, and every precaution taken to prevent accidental contamination.

Analysis.—The first step in the analysis for either arsenic or lead is (1) the destruction of the organic matter of the urine, and the addition of sulphuric acid for the purpose of driving off the nitric acid, thus leaving the residue in the form of sulphates; and (2) the application of independent tests for either lead or arsenic as the case may be.

1. *Destruction of Organic Matter.*—Take at least one liter of urine in an evaporating dish, and evaporate to dryness over a water-bath. Add to this residue about 100 c.c. of concentrated nitric acid (C. P.), and continue the heat until the acid has evaporated, when a yellow cake remains. Transfer this yellow mass—nitrates and nitro-compounds—to a crucible by means of a porcelain spatula, heat with a Bunsen flame until the mass ignites, and continue the heat until a white residue remains. Cool; add 10 to 20 c.c. of concentrated sulphuric acid (C. P.), and heat until all of the nitric acid has been expelled—that is, until the red fumes disappear and dense white fumes are evolved. Cool, and then add from 25 to 50 c.c. of distilled water, and filter, reserving the filtrate for the test for arsenic. The precipitate on the filter is washed several times with distilled water in order to remove all soluble sulphates, and the final residue on the filter reserved for the test for lead.

2. (*a*) *Process for Arsenic.*—The filtrate from the insoluble sulphates, which contains any arsenic that may be present, is then introduced into a Marsh apparatus that has been previously tested and found to be free from arsenic. The approximate quantity of arsenic can be judged from the intensity of the mirror of metallic arsenic obtained in the delivery tube, and should be expressed in hundredths of a milligram.

Great care should be taken to expel *all* of the nitric acid by means of the sulphuric acid, otherwise an explosion will ensue when the solution is put into the Marsh apparatus.

(*b*) *Process for Lead.*—The residue on the filter-paper, which consists of insoluble sulphates, including lead sulphate, is thoroughly extracted with hot dilute ammonium acetate containing an excess of acetic acid, and then filtered. A current of sulphuretted hydrogen is passed through the filtrate for about an hour, the lead acetate being precipitated as lead sulphide. Filter, dissolve the residue in hot dilute nitric acid, run into an evaporating dish, and evaporate to dryness over a water-bath. The residue in the dish is then dissolved in hot dilute acetic acid and filtered. The filtrate, which contains the lead in the form of an acetate, is then treated with either a few drops of a saturated solution of potassium bichromate, or a few cubic centimeters of dilute sulphuric acid, and allowed to stand twenty-four hours. The solution that contains the lead chromate or sulphate is then filtered, and the precipitate, which is usually exceedingly slight, is washed a few times with distilled water. Sulphuretted-hydrogen water, which has been previously filtered, is allowed to pass through the filter-paper holding the precipitate, and the filter then carefully dried. If lead be present, a slight black precipitate will be seen adhering to the surface of the filter-paper near its center.

Mercury.—This substance appears in the urine following the external or internal use of its various compounds. The test is applied in the following manner:

Acidulate a portion of the urine with hydrochloric acid, then add copper filings, and heat to from 50° to 60° C. for about five minutes; let stand until cool. Wash the copper filings, dry, place them in a shallow dish, and at one side of the dish, or on a watch-glass that is to be inverted over the filings, place one drop of a 1 per cent. solution of gold chloride; heat over a low flame. The mercury that is deposited on the copper will be volatilized and will redden the solution of gold chloride. According to Brugnatelli,[1] this test is capable of detecting $\frac{1}{10}$ of a milligram of mercury in one liter of urine.

Chloral.—A simple test for chloral in the urine is the so-called *isocyanphenyl test.* The principle of the test de-

[1] "Journ. de Pharm.," April, 1890, p. 367.

pends upon the fact that an alkali decomposes the chloral into formic acid, which immediately unites with the alkali to form a formiate and chloroform, which in the presence of aniline results in a characteristic volatile compound.

Test.—Take one-third of a test-tube of urine, and add one drop of pure aniline (aniline oil), and about one finger-breadth of an alcoholic solution of sodic hydrate,—or an equal amount of a strong aqueous solution of sodic hydrate and alcohol may be used,—and heat. If chloral be present, a volatile compound, having a very disagreeable odor, is evolved.

In many instances this test is very unsatisfactory; it is, therefore, necessary to resort to other more complicated methods, the one proposed by Duroy [1] being advised.

Iodides and Bromides.—Iodides and bromides make their appearance in the urine after their administration. The presence of iodides is frequently observed in the nitric acid test for albumin. Iodine is set free by the nitric acid, and appears as a reddish-brown color-zone at the juncture of the urine and acid, the color usually becoming gradually diffused through the column of acid. When the presence of an iodide is suspected, the following test may be readily applied:

Test.—Take one-half test-tube of urine, add a small amount of chloroform,—about one fingerbreadth,—then add a few drops of yellow nitric acid, and shake. The chloroform takes up the iodine, which is set free by the nitric acid, and assumes a pink or purple-red color.

The presence of **bromides** is determined in the following manner:

Test.—Proceed exactly as in the test for iodine, care being taken to add more of the yellow nitric acid than in the test for iodine, in order to completely set free the bromine. The chloroform takes up the bromine, and assumes an Indian-red color—a mixture of red, yellow, and brown.

HEMATOPORPHYRIN.

Hematoporphyrin, $C_{16}H_{18}N_2O_3$, is a coloring-matter derived from the blood, and normally present in the urine, but only in traces. It was discovered in 1871 by Hoppe-

[1] Wharton and Stillé, 1884, p. 395.

Seyler, who found that by treating hematin with concentrated sulphuric acid and heating, there resulted a compound whose acid and alkaline solutions showed unusual spectral bands. To this new compound he gave the name "hematoporphyrin." Since its discovery, it has been recognized by a number of observers and under a variety of circumstances.

Hematoporphyrin is identical with iron-free hematin (Nencki). A urine containing this coloring-matter, when viewed by reflected light, is opaque and almost black; or, in a thin layer, it is reddish-brown. In an isolated form

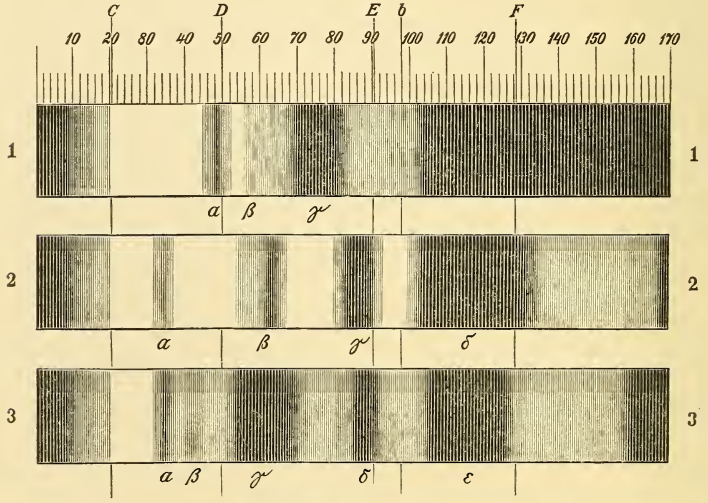


Fig. 20.—Hematoporphyrin spectra: 1, Acid; 2, alkaline; 3, neutral.

hematoporphyrin is nearly insoluble in water, in dilute acetic acid, benzol, and nitrobenzol; it is slightly soluble in ether, chloroform, and amyl alcohol, and readily soluble in alcohol, alkaline hydrates, and carbonates, as well as in dilute mineral acids.

Spectra.—The *acid* alcoholic solution shows (Fig. 20, 1) two absorption bands: one rather dark, situated between Frauenhofer's lines *C* and *D*, with its right border overlapping *D*; and the second, sharply defined, nearly intermediate between *D* and *E*.

The *alkaline* solution presents (Fig. 20, 2) a four-banded

spectrum as follows : A faint and very narrow band about midway between *C* and *D;* two between *D* and *E*, one with its left border near *D*, the other including *E;* the fourth band, which is the darkest of all, but which, however, is not well defined, includes nearly all of the space between *b* and *F*, and incloses *F*.

The *neutral* and *metallic* spectra are represented in the accompanying illustration (Fig. 20, 3); they are less characteristic than the acid and alkaline spectra, and therefore will not be described here in detail.

Clinical Significance.—Since urine normally contains traces of hematoporphyrin, its presence becomes of importance only when it is present in large amounts. It was first discovered in the urine by Baumstark (1874) in a case of leprosy, and then by MacMunn, le Nobel, and others in acute articular rheumatism. Neusser found this pigment in cases of phthisis pulmonalis, and pleurisy with effusion. Perhaps its most frequent appearance in large amounts is following the prolonged use of sulphonal, trional, or tetronal; it is only rarely found after one or two doses of any one of these three drugs.[1] It is commonly found in cases of lead-poisoning, of which Nakarai has reported six; the author has met with it in cases of lead-poisoning, but never in large quantities. This coloring-matter has also been observed in cases of intestinal tuberculosis (Nakarai). The bearing of nervous phenomena upon the production of hematoporphyrinuria is a subject that requires further study. In two cases reported by Rankin and Partington and one by the author, obscure nervous symptoms were prominent, and possibly had some bearing on the cause of the hematoporphyrinuria.

Separation of Hematoporphyrin. — Salkowski's Method.—This method may be employed when the pigment is present in large quantities.

"Take about 30 c.c. of urine, add baryta mixture (equal parts of a 10 per cent. solution of barium chloride and a saturated solution of barium hydrate), until it is completely precipitated. Wash once with water, and once with absolute alcohol, using the latter drop by drop. Transfer the precipitate to an evaporating dish, add from 6 to 8 drops of concentrated hydrochloric acid and sufficient absolute

[1] Ogden, "Boston Medical and Surgical Journal," Feb. 24, 1898.

alcohol to make a thin pap, then stir thoroughly. Heat over a water-bath, filter through a dry filter-paper, and finally add sufficient absolute alcohol to make from 8 to 10 c.c. of filtrate."

Garrod's Method.—This method should be used for the detection of small quantities of hematoporphyrin in the urine.

Process.—Precipitate 100 c.c. of the urine with about 20 c.c. of a 10 per cent. solution of caustic soda. The precipitate of phosphates carries down the pigment with it. Treat the precipitate with absolute alcohol and hydrochloric acid in the manner given above. (See Salkowski's Method.)

The acid solution obtained by either the Salkowski or the Garrod method may be examined directly with the spectroscope for the bands of acid hematoporphyrin, or it may be rendered alkaline, preferably with ammonic hydrate, and examined for the characteristic bands of alkaline hematoporphyrin.

The spectroscopic examination of this alcoholic solution must be made within a few hours after its preparation, since the solution readily decomposes, after which it is useless for observation.

Detection.—This coloring-matter can only be detected with certainty by means of the spectroscope. The four spectral bands of the alkaline solution are most characteristic.

MELANIN.

Melanin is a pigment that is sometimes found in the urine of persons suffering from pigmented tumors. It is usually found in solution in the urine, and more rarely in the form of small black granules which are in suspension. Freshly voided urine containing melanin is usually transparent and of a normal color. When, however, the urine is allowed to stand exposed to the air, the color changes to a brown, and finally to a black. Only in rare instances is the urine black when it leaves the body.

Melanin is eliminated in the form of a chromogen,—*melanogen*,—which becomes oxidized in the air or by oxidizing agents, with a resulting dark or black color due to a deposit of the pigment, melanin. Just where this pigment is converted into a chromogen in the body has not yet been

determined. Ganghofner and Pribram claim that the change takes place in the liver, but this is still a matter of doubt.

Melanin is insoluble in water, ether, amyl alcohol, and dilute acids. It is readily soluble in sodic and ammonic hydrates, sodic carbonate, and monosodic phosphate ; hence it is not precipitated carbon. It contains iron, sulphur, and nitrogen. The chromogen, melanogen, is readily oxidized by potassium bichromate with sulphuric acid, a five per cent. solution of chromic acid, fuming nitric acid, potassium permanganate, and potassium chlorate with hydrochloric acid, with a resulting black color.

Litten observed that urine containing melanin did not undergo ammoniacal fermentation, but, instead, became more acid than normally with the formation of a thick fungus-growth on its surface. He also found that the urine often contained a reducing substance similar to glucose ; such a reaction, however, has not been reported by other observers.

Clinical Significance.—Melanuria is most commonly seen in case of melanotic sarcoma in some part of the body, not necessarily in the kidneys. It has, very rarely, been observed to a marked degree in severe wasting diseases, and has also been observed in persons suffering from repeated attacks of intermittent fever. The urine of individuals suffering from melanotic new growths may be entirely free from melanin while the growth is actively progressing.

Detection.—1. The most sensitive test for the presence of melanin is the addition of bromine water, which causes a yellow precipitate that gradually blackens (Zeller).

2. A few drops of a fairly concentrated solution of ferric chloride will cause the urine to turn gray: if more be added, a precipitate of phosphates falls, carrying the coloring-matter with it, and again dissolves with an excess of the iron solution (v. Jaksch, Pollak).

3. Sodium nitroprusside with caustic potash and acetic acid gives a deep-blue color, probably due to the formation of soluble and insoluble Prussian blue (v. Jaksch). This test, however, can not always be obtained with melanin that has been isolated from the urine, and the reaction must not be regarded as a test for melanin, or only when other tests have shown the presence of melanin or melanogen.

Mörner separated the coloring-matter that was in the

form of a chromogen in the urine by precipitating with baryta water, and then purifying.

PTOMAINES AND LEUCOMAINES.—TOXICITY OF URINE.

Ptomaines may be defined as organic chemic compounds, basic in character, and formed by the action of bacteria on nitrogenous matter. On account of their basic properties, in which they resemble the vegetable alkaloids, ptomaines may be called putrefactive alkaloids. They have also been called animal alkaloids, but this is a misnomer, because, in the first place, some of them are formed in the putrefaction of vegetable matter, and, in the second place, the term "animal alkaloids" is more properly restricted to the leucomaines,—those basic substances which result from tissue metabolism in the body.

While some of the ptomaines are highly poisonous, this is not an essential property, and others are wholly inert. Indeed, the greater number of those which have been isolated up to the present time do not, when employed in single doses, produce any apparent harmful effects. Brieger restricts the term ptomaine to the nonpoisonous basic products, and designates the poisonous ones as "toxines."

Since all putrefaction is due to the action of bacteria, it follows that all ptomaines result from the growth of these organisms. The kind of ptomaine formed will, therefore, depend upon the individual bacterium engaged in its production, the nature of the material being acted upon, and the conditions under which the putrefaction goes on, such as the temperature, the amount of oxygen present, and the duration of the process.

All ptomaines contain nitrogen as an essential part of their basic character. In this they resemble the vegetable alkaloids. Some of them contain oxygen, while others do not. The latter correspond to the volatile vegetable alkaloids, nicotine and coniine, and the former correspond to the fixed alkaloids.

It was formerly supposed that putrefaction was simply oxidation, but the researches of Pasteur and others have demonstrated the fact that countless myriads of minute organisms are engaged constantly in transforming matter from organic to the inorganic form. Hermetically seal the organic matter and it will remain unchanged indefinitely.

According to Pouchet, healthy urine contains traces of certain toxic substances of an alkaloidal nature ; and according to the researches of Bouchard, Lépine, and Guerin, these bodies are more abundant under diseased conditions. They were found by A. Villiers as an invariable manifestation in measles, diphtheria, and pneumonia. Pouchet found in the urine of cholera an alkaloid which was not identical with that observed by him in the feces of the same disease. Feltz found similar bodies in the urine of cancer patients, and Lépine in that of pneumonia. Toxines have been found in the urine of scarlet fever and pneumonia (Albu) ; in carcinoma of the stomach, and in Addison's disease (Ewald, Jacobsen). Bouchard discovered that human urine acted as a poison when injected into the veins of a rabbit, and he referred the toxic effects to various substances, among which were animal alkaloids.

A. B. Griffiths [1] has published a series of unnamed alkaloids which he has isolated from the urine in the following diseases : Parotitis, scarlet fever, diphtheria, measles, pertussis, glanders, pneumonia, epilepsy, erysipelas, puerperal fever, eczema, influenza, carcinoma of the uterus, pleuritis, and angina pectoris.

The experiments of Albu [2] have, in many instances, confirmed those of Griffiths. Albu found alkaloids in the urine of cases of scarlet fever, measles, pneumonia, diphtheria, phthisis with hectic fever, sepsis accompanying carcinoma of the uterus, erysipelas, Basedow's disease, tetanus, pernicious anemia, autointoxication with urticaria following acute gastric catarrh, and in diabetic coma.

Leucomaines are those basic substances which are found in the living tissues, either as the products of fermentative changes other than those of bacteria, or of retrograde metamorphosis. The first attempt at the systematic study and generalization of these basic substances was made by Gautier, who included under this subject all of those substances which are formed in animal tissues during normal life, in contradistinction to the ptomaines or basic products of putrefaction. The distinction between vege-

[1] "Comptes Rendus," CXIII, 656; *loc. cit.*, CXIV, 497; *loc. cit.*, CXV, 185, 667, 668; *loc. cit.*, CXVI, 1205; *loc. cit.*, CXVII, 744; *loc. cit.*, CXVIII, 1350; *loc. cit.*, CXIX, 1382; *loc. cit.*, CXX, 1128; "Chem. News," LXX, 199; "Chem. Centralbl.," 1894, II, 1000.

[2] A. Albu, "Berliner klin. Wochenschr.," XXI, 8 u. 1081, 1894.

table and animal alkaloids is not well defined. Vegetable tissues are known to contain not only what are ordinarily designated as ptomaines, such as choline, but also leucomaines, such as hypoxanthin, xanthin, etc. Under this head must also be placed, on account of their relationship to xanthin, those well-defined alkaloidal bases, caffein and theobromin.

The leucomaines proper may be divided into two distinct and well-defined groups—(1) the uric acid group, and (2) the kreatinin group.

The first of these groups contains a number of well-known bases, which are closely related to uric acid. They are as follows: Adenin, hypoxanthin, guanin, xanthin, (uric acid), heteroxanthin, methylxanthin, paraxanthin, carnin, episarkin, pseudoxanthin, cytosin, gerontin, spermin.

The members of the kreatinin group have all been discovered by Gautier, and by him are regarded as allied to kreatin and kreatinin. They are as follows: Kreatinin and kreatin, crusokreatinin, xanthokreatinin, amphikreatin, and two unknown bases.

Toxicity of Urine.—The question of the toxicity of normal urine has been the subject of much controversy. From the experiments of Feltz and Ritter, Astaschewsky, Schiffer, Bouchard, Lépine, Stadthagen, Gautier, Guinard, and others, it can now be positively stated that normal urine does possess a certain degree of toxicity. It is more difficult to decide upon the nature of this poison.

Feltz and Ritter, and, independently, Astaschewsky, arrived at the opinion that the toxicity was chiefly due to the potassium salts of the urine. Although Schiffer acknowledged the presence and action of the inorganic salts, he maintained that the urine contained a definite organic poison for the reason that the concentrated aqueous solutions from alcoholic extracts of the urine-residue killed large rabbits in doses corresponding to from 1 to 1½ liters of urine deprived of inorganic salts.

Bouchard has shown that from 30 to 60 c.c. of normal urine, injected *intravenously*, will kill a rabbit weighing one kilogram. Hence a man weighing 60 kilograms, and excreting 1200 c.c. per diem, would, if 50 c.c. are necessary to kill one kilogram of living matter, secrete enough poison to kill 24 kilograms of animal. Bouchard claims that

there are five different poisons that may be met with in the urine, each one of which produces a definite symptom: viz., narcosis, salivation, mydriasis, paralysis, and convulsions. He found that the day-urine, which is chiefly narcotic, is from two to four times more toxic than that secreted during sleep, and that the latter induces convulsions and is antagonistic to the former. Further, that the toxicity is independent of the density, since night-urine is denser than that secreted during the day. Bouchard also claims that the greater part of the toxicity of urine is due to organic poisons, especially to coloring-matters; and that the potassium salts are regarded as the cause of only a small fraction of the toxicity.

Lépine also found that about 60 c.c. of urine were sufficient to kill 1 kilogram of animal. To the inorganic salts, however, he ascribed a much greater importance, inasmuch as he estimates that 85 per cent. of the intoxication is due to this cause. Stadthagen has also arrived at practically the same conclusion, that from 80 to 85 per cent. of the toxicity is due to the inorganic constituents. A part of the toxic matter—15 to 20 per cent.—is therefore due to organic substances. No one organic substance in the urine, such as urea, kreatin, kreatinin, etc., possesses this toxicity.

It is now a well-established fact that the urine of certain infectious diseases, such as cholera (Bouchard) and septicemia (Feltz), is far more poisonous than normal urine. That the poisons, basic or otherwise, which are generated within the body by the activity of bacteria can be excreted in the urine is seen in the fact that immunity to the action of bacillus pyocyaneus has been conferred on animals by previous injection of urine taken from animals inoculated with that bacillus (Bouchard), or with filtered cultures of the same (Charrin and Ruffer).

Furthermore, the excretion of the tetanus and diphtheria poisons by the urine has been shown to take place. Thus, Brunner demonstrated the tetanus poison in the urine of experimental animals, but failed with the urine of the disease in man. Bruschettini, however, with the urine of a tetanus patient, produced tetanic symptoms in mice by the injection of from 3 to 10 c.c. subcutaneously. In the urine from diphtheria patients Roux and Yersin demonstrated the presence of the diphtheritic poison by inducing paralysis in animals. Although basic substances are not present in the

urine of cholera, they are present in the intestinal discharges (putrescin in only one of four cases—Roos). From cholera feces Pouchet extracted an oily fluid very poisonous to frogs; whereas Villiers obtained a base which produced convulsions in guinea-pigs.

In the consideration of the toxines in the urine of infectious diseases it must not be forgotten, as pointed out by Jawein, that the poison as well as the specific germ may be present in the urine. Thus, in rabbits that died as a result of infection with anthrax bacillus, erysipelas streptococcus, Eberth's bacillus, and Fränkel's diplococcus, the urine was found to contain these organisms.

CHAPTER VI.

URINARY SEDIMENTS.

It has already been stated that strictly normal, freshly passed urine of *acid* reaction contains no sediment except faint flocculi of mucus, which gradually subside toward the bottom, and entangle a few mucus-corpuscles and an occasional epithelial cell. Should the urine, however, be alkaline, as is frequently the case three or four hours after a meal, it may be more or less cloudy at the moment it is passed, and quickly deposit a flocculent precipitate of *earthy* phosphates, which may occupy considerable bulk. Upon microscopic examination the sediment will be found to consist of amorphous granules, which will quickly disappear on the addition of a few drops of acetic acid.

When a *normal* urine without sediment has stood for some time, especially at a moderate or low temperature, there is frequently observed a deposit of amorphous granular matter, usually of a pink color, and sometimes it is almost colorless. It is readily soluble by heat, and is composed of amorphous urates—a mixture in varying proportions of acid urates of potassium, sodium, and ammonium, with which urates of calcium and magnesium are occasionally commingled. Such a deposit of urates may also contain crystals of uric acid or octahedral crystals of calcium oxalate. Bacteria from the air and other sources frequently make their appearance in the sediment; also, often, spores of torula cerevisiæ—the yeast fungus—and spores of penicillium glaucum are found.

When a urine becomes *alkaline* as a result of the decomposition of the urea into ammonium carbonate, it has an entirely different appearance, and it is at this time that we find myriads of bacteria, together with a deposit of phosphates, both amorphous and crystalline. At the very beginning of the reaction, when the urine may still be

neutral or even faintly alkaline, any crystals of uric acid that may be present begin to dissolve and to change their form so as to become more or less unrecognizable, while on their fragments may often be seen to adhere prismatic crystals of urate of sodium and dark spheres of urate of ammonium. As the reaction becomes more strongly alkaline the uric acid disappears altogether, and the field becomes crowded with granules of amorphous phosphate of lime, beautiful triangular prisms ("coffin-lid" shaped crystals) and irregularly shaped crystals of ammonio-magnesium phosphate, and the dark spheres of urate of ammonium which are often beset with spiculæ. (Fig. 28.)

The methods used for the examination of urinary sediments are both microscopic and chemic. By means of the microscope various deposits are recognized by characteristics that are in themselves diagnostic. But the microscope does not in all instances reveal the exact nature of certain substances, and then it becomes necessary to resort to chemic tests, which, together with the microscope, afford reliable data concerning the substances examined.

METHODS OF OBTAINING URINARY SEDIMENTS.

Two methods are in common use for obtaining urinary sediments—*i. e.*, (*a*) *centrifugal method* and (*b*) *gravity method.*

(a) **Centrifugal Method.**—More recent experience has demonstrated the immense advantages of the centrifugal method of obtaining urinary sediments for purposes of microscopic examination. The principle of this method depends upon the fact that when the urine is placed in tubes and revolved at a high speed upon horizontal rotating arms, a centrifugal force is exerted upon all solid particles in the urine, hundreds of times greater than gravity, and, consequently, the urinary sediment is deposited in the bottom of the tubes almost immediately, irrespective of the specific gravity of the urine or the character of the sediment. Some of the advantages of this method are as follows:

1. Centrifugal sedimentation of the urine permits of an immediate microscopic examination, instead of waiting for from twelve to twenty-four hours as by the old method of gravity.

2. The centrifugal method secures more completely con-

centrated sedimentation, and, therefore, it is better suited for purposes of microscopic diagnosis.

3. Microscopic examination of freshly voided urine may be made before casts or morphologic elements have had time to undergo maceration or solution in the urine, and before the appearance of large numbers of bacteria, which always greatly obscure the microscopic field.

4. It affords the only positive means of distinguishing between *primary* and *secondary crystalline* elements in the urine, since by this method only can the urine be

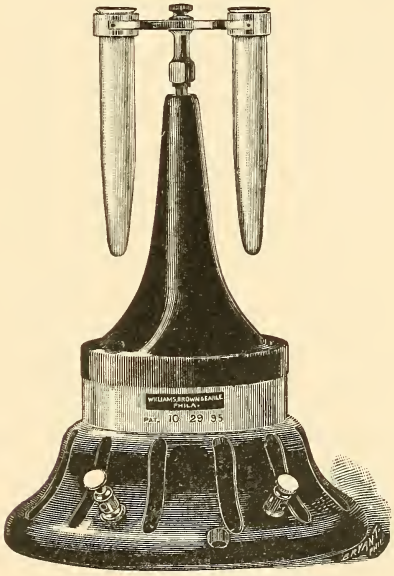


Fig. 21.—The Purdy electric centrifuge.

examined microscopically as soon as voided, and, therefore, before the formation of those crystals that are deposited in nearly all normal urines that are left standing for several hours.

5. By the old method of gravity, it sometimes happens with urines of high specific gravity that the lighter casts (such as those of the narrow, hyaline order) fail to settle, and thus elude detection. The centrifuge precipitates all casts without delay, irrespective of the above-named conditions.

It will, therefore, be readily seen that the centrifuge is destined to supersede the old method of gravitation for all purposes of urinary sedimentation.

Of the various number of centrifugal machines on the market the electric centrifuge devised by Dr. Purdy, of Chicago, is undoubtedly the most serviceable.

The *Purdy electric centrifuge*,[1] shown in figure 21, can be operated on the interrupted incandescent illuminating current, on the constant illuminating current, on the storage

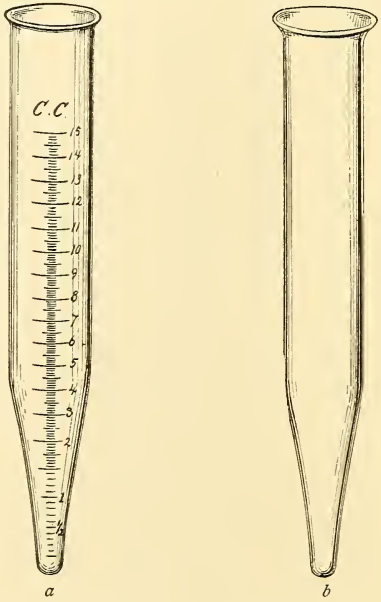


Fig. 22.—Tubes for the Purdy centrifuge: *a*, Percentage tube; *b*, sediment tube.

current, and on the galvanic current (sulphuric cell); and is suitably adjusted for operation at any voltage from 10 to 120 volts, providing the nature and strength of the current be specified.

The apparatus is capable of all grades of speed from 500 to 10,000 revolutions per minute, according to the strength of the current used and the resistance of the arm. When the sediment tubes (Fig. 22), each with a capacity of 15

[1] The Purdy electric centrifuge is manufactured by Williams, Brown and Earle, 918 Chestnut St., Philadelphia.

c.c., are filled and introduced into the aluminium shields of the apparatus, it is capable of sustaining a speed of from 2000 to 2500 revolutions per minute, the tips of the tubes at the same time describing a circle, the diameter of which is 13½ inches. The centrifugal force is from two to three thousand times greater than gravity, so that all the elements of a sediment—organized and nonorganized—are in from three to five minutes forced to the extreme tips of the tubes, where they may at once be utilized for microscopic purposes.

Concerning the *hand centrifuge*, of which there are a large

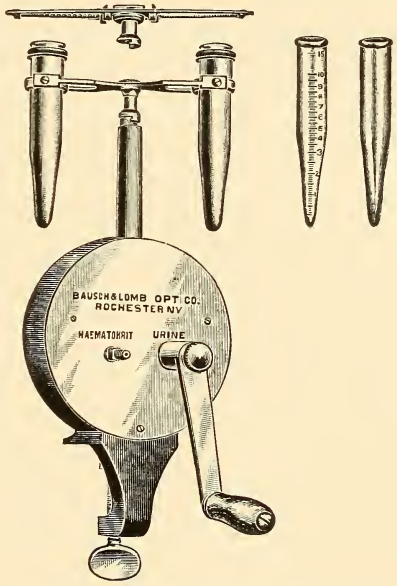


Fig. 23.—The Bausch and Lomb spiral-gear urinary centrifuge with tubes (one-fourth actual size).

number on the market, it is to be said that only a comparatively few are of practical value. The *spiral-gear centrifuge*, manufactured by The Bausch & Lomb Optical Co., of Rochester, N. Y., has been extensively used by the author, and can be highly recommended.

The centrifuge proper (Fig. 23) consists of a small circular case containing a train of gears made of extra hardened bronze, and having teeth spirally cut, three of which are engaged at all times. This form of gearing runs easier and

is more durable than any of the straight gear machines, as it prevents backlash or lost motion. The centrifuge is very small, yet it is strong and capable of a high rate of speed—3000 revolutions per minute.

The glass tubes used for holding the urine are both graduated and plain, and have practically the same shape as those already described in connection with the electric centrifuge. These tubes are carried in aluminium shields, and are supported on elastic cushions to prevent breakage during rotation.

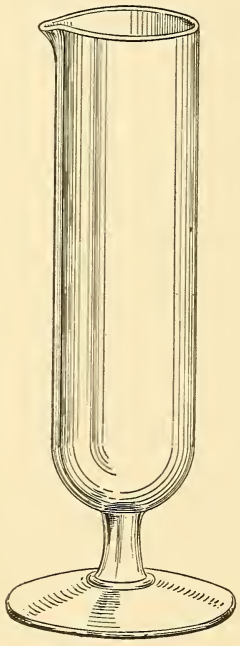


Fig. 24.—Urine or sediment glass.

(b) **Gravity Method.**—The old so-called gravity method of obtaining a sediment, and one that is not without advantages at the present time, consists in placing the urine in a urine glass (Fig. 24) having parallel sides and a concave bottom,[1] then covering with a piece of filter-paper, a glass plate, or other convenient article, in order to keep out dust and other foreign matter. Allow the glass to stand, preferably in a dark and moderately cool place, until the urine is well settled. The time required for a sediment that is suitable for microscopic examination is from one to twenty-four hours; usually a satisfactory sediment is obtained within twelve hours. Occasionally, in a normal urine or one of high specific gravity, the sediment does not fall to the bottom of the glass, but, instead, is suspended in the column of urine; this cloud is sometimes termed the "nubecula."

The chief objection to the use of this method is the length of time required for the urine to settle. Further-

[1] The urine glass, also sometimes termed sediment glass, should be made of perfectly clear, smooth glass which is free from air-bubbles. The bottom of the glass should be concave and without the objectionable upward, nipple-like projection so often found in the ordinary sediment glass. These glasses can be obtained of Richard Briggs Co., 287 Washington Street, Boston.

more, unless preservatives are used, the urine often undergoes alkaline decomposition before a sediment settles, when it becomes unfit for microscopic examination. But preservatives may be used without altering the sediment or otherwise interfering with the microscopic examination. Whenever this method is used, it is the habit of the writer to add to that portion of the urine that is set aside for sediment from 15 to 30 c.c. of a saturated (4 per cent.) solution of *boric acid*, which, under ordinary conditions, preserves the urine until the sediment is satisfactorily settled. A drop or two of *formalin* (formaldehyde gas in water) may be added to the urine, but not always with satisfactory results, since a peculiar crystalline (?) precipitate is often deposited, especially if too much is added, which seriously interferes with the examination of the sediment. Other preservatives, such as chloral, salicylic acid, chloroform, etc., may be used, but with even less satisfactory results.

Fig. 25.—Pipette for sediments.

There can be no question of the many advantages of the centrifugal method over the gravity method for obtaining sediments, and the writer strongly recommends its use for both the practitioner and the student. There are, however, two disadvantages: viz., (1) by the use of the centrifuge the proportion of abnormal elements, such as casts, blood globules, pus-corpuscles, etc., may be very large, since the greater part of the sediment is included in a drop or two of fluid, whereas the sediment obtained by gravity might really contain very few abnormal elements; the examiner is thereby misled as to the extent of the pathologic process. This is particularly the case in judging of the amount of pus which a given urine contains, also the proportion of crystalline elements in a urine. (2) The drop or two of sediment obtained by the use of the centrifuge may contain so much pus, so many crystals, or epithelial cells as to obscure any renal casts that would otherwise be readily detected in a sediment obtained by gravity.

THE PREPARATION OF SEDIMENTS FOR MICROSCOPIC EXAMINATION.

Having obtained a well-settled sediment, either by the use of the centrifuge or by allowing the urine to stand in a urine glass to settle by gravity, the examiner should supply himself with a suitable pipette, slides, and cover-glasses, and a microscope of the best make.

1. Pipette.—Great care should be used in making a pipette, for unless the drawn-out tip is of the proper shape and the opening of the proper size, a suitable sediment can not be obtained. The pipette shown in figure 25 represents the approximate size of the glass tubing that should be used, and the shape of the drawn-out, or, what may be termed the proximal, end. If the proximal tip be abruptly drawn to nearly a point, and the opening be too small, a good sediment can not be obtained. The other end, or distal end, of the glass tube should be rounded off in the flame so as to prevent cutting the finger, and the opening should be nearly as large as the diameter of the tubing.

2. Slides and Cover-glasses.—These should be free from scratches and be *perfectly clean.* The No. 2 square or oval cover-glass is perhaps best suited for the examination of urinary sediments.

3. Microscope.—It will not be necessary here to give a detailed description of the microscope or to refer to its use. The instrument should be one of the best: viz., the Leitz or Zeiss microscope made in Germany, or the Bausch & Lomb microscope made by the Bausch & Lomb Optical Co., of Rochester, N. Y. For the examination of urinary sediments the Abbé condenser can not be satisfactorily used, since too much light is furnished thereby, the ordinary diaphragm supplied with each instrument being most serviceable.

Method.—The pipette, held between the thumb and middle and ring-fingers, is carried to the bottom of the sediment glass with the index-finger (which should be perfectly dry) pressed upon the distal end. When the pipette has reached the heaviest portion of the sediment, it is gently rotated between the thumb and fingers without removing the index-finger from the distal end, and a small amount of the sediment allowed to enter slowly. The pipette is withdrawn from the urine and *carefully wiped from end to end*

to remove all fluid from its outer surface. Two or three slides are then placed on the table, and a drop of the sediment placed on each and covered with the cover-glasses. The preparations are then ready for microscopic examination. The writer, who uses a Leitz microscope, is in the habit of examining the specimen first with a low power,—No. 5 objective and No. 1 eye-piece,—and then with a higher power—7 objective and 1 or 3 eye-piece. Having carefully searched the three preparations, it is probable that most or all of the elements have been seen.

It is sometimes necessary, especially if the sediment is bulky, to first take a sediment from the upper layer, and then one from the bottom layer, in order to be able to detect the lighter elements (casts, etc.) and the heavier substances (crystals).

It sometimes happens that casts and cells do not settle, but are held in suspension in a cloud *near the top* of the column of urine. When such a cloud is present, a drop of sediment from it should always be examined.

URINARY SEDIMENTS.

The urinary sediments are best classified, for the purpose of study, into two groups—*i. e.*, nonorganized or chemic, and organized or anatomic deposits, as follows:

I. NONORGANIZED.

1.	Uric acid	(crystalline).
2.	Urates	(amorphous or crystalline).
3.	Hippuric acid	(crystalline).
4.	Calcium oxalate	(crystalline).
5.	Calcium phosphate	(amorphous or crystalline).
6.	Ammonio-magnesium phosphate—triple phosphate	(crystalline or amorphous).
7.	Calcium carbonate	(crystalline or amorphous).
8.	Cystin	(crystalline).
9.	Cholesterin	(crystalline).
10.	Leucin	(crystalline).
11.	Tyrosin	(crystalline).
12.	Hematoidin—bilirubin	(crystalline).
13.	Xanthin	(crystalline or amorphous).
14.	Indigo	(crystalline).

II. ORGANIZED.

1. Epithelium.
2. Nucleo-albumin (mucin).
3. Blood.
4. Pus.
5. Renal casts.
6. Spermatozoa.
7. Fat.
8. Fibrin.
9. Fungi and infusoria.
10. Morbid growths.
11. Parasites.

III. EXTRANEOUS SUBSTANCES.

NONORGANIZED SEDIMENTS.

The nonorganized or chemic sediments of the urine are usually crystalline, although in a few instances they are amorphous, and are to be distinguished from the organized sediments described under a separate heading.

Uric Acid.[1]—Uric acid crystals are frequently found as constituents of the urinary sediment. They always occur in an acid urine, and usually in one that is strongly acid. They appear in normal as well as in pathologic urine. The crystals are usually colored a deep yellow or orange-red, sometimes a pale yellow, and sometimes brown, and occasionally they are colorless. *Pure* uric acid is very difficultly crystallizable ; therefore, the crystals of uric acid found in the sediment are those of the impure acid.

Uric acid crystallizes in a variety of shapes, but the typical shape may be said to be the rhombic plate. It is, however, comparatively rare to find these typical forms in the sediment, the great majority of the crystals found being modifications of this form. (Fig. 26.) Thus we find the rectangular prisms, the barrel, whetstone, club, spear, wedge, dumb-bell, and diamond shapes ; also the crystal resembling a comb with teeth on two sides, the rosette (coalescence of crystals of varying shapes) and irregularly shaped crystals, all of which have a more or less yellow color, except the diamond form, which is not infrequently

[1] For General Consideration, Properties, and Tests for Uric Acid see pages 59 to 72.

nearly colorless. There are many more forms of uric acid crystals than those mentioned, and practice soon teaches one to recognize these varied forms, even though they may deviate much from the typical shape. The rosette form (Plate 5) may at times be fan shaped; and, again, the individual crystals may have coalesced so as to form a large, solid, compact spherule, often with sharp spicules projecting. These large rosettes and spherules of uric acid frequently have the appearance of particles of sand, hence the term *uric acid sand.* Occasionally, the coalescence of the uric

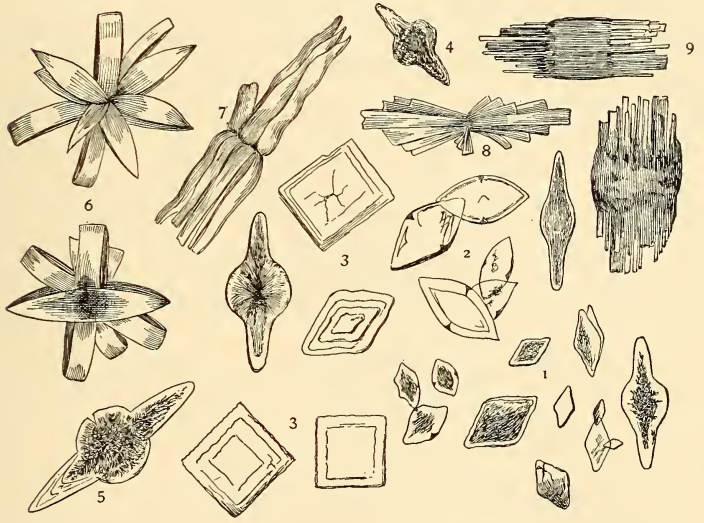


Fig. 26.—Forms of uric acid: 1, Rhombic plates; 2, whetstone forms; 3, 3, quadrate forms; 4, 5, prolonged into points; 6, 8, rosettes; 7, pointed bundles; 9, barrel forms precipitated by adding hydrochloric acid to urine.

acid crystals results in much larger bodies, which have been termed *uric acid gravel*, and still larger, *uric acid calculi*. Ultzmann claims that the irregular forms of uric acid, especially the rough and pointed forms, are almost always an accompaniment of uric acid calculi.

Uric acid crystals may be either *primary* (those separating from the urine inside the body) or *secondary* (those separating from the urine outside the body), but the author knows of no certain means from the appearance of the crystals themselves of distinguishing between the two. The only certain

means of determining the presence of the primary crystals is to obtain a freshly passed specimen and, after thoroughly agitating, centrifugalize while still warm—it may be necessary to centrifugalize several portions in order to obtain the crystals, if present. With these precautions, any crystals found are primary; such crystals are usually highly colored, compact, and in the form of the rosette or spiculated spherule, although other forms may be primary.

All acid urines tend to deposit their uric acid sooner or later. The time of onset of precipitation varies from a few hours to five or six days, or even longer. It possesses a strong tendency to crystallize upon contact with any organic or inorganic substances; thus, upon standing the crystals often cling to the sides of the glass or to threads or specks suspended in the urine. This fact renders it more liable than any other crystalline deposit to form about

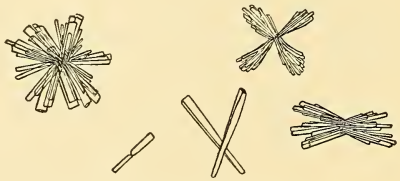


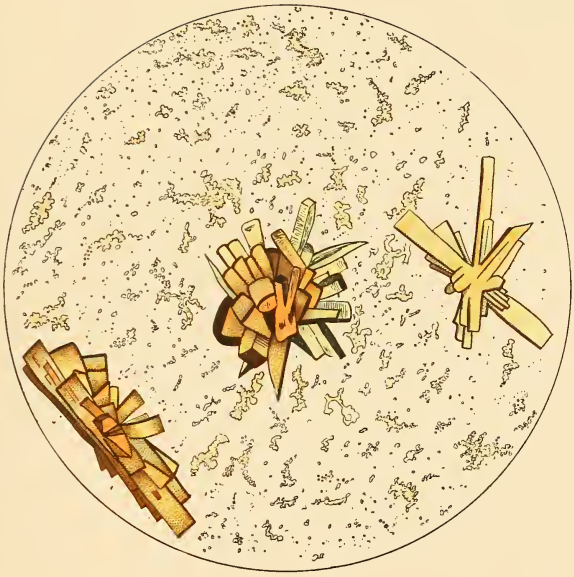
Fig. 27.—Acid sodium urate crystals.

a nucleus in the urinary tract and result in gravel or calculi.

Urates.—(a) **Acid Sodium Urate.**—This salt of uric acid occurs in urine of acid, neutral, or faintly alkaline reaction, and is generally amorphous, but sometimes crystalline. When amorphous, it forms a predominant part of the deposit of *amorphous or mixed urates*, seen in the bottom of the vessel after the urine cools. It crystallizes in colorless, prismatic, needle-like crystals, which are usually arranged in stellate (star-like) clusters. (Fig. 27.) Occasionally, the needle crystals are found alone. Sometimes the clusters have a dumb-bell appearance, each half of which is striated and broad at the extremities; one-half of one of the dumb-bell-like clusters, viewed from above, would be fan shaped.

Acid sodium urate is very insoluble in cold water (1200 parts) but quite soluble in hot water.

Plate 5



Uric-acid Crystals with Amorphous Urates (after Peyer).

(b) **Acid Ammonium Urate.**—This is crystalline and occurs in the urinary sediment as yellowish-red or dark-brown spherules, which are studded with fine, sharp-pointed spicules. To these the terms "thorn-apple crystals" and "hedge-hog crystals" have been given. These spicules may be short or long, sometimes branched, curved, or bent. (See Plate 6.) It also frequently crystallizes in fine needles, which are in clumps, having a sheaf-of-wheat arrangement; and sometimes in the center of a clump a small spherule may be found embedded. These crystals are also colored dark-brown, and should not be mistaken for tyrosin crystals or the groups of colorless crystals of

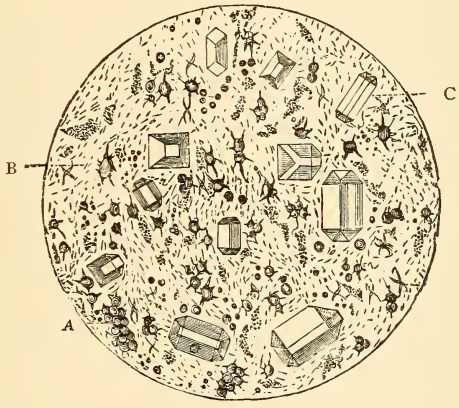


Fig. 28.—Deposits in ammoniacal urine (alkaline fermentation): A, Acid ammonium urate; B, bacterium ureæ; C, ammonio-magnesium phosphate.

acid sodium urate, although by some they are considered identical with the latter.

The crystals of acid ammonium urate are soluble in hot water, and dissolve in hydrochloric acid and other acids, with the subsequent precipitation of uric acid crystals. When they are treated with potassic hydrate, the odor of ammonium is evolved.

The crystals often occur in acid urine with a deposit of amorphous urates. They are very frequently deposited during the alkaline fermentation of the urine, and are found, along with amorphous earthy phosphates and crystals of ammonio-magnesium phosphate. (Fig. 28.) It is, in fact, the only urate found in strongly alkaline urine.

(c) **Acid Potassium Urate.**—This exists in acid urine, is amorphous, and forms a part of a deposit of amorphous urates. Like acid sodium urate, it is very insoluble in cold and quite soluble in hot water.

(d) **Acid calcium urate** is a constituent of acid urine, but occurs only rarely and usually in small quantity in a deposit of amorphous urates. It is an amorphous white powder, difficultly soluble in cold water, faintly soluble in hot water, and is known to have calcium for its base, since, upon incineration, it leaves a residue of calcium carbonate.

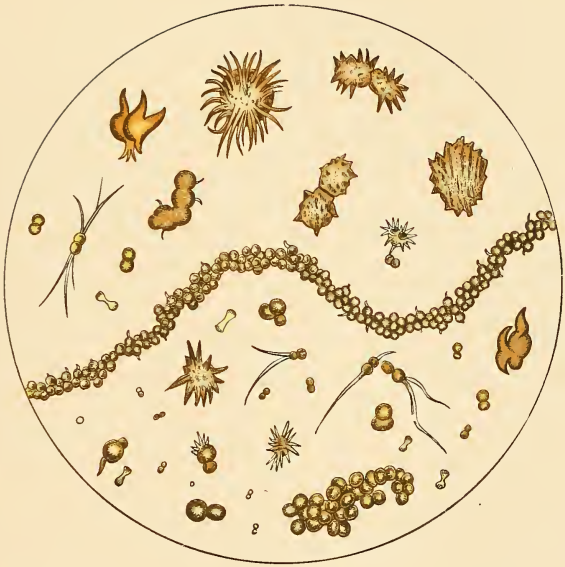
Amorphous or Mixed Urates.—These consist, as mentioned, of acid sodium urate, acid potassium urate, ammonium urate, and sometimes acid calcium and magnesium urates. A deposit of amorphous urates frequently occurs in urine, more especially in concentrated urine, upon cooling to the room-temperature, and particularly if subjected to a low temperature. The deposit usually falls rapidly to the bottom of the urine glass, and when settled, has a pink or yellowish-red color due to uroerythrin; it may rarely be colorless. Occasionally, a portion of the deposit is so finely divided that it will not settle, the urine remaining turbid throughout; but even under such circumstances the greater part settles, forming a heavy deposit.

Detection of Amorphous Urates.—First determine the reaction of the urine, and if acid, pour a small portion of the turbid urine into a test-tube and heat gently, but avoid the boiling temperature. If amorphous urates are present, they are dissolved by the heat, and the urine becomes clear. They are dissolved by an alkaline hydrate, but with the simultaneous precipitation of the earthy phosphates. When amorphous urates are treated with acetic acid or any of the strong mineral acids, they are dissolved, with the subsequent crystallization of uric acid. They also respond to the murexide test.

Treatment of a Sediment Containing Amorphous Urates.—It is obvious that when a sediment consists chiefly of amorphous urates, most of the formed elements will be obscured by the abundance of urate granules; it, therefore, becomes necessary to get rid of the amorphous urates before a satisfactory microscopic examination can be made. This is best accomplished in the following manner:

Fill a urine glass with the urine, allow the sediment to

Plate 6



Ammonium Urate, showing Spherules and Thorn-apple-shaped Crystals (after Peyer).

settle thoroughly ; decant the supernatant urine, and then add warm water to the sediment, using an amount of water equal to the quantity of urine originally taken. The warm water dissolves the urates and, at the same time, dilutes the urine so that they will not reform. Then allow the sediment to settle again, or centrifugalize, and examine in the usual way.

Aside from the solution of the urates, the addition of warm water modifies the sediment in only one particular—*i. e.*, any *normal* blood present will become swollen and lose its color (abnormal blood).

Care should be taken to avoid the use of boiling water, or water having a high temperature, else any albumin present will be coagulated, rendering the sediment unfit for examination.

Clinical Significance.—*1. Uric Acid:* Uric acid crystals are frequently found in the urine of persons who are in perfect health, especially when the urine is concentrated or unusually acid. As has been mentioned, a deposit of uric acid crystals does not necessarily indicate an increase of uric acid in the urine, for, as a matter of fact, a deposit may occur even when the uric acid is much diminished. Any urine upon standing for several hours is apt to deposit crystals of uric acid. Under such circumstances crystals of uric acid are of no clinical importance.

A deposit of uric acid is often the result of a hearty meat diet, especially when coupled with sedentary habits of life and faulty digestion. Likewise, a deposit is frequently a result of increased tissue metabolism and, consequently, an increased formation of uric acid, attended with emaciation, headaches, and nervous debility. An increased formation of uric acid is sometimes the result of conditions in which the oxidizing power of the system is seriously impaired, as in diseases of the respiratory tract and circulatory organs.

Uric acid sediments are often met with in acute febrile conditions, in which there is a marked diminution in the aqueous element and an increased acidity. A deposit of uric acid is of frequent occurrence in gout, especially following a paroxysm ; also in the early stages of chronic interstitial nephritis, particularly when the disease is the result of gout. Given, then, a patient with gouty tendencies, who has habitually taken a hearty meat diet, and whose urine shows a constant deposit of uric acid crystals

and evidences of more or less renal disturbance, an early stage of chronic interstitial nephritis should be strongly suspected. Crystals of uric acid are frequently seen temporarily in the sediment during the convalescent stage of an acute diffuse nephritis.

In the urine of children who are convalescing from scarlet fever or other acute exanthem, uric acid deposits are very apt to occur, and even uric acid gravel may be found under such circumstances.

Primary uric acid, or that formed inside the body, is always of importance. It is frequently accompanied by evidences of marked irritation of the kidney or other portion of the urinary tract. The primary crystals should in all instances be distinguished from those that are secondarily formed. (See p. 211.)

2. Urates: A deposit of amorphous urates, like uric acid, often occurs in any urine that is concentrated or unusually acid, seen especially in acute febrile diseases. In diseases of the liver and heart, also in subacute glomerular (parenchymatous) nephritis, a deposit of amorphous urates often takes place. A primary deposit of acid ammonium urate is of frequent occurrence in the kidneys of the new-born, and crystals of the same may be found in the urine. Further than this, the clinical importance of urates is much the same as that of uric acid. It should be borne in mind that urines that are allowed to stand in a cold place are very apt to deposit amorphous urates.

Phosphates.—The *earthy phosphates* are the only salts of phosphoric acid that appear in the urinary sediment. They consist of (*a*) *ammonio-magnesium phosphate* or *triple phosphate*, and (*b*) *calcium phosphate*. These deposits are found only in *very feebly* acid, neutral, or alkaline urine, and are most abundant following the alkaline fermentation. They appear to the naked eye as bulky, opaque, white deposits, unless they are accompanied by blood, with which they are then more or less tinged. The urine itself is likely to be turbid from the presence of amorphous phosphate of calcium in suspension, especially after a vegetable diet. It often has an ammoniacal and sometimes a fetid odor, though not necessarily. Phosphatic deposits are especially abundant in the urine of some affections of the bladder, and often attend diseases of the spinal cord, because of paralysis of the bladder and consequent retention of urine.

(a) **Ammonio-magnesium phosphate,** $MgNH_4PO_4 \cdot 6H_2O$, or triple phosphate, is a crystalline deposit occurring in two forms :

1. The triangular prism with beveled edges is most typical and frequent. (Fig. 29.) There are many modifications of this type, one of the most common being the so-called " coffin-lid " crystal, which is the triangular prism with one of the three angles wanting. Frequently, the crystals are shortened so as to form squares, and these are the ones already referred to as being possibly mistaken for the octahedral crystals of calcium oxalate.

2. The stellate or feathery crystals of triple phosphate (Fig. 29) are less commonly seen. They predominate in

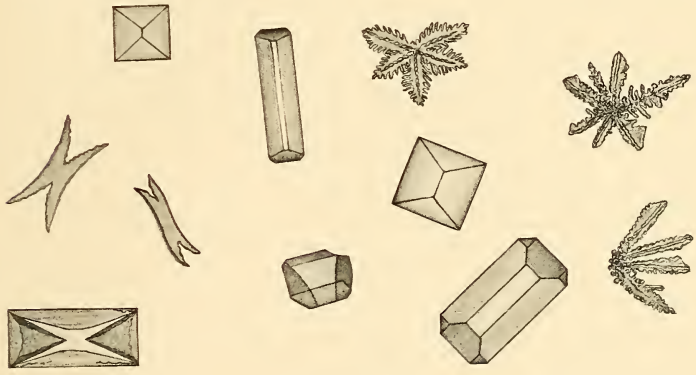


Fig. 29.—Triple-phosphate crystals.

the precipitate that follows the addition to the urine of ammonic hydrate. These crystals gradually undergo conversion into the prismatic form.

(b) **Calcium phosphate** is either amorphous (normal salt, $Ca_3(PO_4)_2$) or crystalline (acid salt, $CaHPO_4$). (1) The *amorphous form* is most frequently found as a whitish flocculent deposit [1] in the *after-meal* urine. It is often precipitated from the urine by heat, and constitutes an important source of error in testing for albumin by heat; this precipitate is readily dissolved by acetic acid. This form of calcium phosphate sometimes occurs in a very feebly acid urine as minute, pale, highly refractive granules,

[1] This deposit usually consists partly of magnesium phosphate.

which are arranged in irregular clumps, and often adherent to renal casts or other organized elements of the sediment. Amorphous phosphate of lime is a frequent accompaniment of triple phosphate in a neutral or alkaline urine.

(*2*) *Acid calcium phosphate*, or the *crystalline form*, is frequently found in urinary deposits, and is often mistaken for the crystals of acid urate of sodium. Crystals of acid phosphate of calcium sometimes occur alone, sometimes with crystals of triple phosphate, and not infrequently with the amorphous form of calcium phosphate. They are also met with in a urine of weak acid reaction, but one that is about to undergo the alkaline fermentation. Acid calcium phosphate crystallizes in the form of prisms that are found either singly or in stellate groups. (Fig. 30.) Frequently, the groups have a fan-like, and sometimes a club-like, arrange-

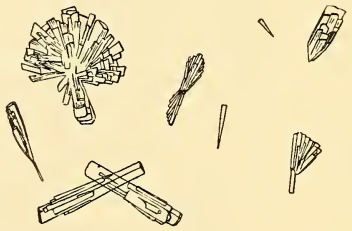


Fig. 30.—Acid calcium phosphate crystals.

ment. Usually, the individual crystals are small, but may be large and thick, with one end beveled to a sharp point, with cutting-edges on each side.

It is often impossible to decide from the microscopic appearance of these crystals whether they are acid calcium phosphate or acid sodium urate, especially when found in a faintly acid urine. These two forms of crystals are distinguished by treating them with acetic acid, which rapidly dissolves the phosphate crystal, while that of acid sodium urate is more slowly dissolved, and is subsequently replaced by crystals of uric acid. The crystals of acid calcium phosphate are often accompanied by crystals of calcium oxalate.

Clinical Significance.—It has already been shown (p. 29) that a deposit of amorphous phosphates may occur in health in a urine alkaline from fixed alkalies, notably two or three hours after a hearty meal. If this deposit be tem-

porary, it is of no clinical importance; if, however, it be permanent, and the twenty-four-hour urine contain a heavy deposit of amorphous phosphates, it becomes of pathologic importance, and in most instances indicates a low general metabolism. Ordinary tonic treatment usually results in a complete disappearance of the deposit.

Crystalline phosphates when *deposited within the body*, often cause much damage to the urinary tract. Such deposits consist chiefly of crystals of ammonio-magnesium phosphate formed as the result of the presence of a volatile alkali—ammonia which arises from the decomposition of the urea in the urinary passages. This is most commonly encountered in cases of chronic cystitis, chronic pyelitis, and pyelocystitis, in which the clinical symptoms are mostly irritant in character. The mechanical irritation by the crystals, *plus* the irritating effect of the ammonia, adds much to the distress of the patient. The most frequent causes of this condition of the urine are obstructive diseases of the lower urinary tract. Likewise, those diseases that affect the contractile power of the muscles of the bladder. Thus, in enlarged prostate, diseases of the spinal cord, paraplegia, etc., the urine is retained, and soon undergoes ammoniacal fermentation with a resulting deposit of triple phosphate. This condition of the urine nearly always precedes the so-called "surgical kidney" and other dangerous septic conditions that also often result from the introduction of unclean instruments into the bladder.

Calcium Oxalate.[1]—Crystals of oxalate of calcium are found in either acid or alkaline urine, but most commonly in acid urine; they are frequently associated with crystals of uric acid. When present in an alkaline urine, they are usually found along with crystals of ammonio-magnesium phosphate, for which they are frequently mistaken.

When crystals of calcium oxalate are constantly present in the urine, the condition is termed *oxaluria*.

Calcium oxalate crystallizes in two typical forms—the *octahedral* and *dumb-bell* crystals. There are, however, various modifications of these two forms, according to the positions of the crystals. (Fig. 31.)

1. **The octahedral crystals** are made up of two four-sided pyramids, placed base to base, and when viewed from

[1] For the properties of Calcium Oxalate see p. 97

the side, their characteristic appearance is that of a square crossed obliquely by two bright lines, forming the so-called "envelop" crystal. If, however, the octahedron be turned with one of its long axes toward the observer while the other is held upright, the short axis will necessarily be transverse, and the crystal will appear as a long and very acute octahedron.

Frequently, the octahedra coalesce in such a way as to have the appearance of an open umbrella, constituting the so-called "umbrella" crystals. Sometimes each half of an octahedron is connected by a short quadrilateral prism, and such have been called "prismatic" crystals of calcium oxalate. A few other irregular forms are occasionally found, but most of them, if not all, are modifications of the typical octahedron. Occasionally, a number of the octa-

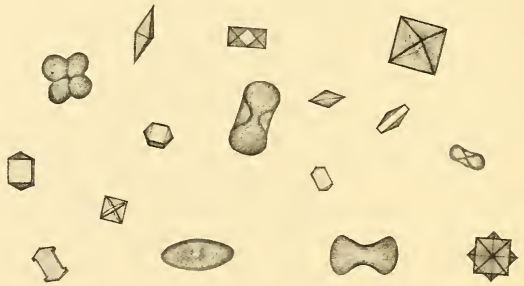


Fig. 31.—Various forms of calcium oxalate crystals.

hedral crystals are found intimately adherent, forming larger or smaller microscopic concretions. Isolated crystals are not infrequently found adherent to renal casts.

2. The **dumb-bell** and **oval crystals** of calcium oxalate are more rarely found in the urinary sediment than the octahedral forms, but when thus met with, are highly characteristic. The dumb-bell crystals are always associated with a larger or smaller number of oval or circular forms, which have bright centers showing their biconcavity. In addition to these are found allied forms, especially those with partial concavities at the sides. Frequently, two dumb-bells are found crossed at their centers, forming a double dumb-bell crystal. These colorless dumb-bell crystals of calcium oxalate should not be mistaken for the yellowish-red

or brown dumb-bells of uric acid and of ammonium urate. The dumb-bells of uric acid and of ammonium urate are readily soluble in alkaline hydrates, while those of calcium oxalate are difficultly soluble; the dumb-bells of uric acid are insoluble in dilute hydrochloric acid, while those of calcium oxalate are soluble. The dumb-bell or oval crystals of calcium oxalate are, like the octahedral forms, quite often found adherent to renal casts, and a number of them may be joined together to form microscopic concretions.

The small circular crystals are sometimes mistaken for normal blood globules. They are readily distinguished by the fact that the oxalate, although biconcave, is very highly refractive, colorless, and insoluble in acetic acid, whereas the normal blood globule has a pale-yellow color, and is rendered abnormal by acetic acid.

Primary and Secondary Crystals of Calcium Oxalate.—The *primary* crystals, or those formed inside the body, are generally the *large octahedra*, and also most of the *oval* and *dumb-bell forms*. *Secondary* crystals, or those formed after the urine has been passed, are usually the *small octahedra* and perhaps some of the *very small oval*, *circular*, and *dumb-bell* forms. These secondary crystals are most commonly found in a urine that has been allowed to stand for some time, when they are frequently accompanied by uric acid. Only rarely are the large crystals deposited secondarily; they may, however, be deposited following the addition of acetic acid to the urine.

Distinction Between Crystals of Calcium Oxalate and Those of Ammonio-magnesium Phosphate.—The fact that, at times, some of the crystals of ammonio-magnesium phosphate (triple phosphate) closely resemble the octahedral form of calcium oxalate often leads to much confusion. These are the small crystals of triple phosphate, modifications of the typical triangular prism, with its beveled ends, in which the body of the prism, instead of being a parallelogram, is nearly square, and in which the line connecting the beveled ends is exceedingly short, but rarely so short as not to be seen by careful focusing. The nature of the crystals may, however, be determined by the characteristic shape of the larger crystals about them, for they never occur alone. As previously mentioned, the octahedron of calcium oxalate is usually a square crossed by two diagonal lines, and therefore has the appearance of an envelop. The

phosphate crystals are promptly dissolved by acetic acid, while those of the oxalate of lime are insoluble in this acid.

Clinical Significance.—Crystals of calcium oxalate may be found in the urine of persons who are typically healthy, as well as in certain diseased conditions. In *health* the presence of an oxaluria is dependent upon the *character of the food* ingested. Thus, it often follows the ingestion of rhubarb, onions, sorrel, tomatoes, grapes, and the like, because of the amount of oxalic acid contained in these substances. It is of frequent occurrence in various disturbances of digestion. It often follows the abundant ingestion of carbohydrates, and the use of an excessive meat diet; this is especially the case when there is any interference with the oxidizing power of the system. We know that oxalic acid is formed as an intermediate product of the metabolism between uric acid and urea; that the process of formation appears to be one of oxidation which, if diminished, results in an oxaluria. Thus, in *diseases of the heart and lungs* an oxaluria is of frequent occurrence. It is commonly seen in diseases of the nervous system, and it is claimed by some that the oxalic acid present in the blood, on account of its poisonous action, causes a certain train of symptoms of which nervous phenomena are especially prominent. This constitutes the theory of so-called "*oxalic-acid diathesis.*" It is true that oxalic acid, when taken internally in considerable amount, exerts a poisonous action upon the organism, not only locally on the digestive tract, but upon the heart and nervous system. However, further evidence is necessary to prove that the symptoms of the so-called "oxalic-acid diathesis" are directly due to an increased formation of oxalic acid, or its retention in the blood.

The primary crystals of calcium oxalate often set up a more or less marked irritation of the urinary tract, especially if they separate from the urine in the kidney or renal pelvis; the mechanical action is usually much less severe if the crystals separate in the bladder. The irritation thereby may be very severe and even be accompanied by abundant hemorrhage. Such a severe mechanical disturbance is invariably accompanied by pain, often frequent and painful micturition, and usually by a more or less concentrated urine. If the separation of these primary crystals continues for some time, the tendency to a calculus-formation

in the pelvis of the kidney or bladder is very great, and especially in those cases in which there is more or less hemorrhage.

In the more severe forms of oxaluria the condition has been incorrectly termed "false Bright's disease," owing to the extreme nervous symptoms, emaciation, dry skin, constant pain or a sense of weight across the loins, frequency of micturition, and other symptoms similar to those that accompany a nephritis.

Cystin.—Cystin, $(C_3H_6NSO_2)_2$, is an amido-acid, and constitutes one of the rarer forms of abnormal urinary sediments. It crystallizes in the form of colorless hexagonal plates (Fig. 32), the angles of which measure about 120 degrees. The sides of these plates are usually equal, although rarely two sides are found to be longer or shorter than the

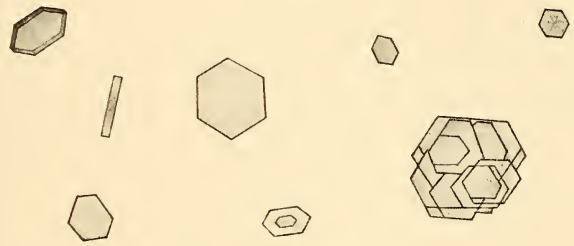


Fig. 32.—Cystin crystals.

other four. It also crystallizes in quadrilateral prisms or groups of prisms. Crystals of cystin have an opalescent luster, and are often arranged in rosettes.

Cystin is insoluble in water, alcohol, and ether; also in acetic and tartaric acids. It is soluble in mineral acids and oxalic acid, in ammonic hydrate and other alkaline hydrates and carbonates, but is insoluble in ammonic carbonate. It is readily precipitated from its alkaline solution by acetic acid. Its solutions rotate the plane of polarized light strongly toward the left.

Cystin contains 26 per cent. sulphur, the odor of sulphuretted hydrogen being evolved when a urine containing cystin undergoes ammoniacal fermentation.

Cystin is probably not a normal constituent of the urine, although Goldmann and Baumann claim to have isolated a substance resembling cystin, in very small quantities as

a benzoyl compound from normal urine. Under pathologic conditions the quantity of cystin in the urine undergoes considerable variation at different times, and it may temporarily disappear. The daily quantity may reach as high as 1.5 grams (Toel); ordinarily, however, it varies between a few milligrams and one gram.

Cause of Cystinuria.—Until recently the cause of cystinuria was thought to be due to abnormal processes of oxidation in the liver, since, in some respects, cystin resembled *taurin.* Marowski [1] considered it a vicarious elimination of taurin because in his case there was an absence of bile in the intestine.

The experiments of Baumann and v. Udránszky, Brieger, and others, threw new light on the causation of this condition. They found that certain products of intestinal putrefaction, called *diamines*, were eliminated in the urine and feces of persons afflicted with cystinuria. Baumann and v. Udránszky [2] made frequent examinations of the urine of a case of cystinuria for diamines, and found them regularly. They were isolated in the form of a benzoyl compound, which varied in amount from 0.2 to 0.4 gram in twenty-four hours. Approximately, one-third to one-fourth of these substances existed as tetramethylendiamine, and the remainder as pentamethylendiamine.[3] According to Brieger, since these diamines arise only as a result of putrefactive processes due to specific bacteria, cystinuria can be considered the result of a specific infection of the intestine. In Baumann's case both diamines were invariably found in the feces as well as in the urine, and he observed that the relative amounts of these substances in the feces, especially the cadaverin, varied inversely as those in the urine. Neither Brieger nor Baumann was able to discover these diamines in the feces of healthy individuals, or in those suffering from other diseases.[4]

So far as has yet been determined, no *definite* relation exists between the formation of cystin and the diamines,

[1] "Deutsches Archiv f. klin. Med.," IV, S. 449.

[2] "Zeitschr. f. physiol. Chem.," 1889, XIII, S. 562.

[3] Brieger gave new names to these two substances, calling the first "putrescin," and the latter "cadaverin."

[4] According to Neubauer and Vogel, these diamines have been found in the intestinal discharges of patients with Asiatic cholera.

although the same conditions that produce diaminuria usually also produce cystinuria.

Clinical Significance.—Hereditary predisposition certainly appears to have some bearing as a cause, since so many cases have been reported of the existence of the affection in several members of the same family. It is difficult, however, to explain the hereditary transmission of cystinuria by the theory of Brieger, unless we assume that such individuals are more susceptible to the action of the "specific bacteria" that produce the intestinal putrefaction than others.

Cystin is met with in the urine of both infants and adults, but only rarely occurs in old age. It does not appear to be connected with any local or constitutional disease. It may be present and continue for years without any noticeable impairment of health, although, as a result of its separation from the urine, there is usually more or less irritation of the urinary tract. It has been occasionally observed in cases of liver disease, and Ebstein has noted the presence of cystin in the urine of cases of acute articular rheumatism.

The danger of a calculus-formation always attends the separation of cystin from the urine inside the body. Where a concretion exists, it is usual to find few (sometimes many) isolated crystals of cystin.

Detection.—The detection of cystin is based chiefly on the recognition of the characteristic crystals in the urinary sediment; also their solubility in weak ammonic hydrate, and their recrystallization upon the evaporation of the ammonic hydrate.

It is always important to distinguish between the crystals of cystin and other like crystalline elements. Cystin can be differentiated from the pale, six-sided crystals of *uric acid* by allowing a drop of weak ammonic hydrate to mingle with the deposit on a glass slide, when either form of crystal will disappear; evaporate, and if cystin be present, the crystals reappear; if uric acid be present, crystals of ammonium urate will be found, instead of those of uric acid. Another simple method consists in treating the crystals with hydrochloric acid, which readily dissolves the cystin, but leaves uric acid unchanged. Cystin is distinguished from *triple phosphate* by its behavior with acetic acid, which quickly dissolves the phosphate crystals while those of cystin remain unchanged.

The evolution of sulphuretted hydrogen from the urine should always lead to an examination for cystin, although H_2S is by no means *always* due to the presence of cystin. Frequently, silver coins carried in the pockets of persons suffering from cystinuria are blackened by the sulphuretted hydrogen evolved, owing to the fact that cystin is sometimes eliminated by the skin, where it decomposes and furnishes H_2S.[1]

Bilirubin and Hematoidin.—*Bilirubin* is frequently deposited in a urine containing bile in an amorphous or crystalline form. The crystals of bilirubin (Plate 7) have two forms—(1) clusters of needles arranged as stellates, occurring either free in the urinary sediment or found attached to cells ; and (2) minute rhombic tablets or plates which vary in color from a yellow to a beautiful ruby red.

They are soluble in caustic soda, and on the application of a drop of nitric acid a green rim forms about them.

Hematoidin, a derivative of hematin, was first discovered by Virchow in extravasated blood. It resembles bilirubin as closely in appearance as in its chemic properties. The crystalline formation of the two is identical. (Plate 7.) According to Hoppe-Seyler, v. Jaksch, and others, they are in all respects indistinguishable, and it is, therefore, safe to say that they are one and the same substance occurring under varying conditions.

As previously stated, these crystals are very commonly found in urine containing bile ; it is not uncommon to find them in the urinary sediment following an extensive hemorrhage, or the evacuation of an abscess, or pyonephrosis in which there has been hemorrhage. Leyden found these crystals in nephritis gravidarium ; Foltanek and Rosenheim in acute yellow atrophy ; and v. Jaksch in phosphorus-poisoning, cirrhosis of the liver, as well as in severe jaundice of the most distinct types. The author has occasionally met with these crystals in hemorrhage from the prostatic region, once in cancer of the bladder, and twice following a traumatic hemorrhage from the kidneys, as well as in jaundice from various causes.

Leucin.—Leucin, $C_6H_{13}NO_2$,—amidocaproic acid,—is one of the products of decomposition of proteid bodies or of their derivatives, and is formed by the activity of certain

[1] For the quantitative determination of cystin see Neubauer and Vogel, "Analyse des Harns," Bd. 1, 1898, S. 807.

Plate 7

Hematoidin (Bilirubin) Crystals.

ferments, especially trypsin. As a urinary deposit it is of very rare occurrence. It is usually accompanied by crystals of tyrosin.

Leucin occurs as highly refractive spherical crystals, which are usually marked with radiating and concentric striæ. (Fig. 33.) When pure, it crystallizes in very delicate, small plates, often of irregular shapes and with a greasy feel, and are usually arranged in groups or found lying one upon another. When very impure, they appear as yellowish, highly refractive globules, apparently without crystalline structure. In this form they may be mistaken for oil-drops, but by careful study it will be found that they are less highly refractive than oil-drops—*i. e.*, not possessing quite so wide a dark border.

Leucin, when pure, is difficultly soluble in cold, but more

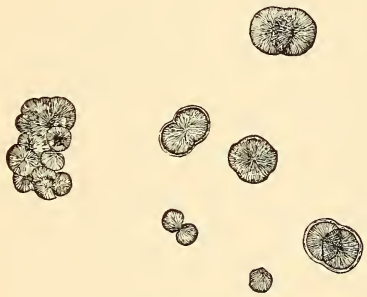


Fig. 33.—Leucin crystals.

readily soluble in hot, water ; it is only sparingly soluble in alcohol ; readily soluble in acids and alkaline hydrates, and insoluble in ether. When impure, its solubility is distinctly increased. Leucin sublimes without melting when heated to 170° C. ; at a higher temperature it is decomposed into carbonic acid and amylamin. It combines with bases and acids to form salts. It can be obtained artificially by decomposing proteids with acids.

Detection.—Leucin may be recognized by the characteristic microscopic appearance of its crystals. Having found crystals resembling leucin, confirmatory tests should always be employed.

1. When leucin is evaporated on a platinum foil with nitric acid, a colorless residue remains, which, if treated

with a few drops of sodic hydrate and heated, furnishes, according to the purity of the leucin, a watery, or more or less colored, fluid. If this fluid be concentrated, there remains an oily fluid that does not adhere to the platinum, but collects in drops of varying size (Scherer).

2. On the addition of a trace of chinon and a few drops of sodic hydrate to a cold aqueous solution of leucin a marked violet color appears. Other amido-acids, as well as certain proteid bodies, give this reaction (Wurster).

3. Leucin does not give a color reaction with furfurol, but tyrosin, on the other hand, gives a decided reaction with an aqueous solution of this substance.

Since leucin nearly always accompanies tyrosin, its clinical importance will be considered under the subject of tyrosin.

Tyrosin.—Tyrosin, $C_9H_{11}NO_3$, like leucin, is one of the products of the decomposition of proteid substances. It crystallizes in the form of exceedingly fine needles, which are arranged in sheaf-like collections, often crossing each other, and intersecting at their constricted middle portions. It also crystallizes in rosettes with the needles radiating from their centers (Fig. 34), especially if crystallized from an alkaline solution.

The crystals are colorless, but when arranged in masses, often look dark, especially near the central portions, because of the compact arrangement of the needles. They are tasteless and odorless, very sparingly soluble in cold water (1 : 2000 at 20° C.), but much more soluble in boiling water (1 : 150). They are almost insoluble in strong alcohol (1 : 135,000), quite insoluble in ether, and readily soluble in acid, alkalies, and solutions of the alkaline salts. Tyrosin readily combines with bases and acids to form distinct compounds. (For details see Neubauer and Vogel, "Analyse des Harns," Bd. 1, 1898, S. 281.)

Tyrosin that has been isolated from the urine or other fluids is readily recognized, even when present in very small amounts, by means of Hoffmann's and Piria's tests.

Hoffmann's Test.—When a solution of tyrosin or a suspected deposit that has been boiled with an *excess* of water is heated with Millon's reagent, a bright crimson or pink color is produced. If much tyrosin be present, a similarly colored precipitate forms, while the supernatant fluid remains red, or sometimes a purple-red.

Piria's Test.—If tyrosin be treated on a watch-glass with a little concentrated sulphuric acid, and heated on a water-bath for from five to ten minutes, there results a compound —tyrosin-sulphuric acid—which has a pink color. This pink solution is then diluted with water, warmed, neutralized with barium carbonate, and filtered while hot. The colorless and neutral filtrate is then treated with a few drops of a very dilute solution of perchloride of iron, which produces a violet color. An excess of the iron salt should be avoided, as it readily destroys the color.

According to v. Udránszky,[1] a characteristic reaction is obtained when an aqueous solution of furfurol is added to a solution of tyrosin.

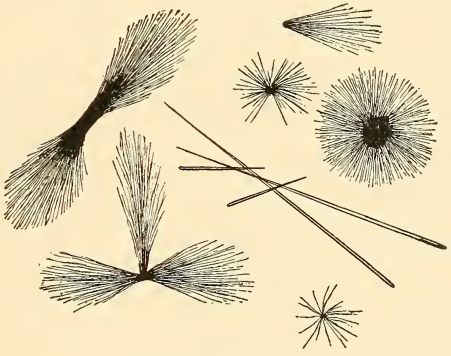


Fig. 34.—Tyrosin crystals.

Furfurol Reaction.—Dissolve a small crystal of tyrosin in 1 c.c. of water, add one drop of a 0.5 per cent. solution of furfurol, and then underlie with concentrated sulphuric acid; the fluid is colored rose-red. The mixture should not have a temperature above 50° C.

The foregoing tests for tyrosin can not be applied directly to the urine with satisfactory results, since various urinary constituents either give the same reactions or obscure the tests. It is, therefore, necessary to isolate the tyrosin, which, according to Blendermann,[2] can be accomplished in the following manner:

Precipitate the urine with basic acetate of lead, filter, and

[1] "Zeitschr. f. physiol. Chem.," XII, 355, 1888.
[2] "Zeitschr. f. physiol. Chem.," VI, 260, 1882.

remove the lead from the filtrate by passing sulphuretted hydrogen through it. Filter, and evaporate this filtrate to a very small volume, and allow it to stand several hours to crystallize. Filter, dissolve the crystals in boiling water, and apply the tests as directed.

If the urinary sediment contains crystals that resemble tyrosin, their presence should always be confirmed as follows: Filter off the sediment, wash with water, dissolve while still on the filter in hot ammonic hydrate to which some ammonium carbonate has previously been added, evaporate the filtrate to crystallization, and examine microscopically.

Care should be taken not to mistake the large hedgehog and sheaf-like crystals of acid urate of ammonium, also the sheaf-like crystals of acid sodium urate, for the rosettes and sheaves of tyrosin.

Clinical Significance.—Leucin and tyrosin are constantly formed as products of the digestion of proteids, particularly by the action of trypsin, and usually, if not always, occur together. The presence of these substances in the urine is of *very* rare occurrence. It is claimed by some observers that they are present in minute traces in normal urine. This, however, is still an unsettled question, as certain reliable observers have been unable to confirm such claims.

Leucin and tyrosin have been found in the urine in considerable amounts in acute yellow atrophy of the liver and in acute phosphorus-poisoning. They have also been observed in the urine in cases of severe typhus fever, severe smallpox, and diseases of the intestines. The appearance of these two substances in disease is invariably accompanied by a very marked reduction in the quantity of urea.

Cholesterin.—Cholesterin, $C_{26}H_{44}O$, is a monatomic alcohol that is normally present in nervous tissue, blood-corpuscles, bile, and elsewhere. It occurs pathologically in gall-stones, as well as in atheromatous cysts, in pus, in tubercular masses, old transudations, excrements, and tumors.

Cholesterin is probably not a constituent of the urine in health, and only occurs in this fluid under pathologic conditions. It crystallizes in large, colorless, transparent plates (Fig. 35), whose angles and sides frequently appear broken, and whose acute angles are often from 76 to 87 degrees. In large quantities it appears as a mass

of white plates having a luster resembling mother-of-pearl, and a greasy feel.

Cholesterin is insoluble in water, dilute acids, and alkalies. It is easily soluble in boiling alcohol, and recrystallizes on cooling. It is readily soluble in ether, chloroform, and benzol, and also in the volatile and fatty oils. It is dissolved to a slight extent by alkaline salts of the bile acids.

Cholesterin crystals are only found in the urinary sediment in cases of extensive fatty degeneration of some part of the urinary tract, as, rarely, in cases of subacute glomerular nephritis and chronic diffuse nephritis, and still more rarely during the fatty stage of an acute nephritis ; also in case of the evacuation of an abscess into the urinary tract.

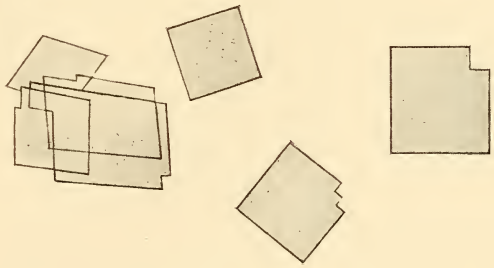


Fig. 35.—Cholesterin crystals.

Detection.—If a mixture of five parts of sulphuric acid and one part of water acts on a cholesterin crystal, first a bright carmine-red and then a violet color appears. This fact is used in the microscopic detection of cholesterin. Another test consists in treating the crystal first with dilute sulphuric acid and then with a solution of iodine. The crystals will be gradually colored violet, bluish-green, and finally a beautiful blue.

Salkowski's Reaction.—Cholesterin is dissolved in chloroform, and then treated with an equal volume of concentrated sulphuric acid. The cholesterin solution becomes first bluish-red, then gradually violet-red, while the sulphuric acid appears dark red with a greenish fluorescence.

Cholesterin is readily detected in the urinary sediment by means of the microscope.

ORGANIZED SEDIMENTS.

The organized or anatomic sediments consist of formed elements coming from various parts of the urinary tract. Some of these elements are present in the urine under normal conditions, while others are found only as the result of functional disturbance or disease.

Blood.—Red blood-corpuscles in the urinary sediment are always abnormal constituents, and indicate a pathologic condition in some portion of the urinary tract. Not infrequently, in the female, blood enters the urine from the genital tract; under such circumstances it is quite unimportant.

Blood-corpuscles vary in their microscopic appearance according to the character of the urine in which they are found, the length of time they have been in the urine, and the location of the urinary tract from which they come. Red blood-corpuscles are conveniently divided, for the purpose of urinary examination, into two classes—*i. e.*, (*a*) *normal* and (*b*) *abnormal* blood globules.

(a) **Normal Blood.**—This refers to the unaltered blood-corpuscles, which are so characteristic in appearance that there is very little, if any, danger of mistaking them for other elements in the sediment. They consist of biconcave discs, which *always* have a yellow color. (Fig. 36, left half.) They are smaller than a leucocyte, being about $\frac{1}{3200}$ of an inch (between 7 and 8 micromillimeters) in diameter, free from nuclei, and perfectly homogeneous—that is, free from granules and other visible cell-contents. These biconcave discs undergo a reversal of light and shadow on careful focusing, the center and periphery alternating in brightness or shadow as the objective is approximated to the slide or removed from it. Normal blood globules that have been in the urine for some time begin to undergo a change. Their edges often become irregular and crenated,—the so-called *crenated blood-corpuscle*,—found particularly in urines that contain a relatively large proportion of sodium chloride. This form still has more or less color, and belongs to the class of normal blood. *In fact, any blood-corpuscle that has the slightest yellowish tint can be considered a normal blood-corpuscle.* Within a few hours after the blood enters the urine the corpuscle begins to swell and lose its color and density, and it is then that we have the—

(b) **Abnormal Blood Globules.**—These are merely blood rings or shadows. (Fig. 36, right half.) The blood globule that was formerly biconcave is now biconvex—in other words, is swollen and has become a sphere, devoid of color or, if any color, the slightest tint of brown at the margin. The corpuscle has also become reduced in diameter, being only about two-thirds of the diameter of the normal blood-corpuscle. There are various forms of corpuscles in the change from normal to abnormal blood, but, since the color is the criterion, any blood-corpuscle that has lost its yellow color is abnormal.

A urine containing *normal* blood is usually more or less reddish in color, depending upon the quantity present. If the amount of blood is excessive, it produces in alkaline urine a bright-red color (oxyhemoglobin), and in highly acid urine more of a brownish-red color (oxy- and methemoglobin). *Abnormal* blood, when present in considerable quantity, imparts a brownish or smoky color (methemoglobin and hematin) to the urine. If present in large amounts, the color is usually very dark and may be black. If the quantity of either normal or abnormal blood in the urine be small, the color may give no indication of its presence, and under such circumstances is not usually detected until the sediment is examined microscopically.

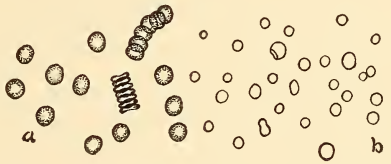


Fig. 36.—Blood-corpuscles: *a*, Normal; *b*, abnormal.

A distinct reaction for albumin is always obtainable in a urine containing blood, even though the quantity of blood be extremely small.

Treatment of a Sediment Containing Blood.—The presence of a large amount of blood in the urinary sediment generally completely obscures other formed elements; on this account the blood globules must be destroyed. The destruction of blood is best accomplished in the following way:

Allow the urine to settle thoroughly in a urine glass, then decant the supernatant bloody fluid, and to the sediment remaining in the glass add a large volume of lukewarm water and a few drops of dilute acetic acid. Stir thoroughly with a glass rod, breaking up all clots, and allow the fluid to settle again. Repeat this process until the wash-water is practically free from blood pigment. Finally, settle and examine. The blood pigment will be found to have been washed from the blood-corpuscles, leaving a very fine network of abnormal blood globules and fibrin, in which other formed elements, such as casts, epithelium, etc., are capable of detection.

The fact that a urine containing a large quantity of blood always contains a considerable number of leucocytes should be borne in mind, especially in drawing inferences as to the presence or absence of a suppurative process that is associated with hemorrhage. If the leucocytes are numerous—in fact, abundant—and more or less arranged in clumps, suppuration in some part of the urinary tract is highly probable.

"Hematuria" is the term applied to a urine that contains blood,—that is, the blood-corpuscles together with the blood pigment,—and should not be confounded with the term "hemoglobinuria," which applies to a urine containing blood pigment *without* blood-corpuscles. (See p. 364.)

Clinical Significance.—The first interest in connection with a hematuria is to locate the source of the hemorrhage. Blood in the urine may come from the kidney, pelvis of kidney, ureter, bladder, prostate, or urethra. Blood coming from the genital tract of the female should in all cases be distinguished from that coming from the urinary tract.

From the Kidney.—In fresh urine blood from the kidney is usually *abnormal* in character, and therefore imparts a more or less smoky color to the urine. Such urines after standing deposit a brown or coffee-colored sediment. But the blood may be *normal*, especially if from the straight tubules or in case of abundant renal hemorrhage when the urine is generally of a bright-red or brownish-red color, and upon standing furnishes an abundant blood-red sediment. Urines containing blood from the kidneys are generally acid in reaction, although if the amount of blood be very large, the reaction may be alkaline. Blood from the kidney is usually accompanied by renal casts, which often have the

blood adherent ; and even blood-casts may be found. This fact constitutes an important element in diagnosis, since the only positive evidence of renal hemorrhage is the presence of blood on casts and true blood-casts. Blood-clots, usually of small size, are not infrequently found in the sediment in cases of abundant hematuria of renal origin. Large clots, however, are generally absent from the sediment unless they be of the long, slender, rod-like variety, which have been molded in passing through the ureters. In case the hemorrhage is very slight blood-clots are usually not found in the sediment.

The most frequent causes of blood from the kidney are the acute diseases and disturbances of this organ, such as active hyperemia (little blood), severe active hyperemia (considerable blood), and acute nephritis (large amount of blood). A *very* small amount of blood is sometimes found in the various chronic diseases of the kidney, but is generally so slight that it is unimportant. In all of the above-mentioned kidney affections the blood is usually abnormal. In an *exacerbation* of an acute or an *acute exacerbation* of a chronic kidney disease the blood is generally abundant and normal in character, this condition being characterized by the *sudden* appearance of normal blood and a rapid fall in the twenty-four-hour quantity of urine. (See p. 300.) This form of renal hemorrhage is most common in the parenchymatous forms of renal disease, such as acute nephritis, subacute glomerular nephritis, and chronic diffuse nephritis. Hematuria is not uncommon in chronic interstitial nephritis as the result of vascular changes, including cardiac disease and atheromatous arteries. It is by no means rare in amyloid infiltration of the kidneys, on account of the extensive infiltration about the smaller blood-vessels.

In *tuberculosis* of the kidney hemorrhage is a common symptom. The attacks are usually intermittent, although at times constant for a long period. An abundance of pus frequently accompanies a hematuria of this origin. A very thorough search for *tubercle bacilli* in the urinary sediment should always be made before eliminating this possibility of hemorrhage. *New growths* of the kidney also give rise to repeated attacks of hematuria, and at times the quantity of blood is profuse. There is generally more or less pus in the sediment, and also an abundance of small round and

degenerated cells. Such cases are to be recognized by renal tumor, more or less pain, and general cachexia of the patient.

A *calculus* in the substance of the kidney or in the renal pelvis of the kidney is a frequent cause of hemorrhage. The blood is generally accompanied by more or less pus. There is usually pain in the region of the affected kidney, tenderness on deep pressure, and pain extending down the leg or into the testicle. There may be renal colic when there is a small stone in the renal pelvis, the blood often being accompanied by small caudate cells from the superficial layer of the pelvis. In the light of these symptoms a hematuria resulting from a calculus should be suspected. The sediment should be carefully searched for crystalline deposits, which may or may not be present.

The ingestion of certain drugs such as cantharides, turpentine, as well as certain other poisonous substances, may give rise to renal hematuria. It may also be due to trauma involving the kidneys, either directly as by wounds or blows, or indirectly from concussion. In tropical countries renal hematuria is frequently the result of an invasion of the kidney by a minute parasite—distoma hæmatobium. (See p. 269.) Of the various other causes of hemorrhage of renal origin, renal embolism, purpura hæmorrhagica, hydatids, abscess, and cystic disease of the kidneys may be mentioned.

From the Lower Urinary Passages.—Abundant hemorrhage from the *bladder* is not uncommon, and is most liable to be the result of one of three abnormal conditions—*i. e.*, vesical calculus, tuberculosis, or new growth. A moderate amount of blood usually accompanies all acute and chronic inflammations of the bladder. Blood from the bladder is generally normal in character, but if present in small amounts, may be abnormal, particularly if the urine in which it is contained be highly acid or strongly akaline. The quantity of blood may be so abundant as to cause coagulation within the bladder or, as is more frequent, shortly after the urine has been voided. Blood-clots are more common in vesical hematuria than in other forms of hemorrhage, and are invariably associated with profuse bleeding. The clots are usually small and irregular in shape, but may be large and regular. A clot in the bladder may completely obstruct the outflow of urine. Rarely, long, smooth, cord-like blood-clots are passed by the urethra. One instance

of this was observed by the author, the clot being seventy-two inches in length.

Blood of vesical origin is generally accompanied by more or less pus, and in cases of long-standing cystitis the urine is frequently alkaline, although not invariably so. For purposes of diagnosis the blood must be destroyed before microscopic examination is undertaken, and then a search made for characteristic cells of new growth, or crystalline elements; or the sediment prepared, and carefully examined for tubercle bacilli.

Hemorrhage from the *neck of the bladder* is probably most commonly the result of tuberculosis, although it may be due to various other pathologic conditions of this region. In most respects it resembles hemorrhage from the fundus of the bladder, although accompanied by symptoms suggestive of neck-of-bladder trouble.

Hematuria of urethral origin may arise from traumatism, acute gonorrhea, urethral chancre, or following surgical operations on strictures of the urethra. The blood is generally normal in character, and precedes the flow of urine, and also oozes from the meatus between the acts of micturition.

Teichmann's Test for Blood Pigment.—In the application of this test to urine it is necessary to coagulate the albumin, which carries down with it the blood pigment. This is best accomplished for the purpose of this test (1) by strongly acidulating the urine with acetic acid, and then adding a saturated solution of sodium tungstate also acidulated with acetic acid. Upon heating this mixture a brownish precipitate of albumin and blood pigment is obtained, which is collected on a filter and dried. (2) The albumin can also be coagulated by boiling the urine, which has been faintly acidulated with acetic acid, as described on page 131. This precipitate is placed on a filter, washed, and dried.

Method.—A small portion of the dried and powdered precipitate containing the blood pigment is placed on a microscopic slide, and moistened with a weak solution of potassium iodide or sodium chloride, and evaporated to dryness. The residue is covered with a cover-glass, and *glacial* acetic acid allowed to flow underneath in contact with the powder. This preparation is then gently heated until the acid begins to boil, when it is cooled, and examined

by means of the microscope. If blood pigment be present, brown rhombic plates (Fig. 37) of iodide or chloride of hematin (also known as *hemin crystals*) will be found. These rhombic crystals are generally isolated, but they occasionally cross each other to form more or less characteristic groups.

This test affords one very important means of determining the presence of blood or blood pigment in the urine and other fluids of the body. It is also of great importance in distinguishing between the dark or black urines due to hemoglobin (see Hemoglobinuria, p. 364) and those that are dark or black from other pigments. Further-

Fig. 37.—Teichmann's hemin crystals.

more, this test is of great practical value in the medicolegal detection of blood.

Pus.—Pus-corpuscles, also termed leucocytes, are round, well-defined bodies, which are usually extremely granular. (Fig. 38, *a*.) They vary a little in size, but are usually quite constant and a trifle less than twice the size of the average normal blood globule. Although generally round, they vary somewhat in shape according to the age of the pus, the reaction of the urine, and the pathologic process that they accompany. Pus-corpuscles usually contain two or three nuclei,—polymorphonuclear leucocytes,—which constitute the chief characteristic of the typical pus-corpuscle. There is also the *mononuclear leucocyte*, which is less common in the urinary sediment, and not easily distinguished from the small round cell.

The nuclei of the pus-corpuscle are not usually distinct, on account of the very granular character of the body, but if the corpuscle be not decomposed or disintegrated, two or more nuclei can be made out upon focusing closely. The distinctions of the nuclei, and, in fact, the general appearance of the pus-corpuscle, depend largely upon the reaction of the urine in which they are contained and the age of the pus.

In Acid Urine.—Fresh pus in an acid urine is very dense and the nuclei are seen with difficulty, if at all ; this constitutes the so-called "*normal pus.*" On the other hand, pus which has been suspended in the urine for some period, either within or outside the body, has a different appearance ; the body of the corpuscle becomes less distinct and the nuclei more prominent ; this is sometimes termed

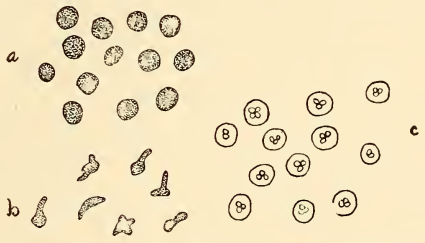


Fig. 38—*a*, Pus-corpuscles as ordinarily seen ; *b*, ameboid pus-corpuscles ; *c*, pus-corpuscles showing the action of acetic acid.

"*abnormal pus,*" *or* "*washed-out pus.*" In the abnormal pus-corpuscle the nuclei, instead of being separate bodies, are often fused, forming a single horseshoe-shaped nucleus, which is not so dense as the individual nuclei of the normal pus-corpuscle. These abnormal pus-corpuscles may come from any part of the urinary tract, and are most common in cases of long-continued chronic inflammation.

In Alkaline Urine.—When a urine containing pus becomes alkaline by a volatile alkali or alkaline hydrate, such as ammonium carbonate or hydrate resulting from the decomposition of the urea, the pus-corpuscles become destroyed. By the action of the alkali the pus becomes converted into a gelatinous, tenacious mass (see Donnè's Test for Pus), which in many respects resembles white of egg. If a portion of this mass be examined microscopi-

cally, the pus-corpuscles will be found to have been destroyed, while only a dense mucus-like mass with adherent amorphous phosphates, crystals of triple phosphate, and bacteria remains. Some of the nuclei of the pus-corpuscles may still be found.

Pus-corpuscles are practically identical with the white corpuscles of the blood and lymph. In a fresh state they often present protoplasmic processes,—ameboid movements,—and under such circumstances should not be mistaken for small caudate cells.

It is very important to determine the exact nature of all small, round, or irregular bodies whose nuclei are not distinct, to distinguish between leucocytes and small round cells, and also between ameboid leucocytes and small caudate cells. This is best accomplished by treating the urinary sediment with dilute acetic acid, as follows : Moisten the microscopic slide with a fraction of a drop of the acid, then place a drop of the sediment on the drop of acid ; mix thoroughly by means of a glass rod, and cover with a cover-glass.

Action of Acetic Acid.—When dilute acetic acid (20 per cent.) is added to a fluid containing pus, the changes in the corpuscles are very rapid ; the first effect being to cause them to swell up, and next to dissolve the granules, the body of the corpuscle becoming smooth and the nuclei very distinct. In a short space of time the body of the corpuscle becomes almost invisible, while the nuclei remain a much longer time.

Epithelial cells are affected by acetic acid in much the same manner as leucocytes, but to a less marked degree. The first effect is a solution of the granules, making the nucleus very prominent, and, finally, after prolonged action of the acid, the cell begins to swell. The body of the cell does not usually become faint or invisible by the action of this acid.

The *action of water* on the pus-corpuscle and epithelial cell is identical with that of acetic acid, except that it is very much slower and the stage of distinct nuclei is reached much later.

Characteristics of Urine Containing Pus.—An acid urine containing pus is turbid except when the corpuscles are only few in number. It very soon deposits an opaque white sediment, which rapidly settles to the bottom of the

sediment glass. This deposit should not be mistaken for a deposit of amorphous urates or phosphates. The distinction is easily made by means of the microscope, also by the fact that the phosphatic deposit is readily dissolved by acetic acid, while the deposit of pus undergoes the changes already described. On the other hand, a deposit of amorphous urates is readily dissipated by gentle heat.

A purulent urine that has undergone alkaline fermentation is invariably turbid and often contains a large, ropy mass, consisting of decomposed pus, etc., as previously mentioned.

Donnè's Test for Pus.—This depends upon the reaction that takes place between alkalies and the pus, and consists in the addition of an alkaline hydrate—potassic, sodic, or ammonic hydrate—to the suspected urine, or its sediment after the supernatant urine has been poured off. If pus be present, the urine becomes viscid, or the sediment is promptly converted into a viscid, gelatinous, mucus-like mass, which adheres to the bottom and sides of the test-tube. If some of this viscid substance be examined under the microscope, the pus-corpuscles will be found to have been destroyed or, rather, converted into the substance itself. If the action has not been very long or the proportion of the alkali to the pus is small, the outline of the pus-corpuscles may still be seen; so, also, the nuclei of the corpuscles may still be discernible, embedded in the mucus-like mass.

According to v. Jaksch, leucocytes are stained a deep mahogony-brown (glycogenic reaction) by a solution of potassic iodide. This serves to distinguish them from small round cells, which are stained a light yellow color.

A. Vitali recommends the following test for pus: The suspected urine, if alkaline, is acidulated with acetic acid, and filtered through a thick filter. The deposit on the filter is then treated with a little guaiacum tincture, which has been kept in the dark. If pus be present, the inner surface of the filter takes a blue tint. The result is obtained even with a small number of leucocytes.

Clinical Significance.—A perfectly normal urine may contain isolated leucocytes. It is only when they occur in considerable numbers or in conjunction with other formed elements (casts, etc.) that their presence becomes important.

Pus is one of the most common elements found in the

urinary sediment. It may be derived from the substance of the kidney or pelvis of the kidney, the ureters, the bladder, the prostate gland, the urethra, or from the rupture of an abscess into some part of the urinary tract. Given, then, a urine containing pus, the first effort should be directed toward determining its source. The character of the elements (cells, casts, etc.) that accompany the pus is of the utmost importance in locating the suppurative process.

Pus coming from the kidney is found in cases of *chronic suppuration in the tubules*, such as may result from the presence of a calculus, the existence of a tubercular process, or the extension of an inflammation from the pelvis of the kidney into the renal tubules. In these conditions the pus is usually present in large quantity, and is sometimes accompanied by a few or numerous renal casts, including pus-casts, which come from the suppurating area or the neighborhood of the diseased area in the kidney. In acute nephritis and following acute exacerbations of chronic renal diseases pus is usually present in greater or smaller quantities, and often found adherent to casts, but in these conditions true pus-casts are only rarely found.

The diagnosis of *abscess of the kidney* can not be positively determined until the abscess has evacuated its contents into the urinary passages. Previous to rupture of the abscess the urine usually presents evidences of a renal congestion—active hyperemia—that is going on in the renal tissue around the abscess pocket. A urine that suddenly contains a large quantity of greenish pus strongly suggests abscess of the kidney.

In *chronic pyelitis* the urine is generally acid in reaction; the pus is not only free, but is often arranged in clumps, and is mixed with small round cells from the deep layer of the pelvis of the kidney. Any obstruction to the outflow of pus causes a pyonephrosis; if the back pressure becomes sufficient to force an opening, a sudden gush of greenish pus follows. So far as the author is aware an abundant deposit of greenish-colored pus is indicative only of abscess of the kidney, the evacuation of an abscess into the urinary tract, or pyonephrosis.

Numerous leucocytes usually accompany an acute pyelitis, but ordinarily they are insignificant as compared with the other formed elements, which are, in themselves, diagnostic.

Acute and chronic inflammations of the bladder—cystitis—are always associated with purulent urine. In acute cystitis the urine is generally acid, but in chronic inflammation of this membrane the urine is often alkaline—ammoniacal—when voided. This is by no means true of every chronic inflammation of the bladder, since in tubercular cystitis and also in some cases of calculous cystitis the urine is acid in reaction. Purulent urines in general, and especially those from the bladder, readily become alkaline upon standing exposed to the air, if not already alkaline when voided. In cystitis the ropy, glairy mass consisting of decomposed pus, amorphous and crystalline phosphates, as well as epithelial cells, is not infrequently found.

Pus from the *neck of bladder* or *prostatic region* is often found free, and arranged in clumps and mixed with neck-of-bladder cells. Oftentimes spermatozoa are found free and mixed with the pus in shreds.

In *urethritis* the pus is usually very dense, and found chiefly in long threads or shreds, mingled with urethral cells, especially when of gonorrheal origin. When the amount of pus is abundant, it is generally free, no shreds being found. In acute gonorrhea the pus is usually yellowish in color. If any doubt exists as to the exact source of this pus, the question is often settled by directing the patient to pass the first portion of his urine into one vessel and the last portion into another; if urethral, the first portion will contain much pus, while the second will be practically free from it.

Pus from the *uterus* or *vagina* is usually accompanied by an abundance of squamous epithelium. If, in the case of a female, there is any doubt as to the source of the epithelium and pus,—whether bladder or vaginal,—a catheter specimen or one voided after a thorough vaginal douche should be procured. If pus be present in such a specimen, it must have originated in some portion of the urinary tract; but if no pus be present, then it must have come from the genital tract. In *blennorrhea* a considerable quantity of pus may find its way into the urine.

Epithelium.—Epithelial cells from various parts of the urinary tract usually form a part of the sediment of every normal and pathologic urine. Epithelium is the normal product of the mucous membrane, and represents the "wear and tear" of such surfaces. In disease the desqua-

mation is usually much increased; the recognition of the cells from the various parts of the urinary passages is, therefore, of the *greatest* importance, for it is often only by this means that abnormal processes can be located. The student should familiarize himself, as far as possible, with the cells that are characteristic of certain areas, before drawing inferences as to pathologic states; he should also bear in mind that every normal urine contains a certain number of cellular elements.

The epithelial cells found in the urinary sediment coming from a given part of the tract usually have entirely different shapes from those found in prepared histologic specimens of that part. For example, some of the renal epithelium *in situ* is cuboid in shape, while that found in the urine is usually round. Other similar examples could be cited in which the shapes of the original cells have become changed, apparently by the action of the urine.

In the detailed study of the cells that follows, the *leucocyte will be used as a standard for comparison*, since this body is nearly constant in size. (Fig. 39, *a*.)

Renal Epithelium.—These are epithelial cells from the tubules of the kidney. They are essentially small round cells, which are usually more or less granular, and present a single nucleus. (Fig. 39, *b*.) There are three sizes of renal cells: *i. e.*, the first, which is smaller than a leucocyte, and probably comes from the smaller tubules in the cortical portion of the kidney; the second, which is about the same size as the leucocyte, and constitutes the average renal cell, which is probably from the convoluted tubules; and the third, which is larger than the leucocyte, and probably comes from the straight or collecting tubules. Renal cells are frequently adherent to casts which, when practically covered with them, form the so-called *epithelial cast.* Renal cells are often *very* granular, and sometimes much distorted, as a result of degenerative processes in the kidney; such are seen especially in cases of advanced chronic interstitial nephritis.

Fatty renal cells are those which contain fat-drops (Fig. 39, *o*), and are the result of degenerative processes in the tubules of the kidney. Such cells may contain only one or two fat-globules, or they may be entirely fatty degenerated. They do not usually differ in size from the renal cells already mentioned, and are not to be mistaken for the

larger, so-called compound granule cell, to be described later. Not infrequently some or all of the fat is washed out of the cell, when it will be found to contain one or more vacuoles. Fatty renal cells are found in the urinary sediment in cases of subacute glomerular nephritis, chronic diffuse nephritis, during the fatty stage of acute nephritis, and not infrequently in the severer forms of renal congestion.

Renal cells always accompany renal casts, although at times they are present only in small numbers. Any small round cell that is adherent to a cast can be safely considered a renal epithelial cell.

Pelvic Epithelium.—Epithelial cells from the pelvis of the kidney vary in shape according to the parts from which they come. (*a*) Those from the *superficial layer of the pelvis* are small caudate cells. (Fig. 39, *c*.) The tails are often curved and at times are bifurcated. The body is the same size or perhaps a little larger than that of the leucocyte, and usually has a distinct nucleus, a brown color, and is quite granular. These cells are sometimes arranged in groups, overlapping "like shingles on a roof," but are usually found singly. They are invariably accompanied by more or less blood, and indicate either a simple irritation of the renal pelvis or a more extensive inflammatory process —an acute pyelitis. They are of frequent occurrence, and often occur in very large numbers in cases of acute pyelonephritis, especially those cases that are of toxic origin. (*b*) The cells from the *deep layer of the pelvis* of the kidney are merely small round cells (Fig. 39, *d*), usually about the size of the leucocyte, and having much the same appearance as the renal cells, although frequently not quite so dense. These cells are often arranged in clumps, and are always accompanied by pus which is both free and mixed with the cells in clumps. Deep pelvic cells are always found in cases of chronic pyelitis. (*c*) The cells from the *calices of the kidney* (Fig. 39, *e*) are only rarely found in the sediment. They belong to the class of small round cells, but are considerably larger than the deep pelvic cells. They are also somewhat larger than the cells from the straight tubules of the kidney, and are generally found in clumps, overlapping one another. These cells have large, round, prominent nuclei, and are less granular than the cells from the deeper layer of the pelvis. They are usually found in cases of acute pyelitis.

Ureteral Epithelium.—The author has had exceptional opportunities for the study of cells from the ureter in specimens obtained by the ureteral catheter. Epithelial cells from the ureter are of two forms (Fig. 39, *f*)—*i. e.*, (1) *small caudate cell*, which is somewhat larger and denser than the cell from the superficial layer of the pelvis of the kidney, also with a larger and more prominent nucleus and a somewhat larger tail; and (2) a *small spindle cell*, which is generally very narrow and with a small nucleus. These two forms of cells are usually quite granular and *small*, and

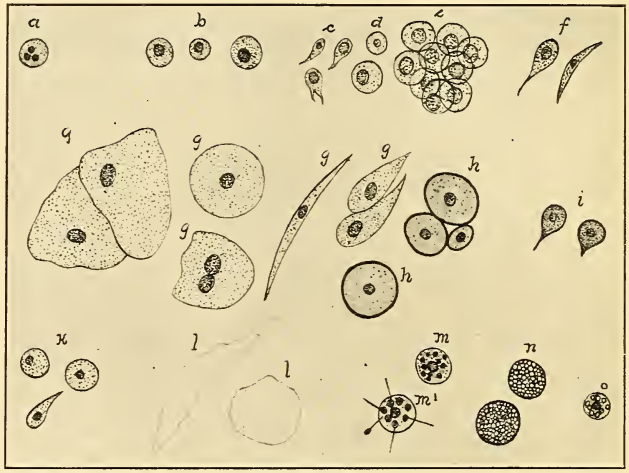


Fig. 39.—Epithelium from various parts of the urinary tract: *a*, Leucocyte (for comparison); *b*, renal cells; *c*, superficial pelvic cells; *d*, deep pelvic cells; *e*, cells from calices; *f*, cells from ureter; *g*, *g*, *g*, *g*, *g*, squamous epithelium from the bladder; *h*, *h*, neck-of-bladder cells; *i*, epithelium from prostatic urethra; *k*, urethral cells; *l*, *l*, scaly epithelium; *m*, *m'*, cells from seminal passages; *n*, compound granule cells; *o*, fatty renal cell.

should not be confounded with similar cells of larger size, which come from the bladder. The diagnosis of an inflammatory process in the ureter is generally not easily made from the urinary sediment, since the number of cellular elements from this membrane is often small, and the inflammatory condition is usually accompanied by either a pyelitis or a cystitis. In case there is marked irritation of the mucous membrane of the ureter by crystalline elements or small calculi, ureter cells may be found in large numbers, and the diagnosis more easily determined.

Bladder Epithelium.—The epithelial cells from the *fundus* of the bladder are, for the most part, of the squamous or pavement variety. They are large, flat, thin, polygonal cells (Fig. 39, *g*), having a distinct and usually a central nucleus, which is prominent without the aid of acetic acid. When arranged in groups, the cells are frequently found joined by their edges and not overlapping, although at times they are found overlapping to a slight extent. Squamous cells from the bladder are generally moderately granular, but may be entirely free from granules. Those cells that come from near the *openings of the ureters* are usually large, thin, and circular in shape. Epithelial cells from the *mouth* are not unlike those from the fundus of the bladder, but differ by having small nuclei and containing small particles of carbon. Cells from the mouth are generally clumped, and accompanied by a large amount of mucin in which they are entangled, and often by particles of food.

Epithelial cells from the *neck* of the bladder (in the male) are thicker, smaller, and much denser than those coming from the fundus. They are generally round or oval, and have a small, prominent nucleus. (Fig. 39, *h*.) They are usually not granular, and are from three to five times the size of a leucocyte. Cells from the neck of the bladder are often arranged in clumps of three or five, but are usually not found overlapping. An occasional cell from this region may be found in a perfectly healthy urine, but when found in excess with leucocytes, they indicate an irritation, and when mixed with pus, an inflammatory process at the neck of the bladder.

Prostatic Cells.—Epithelial cells from the prostatic ducts are small round cells, which are not unlike renal cells in size. They are usually less granular and somewhat denser than renal cells, and present a single distinct nucleus. They are often adherent to long shreds of mucin,—so-called "*prostatic casts*,"—and are generally accompanied by leucocytes and often by spermatozoa.

Seminal Cells.—These are cells from the seminal passages, and are medium round cells, which are highly granular, rather dense, and contain an ill-defined nucleus. (Fig. 39, *m*, *m'*.) Spermatozoa are often found within the body of the cell or projecting from it. These cells are invariably accompanied by free spermatozoa.

Urethral Cells.—Epithelial cells from the urethra vary

in shape according to the portion from which they come. Those from the *prostatic portion* are usually *dense*, pyriform, round, or irregular cells with a single distinct nucleus. (Fig. 39, *i*.) They are smaller than those from the neck of the bladder, and from one and one-half to twice the size of a leucocyte. They are usually not clumped unless entangled in shreds of mucin with pus, as is often the case in stricture of this portion of the urethra. Cells from the *pendulous portion* of the urethra are either small round or small caudate in shape (Fig. 39, *k*), but somewhat denser than renal and superficial pelvic cells, but not so dense as those from the prostatic urethra. These cells are most frequently seen in the discharge that results from a gonorrheal inflammation, and are usually intimately mixed with mucin and pus. The recognition of the cells from this portion of the urethra is of no great consequence, as the diagnosis of a urethritis is generally made by other means.

Vaginal Epithelium.—The urine of the female nearly always contains more or less epithelium from the genital tract—that is, the vaginal secretion, generally consisting chiefly of epithelium with a greater or smaller number of pus-corpuscles, is washed from the vulva and often causes a very abundant sediment. Vaginal epithelium consists chiefly of the squamous or pavement form, although many other varieties of cells are usually present, such as the spindle, large and medium round, large and small caudate, and irregular cells. These cells are mononuclear, and usually only slightly granular, and generally somewhat larger than the average sized bladder cell. Vaginal cells are often arranged in large clumps, and on careful focusing will be found to be overlapping, "like shingles on a roof," and often several layers in depth. Very often the so-called *scaly epithelial cell* (Fig. 39, *c*) is found, which represents the old epithelium from the vulva, and is a very thin, degenerated cell, containing only a remnant of a nucleus, if any nucleus at all. A urine holding a large amount of squamous epithelium and only a few leucocytes generally contains a vaginal secretion, which, in the majority of instances, is not abnormal.

Compound Granule Cells.—These are medium and large round cells that have undergone complete fatty degeneration. They are entirely filled with fat globules of varying size, and do not show a nucleus. (Fig. 39, *n*.) Com-

pound granule cells should not be mistaken for fatty renal cells, the former being always larger than the latter, and usually more completely degenerated. Not infrequently they have prismatic or long hair-like crystals of the fatty acids protruding from them. They may be found free in the sediment, or adherent to casts. Compound granule cells are the result of extensive fatty degeneration, and come not only from the urinary tract but from other mucous membranes as well, especially those that are chronically diseased. When of renal origin, they are found in the sediment during the fatty stage of an acute nephritis, also in subacute glomerular and chronic diffuse nephritis, and rarely in active hyperemia. They may be found in the sediment in chronic pyelitis, chronic cystitis, chronic prostatitis, and in urethritis ; also as a result of ulcerations in any part of the urinary tract, and often in large numbers in the contents of an abscess or cyst cavity that has evacuated into the urinary passages. They are sometimes found in vaginal secretions, and also in expectorated matter that has been introduced into the urine. Compound granule cells are, therefore, of no great practical importance unless found in the presence of, and adherent to, renal casts.

Renal Casts.—Renal casts, also termed "tube-casts" and "cylinders," are molds of the uriniferous tubules. They are produced by the admission into the tubules of a coagulable (?) substance, which there solidifies, and, entangling whatever it may have surrounded in its liquid state, subsequently contracts, and is forced from the renal tubules by the urine. It is then carried into the pelvis of the kidney, thence into the bladder, and voided with the urine.

The origin of renal casts has been the subject of much discussion and must still be considered an unsettled question.

Three theories have been advanced as to their probable nature and mode of formation :

(*a*) That they are composed of coagulable elements of the blood that have transuded into the renal tubules through pathologic lesions of the latter, and have there solidified, to be later voided with the urine as molds of the tubules.

(*b*) That they consist of a secretion of the pathologic epithelium lining the renal tubules, this secretion solidifying to form molds or tube-casts, which are forced out by the urine.

(*c*) That they are the direct result of the disintegration of the renal cells, whose products become formed into casts of the tubules in which they are formed, and being forced out by the urine make their appearance in the sediment.

The first theory (*a*) is the most plausible of the three; at least, it is applicable to the nature and mode of formation of most of the casts found in the urinary sediment.

Renal casts have been variously classified, but the simplest division is the following, which is based upon their microscopic appearance:

I. Hyaline (transparent) casts { (1) Pure hyaline. (2) Fibrinous. (3) Waxy.
II. Granular " { (1) Fine. (2) Coarse. (3) Brown.
III. Epithelial "
IV. Blood "
V. Fatty "
VI. Pus "
VII. Crystalline " { (1) Urate. (2) Oxalate. (3) Cystin.
VIII. Bacterial "
IX. "Mucous" (nucleo-albumin) casts, also termed *false casts.*

1. **Hyaline Casts.**—Hyaline[1] casts are of three varieties: (1) Pure hyaline, (2) fibrinous, and (3) waxy casts.

(*1*) *Pure hyaline casts* are pale, transparent, homogeneous cylinders, generally with rounded ends. (Fig. 40.) They may be short or very long, even extending through six or more fields of the microscope.[2] They are found of varying diameters, some narrow and others wide, but always presenting a cylindric appearance. Their sides are usually parallel and straight, but they may be indented, presenting a scalloped appearance. They are often twisted upon themselves, and not infrequently have a serpentine shape. One end of the cast may be ragged and irregular, showing that the original cylinder has been divided, and occasionally a

[1] The term hyaline is here used in the broad sense of transparent.

[2] Leitz microscope, No. 1 eye-piece and No. 7 objective.

segment is seen with both ends ragged. Pure hyaline casts are free from granules, and are therefore often very difficult to detect in the sediment. They are best discovered by reducing the amount of light entering the microscope, either by manipulating the mirror, or by interposing the hand between the source of light and the mirror, thus shading the microscopic field. As a rule, the casts of large diameter are somewhat more refracting, and thus more readily detected than the small narrow casts.

Not infrequently hyaline casts contain a few *very* fine granules of a pale color. They sometimes exhibit here and there upon their surfaces a renal cell or a blood globule or droplet of oil. Such casts are considered strictly of the

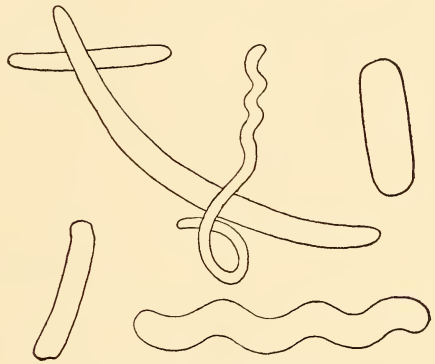


Fig. 40.—Pure hyaline casts.

hyaline order, and are referred to as hyaline casts with a renal cell or a blood globule or fat-drops adherent, as the case may be.

The narrow hyaline casts doubtless have their origin in the smaller undenuded tubules, while those of large diameter come chiefly from the large straight, or collecting tubules of the kidney. In advanced disease of the kidney, notably chronic interstitial nephritis, we find an exception to the rule—*i. e.*, the majority of the casts emanating from high up in the kidney are of large diameter, while those from the collecting tubules are *very* large. Such casts are from extensively denuded tubules, the result of the advanced disease.

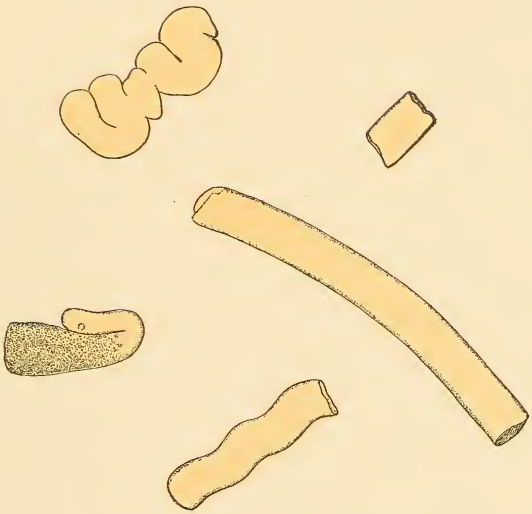
Hyaline casts are common to all diseases and disturbances of the kidney, and not pathognomonic of any one abnormal condition. They are, however, predominant in the sediment in cases of chronic interstitial, chronic diffuse nephritis, amyloid infiltration, and in passive hyperemia; while their relative proportion is much smaller in comparison with the other forms of casts present in active hyperemia, acute nephritis, and subacute glomerular nephritis.

(*2*) *Fibrinous Casts.*—These are very *dense or highly refractive casts*, usually of the transparent variety and *always of a yellowish color*, which ranges between a pale yellow and a deep brown. (Plate 8.)

Fibrinous casts are, however, sometimes granular, and often have renal epithelial cells and blood globules, and, not infrequently, oil-drops adherent. Like the pure hyaline casts, they are of various shapes and sizes, but being heavier and denser than the hyaline form, show a greater tendency to crack and break, thus becoming divided into rather short segments, the ends of which are usually thick and ragged. They are also frequently found of moderate length, with rounded ends; they are, as a rule, of larger diameter than the average hyaline cast found in the sediment. Fibrinous casts sometimes have so little color as to be distinguished with difficulty from the waxy cast that is always perfectly colorless. If any doubt exists in the mind of the observer as to their true character, the term "highly refractive casts" should be used, until, upon further study, the observer is convinced that they are fibrinous and not waxy casts. The bearing of this suggestion is seen in the following paragraph:

Fibrinous casts usually accompany blood in the sediment—in other words, are found in acute diseases or disturbances of the kidney, such as acute nephritis, and sometimes active hyperemia; also in acute exacerbations of either acute or chronic renal diseases. The fibrinous cast is simply one of the elements of an acute condition, and as this condition subsides, it disappears from the sediment. Fibrinous casts do not, therefore, indicate an unfavorable prognosis. Waxy casts, on the other hand, are practically unheard of in active hyperemia and acute nephritis, but are most often found in the sediment in the advanced forms of kidney disease, their presence being always an unfavorable prognostic sign.

Plate 8



Fibrinous Casts.

The term *fibrinous* as applied to these casts is inappropriate, as they do not consist of fibrin, nor do they have any relation to it, only resembling fibrin in their yellow or brownish color.

(*3*) *Waxy Casts.*—These, like the fibrinous casts, are *very highly refractive casts* of the transparent variety, and are *always perfectly colorless.* (Fig. 41.) They are usually of large diameter and often very long, and their surfaces may be marked by indentations showing imperfect vertical segmentations ; they often have a serpentine appearance. Not infrequently, waxy casts are coarsely granular, the granules apparently having the same composition as the cast itself. (Fig. 41.) They may have fat-drops, or fatty

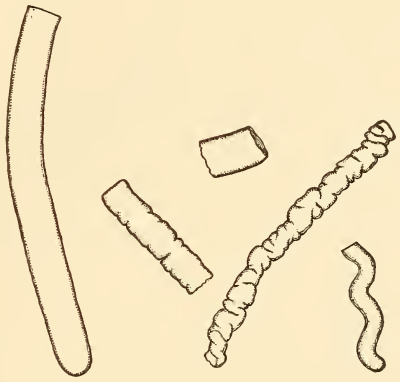


Fig. 41.—Waxy casts.

renal cells, or compound granule cells adherent to them. On account of their thickness and density, waxy casts are often found with cracks on their surfaces, also frequently found in segments, with one or both ends rough and irregular, showing that the long casts have become broken into several small pieces.

Waxy casts should, in all instances, be distinguished from fibrinous casts, since, as has already been explained, they have an entirely different significance.

Waxy casts are found in the sediment in the advanced stages of all chronic diseases of the kidney, such as chronic interstitial, chronic diffuse, and subacute (parenchymatous) nephritis. and are of bad omen, indicating that death will

probably occur within a comparatively short time, usually a year. This rule, however, is not invariable, as was well demonstrated by a case that the author observed for a period of over two years, in which waxy casts were constant, and, as was shown at the autopsy, there existed a marked chronic diffuse nephritis of the parenchymatous variety. Waxy casts are a frequent accompaniment of amyloid infiltration of the kidneys, in which they appear earlier than in other chronic renal diseases, and are of decided diagnostic value. They are of much less importance as a prognostic sign than in other chronic renal affections.

The term *waxy*, as applied to these casts, is a misnomer. It was formerly supposed that waxy casts were characteristic of amyloid infiltration of the kidneys, but, as has been shown, they are often found in other chronic diseases of the kidney. These casts rarely show the amyloid reaction with methyl-violet and with iodopotassic-iodide solution, even when amyloid disease of the kidneys is present.

The hyaline cast constitutes the basis or groundwork of all other casts to be described, each cast being named according to the elements adherent to or embedded in it. Thus, a cast covered with granules is called a *granular cast;* with epithelium, an *epithelial cast;* with blood, a *blood-cast*, etc.

II. Granular Casts.—These casts consist of a hyaline basis in which granules are embedded. Various terms are applied to these casts—*i. e.*, when covered with fine granules, *finely granular;* with coarse granules, *coarsely granular;* and when the granules are colored so as to give the cast a brown color, *brown granular*, etc. (Fig. 42.)

The granules found on these casts probably come from the renal tubules, and are the result of the degeneration and disintegration of the renal epithelium. At times, these granules appear to result partly from the destruction of blood-corpuscles and leucocytes. This is particularly the case in connection with the *brown granular* casts, which appear to derive their color from the blood pigment. Bile naturally stains granular casts yellow or it may give them a brown color. Brown granular casts nearly always accompany blood-casts.

Granular casts, like the hyaline forms, have a variety of shapes, and may be of small, medium, or large diameter. They are usually rather short and have rounded ends ; not

infrequently, however, fragments of granular casts are found with rough and irregular ends. They may have renal epithelium, blood globules, fat, or leucocytes adherent to their surfaces or embedded in them.

Finely granular casts are found in every disease or disturbance of the kidney; they, therefore, can not be considered pathognomonic of any one disease or class of diseases.

III. Epithelial Casts.—These are casts that are practically covered with renal epithelium. (Fig. 43, 1.) The renal cells may be embedded in, or firmly adherent to, either hyaline or granular casts. A hyaline cast that holds one, two, or three renal cells is best termed a *hyaline cast*

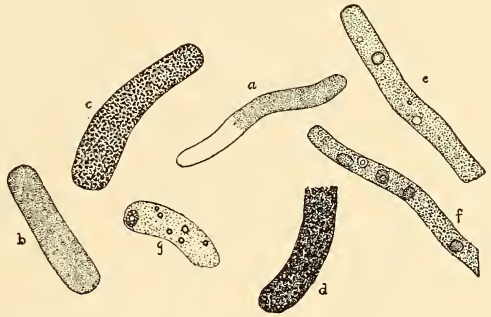


Fig. 42.—*a*, Hyaline and finely granular cast; *b*, finely granular cast; *c*, coarsely granular cast; *d*, brown granular cast; *e*, granular cast with normal and abnormal blood adherent; *f*, granular cast with renal cells adherent; *g*, granular cast with fat and a fatty renal cell adherent.

with a renal cell or cells adherent; the same applies to a granular cast. This term serves to distinguish such casts from those that are covered with renal cells and properly called epithelial casts. Renal cells on casts are usually more or less granular and swollen, and sometimes they are so firmly embedded in the cast that their outlines are ill defined. The nuclei of the cells often stand out prominently, although at times the cells are so granular as partially or entirely to obscure the nuclei. These cells may also contain fat globules. In an epithelial cast leucocytes are frequently found mixed with the epithelial cells; such a cast, which consists chiefly of epithelium, should not be mistaken for a true pus-cast.

Epithelial casts are most commonly found in those pathologic conditions that cause an exfoliation of the renal epithelium, such as severe active hyperemia, acute nephritis, and subacute glomerular nephritis. They are only rarely found in the urine of chronic interstitial nephritis and amyloid infiltration of the kidneys. In cases of extreme renal irritation and congestion the epithelial lining of the tubules is sometimes thrown off intact for short distances, an epithelial cylinder possessing a lumen resulting.

IV. Blood-casts.—These are of two kinds—*i. e.*, (*a*) a hyaline or granular cast, which is practically covered with blood globules; and (*b*) the cylinder, which consists of coagulated blood—fibrin with blood globules firmly embedded.

Blood-casts are found in the urine in those conditions in

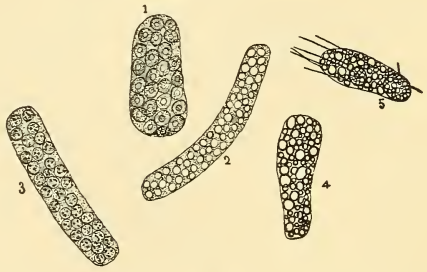


Fig. 43.—1, Epithelial cast; 2, blood-cast; 3, pus-cast; 4, fatty cast; 5, fatty cast with a compound granule and fatty renal cell adherent (crystals of the fatty acids protruding).

which there is more or less hemorrhage into the renal tubules. In the majority of instances the blood-cast is made up of *abnormal* blood (Fig. 43, 2), in which case the inference is that either the blood comes from high up in the kidney or the hemorrhage into the tubules is very slow. In casts of this kind the blood-corpuscles are unusually distinct, but, at times, indistinct, requiring careful focusing in order to make out the faint, deeply embedded globules. Not infrequently blood-casts consist of *normal* blood; under such circumstances the hemorrhage is usually either from the pyramidal portion of the kidney—straight tubules—or is very abundant and from higher up in the kidney. These normal blood-corpuscles, which still have their pale-yellow color, are often observed agglutinated,

at times forming a solid mass on the cast. Ordinarily, however, they are not so agglutinated but that the outlines of the individual corpuscles can be readily seen. Blood-casts are generally short, of medium diameter, and quite uniform throughout, usually having rounded ends. One portion of the cast may be hyaline or granular, and the remainder covered with blood.

Blood-casts are found in the urine in hematuria of renal origin, acute diffuse nephritis, acute renal congestion, and hemorrhagic infarctions of the kidneys. Blood-casts do not in themselves furnish positive evidence of organic renal disease, since any hemorrhage from the kidney may be associated with blood-casts in the urine. On the other hand, it may be stated that the presence of blood-casts constitutes the only positive evidence of the existence of renal hemorrhage.

V. Fatty Casts.—These are casts that are *thickly studded* with fat drops. (Fig. 43, 4.) It has already been stated that a hyaline or granular cast may have oil globules attached, but the term *fatty cast* only applies to those that are practically covered with fat. At times, fine needle- or hair-like crystals of the fatty acids are found protruding from these casts, and they may have fatty renal cells and compound granule cells embedded in or attached to them. (Fig. 43, 5.) Generally, the fat-drops are small and appear as glistening points; such should not be mistaken for the less highly refracting granules not fat. Sometimes the globules are large, when they are easily recognized. Fatty casts indicate that a fatty degeneration of the kidney is in progress, since the fat is probably the result of extreme degeneration of the renal cell protoplasm. They are not necessarily indicative of a chronic kidney disease, although most common in subacute glomerular (chronic parenchymatous) and chronic diffuse nephritis. They are also found during the fatty stage of an acute nephritis, and occasionally in severe renal congestion.

VI. Pus-casts.—Pus-casts are those that are covered with pus-corpuscles or leucocytes. (Fig. 43, 3.) The corpuscles are generally highly granular, and often so much so that their nuclei are entirely obscured. Under such circumstances, because of failure to make out the nuclei, casts that are covered with pus-corpuscles are often considered to be epithelial casts. Such inference should not be drawn without first thoroughly treating the sediment with dilute

acetic acid, which dissolves the granular matter, thus causing the nuclei of the leucocytes and the nucleus of the cell to stand out prominently.

Hyaline or granular casts with one, two, or three leucocytes adherent are frequently found in acute diseases and disturbances; also in acute exacerbations occurring during the course of a chronic disease of the kidneys. True pus-casts, on the other hand, are quite uncommon, and, when present, indicate a chronic suppurative process in some portion of the kidney. Pus-casts may be formed in case there is an abscess of the kidney or tuberculosis of this organ; also in cases of chronic pyelitis with extension into the straight tubules, in which instance they are usually of large diameter.

Bacterial Casts.—True casts when covered with bacteria have received the name "*bacterial casts.*" Accidental aggregations of bacteria that closely resemble renal casts in shape and size, and seen particularly in urines that have been exposed to the air for a long time, should not be mistaken for bacterial casts. True bacterial casts closely resemble the brown granular casts, and are distinguished from the latter by their resistance to certain chemicals, such as acetic acid, mineral acids, and strong alkalies. It is almost impossible to distinguish between them by means of the microscope, particularly if the bacteria belong to the class of micrococci as is usually the case. Bacterial casts are very uncommon, and are chiefly found in the septic forms of renal disease, especially those accompanied by embolism, and are therefore a grave prognostic sign. They are sometimes found in the ascending form of chronic pyelonephritis or "surgical kidney."

VII. Crystalline Casts.—These are of three kinds, and are named according to the form of crystal adherent to or embedded in them. Thus, a *urate cast* is one that is covered with crystals of ammonium urate, usually the hedgehog crystals; the *cystin cast*, covered with hexagonal crystals of cystin, as seen rarely in cases of cystinuria; and the *calcium oxalate cast*, covered with the octahedral, oval, or dumb-bell crystals of calcium oxalate. As a rule, crystalline casts show that the crystals deposited thereon were separated in the kidney, and therefore primary. Occasionally, crystals are deposited on casts secondarily—that is, after the urine has been voided.

False Casts.—False casts, also termed *mucin casts*, *shreds*, or *cylindroids*, are not infrequently found in the sediment. They are long, flat structures, usually with fine, wavy, longitudinal striations, and long tapering ends. (Fig. 44.) They are colorless, often twisted or folded, and usually free from adherent elements, although they may have cells, leucocytes, and blood globules adherent. False casts are usually longer than the true renal casts just described, and appear to be flat and not cylindric. It is probable that these structures consist only of coagulated nucleo-albumin or mucin, although the subject requires further investigation in order to determine their true nature. It is sufficient to say that they are, apparently, not true casts, that they are frequently present in a urine that is free from albumin, and that they are of little clinical importance.

False casts may originate in the kidney, but they are most commonly found in the sediment in connection with

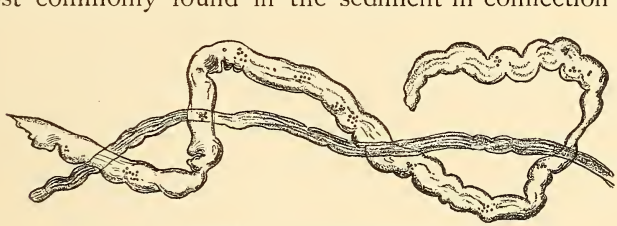


Fig. 44.—False casts or cylindroids (after von Jaksch).

irritation or inflammation of the lower urinary passages, particularly of the bladder, prostatic region, and urethra. They may be found in the prostatic ducts as a result of mild or severe inflammatory processes, when they are usually accompanied by a large number of mucin (nucleo-albumin) threads or shreds. It is often exceedingly difficult to distinguish these so-called *prostatic casts* from true renal casts; in fact, these two structures may exist in the same urinary sediment.

Prostatic Plugs.—These bodies, occasionally found in the urinary sediment, are evidently formed in the prostatic ducts. They appear to be cylindric, often with rounded ends, and are usually of large diameter, but may be of irregular shape, as from a dilated duct or cavity. They are either colorless or colored yellow, when they have much the appearance of fibrinous casts. Prostatic plugs usually have spermatozoa embedded in them, and, at times, leuco-

cytes or epithelial cells from the prostatic ducts are firmly adherent to them.

These bodies are found most commonly in mild inflammatory processes that involve the region of the neck of the bladder and the prostatic ducts.

Spermatozoa.—Spermatozoa are frequently found in the urine of healthy men. They are bodies about 50 μ in length, and consist of an oval head, or body, about 4.5 μ in length, to which is attached a long, tapering whip-like tail of extreme delicacy. (Fig. 45.) When freshly ejected, they exhibit active eel-like movements, strongly suggestive

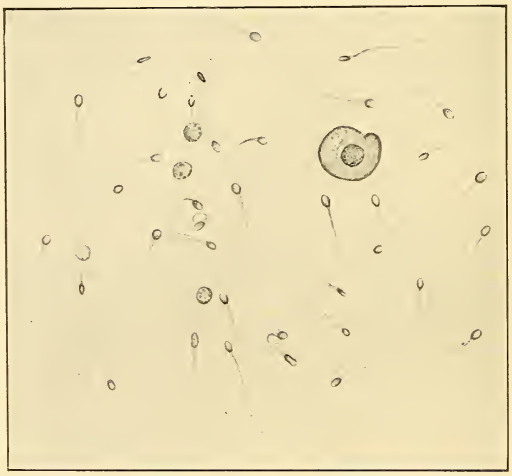


Fig. 45.—Spermatozoa.

of volition; but as seen in the urine they are always motionless. The cause of the movements in spermatozoa is unknown, although Roberts claims that they are floating cilia and resemble the oscillating sperm-cells of the antheridæ of mosses. Their movements are arrested by water, alcohol, ether, drying, etc. They resist putrefaction, and when once dried, may, after years, be restored to their original form by moistening them with a weak solution of sodium chloride or potassium acetate. Spermatozoa are often accompanied by medium-sized, highly granular cells (Fig. 39, *m*, *m'*); also by finely granular cells with one or more nuclei; more rarely, by lecithin corpuscles and spermatic crystals.

Clinical Significance.—A certain number of spermatozoa necessarily find their way into the urine of both sexes after coitus; also into the urine of men after involuntary nocturnal emissions. The persistent absence of spermatozoa from the seminal fluid indicates sterility. The recognition of spermatozoa is most important in connection with medicolegal cases—suspected rape. Their presence in vaginal secretion soon after coition and in stains upon linen is easy of demonstration. Spermatozoa are sometimes found in the urine in cases of severe acute febrile disease, such as typhoid fever, pneumonia, and acute septic conditions, also following convulsions. They are of frequent occurrence in cases of acute or chronic prostatitis or irritation in the prostatic region. The condition of spermatorrhea is characterized by the constant presence of spermatozoa in the urine.

Detection.—Spermatozoa are best detected by their characteristic appearance under the microscope. Florence,[1] of Lyons, has recently described a characteristic reaction that takes place between iodine-potassium iodide and seminal fluid, and which is probably dependent upon the presence of cholin.

Florence Reaction.—The reagent is prepared as follows:

Potassium iodide,	1.65 grams.
Iodine,	2.54 "
Distilled water,	30 "

The iodine-potassium iodide in this mixture corresponds to the formula KI_3.

A small portion of the suspected seminal fluid is treated with a drop of the foregoing reagent. If semen be present, small, dark, rhombic crystals appear, which are very similar in their general appearance to the hemin crystals obtained in Teichmann's test for blood.

Corpora Amylacea.—The so-called amyloid bodies, or corpora amylacea, have somewhat the appearance of starch granules, but they differ from starch in their chemic reactions. They are microscopic, spheroid, homogeneous, or lamellated bodies (Fig. 46), usually containing within them a core, which is also frequently lamellated and sometimes colored. They do not swell when soaked in hot

[1] Florence, "Du Sperme et des Taches de Sperme en Medécine Légale," 1897.

water, and are not split up by boiling with dilute mineral acids ; they are not dissolved by fuming nitric acid. Amyloid bodies are colored red by methyl-violet, while starch is colored blue. When the former are treated with iodine or iodine-potassium-iodide solution, they not infrequently show a violet to a blue color, which becomes distinctly blue by the subsequent action of sulphuric acid. These bodies seem to have no connection with amyloid infiltration, although they sometimes resemble its products. They may occur normally as well as under pathologic conditions, and are apparently of little clinical importance.

Corpora amylacea are frequently found in the acini of the prostate gland, from which they may find their way into the urine, sometimes in large numbers. They are also found in the ependyma of the ventricles of the brain and in

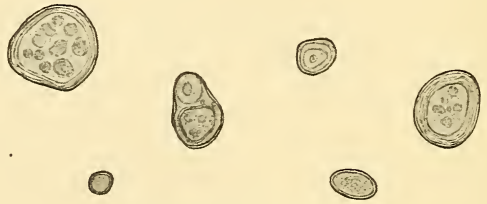


Fig. 46.—Corpora amylacea.

areas of sclerosis of the brain and cord ; also in extravasations of blood in various other situations. The amyloid bodies represented in figure 46 were found by the author in the urine of a man who, several days before, had had an extensive hemorrhage from the prostatic region. At the time these bodies were found, the urine was, however, free from blood. In the experience of the writer these so-called amyloid bodies are a rare constituent of the urinary sediment.

Amyloid Concretions.—These are frequently found in the prostate gland of old people. They are sometimes large enough to be detected with the naked eye, and are usually hard, and often have a dark color due to the deposition of pigment. (See Prostatic Concretions, p. 282.)

EXTRANEOUS SUBSTANCES FOUND IN URINE.

These are very numerous, and include, indeed, all substances that are liable to get into vessels containing the urine. The most common of these are fibers of cotton and linen, hair of blankets, worsted, wool, human hair, cats' hair, splinters of wood, oil globules, starch granules, lycopodium and other pollen, tea leaves, bread crumbs, particles of glass, dust, etc. It is a common custom with some persons to expectorate into the vessel that is to contain the urine or into the urine after it has been voided, hence pavement epithelium containing pigment granules, particles of food, free oil, etc., will be found. It is very important that the student should become familiar with the microscopic appearances of all these extraneous elements before he begins the examination of urinary sediments.

PRESERVATION OF URINARY SEDIMENTS.

In order to preserve urinary sediments it is necessary to treat the urine and its sediment in such a way as to prevent subsequent changes, of which the most common are ammoniacal decomposition and the formation of vegetable growths. To accomplish this end, the coloring-matters and the salts of the urine must be removed by washing with those media that will take up the soluble urinary constituents and, at the same time, leave the sediment—cells, casts, crystals, etc.—in the same condition as found in the fresh urine.

Epithelial cells, *renal casts*, *blood*, *pus*, *fat*, *and fibrin*, are best preserved in the following manner: Allow the urine to settle thoroughly in a urine glass, or centrifugalize, and wash by decantation twice with a saturated aqueous solution (4 per cent.) of boric acid, and then three times with an aqueous solution of potassium acetate (specific gravity, 1030) containing ¼ of 1 per cent. of formalin. The sediment is left in the last washing of potassium acetate and formalin, and is then placed in a *tightly stoppered* bottle, where it will keep for months and years. By this process the sediment suffers very little, if any, change, excepting that any blood that was originally in the sediment as *normal* blood will be changed to *abnormal* blood.

Crystalline sediments on account of their solubility in the media already given require different treatment, the pre-

servative used varying with the form of crystal to be preserved.

Uric acid, *calcium oxalate*, *hippuric acid*, *cystin*, and *cholesterin* crystals should be washed, by decantation, several times with a *small* volume of very dilute acetic acid (1 to 2 per cent.); finally, after all of the soluble urinary salts have been removed, they are left in the last washing, which is then placed in a perfectly clean, tightly stoppered bottle.

Acid ammonium urate and acid sodium urate crystals should be washed, by decantation, several times with a small volume of 33 per cent. alcohol, and, after all of the soluble urinary salts have been removed, left in the last washing, and then placed in a clean, tightly stoppered bottle.

Triple phosphate and acid calcium phosphate crystals should be washed, by decantation, several times with a *small* volume of very dilute ammonic hydrate (1 to 2 per cent.); finally they are left in the last washing, and placed in a clean, well-stoppered bottle.

Some of these crystals, such as the oval and dumb-bell forms of calcium oxalate, cystin, triple phosphate, and acid calcium phosphate, frequently undergo partial solution in their respective media, particularly when kept in the bottle for several months or years. All crystalline sediments keep better when mounted on glass slides; it is, therefore, advisable to mount them as soon as possible after washing.

The washing can be done by the centrifugal or the gravity methods, the former having the advantage of completing the washing in a few hours and before bacteria or other foreign substances enter the fluid.

The Mounting of Urinary Sediments.—After the sediments have been prepared in the manner described they can be mounted on glass slides, and thus preserved for years.

Method.—Place a glass slide on a turn-table and make a cell by the use of Bell's cement and a camel's-hair brush. Allow the cement to dry thoroughly. Place a drop of the prepared sediment within the cell, and cover with a circular cover-glass of such a size that its margin rests well on the ring of cement. Take up the excess of fluid from around the cover-glass by means of a piece of filter-paper, care being taken not to admit air to the cell, and also to remove all air-bubbles that may be present. Return the slide to the turn-table, and carefully cover the margin of the cover with the

cement so as to make the cell air-tight. Allow this layer of cement to dry, and in two or three days apply another coat. Mounts prepared in this manner will in most instances keep several years, and are very useful for purposes of demonstration or for reference.

MICRO-ORGANISMS.

The micro-organisms that are found in the urine belong to the following different classes : *Bacteria* (nonpathogenic and pathogenic), *molds*, and *yeasts*, all of which properly belong to one general class called *fungi*.

Fresh normal urine is free from bacteria or other micro-organisms, and, as has been repeatedly demonstrated, is a sterile fluid. Numerous investigations have shown that bacteria are usually, if not always, present in the urethra of both the male and female, particularly near the meatus ; therefore urine that was sterile *intra vesicam* becomes contaminated as it passes through the urethra.

Bacteria, being vegetable in their nature, belong to the class of fungi, and for purposes of study are more conveniently divided into two classes : (*a*) *nonpathogenic* or those that are innocuous, and (*b*) *pathogenic forms* or those that are pyogenic in their nature.

(a) **Nonpathogenic Forms.**—As already stated, fresh normal urine is free from bacteria, but when such urine is allowed to stand exposed to the air for some time, it soon becomes crowded with micro-organisms of various kinds, rendering the urine turbid and, for the most part, unfit for a satisfactory examination.

The microscopic appearance of fermenting normal urine is subject to much variation. The conversion of urea into ammonium carbonate is probably effected through the agency of several forms of micro-organisms (Leube, C. Flügge, v. Jaksch, v. Limbeck), of which the *micrococcus ureæ* (Fig. 47) is the most prominent, and at times may be seen in almost pure culture upon the surface of the decomposing fluid. These micrococci form in long chain-like series, although they may occur as free, round, highly refracting dots ; they are usually of comparatively large size, and are constant inhabitants of the air. Of the other micro-organisms that have a part in the decomposition of urea, the *staphylococcus ureæ candidus* and *staphylococcus ureæ lique-*

faciens (Lundstrom), *bacillus ureæ* (Leube), *urobacillus Freudenreichii*, and the *urobacillus Maddoxii* should also be mentioned. It is claimed that the urobacillus Maddoxii is the micro-organism that renders the urine viscid and stringy. A number of other bacteria have been isolated from decomposing urine, but little is yet known of their importance. Occasionally, long spiral bacilli with large

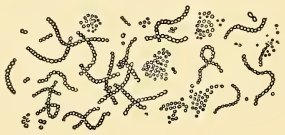


Fig. 47.—Micrococcus ureæ (after v. Jaksch).

spores, and cocci that group themselves in globular masses of varying sizes are met with in the urine.

Molds are, under normal circumstances, a very rare manifestation in decomposing urine. In diabetic urine, however, they not infrequently make their appearance, especially after the alcoholic fermentation has ceased. They are then found floating in a layer on the surface of the urine. The urine is at the same time more or less turbid with bacteria and yeast fungi.

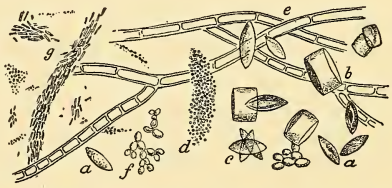


Fig. 48.—Sediment from fermenting diabetic urine with casts of micrococci: *a*, *b*, *c*, Various forms of uric acid; *d*, micrococci in form of casts; *e*, molds; *f*, yeast fungi; *g*, bacilli and micrococci (after v. Jaksch).

The *yeast fungus* of the urine (saccharomyces urinæ) consists, in the sporule stage, of transparent oval cells, which are seen both singly and in rows of two, three, or more. (Fig. 48, *f*.) They are found in saccharine urine, and are identical with the yeast fungus (saccharomyces cerevisiæ). They grow in acid urine, but cease to multiply as soon as the urine becomes alkaline.

Yeast spores are distinguished from *normal blood-corpuscles* by the fact that the former are smaller, perfectly colorless, and have usually a focal point. They differ from *abnormal blood-corpuscles* in having an oval shape, a focal point seen especially in the larger sporules, and a cell-body, the abnormal blood globule appearing simply as a ring —that is, apparently without a cell-body. (Compare p. 233.)

The presence of the yeast fungus in the urine is always suggestive of the presence of sugar, but in the experience of the writer this rule is by no means invariable. It occasionally happens that the urine to be examined has been placed in a bottle containing a mere trace of syrup; in such a urine the yeast fungus grows rapidly.

Penicillium glaucum is not infrequently met with in acid urine with or without sugar or albumin. The sporule stage furnishes cells very similar to those of the yeast fungus, but later the penicillium multiplies by linear division of cells, forming threads that have a characteristic appearance.

The *sarcina urinæ* is a fungus only occasionally seen in the urine. It is smaller than that which forms in the stomach (sarcina ventriculi), being in point of size comparable to the sarcina of the lung. They are cubes, each group of eight cells being so arranged as to resemble a "bale of goods."

(b) **Pathogenic Forms.**—The pathogenic micro-organisms found in the urine may be divided into two classes—*i. e.*, *micrococci* and *bacilli*. Of the *micrococci* the *streptococcus pyogenes*, the *staphylococcus pyogenes albus*, *citreus*, and *aureus*, and the *gonococcus of Neisser* are the most important. The most common bacilli found in the urine are the *bacillus coli communis*, the *urobacillus liquefaciens septicus*, and the *tubercle bacillus*.

When recently voided urine is found to contain pathogenic micro-organisms, the condition becomes serious on account of the marked tendency to decomposition of the urine within the bladder. These micro-organisms occur in the freshly voided urine in connection with certain specific diseases, such as *typhoid fever*, *erysipelas*, *relapsing fever*, *ulcerative endocarditis*, *glanders*, *malignant pustule* (bacillus of anthrax), *septic processes*, and *tuberculosis*. The spirilla of relapsing fever occur very rarely and only when hemorrhage takes place in the kidney during an exacerbation (v.

Jaksch). According to Horton-Smith,[1] the freshly voided urine of typhoid fever is usually turbid from the presence of the typhoid bacilli. Richardson [2] has recently shown that the virulence of these bacilli is destroyed by the ingestion of urotropin (a formaldehyde compound). Actinomyces may also occur in the urine in instances in which the genito-urinary tract is infested with it, or in those cases in which it enters this tract from other parts (Braatz). Lustgarten and Mannaberg have found cocci in the urine in acute nephritis; and Letzerich has found bacilli in the "primary nephritis" of children. Mircoli also determined the presence of pneumococci-like forms in the urine of children suffering from acute nephritis. Schweiger has demonstrated that in scarlet fever the urine is distinctly contagious; and he claims that all renal lesions arising in the course of infectious fevers are caused by micro-organisms.

In recent years the recognition of the *tubercle bacillus* in the urine or urinary sediment has been attended with great pathologic interest. A detailed consideration of this subject, together with the method best adapted to the detection of tubercle bacilli, will be found on page 325. It is of great importance to differentiate the tubercle bacillus from the *smegma bacillus*, which is frequently present in the urine.

Gonococci consist of diminutive kidney-shaped cocci aggregated in large groups. They are, for the most part, diplococci with the flattened surfaces of the kidney-shaped cocci presenting to each other. They are often found in abundance in the gonorrheal discharge from the urethra, within the pus-corpuscles and exfoliated epithelial cells, as well as free in the shreds of mucin. It has been satisfactorily demonstrated that diplococci, in all respects resembling gonococci, exist in the genital tract. It is, therefore, exceedingly important from a diagnostic point of view to distinguish the gonococci from those that closely resemble them. This is best accomplished in the following way: First, stain a preparation with Loeffler's solution of methylene-blue. If the characteristic groups of diplococci are found in the cells and pus-corpuscles, then stain a new preparation by *Gram's method*, as follows: (1) Cover the preparation with aniline-gentian-violet solution (without

[1] "Transactions of the Medical and Surgical Society," London.

[2] "The Journal of Experimental Medicine," vol. IV, No. 1, 1899.

heat) for thirty seconds; (2) wash in water for two or three seconds; (3) cover the preparation with Gram's solution of iodine (iodine, 1 part; potassium iodide, 2 parts; water, 250 parts) for thirty seconds; (4) wash with 95 per cent. alcohol until the color ceases to come out of the preparation; (5) wash in water for two or three seconds; (6) counterstain with saturated aqueous solution of Bismarck brown ten seconds; (7) wash in water, mount, and examine. Gonococci are stained brown, while other diplococci are stained blue by this method.

PARASITES.

Filaria Sanguinis Hominis.—This is the parasite that causes the condition of *chyluria.* This parasite was first dis-

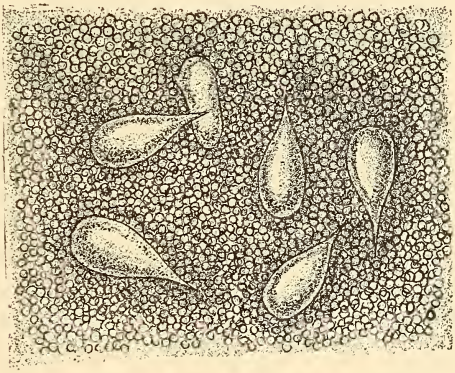


Fig. 49.—Eggs of distoma hæmatobium in sediment (after v. Jaksch).

covered and described by Lewis, of Calcutta, who found them in large numbers in the urine and blood of persons who were passing milky or chylous urine.[1]

Distoma Hæmatobium.—The eggs of this parasite are often found both in the urinary passages and in the urine of inhabitants of tropical climates. This worm infests the north and east coasts of Africa, and, according to Brock, is found also in South Africa. The eggs are oval, slender bodies, about 0.12 mm. long and 0.04 mm. broad, and furnished with a small spike, which projects from the ex-

[1] A detailed account of this parasite, together with an illustration of the same, will be found under the subject of Chyluria, p. 362.

tremity or from the side. (Fig. 49.) Both the male and female parasites have been found in the branches of the portal vein, the splenic vein, the vesical plexus, etc., and are nourished by the blood. The male is from 12 to 14 mm. long, and the female is from 16 to 20 mm., and nearly cylindric in shape. (Fig. 50.) In case the individual is infested with this parasite the most prominent symptom is

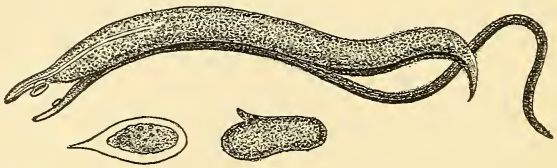


Fig. 50.—Distoma hæmatobium; male and female, with eggs (after v. Jaksch).

severe burning pain during micturition. The pain is usually momentary, and caused by the passage of the eggs along the urethra, which they irritate by their sharp angles. The urine usually contains blood- and pus-corpuscles, with eggs of the parasite, and sometimes a considerable quantity of fat. There are often marked cystitis, pyelitis, sometimes nephritis, and septic processes.

Echinococci.—Echinococcus cysts have been found in

Fig. 51.—Echinococcus scolices and hooklets (after Heller).

the kidney, although rarely. Usually, only one kidney is affected. The hydatid growth is made up of an outer capsule, within which the mother cysts are found. Within the mother cysts are the daughter cysts. Both the large mother cysts and the smaller daughter cysts float freely in the liquid contents of the capsules holding them. This peculiar growth is caused by a very small tapeworm,—the

tænia echinococcus,—whose natural size is about that of a millet seed. (Fig. 52.) This worm consists of a head much like that of the ordinary tapeworm, four mouths or suckers, and a double row of hooklets.

The scolices and hooklets (Fig. 51) occasionally find their way into the urine, either from the cysts in the kidney or from some neighboring organ, as the result of rupture. The hooklets are usually accompanied by more or less blood, leucocytes, and at times shreds of membrane forming the hydatid cyst. The diagnosis of echinococcus growth of the kidney is only made with certainty by finding characteristic hooklets in the urinary sediment.

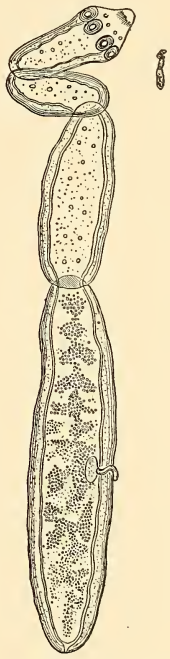


Fig. 52.—Tænia echinococcus, enlarged. Above, at the right, echinococcus of natural size (after Heller).

Hydatid disease of the kidney in man is most commonly contracted from the dog, whose intestinal tract is often infested with large numbers of echinococci. The eggs that are passed with the stools find their way into the food, thence to the stomach of man; as the embryo hatches it enters the blood, is carried to the liver or kidneys, where it forms the hydatid cyst. This disease is most common in the arctic regions, where the natives live with their dogs, and it is said that in Iceland approximately one-seventh of the mortality is due to hydatid disease.

Eustrongylus Gigas.—The presence of this parasite in the urine is a very rare occurrence. According to the researches of Leuckart,[1] the existence of this parasite in man is a matter of some doubt.

Ascarides.—In rare instances ascarides have been found in the urinary passages. Their presence in the urine is usually explained by an abnormal communication between the intestine and the urinary tract. Scheiber[2] reports having found in the urine of a woman worms that he considered had been derived from the genital organs, and he has named them *rhabditis genitalis*.

[1] Leuckart, "Deutsche med. Wochenschr.," XIII, S. 390.
[2] Scheiber, "Virchow's Archiv," LXXXII, 161, 1884.

CHAPTER VII.

URINARY CONCRETIONS.

Urinary concretions or calculi consist of an aggregation of solid matter that has become separated or precipitated from the urine. They may form in any part of the urinary tract, from the tubules of the kidney to the meatus urinarius. They vary very much in their composition, but invariably consist of certain constituents of the urine—either normal or pathologic—that have separated or become precipitated from it. The nucleus may, however, consist of a foreign body that has been introduced into the urinary passages, or of certain substances that have their nativity in the body, such as mucous or blood coagula, or fragments of morbid tissue that have become detached. Of the foreign substances that have been found to form the nucleus of urinary calculi may be mentioned peas or beans that have been introduced into the urethra by the insane or by children, pieces of catheters or bougies that have been accidentally broken off in the urethra or bladder, pieces of soap or candles, hairpins, pins, needles, and bullets that have lodged in some portion of the urinary tract. From this it is seen that the nucleus of a urinary calculus may be any substance that has its origin in the body and that exists in solid form in the urinary passages, or a foreign body that may have been accidentally or intentionally introduced into them.

The conditions of the urine favoring the growth of calculi are variable. Among the causes may be mentioned (1) a diminution in the amount of water excreted; (2) a change in the reaction of the urine, whether abnormally acid or alkaline; (3) an increased formation of some of the less easily soluble constituents of the urine. Changes in the

reaction embrace hyperacidity, which favors the deposition of uric acid and urates and of calcium oxalate by diminishing the solvent action of the urine over these substances; and an alkaline condition of the urine, which causes the separation of the phosphates and carbonates of calcium and magnesium and of ammonium urate. The chief effect of an increased acidity of the urine is to lessen the solubility of the uric acid by diminishing the amount of alkali with which it may enter into combination. Uric acid is usually present in the urine in solution in the form of normal urate of sodium or potassium, which is very soluble in water. In case the uric acid is deprived of a part or the whole of its base, either the acid urate of potassium or sodium or uric acid is the result. These substances, being much less soluble in water than the normal urates, separate from the urine, and tend to become aggregated in the form of concretions. An alkaline reaction of the urine may be due to the presence of either a fixed alkali or to free ammonia and ammonium carbonate. It rarely happens that a calculus forms as a result of a deposition of the earthy phosphates by a fixed alkali, as is well demonstrated in those cases in which alkaline remedies are given for a long time, as in the treatment of acute rheumatism, and also in those cases in which the urine is habitually alkaline, as in some cases of faulty metabolism.

Of much greater importance is an ammoniacal reaction that frequently results in a calculus formation by the deposition of triple phosphate, amorphous phosphates, and ammonium urate. (See Reaction, p. 31.) Concretions from this cause are quite commonly met with in cases of irritation or inflammation of the bladder, the change from a normally acid to an alkaline reaction being due to the presence of the urea ferment that decomposes the urea. A deposit of phosphates always tends to increase the size of any calculi that may already exist.

A diminution in the amount of water excreted, particularly when coupled with an increased formation of any of the slightly soluble constituents of the urine, such as uric acid and acid urates, calcium oxalate, cystin, and very rarely xanthin, favors the tendency to the formation of concretions within the urinary passages, since these substances do not find a sufficient amount of urine to hold them in solution.

CONSTITUENTS OF URINARY CALCULI.

These are either organic or inorganic or a mixture of the two. They are conveniently divided into two classes, as follows: (1) *Primary constituents*, or those which separate from the urine without any material change in the character of the urine, other than changes referable to altered metabolism; and (2) *secondary constituents*, or those which separate from the urine as a result of ammoniacal fermentation.

Primary Constituents.	*Secondary Constituents.*
Uric acid and urates of sodium. ammonium. potassium. calcium. magnesium.	Calcium phosphate.
Calcium oxalate.	Calcium carbonate.
Calcium phosphate, both crystalline and amorphous.	Ammonio-magnesium phosphate (triple phosphate).
Calcium carbonate.	Ammonium urate.
Cystin.	
Xanthin.	
Indigo.	
Urostealith (Heller).	
Silica.	
Albuminous substances (blood, pus, etc.).	
Bilirubin (hematoidin).	

Urate of ammonium, calcic carbonate, and calcic phosphate may, therefore, be either primary or secondary constituents.

Urinary concretions are most commonly found in the pelvis of the kidney and in the bladder, but they may form in any part of the urinary tract. In the Warren Museum at the Harvard Medical School is a rare specimen showing a number of medium-sized concretions in the pelves of both kidneys and in both ureters, also a large calculus in the bladder. Calculi are also sometimes formed in sinuses connecting the urinary passages with the intestines, uterus, or vagina.

The *number* of concretions that may be present in the urinary passages is almost unlimited; often there is only a single stone, but there may be several hundreds.

Urinary concretions vary in size from that of a pinhead to that of an orange or even larger. Those of small size

have been somewhat arbitrarily termed *sand* or *gravel*, while those of large size are called stones or calculi. The size of a calculus is limited only by the dimension of the cavity in which it is formed. The smaller concretions usually emanate from the kidney or pelvis of the kidney, while those of large size generally come from the bladder. Concretions vary in weight from a few milligrams to several grams; in the Dupuytren Museum, at Paris, is a calculus weighing 1596 grams.

The *surface* of a urinary calculus varies with its composition and its location in the urinary tract. Those consisting of uric acid, phosphates, and cystin are usually smooth, while those made up of calcium oxalate are generally rough and lobulated—*mulberry calculi.* In case several concretions occupy a single cavity—for example, the bladder—their surfaces are often polished in those portions that rub against each other during the natural movements of the bladder wall or during the changes in position of the body. The smooth or polished surfaces are termed *facets.*

The *shape* of urinary calculi varies as the location. Those in the kidney proper are generally very irregular; they often have small projections that have extended into cavities formed by the destruction of the renal tissue. Calculi in the pelvis of the kidney when large usually assume the form of that cavity, projections taking place into the calices, and giving the calculus in some cases a shape not unlike that of an elephant; small concretions in the pelvis are generally round or oval. Calculi in the bladder vary greatly in shape. If only a single concretion be present, it is usually round, oval, or sometimes flat. If numerous calculi are present, their form may be modified by constant pressure against each other. Occasionally, a calculus becomes partially encysted in the bladder, so that the deposit takes place only upon one portion, thereby causing the growth of the calculus to take place in one direction only, and giving it a very irregular shape. Those that have formed in the urethra are generally oblong or cylindric in shape, and when there are several, the ends of those that are adjacent are often highly polished.

The *color* of calculi varies with their composition and the admixture of organic subtsances such as blood, pus, fibrin, etc. Those consisting of uric acid and urates are always colored, varying between a pale straw and a dark brown,

the coloring-matter being derived chiefly from the urine. Calculi consisting of calcium oxalate are often of a dark-brown color due chiefly to the presence of decomposed blood and of fibrin. Phosphatic calculi are generally grayish or white, while those made up of cystin are usually yellow in color.

The composition of urinary calculi may be *simple*, consisting of only one constituent of the urine, such as uric acid or calcium oxalate, or it may be *compound*, with two or more primary deposits occurring in separate and alternate layers, the most common of these constituents being uric acid and calcium oxalate. Several of the constituents may be mixed in any portion of the stone. It is not uncommon to find a calculus with a central portion composed of alternate layers of two or more of the primary constituents and an outer layer of some one of the secondary constituents.

Most urinary calculi consist of three distinct parts—*i. e.*, the nucleus; the body; and the crust. The *nucleus* occupies the center and may have the same composition as the rest of the concretion, but it often consists of some albuminous body, such as a coagulum of fibrin, or mucus or pus mixed with uric acid, urate, or calcium oxalate crystals about which are deposited other similar or perhaps entirely different urinary constituents. A concretion may have several nuclei, as, for example, when two or more small calculi become united to form a single stone; these nuclei are readily seen when a section is made through the calculus. The nucleus varies much in size and usually occupies the center of the concretion, but it may be excentrically placed especially if the growth of the calculus is only in one direction.

The *body* comprises the greater part of the calculus and surrounds the nucleus; it may or may not have the same composition as the nucleus. The body may consist of concentric layers of two or more urinary constituents, such as a layer of uric acid and urates, another of calcium oxalate, and so on for several layers. The several layers of the body may be differently colored; even those having the same composition may be variously colored.

The *crust* or external envelop of the calculus is deposited upon the body, and always consists of one or more of the secondary constituents of the urine, the phosphates usually predominating; in other words, the crust is always found

after ammoniacal fermentation of the urine has taken place, and it usually forms upon vesical calculi. Concretions that have formed in an acid urine do not, therefore, have a crust. Calculi that have smooth surfaces like the uric acid and urate may not have a crust formation even when present in an ammoniacal urine, but calculi consisting of calcium oxalate, on account of their rough surfaces, usually have a crust formation and sometimes the deposit begins while they are quite small. As a rule, the time required for the beginning of formation of a crust depends largely upon the time necessary for the calculus to produce a cystitis.

URIC ACID AND URATE CONCRETIONS.

Calculi consisting partly or entirely of uric acid and urates comprise the great majority of concretions found in the urinary tract. They are very common as renal calculi in children, especially those consisting chiefly of ammonium urate. They are generally smooth, oval, or round and of a yellow or brown color. When such concretions are formed in the kidney or pelvis of the kidney, they may be washed out with the urine singly or in numbers, and are then found to vary in size from a pinhead to that of a kernel of wheat, or to that of a pea. Their passage down the ureter is accompanied by more or less pain, so acute at times as to cause the symptoms of *renal colic*. If these small concretions are retained in the bladder, they usually grow more or less rapidly, and then instead of being perfectly smooth are often irregular, and vary in weight from a few grains to several ounces. When uric acid and urate concretions are forming, the urine is usually found to be concentrated, highly colored, of strongly acid reaction, and of high specific gravity. The sediment generally contains crystals of uric acid or the hedgehog forms of acid ammonium urate, or the stellate groups of sodium urate; there is usually also evidence of more or less irritation of the kidneys and frequently signs of mechanical irritation of the bladder that has been set up by the crystalline elements.

Concretions that consist chiefly of urates do not usually attain the large size of the mixed uric acid and urate calculi, rarely being found larger than an average sized marble. They are usually lighter in color and not so hard as the

mixed concretions. When some of the powdered calculus is heated on platinum foil, it chars and completely disappears if uric acid or ammonium urate be the only constituent; but if sodium urate be present, there remains a residue that is soluble in water and has an alkaline reaction (carbonate of the alkali).

CALCIUM OXALATE CONCRETIONS.

These are met with most often as medium or large, dark brown, rough, trabeculated bodies having a mulberry-like surface, hence the name "*mulberry calculi*." They are very hard and can be crushed only with difficulty. Calcium oxalate concretions are composed chiefly of calcium oxalate which is mixed with more or less organic matter. Occasionally the body of the calculus consists of alternating layers of calcium oxalate and uric acid. The nucleus often consists of uric acid and urates, or a coagulum of blood or mucus; it may, however, be made up entirely of calcium oxalate. As previously stated, calcium oxalate concretions are very apt to have a crust consisting chiefly of phosphates.

The characteristics of the urine from which oxalate concretions are being deposited are very much the same as when uric acid and urate concretions are forming. The sediment will contain crystals of calcium oxalate and evidences of a more or less marked irritation of the kidneys and bladder. If the stone is forming in the bladder, a typical chronic cystitis may exist. When some of the powdered calculus is heated on platinum foil, it chars slightly, on account of the organic matter that is mixed with it; there remains a white residue of calcium oxide or calcium carbonate, according to the amount of heat used. If the former, it will be found to be only slightly soluble in a drop of water, which will have an alkaline reaction; if the latter, it will dissolve with effervescence in a drop of acetic acid.

PHOSPHATIC CONCRETIONS.

These always form in neutral or alkaline (ammoniacal) urine and originate chiefly in the bladder. They are usually

white or of a grayish color, quite soft and easily crushed. They are often covered on their surface with bright, glistening points representing large crystals of triple phosphate. The surface may be smooth or rough; if it is smooth it frequently has the feeling of chalk. Phosphatic concretions having a grayish color are usually harder than the white or chalky calculi. The former consist chiefly of calcium phosphate, while the latter are composed chiefly of triple phosphate. Concretions that consist solely of calcium phosphate, or triple phosphate are very uncommon, the mixed phosphatic calculus being the one met with most frequently.

If some of the powdered calculus be heated on platinum foil it does not char or burn, but a bulky residue remains which dissolves in acetic acid without effervescence, as does the original powder.

CALCIUM CARBONATE CONCRETIONS.

Concretions composed of calcium carbonate are very rare in man, very few cases having been reported. They are not uncommon in the herbivora. They are usually small, of a grayish color, of smooth surface and very hard. Calcium carbonate concretions are generally spherical in shape, and on section they present concentric lines. When some of the original powder is treated with a drop of acetic acid it dissolves with effervescence; when the powder is heated on platinum foil to a white heat it is converted into calcium oxide, which is but slightly soluble in a drop of water, the solution having an alkaline reaction.

CYSTIN CONCRETIONS.

These are among the rarer forms of calculi. They are quite soft and of a pale-yellow color. As a rule, they are oval or cylindric in shape with a rough—finely granular—surface. They may form in the kidneys or bladder, the latter location being perhaps the more common.

Cystin calculi when taken from the body usually have a yellow color not unlike beeswax, but after being exposed

to the light for a long period the color changes to a green. They are generally of light weight and vary much in size.

Probably the largest cystin calculus in existence is the one reported by Dr. E. S. Wood.[1] It was removed from the bladder by Dr. J. C. Warren, and weighed, after drying, 101.883 grams. It was in the form of a flattened oval, and measured $2\frac{5}{8} \times 2\frac{3}{8} \times 1\frac{3}{8}$ inches.

Upon section they are found to be crystalline and present a radiating appearance. When some of the powdered calculus is heated on platinum foil it burns with a blue flame, and the odor of burning sulphur is evolved; no residue remains after ignition. Cystin is recognized by its solubility in alkaline hydrates and in strong acids, also by its insolubility in acetic acid. If some of the powder be treated with a drop of ammonic hydrate on a glass slide, it will dissolve; and if the mixture be allowed to stand until the ammonia has escaped, the residue will be found to consist of the colorless hexagonal crystals of cystin.

XANTHIN CONCRETIONS.

These are very rare, being probably the rarest of all of the urinary calculi. They may consist entirely of xanthin, or the xanthin may be mixed with uric acid and urates. The cases of xanthin calculi thus far reported have occurred in children. Xanthin concretions vary in color from a white or pale yellow to a brown, and they range in size from a bean to a hen's egg.

When some of the powdered calculus is heated on platinum foil, it chars and entirely disappears; in this respect it resembles uric acid. But xanthin can readily be distinguished from uric acid by a modification of the murexide test (see p. 66). If some of the powdered calculus be treated with a drop of nitric acid on a porcelain surface and evaporated to dryness, and the residue treated with a drop of potassic hydrate, a pinkish tint appears which, if xanthin be present, deepens to a violet on warming. Uric acid gives a violet with potassic hydrate, the color disappearing on warming.

[1] "Journ. Boston Soc. Med. Sciences," Feb., 1898, p. 82.

INDIGO CONCRETIONS.

These are also exceedingly rare. Ord [1] has reported a case in which an indigo calculus was found in the pelvis of the right kidney of a woman whose left kidney was destroyed by sarcoma. The stone weighed 40 grams, and had a nucleus consisting of a coagulum of blood and a deposit of calcium phosphate. Indigo derived from a decomposition of the indican of the urine was deposited upon one side of the calculus. Forbes [2] has also reported an indigo calculus which was found in the pelvis and a calyx of one kidney. The stone weighed 147 grains; its greatest thickness, fore and aft, was $\frac{19}{32}$ of an inch; it measured across its base 1 $\frac{1}{8}$ inches, and from base to apex 1 $\frac{1}{2}$ inches. It was dark brown in color; and when it was drawn across white paper, it left a rough, blue mark. The specimen can be seen in the Museum of Jefferson Medical College, Philadelphia.

So far as the author is aware these two cases of indigo calculus are the only ones that have thus far been recorded.

UROSTEALITH CONCRETIONS.

Urostealith, or fatty concretions, are very rare. They are soft and elastic when fresh; but when dry they are hard and brittle. They are generally of a yellowish or brownish color, and are frequently enclosed within a phosphatic crust. When some of the calculus is heated on platinum foil it burns with a yellow flame and gives off an odor not unlike that of benzoin or shellac.

FIBRIN OR BLOOD CONCRETIONS.

These are formed as a result of the coagulation of blood in the urinary tract. They are commonly found as nuclei of other calculus growths, and not infrequently contain a deposit of uric acid, calcium oxalate, or phosphates. When

[1] Ord, "Influence of Colloids upon Crystalline Form and Cohesion in Urinary and Other Calculi," London, 1879, p. 144.

[2] "Medical News," Aug. 18, 1894.

portions of calculi containing a large proportion of organic matter are heated on platinum foil, they give off the odor of burnt horn and burn with a yellow flame.

Concretions containing crystals of *hematoidin* are occasionally seen. These crystals are most commonly seen in fibrin concretions, or in those calculi that have formed in the presence of a considerable amount of blood.

PROSTATIC CONCRETIONS.

Concretions emanating from the follicles of the prostate are occasionally discharged with the urine. They usually have a laminated nucleus consisting of amyloid bodies (*corpora amylacea*) about which is deposited a mixture of ammonio-magnesium phosphate and calcium phosphate. They do not, as a rule, produce symptoms until they have attained a large size; prostatic concretions of large size are, however, rare.

CHEMIC EXAMINATION OF URINARY CALCULI.

Before beginning the chemic examination of a calculus, its size, shape, color, and density should be observed, as these properties often suggest the probable composition of the concretion. Since a calculus may consist of alternate layers of two or more substances, it is first necessary to make a section through the center of the stone by sawing, in order to determine the composition of each layer. If several different strata are found, it is essential that a portion of each layer be subjected to chemic examination; that portion to be tested should always be in the form of a fine powder, which can be obtained by scraping a very small amount of the stone from its cut surface by means of a knife-blade, or by placing small particles of the calculus in a mortar and grinding them to a powder with a pestle. If the section of the stone is found to have a homogeneous appearance, it is only necessary to examine the sawdust; it is, however, advisable to make a separate examination of the nucleus in every instance, since this portion of a concretion is subject to marked variation.

The chemic examination is best conducted in the following manner:

1. **Preliminary Examination.**—Heat on platinum foil:
Albumin = a flame with odor of burnt horn.
Urostealith = a flame with odor of shellac and benzoin.
Cystin = a blue flame with odor of SO_2.
Xanthin and uric acid = char without a flame.
Alkaline urates = alkaline residue soluble in H_2O.
Earthy phosphates = a residue soluble in acetic acid *without* effervescence.
Calcium oxalate and calcium carbonate = a residue soluble in acetic acid *with* effervescence.
Calcium carbonate = original powder soluble in acetic acid *with* effervescence.
Calcium oxalate = original powder insoluble in acetic acid.
Silica = residue insoluble in HCl.
Murexide Test for Uric Acid.—Original powder + HNO_3 and evaporate = pink residue + NH_4OH = purple color = uric acids and urates.
Original powder + HNO_3 and evaporate + KOH = violet color, which disappears on heating = uric acid. Violet increases on heating = xanthin.

2. **Systematic Examination.**—Presence of uric acid shown by (1). Boil in H_2O and filter.

A. Filtrate + HCl. Let stand 24° = crystals of uric acid. Bases in solution. Concentrate.
Calcium urate = one drop of solution + solution ammonium oxalate = crystals calcium oxalate.
Magnesium urate = one drop of solution + NH_4OH + Na_2HPO_4 = crystals ammonio-magnesium phosphate.
Sodium urate = one drop of solution + $Pt.Cl_4$ = after concentrating, prisms of sodioplatinic chloride.
Potassium urate and *ammonium urate* = one drop of solution + $Pt.Cl_4$ = dodecahedra of potassioplatinic chloride and ammonioplatinic chloride.
Potassium Urate.—Evaporate solution and ignite on mica. Residue + HCl + $Pt.Cl_4$ = potassioplatinic chloride.
Ammonium Urate.—Evaporate solution and ignite on mica. Residue = no crystals with $Pt.Cl_4$.

B. Portion insoluble in H_2O. Add HCl.
Uric acid = insoluble.
Calcium carbonate = soluble with effervescence. Filter + NH_4OH = precipitate of calcium oxalate, calcium phosphate, and ammonio-magnesium phosphate. Wash. *Calcium oxalate* = insoluble in acetic acid. Filter + ammonium oxalate to filtrate. *Calcium phosphate* gives precipitate of calcium oxalate. Filter + NH_4OH to filtrate = precipitate of ammonio-magnesium phosphate.

PART II.

DIAGNOSIS.

CHAPTER VIII.

DISTURBANCES AND DISEASES OF THE KIDNEYS.

ACTIVE HYPEREMIA.

Active hyperemia—active congestion—is essentially *not* a disease of the kidneys, but a disturbance of the functions of these organs. This condition is invariably due to the presence of some irritant that is within or is passing through the kidneys, or to some alteration in their circulation—in other words, it is always secondary in its nature.

Causes.—The causes of active hyperemia may be divided into three general classes:

I. Any general disease or disturbance, which is not primarily renal, but which may cause a change in the renal circulation, as in severe nervous diseases, notably delirium tremens and acute mania; also in other serious affections that act by causing a change in the pressure of the blood in the renal vessels.

Exposure to cold and wet may set up an active hyperemia of the kidneys or an acute nephritis. The reason for a renal disturbance under such circumstances probably is that the superficial blood-vessels and the capillaries of the skin suddenly contract, due to vasomotor changes, congesting the internal organs, and, since the function of the skin is interfered with, the renal congestion is augmented by the necessity for increased activity of the kidneys.

II. Irritants Within or Passing Through the Kidneys.—These may be divided into two distinct classes—viz., insoluble and soluble.

(*a*) *Insoluble Irritants.*—These are crystalline substances that may be separated from the urine in the kidneys, and may set up a mechanical disturbance in the renal tubules—*e. g.*, uric acid, acid ammonium or sodium urate, calcium oxalate, acid calcium phosphate, and cystin.

(*b*) *Soluble Irritants.*—Of these there are—

1. The *toxines*, which are soluble poisons formed and eliminated during the progress of disease. Their irritating effect is especially seen in the acute diseases—viz., pneumonia, typhoid fever, erysipelas, measles, scarlet fever, diphtheria, acute rheumatism, acute miliary tuberculosis, cerebrospinal meningitis, malaria, etc.; and not infrequently in chronic diseases, such as pulmonary tuberculosis, chronic rheumatism, chronic malaria, etc. Irritant toxines may also be formed in the intestines as a result of faulty processes going on there. These are absorbed by the blood and eliminated by the kidneys, causing an active hyperemia. This is especially seen in children who are suffering from diarrhea or an enterocolitis.

Toxines may also be formed in those acute and chronic local diseases that are attended with suppuration, notably urethritis, prostatitis, vesiculitis, bone diseases, abscesses (from which there is absorption), and diseases of the female genitalia, the disturbing element being a toxine that is absorbed from the seat of the disease by the blood and eliminated by the kidneys.

2. Drugs.—The elimination of any irritating drug, such as arsenic, lead, mercury, cantharides, salicylic acid, potassium chlorate, phenol and its compounds, volatile oils, etc.

3. Concentrated Urine.—Not infrequently the passage of a concentrated urine sets up an active hyperemia that varies in intensity from a very mild condition to one that is quite severe. It is especially seen if the urine has been in a state of concentration for a long time. An active hyperemia from this cause rapidly disappears when the patient is given plenty of diluent drinks, the urine becoming diluted and less irritating.

4. Bile.—This substance acts as an irritant in its way through the kidney. It is obvious that the merest trace of bile would not, as a rule, produce any active hyperemia, whereas larger amounts generally set up a more marked form of this disturbance.

5. Sugar.—What has been said of bile may also be credited to sugar. The author has yet to see a urine containing bile or sugar—especially if one or the other were present for more than a day or two and in more than the slightest trace—where there was not evidence of an irritation of the kidneys.

III. Irritants Extending Upward from the Lower Urinary Tract.—It is not uncommon to have a gonorrheal inflammation extend upward from the urethra and bladder, and involve the straight or collecting tubules of the kidney. The same danger exists in an inflammation of the bladder from any other cause.

In case there is some obstruction to the outflow of urine, as by a urethral stricture or an enlarged prostate, the collecting tubules may dilate, and finally result in a "surgical kidney."

Various bacteria, more especially tubercle bacilli, whether coming from the lower urinary passages by extension or by way of the blood-vessels, may set up a focal active hyperemia of the kidneys. The disturbance is principally confined to the pyramidal portion with more or less evidence of extension into the cortical portion of the kidney. Reference will again be made to this under the heading of Tuberculosis of the Kidney.

Character of the Urine.—This varies as the cause: *e. g.*, if the hyperemia is due to the elimination of toxines that are produced in the course of an acute febrile disease, we will generally find a highly colored, concentrated urine, whereas if the cause of the irritation is not accompanied by fever, the urine may have about a normal concentration, or it may be dilute.

It is, of course, impossible to give the characteristics of the urine that will apply in every case of active hyperemia, yet a few general rules may be laid down concerning the average urine in this disturbance.

Quantity in Twenty-four Hours.—Usually less than 1500 c.c.; average, from 800 to 1200 c.c. It may be as low as 300 or 400 c.c., and may exceed 1500 c.c., but only for a short time.

Color.—Normal or high. Not infrequently it is paler than normal. It may be slightly smoky (usually seen, however, in severe active hyperemia, or catarrhal nephritis). (See p. 288.)

Reaction.—Almost always acid, and frequently strongly acid.

Specific Gravity.—This varies according to the metabolism and quantity of urine; it is generally normal or high (1018 to 1030), sometimes less than normal. It usually bears an inverse relation to the quantity of urine passed—*e. g.*, quantity of urine in twenty-four hours 800 c.c., specific gravity 1030; or quantity 2000 c.c., specific gravity 1014. This, however, is not always the case, for both the quantity and specific gravity may be below the normal at the same time—*e. g.*, quantity 1200 c.c., specific gravity 1012.

Normal Solids (Urea, Uric Acid, Chlorides, Phosphates, and Sulphates).—*Absolutely*, about normal or slightly diminished, depending upon the metabolism. In case the metabolism is much reduced, as by an acute infectious disease, the solids may be found, absolutely, very much diminished. In diabetes mellitus they are usually absolutely increased. They are *relatively* increased if the urine is concentrated; and relatively diminished if the twenty-four-hour quantity is near the normal and the metabolism is low.

Albumin.—The quantity varies as the cause and the severity. If the irritation is slight, there may not be more than the *slightest possible trace* or a *slight trace*. On the other hand, if the hyperemia is severe, as following exposure to cold and wet, the quantity of albumin may go as high as ¼ of 1 per cent., but such an amount rarely continues for more than a day or two, when it will fall to a trace, slight trace, or even the slightest possible trace. (See Severe Active Hyperemia.) Very soon after the removal of the cause of the irritation the albumin entirely disappears, but not until all of the renal epithelium that has been denuded by the irritant or other active process has been restored to the tubules.

Sediment.—Usually considerable in quantity, and in the average mild case consists of an occasional (or few) hyaline and finely granular cast, with blood and renal cells adherent. An occasional (or few) free renal cell and blood globule.

If crystalline elements, such as uric acid or calcium oxalate, are the cause of the disturbance, they will generally be found in the sediment, and occasionally embedded in the casts. Normal blood also is very apt to be found under these circumstances, as a result of the mechanical irritation by the crystals.

Long-continued Active Hyperemia.—If the source of irritation has not been removed, and the hyperemia continues for months or years, fatty elements, such as fatty renal cells, fat drops adherent to the casts, compound granule cells, and rarely a small fatty cast, may be found in the sediment. These fatty changes evidently result from the interference with the nutrition of the renal epithelium. Besides the fatty elements there is not infrequently a little more abnormal blood than in the average mild hyperemia of short duration.

The solids will usually be found to be absolutely more diminished than in the average temporary irritation.

Severe Active Hyperemia ("Catarrhal Nephritis").—A mild active hyperemia may gradually or suddenly become intensified, especially during the progress of acute infectious diseases, and a mild but true inflammatory process exist. A severe irritation of the kidneys may, however, be severe from the start, as is sometimes seen in cases of *exposure to cold and wet.*

Causes.—Any of the causes of an active hyperemia already enumerated may result in a severe renal congestion; toxines are especially liable to produce this condition.

Character of the Urine in the Acute Stage.

Quantity.—Usually below the normal—600 to 1000 c.c.

Color.—Smoky, because of the altered blood pigment (methemoglobin or hematin). If there is very much normal blood present, the urine may have a blood-red color.

Reaction.—Generally strongly acid. It may, however, have the normal acidity.

Specific Gravity.—This varies from 1018 to 1025—in other words, not far from the normal. Of course, if the metabolism is much diminished, it may be as low as 1012 to 1015.

Solids.—*Absolute.*—The absolute solids are usually somewhat below the normal, but dependent upon the metabolism. In pneumonia they may be high during the first few days of the acute stage, but later on they may be very low, when not only the metabolism is low, but there is a serous exudation or effusion, into which to a greater or less extent the chlorides and urea go. *Relative.*—As a rule, the relative solids are about normal. They may be a little high or even below normal, depending upon the degree of concentration of the urine.

Albumin.—This varies in quantity from a slight trace to

¼ of 1 per cent. The large quantity of albumin, however, is usually present only for a short period (a day or two), and then falls to about a trace. The comparatively small quantity of albumin (slight trace or trace) is one of the important elements in the diagnosis of a catarrhal nephritis as distinguished from an acute nephritis, which is characterized by a large amount of albumin (¼ to 1 ½ per cent.).

Sediment.—Usually considerable in quantity and consists chiefly of abnormal blood (possibly some normal blood if the irritation is at its height); few (or numerous) granular and brown granular, an occasional blood, epithelial, and fibrinous cast; numerous renal epithelial cells, often colored brown, and a few leucocytes.

Frequently there is evidence of a coexisting acute inflammation of the pelvis of the kidneys, in which case small caudate cells from the superficial layer of the pelvis and clumps of cells from the calices will be found.

Convalescence from a Severe Active Hyperemia.—In the severe forms of active hyperemia or catarrhal nephritis there is frequently a distinct convalescent stage, especially in those cases in which the source of irritation has been partly or entirely removed by natural means or by treatment.

Character of the Urine.—*Quantity.*—The quantity is usually found to be above the average normal (1500 c.c.), varying from 1600 to 2000 c.c.

Color.—Slightly smoky or pale.

Reaction.—Usually acid, unless mild diuretics, such as potassium acetate, may have been taken, when the reaction will be found alkaline from fixed alkalies.

Specific Gravity.—This varies as the twenty-four-hour quantity. It is generally between 1012 and 1018.

Normal Solids.—*Absolute.*—The solids, especially the urea, are absolutely about normal. If for any reason the patient be kept on a low diet, of course the solids will be absolutely lower than when a liberal amount of nitrogenous food is given. *Relatively*, the solids are diminished.

Albumin.—This varies from the slightest possible trace to a large trace, usually the former. If the process be still rather active, the albumin may reach a large trace (about 1/10 of 1 per cent.).

Sediment.—A few (sometimes numerous) abnormal blood globules. An occasional (or few) hyaline, finely granular, and brown granular casts, some with a little blood and fat,

and a few with renal cells adherent. Few free renal cells, an occasional one slightly fatty.

If there was a mild pyelitis during the acute stage of the disturbance, evidence of it may still be found—viz., little pus, free and in clumps; small round cells, free and in the clumps of pus; and, possibly, an occasional small caudate cell from the superficial layer of the pelvis of the kidney. In such a case leucocytes may be found on an occasional cast, especially those coming from the straight tubules.

If the irritant has been entirely removed, the quantity of urine gradually falls to the normal, the casts disappear and finally the blood, at which time the urine will be found free from albumin—in other words, complete recovery.

A circumscribed inflammation of one or both kidneys may take place, especially as a result of the extension of a gonorrheal or tubercular inflammation or other bacterial infection of the bladder and lower urinary passages to the renal pelvis, and then to circumscribed areas of the kidney. A circumscribed inflammatory process may also be set up around a crystalline deposit or morbid growth in the kidney. Under these circumstances the urine has the usual features of an active hyperemia, and not those of acute nephritis.

There are very few **clinical symptoms** aside from the abnormal features of the urine, which are directly referable to this disturbance of the kidneys. In the majority of instances of mild active hyperemia renal symptoms are entirely wanting. Since an active hyperemia is always secondary, it may be stated in general that the symptoms encountered are those of the disease or abnormal condition that causes it, and not those that are referable to the kidneys themselves.

In the severer forms of this condition, particularly when due to mechanical irritants (crystals), pain in the loins is not uncommon. When due to *exposure to cold and wet*, pain in the loins, languor, headache, neuralgic pains in various parts of the body, and more or less frequency of micturition are sometimes present.

It is probable that an active hyperemia or active congestion of the kidneys always becomes a part of the initial stage of an acute nephritis.

Dropsy never exists as a result of an active hyperemia of the kidneys, even when it is severe.

Differential Diagnosis.—From the urine alone it is often difficult, if not impossible, to distinguish between a severe active hyperemia (during its height) and an acute nephritis, owing to the fact that the albumin may be temporarily high, and the amount of blood and number of renal elements (casts and renal cells) abundant. By observing the urine for a period of a few days, if a severe hyperemia, the amount of albumin and blood and the number of casts will be found to diminish rapidly. The urine will then have the characteristics of an ordinary active hyperemia, or the convalescent stage of this disturbance. In case the condition is one of acute nephritis the changes in the urine will be more gradual, and the three stages—*i. e.*, acute, fatty, and convalescent, are easily distinguished. The albumin will be abundant usually for a period of ten days or two weeks, and the amount of blood and the number of casts and renal cells will remain large.

A urine secreted just before the fatal termination of a chronic interstitial nephritis may have all of the characteristics of a mild active hyperemia. The only features of such a urine pointing to a chronic nephritis are the low quantity of urine and the very low total solids. A consideration of the clinical history and the symptoms is of the greatest importance in differentiating between these two conditions.

PASSIVE HYPEREMIA.

Passive hyperemia of the kidneys, also termed *chronic passive congestion*, is, like active hyperemia, not a disease of the kidneys, but a disturbance that is always secondary to some obstruction to the venous circulation. As a result of this, the kidneys are engorged with blood, and the urine becomes modified to a greater or less extent.

Causes.—(1) *Disease of the heart* accompanied by obstruction to the flow of blood through it. (2) *Liver disease* with obstruction to the passage of blood through the ascending vena cava, whether due to marked enlargement or extensive atrophy (cirrhosis). (3) *Tumors of the abdomen*, including the *pregnant uterus*, may cause sufficient obstruction to the circulation in the kidney to cause a passive hyperemia.

Character of the Urine.—Quantity.—In uncomplicated cases the twenty-four-hour quantity of urine is diminished,

usually varying from 400 to 1200 c.c., but is largely dependent upon the degree of obstruction and the character of the disease producing it.

Color.—Generally high, especially if due to disease of the liver, or a markedly uncompensated heart. It may be normal or pale if due to a *long-standing* organic disease, or following treatment by diuretics.

Reaction.—Usually strongly acid; when the urine is dilute and of low specific gravity, the reaction is either normal or faintly acid.

Specific Gravity.—This varies inversely as the quantity, and directly as the metabolism. If the urine is high colored and concentrated, it will have a specific gravity varying between 1025 and 1035. On the other hand, if the urine is pale and less concentrated, it will vary between 1012 and 1020.

Normal Solids.—*Absolute.*—Usually considerably diminished, especially if the cause of the disturbance is marked. Since there is more or less dropsy accompanying the heart or liver disease, the chlorides and urea will be found absolutely diminished. (See Effect of Dropsy upon the Solids.) *Relative.*—Increased, especially the uric acid. In extreme cases accompanied by marked dropsy the urea and chlorides will be relatively diminished.

Albumin.—This varies between the *slightest possible trace* and $\frac{1}{10}$ of 1 per cent. (except in pregnancy, when it may exceed this quantity). The amount of albumin is generally a *very slight trace* or a *trace.*

Sediment.—Frequently there is a deposit of amorphous urates. An occasional (or few) hyaline and finely granular cast of small diameter. Rarely, a renal cell, and *very* rarely, a blood globule (blood is often absent). If more than a stray blood globule be present, it is usually either accidental or the result of some slight complication. Fat globules are not found in the cells or adherent to the casts, except in case there is some active parenchymatous change as a complication.

Not infrequently a passive hyperemia is complicated by an active hyperemia, in which case a few blood globules (abnormal) will be found free and adherent to casts. (See Differential Diagnosis.)

Passive Hyperemia of Pregnancy.—The urine of a pregnant woman, especially between the seventh and ninth

months, will almost invariably show more or less evidence of a passive hyperemia of the kidneys. Most of these cases pass a urine having the characteristics of passive hyperemia already described, except that in pregnancy it is not common to find a highly concentrated or highly colored urine, but rather one having a normal or pale color, and a normal or slightly low specific gravity.

Occasionally, the renal disturbance is severe, when the albumin usually exceeds $\frac{1}{10}$ of 1 per cent., and may go as high as $\frac{1}{4}$ of 1 per cent.

The renal casts in the sediment are frequently of larger diameter than those found in the sediment of an ordinary passive hyperemia due to heart or liver disease.

The **symptoms** encountered in passive hyperemia are those of the disease or disturbance that causes the passive congestion of the kidneys ; there are usually no symptoms that are directly referable to the kidneys themselves. There is generally dropsy, mostly of the feet and legs ; dyspnea ; edema of the lungs, which causes a hacking cough ; and prominence of the veins of the abdomen.

Differential Diagnosis.—The diagnosis of an uncomplicated passive hyperemia of the kidneys can usually be made from the urine without a knowledge of the clinical history or physical examination. If, however, the condition is complicated in any way, either by an active hyperemia, acute nephritis, or by some chronic disease of the kidneys, the diagnosis of passive hyperemia can not be made with certainty from the urine alone.

In the passive hyperemia of pregnancy a rapid increase in the quantity of albumin and an increase in the number of hyaline and finely granular casts in the sediment are always important, as these changes frequently serve as a "danger signal" to the approach of puerperal eclampsia. It must be borne in mind, however, that puerperal convulsions may occur without there being necessarily any marked change in the quantity of albumin or the appearance of blood. Nevertheless, this fact does not lessen the importance of carefully watching the urine for such changes as may indicate the approach of this serious complication. It is a well-known fact that chronic diseases of the kidney do not predispose to the occurrence of puerperal eclampsia, even though a passive hyperemia is superimposed.

Passive congestion of the kidneys is to be distinguished

from a chronic interstitial nephritis chiefly by the large quantity of urine and the low absolute quantity of urea in the latter disease. Also by the predominance in interstitial disease of the quantity of urine passed at night over that passed during the day, and by the prominent symptoms of interstitial nephritis—*i. e.*, a full, hard pulse, cardiac hypertrophy, absence of dropsy until late in the disease, etc.—all of which, except dropsy, are absent in passive hyperemia. In chronic interstitial nephritis near death, when the quantity of urine has fallen to the normal or below, it is frequently impossible to distinguish between these two conditions.

ACUTE DIFFUSE NEPHRITIS (ACUTE NEPHRITIS).

This condition consists of an acute inflammation or degeneration of the kidneys; the pathologic process is usually present in both kidneys, although it may be entirely confined to one of these organs. According to Councilman,[1] an acute diffuse nephritis includes a number of pathologic conditions : *i. e.*—

"(a) **Acute Degenerative Nephritis.**—In this are included degenerative lesions of the epithelium, embracing cloudy swelling, hyaline, fatty, and dropsical degeneration, and often complete necrosis, without lesions other than degenerative, in the glomeruli or in the interstitial tissue. This occurs chiefly in infectious diseases, in jaundice, in anemia, and as the result of the action of certain poisons. The kidney is slightly swollen or unchanged in size, rather paler and more opaque on section ; the markings may be obscure or more prominent than normal. There is often albuminous exudation in the glomerular capsules and in the tubules.

(b) **Acute Glomerular Nephritis.**—The essential changes consist in acute lesions in the glomeruli. There may be acute proliferation of the endothelium of the vascular tufts, hyaline and fibrinous thrombi in the vessels, accumulation of leucocytes in the vessels, degeneration of the vessel wall, etc. These changes in the vascular tufts of the glomerulus can occur with or without changes in the capsular epithelium. The changes in the capsular epithelium consist in degeneration and proliferation. The capsular space may contain an albuminous hemorrhagic or fibrinous exudation.

[1] "Amer. Journ. Med. Sciences," July, 1897.

The changes in the vascular tufts and in the capsule are so frequently combined in various degrees that they can not be separated into two subclasses. The glomerular lesions are accompanied by degeneration of the tubular epithelium, necrosis, and exfoliation. Often there are dilatation of the tubules and edema and cellular proliferation of the intertubular tissue. There may be more or less hemorrhage into the tubules.

This affection occurs in infectious diseases, notably in acute endocarditis, measles, and diphtheria, or as an independent affection. The kidney is usually increased in size. The capsule easily strips off; the surface is pinkish and mottled with points of ecchymosis. On section the cortex is wide, rather paler and more opaque, markings obscure; glomeruli pale, enlarged, and prominent. Pyramids often congested. The tissue moist and pits on pressure. While these appearances are usually marked, lesions of the glomeruli may be found with but little macroscopic change in the kidney.

(c) **Acute Hemorrhagic Nephritis.**—The essential change consists in hemorrhage in the tissue combined with degeneration of the epithelium. The hemorrhage is chiefly found in the capsule of the glomeruli and in the tubules. The degenerative lesions may be extensive and lead to necrosis and exfoliation. Edema, hemorrhage, and cellular infiltration are often found in the intertubular tissue. The kidney is enlarged, hemorrhages are found in the capsule; the surface is dark red, with numerous ecchymoses. On section the cortex is swollen and sprinkled with dots and streaks of ecchymosis.

(d) **Acute Interstitial Nonsuppurative Nephritis.**—The essential lesion consists in acute proliferation of the cells in the intertubular tissue. The proliferation takes place mainly from the vascular endothelium. The cells lie within and without the vessels. They are large and similar to the endothelial cells of young granulation tissue. They are found chiefly in the intermediate zone of the kidney between the pyramids and the cortex. In the cortex they are both generally diffused and in areas chiefly around the glomeruli. There is more or less degeneration and necrosis of the tubules, affecting chiefly those in the areas of cellular infiltration. Leucocytes in small numbers may be found in the intertubular tissue among the other cells, in the degenerated epithelium, and in the lumen of the tubules. The glomeruli

are not affected. This affection occurs in acute infectious diseases, notably in diphtheria and scarlet fever. The kidney is large, pale, somewhat mottled ; on section, moist, opaque, markings obscure, and milky fluid can be pressed from it."

From a clinical point of view we are unable at present to distinguish with certainty between these four forms of acute nephritis, either by the characteristics of the urine or by a consideration of the urine in connection with the clinical history and symptoms. The description that follows applies to an acute nephritis as seen clinically, and is without reference to these different forms of the disease. It is probable, however, that the form which Councilman designates as "acute degenerative nephritis" corresponds to the condition which the author has described as *active hyperemia.*

Causes.—An acute nephritis may be caused by any irritant or abnormal condition, such as causes an active hyperemia (see Causes of Active Hyperemia) ; in fact, an active hyperemia from any cause may end in a true acute nephritis. Of the causes *exposure to cold and wet* is probably the most common. *Toxines,* notably those of diphtheria and scarlet fever, are very apt to cause acute nephritis. *Bacterial infection* is sometimes a cause, and when present, generally produces the disease in its most virulent form. *In pregnancy* there may be an acute nephritis, which is usually accompanied by puerperal convulsions, and not infrequently this complication proves fatal.

An acute nephritis may be divided into three stages : *First* or *acute, second* or *fatty,* and *third* or *convalescent* stage.

First or Acute Stage.—

Character of the Urine.—Quantity.—Much diminished —usually 200 to 400 c.c. There may be almost complete anuria, the patient frequently passing not more than 100 c.c. in forty-eight hours.

Color.—Very smoky (dark) or, in the first day or two, almost black ; if much normal blood, a blood-red color.

Reaction.—Usually acid ; sufficient blood may be present to give a slightly alkaline reaction.

Specific Gravity.—Generally high, although it may be low. If albumin be present in large amount (and it generally is excessive), it will raise the specific gravity to 1030, even though the normal solids are diminished.

Normal Solids.—*Absolutely,* much diminished, espe-

cially the urea and chlorine. (See Effect of Dropsy on Normal Solids.) If the dropsy is increasing, as is the rule during this stage, the chlorine may be found absent. *Relatively*, diminished, especially the urea and chlorine.

Albumin.—Generally ¼ to ½ of 1 per cent. It may exceed this quantity, going as high as 1½ per cent. The amount varies with the severity of the disease and the degree of obstruction in the tubules.

Sediment.—Abundant and of a dark-brown or chocolate color. It consists of a large number of abnormal, and perhaps some normal, blood globules. Many brown granular renal epithelial cells. Many brown granular, epithelial, blood, and fibrinous casts, and perhaps a few hyaline and finely granular casts. A large amount of granular debris from the broken-down renal cells and blood globules. There are usually numerous leucocytes, free, in clumps, and adherent to the casts ; also small caudate cells from the superficial layer of the pelvis, as well as an occasional clump of round cells from the calices of the kidney —an acute pyelitis.

The **duration** of this stage is usually from five to ten days. The urine then commences to show signs of improvement, the dropsy begins to diminish, the absolute solids are a little higher, the quantity of urine gradually increases, and fatty elements begin to appear or have already appeared.

Second or Fatty Stage.—

Character of the Urine.—Quantity.—This varies between 800 and 1500 c.c., according to the amount of improvement that has taken place.

Color.—Still very smoky.

Reaction.—Usually acid.

Specific Gravity.—This generally ranges between 1015 and 1020. It is still influenced by the considerable amount of albumin that is present.

Normal Solids.—*Absolutely*, somewhat diminished, although higher than in the first stage. *Relatively*, diminished. The urea and chlorine will be found relatively higher as the dropsy diminishes.

Albumin.—This varies between ⅛ and ¼ of 1 per cent. As a rule, the diminution in the quantity of albumin is in inverse proportion to the increase in the twenty-four-hour

quantity of urine. In the first part of this stage the quantity of albumin may exceed ¼ of 1 per cent.

Sediment.—This is still abundant in quantity, and of a brown color. The elements are practically the same as in the acute stage, but with the addition of fatty renal cells, fatty casts, and compound granule cells. The amount of fat at this time follows quite closely the degree of severity of the disease during the acute stage—that is, if there was a rather mild acute stage, the number of fatty elements and the degree of degeneration will not be extensive; but if there was a severe acute stage, the quantity of fat will be excessive. Furthermore, from a single examination of the urine at this time, and without a knowledge of the previous history, it may be impossible to determine whether we are dealing with the fatty stage of an acute nephritis or a subacute glomerular nephritis that is complicated by an acute process.

The evidences of a pyelitis seen in the acute stage will probably be present to a greater or less extent in this stage, although it occasionally happens that the acute pyelitis has developed into a subacute or chronic pyelitis. The latter is shown by the presence of a larger quantity of pus, free, arranged in clumps, and adherent to casts of large diameter; also a large number of small round cells, free and in the clumps of pus.

The **duration** of this stage is about the same as that of the first,—viz., five to ten days,—providing there is steady improvement.

With the favorable progress of the disease the character of the urine gradually changes still more, and we have the third or convalescent stage. The edema has entirely disappeared.

Third or Convalescent Stage.—

Character of the Urine.—Quantity.—This generally varies between 1500 and 3000 c.c. There is usually a gradual rise in the quantity, as high as 4000 c.c., where it generally remains for a few days or even weeks. As the condition approaches complete recovery, the quantity falls gradually, and in some cases there is a sudden fall to about the normal.

Color.—Usually, the urine has lost its smoky color and is pale. Occasionally, the smoky color continues, especi-

ally in the early part of this stage, and as long as the urine contains a large amount of abnormal blood. As the amount of blood diminishes, the color becomes pale.

Reaction.—Faintly acid.

Specific Gravity.—This varies as the quantity—*i. e.*, if the twenty-four-hour amount is between 3000 and 4000 c.c., it will be not far from 1008 to 1010. On the other hand, if the quantity is between 1800 and 2500 c.c., it will be between 1012 and 1018.

Normal Solids.—These are *absolutely* normal. They may be increased for a time, especially the urea and chlorides, due to their reabsorption from the serous transudations and their elimination in the urine. They are *relatively* diminished, the degree of diminution being dependent upon the dilution of the urine.

Albumin.—This is usually between ⅛ of 1 per cent. and a *very slight trace*, according to the extent of the convalescence and the twenty-four-hour quantity of urine. The larger the quantity of urine, the smaller the amount of albumin. The average quantity in this stage will be not far from a *trace*.

Sediment.—Generally, slight in quantity and colorless, although it may still have a brownish color if much abnormal blood be present. It consists of numerous (or few) abnormal blood globules. Few (or occasional) hyaline, granular, and brown granular casts, and rarely a blood, epithelial, and fibrinous cast. Most of the casts with abnormal blood and a little fat adherent. Few renal cells, some fatty. Rarely there may be a small fatty cast. The brown granular and fibrinous casts are the first to disappear.

If there was a chronic pyelitis in the second stage, evidence of it will probably still be found. As the convalescence advances, the pyelitis usually disappears rather suddenly, if it has not entirely recovered during the second stage.

The **duration of the convalescent stage** is from one to four months, but not infrequently it lasts for a longer period, even from one to two years, followed by complete recovery.

In a perfectly favorable convalescent stage, without complications, after the lapse of a month or two, the quantity of urine falls to the normal, the albumin diminishes to a *very slight trace* or the *slightest possible trace*, the quantity of blood diminishes, the brown granular and fibrinous casts disap-

pear and then the majority of the fatty elements. In well-advanced convalescence, only hyaline and granular casts, an occasional blood globule free and adherent to some of the casts, an occasional renal cell, and rarely a fatty renal cell remain. If the urine is first examined at this time and without a knowledge of a previous history of the case, it is often impossible to determine whether the condition is one of active hyperemia or a well-advanced convalescence from an acute nephritis, for the urine is the type of one of simple active hyperemia. When complete recovery has taken place, all abnormal elements disappear from the sediment, and the urine is normal in character.

The **prognosis** in a case of acute nephritis is usually good, although there is always a liability that it may result in a chronic disease of the kidneys. It is certainly the exception, and not the rule, for an acute nephritis to run as favorable a course as has just been outlined.

Exacerbations (relapses) are very liable to occur, especially during the convalescent stage.

Causes.—Probably the most common cause is exposure —a draft of air on the head and neck, too little clothing, cold and wet feet, etc. Since the skin is usually very active at this time, any sudden exposure stops its action and increases the congestion or inflammation of the kidneys. Occasionally, the ingestion of highly nitrogenous food (meats, etc.) is apparently an element in causing an exacerbation. Sometimes an exacerbation occurs without a discernible cause, even when the patient has taken every precaution. The onset is usually sudden, and the patient realizes that he does not feel as well as usual, having a recurrence of the symptoms of the acute stage—*i. e.*, diminished quantity of urine, frequent micturition, and generally some headache and pain in the back. There is usually more pallor than before the attack, and often swelling of the face and extremities.

Character of the Urine.—The urine of an exacerbation is characterized (1) by a sudden fall in the quantity, (2) a blood-red color, and (3) the presence in the sediment of a large quantity of normal blood. It may be either mild or severe, and the severity of the attack governs the extent to which the quantity of urine is diminished, and the amount of normal blood found ; in other words, if severe, the quantity of urine is greatly reduced and the amount of normal blood large ; if mild, a moderately diminished quantity and com-

paratively little blood. The quantity of albumin increases and the normal solids diminish according to the severity. The blood, epithelial, and fibrinous casts are again present in moderately large numbers. In the course of two or three days, possibly a week or ten days, the urine again increases and the normal blood disappears, although the latter may continue in small amount (not sufficient to give the urine a bloody color) for weeks. Following the disappearance of the greater part of the normal blood, the urine generally contains a larger quantity of abnormal blood than before the exacerbation, hence a smoky color again for a few days. After a short time has elapsed the urine again presents the characteristics of the third, or convalescent, stage of an acute nephritis.

Any number of exacerbations may occur, the average being from one to four, and the larger the number, the more prolonged the convalescence. Likewise, the greater the number of exacerbations, the more extensive the pathologic changes in the kidney, and hence the more unfavorable the prognosis, since the acute nephritis may end in a chronic disease of the kidneys. An unfavorable prognosis is not necessarily warranted, however, as cases of acute nephritis accompanied by frequent exacerbations have recovered after a lapse of two years.

Symptoms of *uremia* may appear at the time of a severe exacerbation because of the interference with the elimination of the toxic material from the body; but, fortunately, this complication is only rarely seen.

Prominent Symptoms.—The onset of an acute nephritis is usually very rapid and, like other acute processes, is frequently ushered in by a chill. There is usually rapid pallor, swelling of the lower eyelids and face, also edema of the legs, and often general dropsy; intense headache, thirst, nausea, and often vomiting; pain in the back and limbs, and frequency of micturition. Because of the last-mentioned symptom the patient often has the firm impression that he is passing a large quantity of urine, but when the total quantity is measured, it will be found to be abnormally diminished. There is usually at first some elevation of temperature, also a high tension pulse. Acute uremic symptoms are not uncommon, the most prominent of which are nausea and vomiting, stupor, and sometimes convulsions. Acute visual disturbances are occasionally seen.

Differential Diagnosis. — The distinction between a *severe active hyperemia* and *a mild acute nephritis* is, in some instances, not easily deduced from the urine alone. However, the history of a sudden onset and the prominent symptom of edema,—swelling of the face and legs,—together with the chief characteristics of the urine—viz., the persistence of a considerable amount of albumin, considerable blood, and numerous casts—will serve to distinguish an acute nephritis from a severe form of active hyperemia.

The urine of the *second stage of acute nephritis* may not differ materially from one of *subacute glomerular nephritis* (*active stage*) *complicated by an acute process.* In the latter condition the albumin is usually present in larger amounts, and the total quantity of urea is generally much lower than in the former disease. In an acute nephritis the clinical symptoms will show that the condition is gradually improving, while in a case of a complicated subacute glomerular nephritis the patient is at his worst. In doubtful cases, however, the urine should be carefully watched for several days; if an acute nephritis, the third or convalescent stage will appear; if a subacute glomerular nephritis complicated by an acute process, the acute complication will gradually subside, leaving the disease in its uncomplicated form; or the patient may have symptoms of uremia and succumb to the disease.

The urine of the *convalescent stage of an acute nephritis* should not be mistaken for the urine of *chronic interstitial or chronic diffuse nephritis.* The acute history, the characteristic first and second stages of an acute nephritis, the presence of blood in the sediment, and the normal total solids will serve to distinguish an acute from a chronic form of renal disease.

SUBACUTE GLOMERULAR NEPHRITIS.

Subacute glomerular nephritis, also termed "chronic parenchymatous nephritis," "fatty degeneration of the kidneys," and "chronic diffuse nephritis of the parenchymatous type," is a disease characterized by marked degenerations of the glomeruli as well as of the epithelial lining of the renal tubules.

The essential lesions are in the glomeruli. They consist in swelling and nuclear increase in the vascular tufts and obliteration of the vessels by hyaline degeneration, both of

the cells and the vascular walls. These changes in the tufts are often combined with proliferation and desquamation of the capsular epithelium with connective-tissue ingrowth. There is extensive degeneration, necrosis, and desquamation of the tubular epithelium. The intertubular tissue is the seat of edema and connective-tissue formation. The kidney is enlarged, and the capsules may cling slightly to the surface, which is pale and slightly mottled. On section, the cortex is increased in width, pale, opaque, markings obscure, glomeruli pale, and its consistency is increased (Councilman).

Causes.—This disease is sometimes the result of a previous acute nephritis, during the course of which frequent exacerbations have occurred, and when the convalescence has been extended over a long period (years). It is, perhaps, more common for the disease to accompany chronic wasting diseases, such as phthisis, syphilis, and chronic suppurative bone diseases; also in cases of prolonged malaria. When the disease is an accompaniment of these conditions, the changes in the kidney are gradual, and the disease appears to be chronic from the beginning. The reason for a subacute glomerular nephritis under these circumstances is not known.

The disease can be conveniently divided into two stages—*i. e.*, *active* and *inactive stages*.

ACTIVE STAGE.

This stage is seen at the time when the patient is at his worst. The urine is concentrated and highly characteristic, and there is marked dropsy.

Character of the Urine.—Quantity.—Very small, varying from 200 to 800 c.c., the average being not far from 400 c.c.

Color.—High, like that of a fever urine, and often turbid because of the presence of amorphous urates. In case of a recent acute exacerbation, the color will be bloody.

Reaction.—Usually strong acid.

Specific Gravity.—High—1026 or 1028, and often as high as 1030 or 1035.

Normal Solids.—*Absolutely*, much diminished, especially the urea and chlorides, which are low because of the very extensive and increasing dropsy. The chlorides may be

nearly absent. *Relatively*, the uric acid and the urea are increased, unless the disease has been going on for a long time, in which case the urea will be relatively diminished. The chlorides are much diminished or nearly absent.

Albumin.—In this form of kidney disease, and especially in this stage, the quantity of albumin is the largest ever found in the urine. It varies between ½ of 1 and 3 or 4 per cent. by weight, but the average quantity is usually from ½ of 1 to 1 per cent. The maximum amount ever reported was as high as 5 per cent. Upon performing the heat test for albumin it is not very uncommon to find that the urine completely solidifies, in which case the quantity of albumin exceeds 2 per cent. The average quantity in this stage is between ½ of 1 and 1 per cent., usually nearer the latter figure.

Sediment.—If a deposit of amorphous urates is present, the sediment will be abundant and usually of a pink or reddish-brown color. If there is not a deposit of urates, the amount of sediment will be "considerable" and practically colorless. If the disease be complicated by an acute process, normal blood may be present in sufficient quantity to color the urine and sediment red. The sediment consists of many hyaline, granular, and fatty casts, some of which have fatty renal and compound granule cells adherent; numerous *free* fatty renal and compound granule cells. Crystals of the fatty acids are often seen projecting from the fatty renal and compound granule cells, and the fatty casts. Cholesterin crystals are occasionally seen, but usually only in the late stages of the disease. If the disease is well advanced, waxy casts may be seen in the sediment. When present, they are of bad omen. In an uncomplicated case the sediment is free from blood and renal blood elements. As a matter of fact, chronic diseases of the kidneys are usually more or less complicated by either a mild or severe acute process, so that usually an occasional (or numerous) blood globule will be found. If there is very much blood present, a few leucocytes are often found free and adherent to some of the casts.

With the improvement that usually follows rest in bed, a milk diet, and mild diuretic treatment, providing the disease is not near its termination, there is a distinct change in the character of the urine. The dropsical effusions have diminished, the edema of the extremities has largely disappeared, although usually not entirely, and the process in the

kidneys appears to be quiescent. Then we have the inactive stage of the disease.

INACTIVE STAGE.

Character of the Urine.—Quantity.—Usually, from 800 to 1200 c.c. It may exceed the normal quantity for a day or two at the time the edema is being absorbed, but it soon falls to about 1200 c.c.

Color.—The color is pale and not infrequently the urine has a greenish tint.

Reaction.—Generally, acid.

Specific Gravity.—This varies as the twenty-four-hour quantity, but in the early part of the disease it will generally vary between 1010 and 1015.

Normal Solids.—They are both *absolutely* and *relatively* diminished. The solids may be absolutely somewhat higher than in the active stage, especially at the time of the greatest absorption of the edema, but the increase is usually slight.

Albumin.—The quantity of albumin is smaller than in the active stage, but it is still present in large amount, generally from ¼ to ½ of 1 per cent. Occasionally, it is a little less than ¼ of 1 per cent., particularly if the twenty-four-hour quantity of urine is about 1500 c.c.

Sediment.—This is "considerable" in quantity, and colorless. A deposit of amorphous urates is usually not present. It consists of the same elements that were found in the active stage, but they are less in number: numerous hyaline, granular, and fatty casts, fatty renal and compound granule cells. If waxy casts were present in the active stage, they will be found at this time, although fewer in number. Crystals of the fatty acids and cholesterin will also be found if they were present in the active stage.

ATROPHIC STAGE.

This stage is only very rarely seen, since death usually occurs before atrophy of the kidneys has taken place. The kidneys become very small, have a yellow color, consist principally of fat, and there is a marked increase in the connective tissue.

Character of the Urine.—The *quantity of urine* is usually not far from the normal, and it may be slightly increased.

The *specific gravity* and the *normal solids* are very low; the *quantity of albumin* falls to about ¼ of 1 per cent. or less; and the *sediment* consists of practically the same elements as in the inactive stage of the disease, except a smaller number of fatty elements and a larger proportion of waxy casts.

A subacute glomerular nephritis is characterized by frequent alternations of the active and passive stages, without there being necessarily a true acute exacerbation. But acute exacerbations are as likely to occur in this disease as in an acute diffuse nephritis. When present, the urine has the additional elements of the acute disease, together with the normal blood and renal blood elements—blood-casts, etc.

Prominent Symptoms.—The patient usually suffers from indigestion (early symptom), often attended with vomiting; almost constant headache, which gradually increases in intensity from month to month; marked pallor ("pasty") and, usually, swelling of the face; and invariably marked edema of the extremities, which finally extends and increases to a condition of extreme general dropsy (ascites, pleuritic effusion, etc.). There is frequency of micturition, but a small quantity of urine is passed. Palpitation and dyspnea on exertion are often present to a marked degree. The disease is characterized by periods of *activity* in which the edema is increased, the quantity of urine is very small, and there are uremic symptoms. It is also characterized by *quiescent* periods, in which the patient improves, the edema diminishes, and the quantity of urine increases, although generally not above the normal except for a day or two.

The **duration** of the disease is usually from two to five years, but this depends upon the care of the patient and the hygienic surroundings. If the circumstances are such that he can have the very best care, life may be prolonged a year or two longer; on the other hand, an early end is often the fate of such cases among the poorer classes.

The **prognosis** is invariably unfavorable. So far as is known, recovery never takes place after the disease has become well established. Death may result from uremia or, as is not infrequent, from some secondary acute disease, such as pneumonia, erysipelas, diphtheria, etc. The low physical state of the patient renders him very susceptible

to other diseases, especially those of an acute infectious nature.

Differential Diagnosis.—The diagnosis of a subacute glomerular nephritis from the urine alone is generally not difficult, providing the condition is uncomplicated. In case the disease is complicated by an acute process it can not be readily distinguished from the *second stage of an acute nephritis.* Under these circumstances the history of the case should be considered, and the character of the urine should be carefully watched for several days. If a complicated subacute nephritis, the acute process will generally subside in the course of from two to three weeks, when the urine will have the characteristics of an uncomplicated subacute nephritis. The edema that was extreme at first usually continues after the acute process has subsided—viz., after the blood has entirely disappeared. On the other hand, if the disease is an acute nephritis passing through the second stage, the third or convalescent stage will soon appear, the edema will entirely subside, and the patient will gradually improve until there is complete convalescence.

CHRONIC INTERSTITIAL NEPHRITIS.

This condition has been variously termed *chronic nephritis, chronic diffuse nephritis of the interstitial type, sclerotic kidney, gouty kidney, small granular kidney, chronic diffuse nephritis without exudation,* etc. It is a chronic disease of the kidneys, which is characterized chiefly by an increase in the connective tissue of those organs. The disease develops very slowly and insidiously, usually having been in progress for years before it is recognized, and then often only accidentally discovered by the physician who is consulted for the relief of headaches or some annoying stomach difficulty; or perhaps it is first encountered by the life insurance examiner or oculist.

According to Councilman, some of the pathologic processes found in chronic interstitial nephritis, such as *chronic arteriosclerotic nephritis,* and *chronic degenerative and interstitial nephritis* really belong under the heading of chronic diffuse nephritis.

In *chronic arteriosclerotic nephritis* the essential lesions occur in the arteries, and consist in those changes known as arterioscleroses. There is degeneration of the epi-

thelium of the tubules, with more or less complete destruction. The degeneration takes place slowly, and at any given time sections may show only a slight degree. Atrophic changes in the epithelium are common. The lesions may affect almost equally all parts of the kidney, or appear in areas corresponding to the vascular territories of those arteries that are most affected. There is a general increase in the connective tissue, though large areas of tubules may be found with no increased tissue between them. This condition of the kidney is found accompanying a general arteriosclerosis affecting all the arteries of the body, or the vascular lesions may be most marked in the renal arteries. The kidney varies in size; it may be slightly larger or of normal size, but is usually very much smaller than normal. The capsule may or may not be adherent. The surface is more or less irregular and granular; the color is red and often cyanotic. On section, the cortex may be much diminished in size, of a dark-red color, the markings obscure, and the glomeruli injected; the arteries in the intermediate portion are evident, and often project above the cut surface. The pyramids show venous congestion; the consistency of the kidney is greatly increased. Most of the cases of contracted kidney belong to this class.

To the class of *chronic degenerative and interstitial nephritis* belong those cases of contracted granular kidney that occur without primary arterial lesions. It is difficult to give a name to the condition, for there is no single change that predominates. Degeneration, atrophy, and destruction of the epithelium in various degrees are found. There is a general increase in connective tissue more diffuse than in the arteriosclerotic nephritis, but not so diffuse as in the chronic glomerular form. The increase in the connective tissue is most intense where the degeneration of the epithelium is most marked. Lines of connective tissue extend to the surface, and by their contraction produce depressions. Very minor degrees of change, which may consist in small areas of cellular infiltration with hyperplasia of the connective tissue extending down from the capsule, are very commonly found. The essential lesion seems to be a slow degeneration of the epithelium, followed by connective-tissue hyperplasia. The microscopic appearances of the kidney vary extremely, following the different degrees of the

lesions. The gross and microscopic condition may be complicated by lesions of another character (Councilman).

Causes.—There are three toxic agents that are probably causes of this disease:

1. **Lead.**—Chronic lead-poisoning is usually met with in type-setters, painters, those handling lead, and others exposed to its influence. The damage to the kidneys is apparently due to the constant elimination of the lead, which acts as a chemic irritant. The connective-tissue changes do not usually appear until after years of almost constant poisoning.

2. **Alcohol.**—Those persons who are addicted to the moderate use of alcohol, especially if continued for years, may have a chronic interstitial nephritis, which may lead to their death or be an accompaniment of some other acute or chronic disease that proves fatal.

3. **Uric Acid.**—The gouty individual is often the victim of this disease—the so-called "gouty kidney." The manner in which uric acid produces a chronic interstitial nephritis can not be well explained unless we assume that it is the result of the constant irritation set up by the elimination of excessive amounts of uric acid and other products of diminished metabolism.

Arsenic.—Chronic arsenic-poisoning probably leads to this form of disease, especially in those persons who have been exposed to the influence of the substance for a long period of years.

Syphilis and chronic malaria are also considered causes of this disease. It is certain that these conditions are often accompanied by a chronic interstitial nephritis, but not invariably. It is probable that any long-continued irritation of the kidneys gradually results in renal changes that finally terminate in a chronic interstitial nephritis.

Arteriosclerosis.—There can be no doubt that this disease of the blood-vessels results in those changes that characterize this form of kidney disease. It is common in middle-life, and, as before stated, most of the cases of contracted kidney belong to this class.

Chronic interstitial nephritis can be divided, clinically, into three stages according to the degree to which the urine becomes modified from the normal and the extent of the renal changes: first or early stage, second or advanced stage, and third or late stage.

FIRST OR EARLY STAGE.

This stage is seen at the time when the individual is capable of attending to business and, with the exception of headaches and frequent attacks of indigestion, enjoys a fair degree of health. There may not be any noticeable frequency of micturition at this time, although the patient will probably find it necessary to urinate once or twice during the night.

Character of the Urine.—Quantity.—This is a very important element in the diagnosis. It is moderately increased above the normal at this time—usually, between 1500 and 2000 c.c. Frequently, the quantity of urine passed at night exceeds that passed during the day; this is much more marked during the advanced stage of the disease.

Color.—Normal or slightly pale.

Reaction.—Acid.

Specific Gravity.—This varies inversely as the quantity of urine, but will usually be found to vary between 1012 and 1018.

Coloring-matters.—All somewhat diminished except the indoxyl, which is generally increased.

Normal Solids.—The *absolute* solids are somewhat diminished, although not markedly. The total quantity of urea eliminated by an average-sized adult will be about normal, or it may be higher than normal, especially if the individual is having a liberal nitrogenous diet. *Relatively*, they are nearly normal or somewhat diminished, depending on the dilution of the urine. The percentage of urea will probably be found to be not far from 1.5 per cent.

Albumin.—This varies between the *slightest possible trace* and a *trace*. It is at this time that the presence of albumin is sometimes overlooked, because of the failure to detect the slightest possible traces. (See Detection of Albumin.) The author's experience leads him to believe that albumin is always present in the urine of chronic interstitial nephritis, even in the early stages.

Sediment.—This is usually very slight in quantity and requires very careful sedimentation in order to be able to obtain a satisfactory preparation for examination. Oftentimes it is necessary to centrifugalize the urine in order to obtain the best results from the microscopic examination.

It will be found to consist of an occasional hyaline and finely granular cast. No excess of renal cells and, unless complicated, no blood or fat are present.

In this stage the diagnosis of chronic interstitial nephritis from the urine alone is usually extremely difficult, but when combined with the clinical history and physical examination, it becomes less difficult, although often doubtful until the case has been carefully watched for some months.

SECOND OR ADVANCED STAGE.

The patient at this time usually finds it necessary to discontinue business, because of lack of strength, habitual headache, more or less marked gastric disturbance, and perhaps other more serious symptoms; in other words, the disease is at its height, and the patient requires almost constant attention.

Character of the Urine.—Quantity.—This gradually but steadily increases from 2000 to 3000 or 4000 c.c. Rarely, it may go as high as 6000 c.c. in twenty-four hours.

Color.—Pale and sometimes almost colorless.

Reaction —Faintly acid.

Specific Gravity.—This has fallen from 1012 or 1015 to 1010 or lower.

Normal Solids.—*Absolutely*, much diminished. Occasionally, if the disease is not very far advanced and the patient is having the best of care and can take a moderately nitrogenous diet, the urea may be nearly or quite normal, but this does not continue for a very long time. *Relatively*, much diminished.

Coloring-matters.—These are all diminished, except the indoxyl, which is often normal or increased.

Albumin.—This has increased, and usually varies between *a trace* and $\frac{1}{8}$ of 1 per cent. It may rarely reach $\frac{1}{4}$ of 1 per cent.

Sediment.—This is much the same as in the early stage, except that the casts are more numerous and usually more granular. The renal cells, which are only few in number, will be found to be quite granular. Oftentimes the abnormally formed renal elements are found with some difficulty, since the amount of sediment is so slight. As in the early stage, the urine may require centrifugalization in order to obtain a satisfactory sediment for examination.

THIRD OR LATE STAGE.

This is at a time when the disease has advanced to a late stage, and the patient is more or less uremic—*i. e.*, suffering from intense headache, nausea, vomiting, and often convulsions. General weakness is marked. Dyspnea is often a prominent symptom. There is considerable vertigo and disturbance of vision—the so-called *albuminuric retinitis.* There may be some edema of the feet at this time, due to an uncompensated heart.

Character of the Urine.—Quantity.—This has gradually fallen from the large quantity to about 1500 c.c. The quantity of urine passed at night is usually greater than that passed during the day.

Color.—Very pale (watery).

Reaction.—Faintly acid.

Specific Gravity.—Usually between 1005 and 1010; even when the twenty-four-hour quantity of urine is much below the normal—*e. g.*, with a quantity of 500 c.c. the specific gravity may be as low as 1005.

Normal Solids.—Both *absolutely* and *relatively* much diminished.

Albumin.—Usually, a distinct *trace;* rarely, the *slightest possible trace.* It may, on the other hand, reach as high as ¼ of 1 per cent.

Sediment.—This is still slight in quantity, and consists of numerous (or many) hyaline, finely and coarsely granular, and a few waxy casts. Most of the renal cells will be found to be very granular. No fat nor blood unless complicated. Often in the late stage a few abnormal blood globules will be found. It, therefore, may be difficult from the urine alone and without a previous knowledge of the case to make a diagnosis of a primary renal disease, especially if the quantity of urine is small and the waxy casts are stained by the blood so as to resemble fibrinous casts. The blood may be due to a slight acute exacerbation, or it may be the result of either a circumscribed acute nephritis or a more or less general active hyperemia. If the disease is the result of some active irritant (lead or arsenic), blood may be found in the sediment in all stages of the disease.

Prominent Symptoms.—Owing to the latency of the disease, symptoms are frequently not noticed until the occurrence of one of the serious or fatal complications.

Even an advanced grade of chronic interstitial nephritis may be compatible with great mental and bodily activity. There may have been no symptoms whatever to suggest to the patient the existence of a serious disease. In other cases the general health is greatly disturbed. The patient complains of lassitude, sleeplessness, has to arise two or three times at night to micturate, the digestion is disordered, and there are complaints of headache, failing vision, and shortness of breath on exertion. The pulse is usually hard, the tension increased, and the vessel-wall, as a rule, thickened. Hypertrophy of the left side of the heart occurs, to overcome the resistance offered in the arteries; and in many cases a systolic murmur develops at the apex, probably as a result of relative insufficiency. Bronchitis is a frequent accompaniment, especially in winter. Sudden attacks of oppressed breathing, particularly at night, are not infrequent. Cheyne-Stokes breathing may be present, most commonly toward the close, but the patient may be walking about and even attending to business. Dyspepsia and loss of appetite are common; in fact, severe vomiting may be the first symptom. Severe and fatal diarrhea may develop; the breath is often heavy and urinous. Headache is frequently an early and persistent feature of chronic interstitial nephritis. Hemorrhages may take place into the meninges or the cerebrum; such are usually associated with marked changes in the walls of the vessels. Disorders of vision may be one of the first symptoms of the disease, and the oculist may be the first to make the diagnosis of a chronic form of renal disease. Ringing in the ears, with dizziness, is not uncommon.

Edema, except *very slight* swelling of the ankles, is very uncommon in chronic interstitial nephritis until late in the disease, when it is probably due to an uncompensated heart. The skin is often dry and pale. Epistaxis may occur and prove serious. Uremic symptoms, some of which have been mentioned, are common in the advanced stage of the disease. Uremic convulsions may be frequent and severe.

Duration.—A chronic interstitial nephritis is usually in progress for many years—from ten to thirty, or a longer time. It is most common in middle life, and if discovered early and the source determined, by good care the patient may have fair health for many years.

Prognosis.—The prognosis is very unfavorable, although, as has been stated, if the disease is discovered during its early stages, the patient may live many years. Occasionally, the patient dies of some intercurrent disease such as pneumonia, or, perhaps more commonly, cerebral hemorrhage because of the diseased arteries. Frequently, a sudden attack of uremia results fatally. The appearance of waxy casts usually indicates that the fatal termination will occur within one year, and often within six months.

Clinically, an uncomplicated case of chronic interstitial nephritis—that is, one that does not present some evidence of a slight parenchymatous change (presence of fat)—is quite uncommon, it being the rule to find rarely a fat globule adherent to an occasional cast.

Differential Diagnosis.—The diagnosis of an *early stage of chronic interstitial nephritis* from the urine alone is often difficult, owing to the fact that the urine is so slightly altered from the normal. It is at this time that a very careful consideration of the clinical history and the physical examination are of infinite importance. It is needless to say that an early recognition of this form of nephritis is very important, for if it is the result of some chronic irritation, as by lead or uric acid, the same should be recognized and the irritant removed as early as possible.

The so-called "cardiac and renal" cases are worthy of consideration here because of the differential diagnosis between a *chronic interstitial nephritis* and *passive hyperemia.* The latter condition is sometimes superimposed on the former because of an uncompensated heart. From the urine alone it is often impossible to decide which condition is the more prominent. A very small twenty-four-hour quantity of urine, a comparatively small amount of albumin (trace), and the presence of marked edema are all against a chronic nephritis. On the other hand, if the sediment contains waxy casts, or casts from extensively denuded tubules, very granular renal cells, and, clinically, a high tension pulse, and other evidences of increased blood pressure, the condition may be a chronic interstitial nephritis in a late stage, and at a time in the disease when the edema is the direct result of the secondary disease of the heart. It is sometimes necessary to watch the effect of treatment by digitalis or other drugs that act chiefly on the diseased heart before deciding as to the probability of an underlying

chronic interstitial nephritis. If the original abnormal features of the urine were the results of a passive congestion, such abnormalities will usually largely disappear as the condition of the heart improves by treatment.

It is often difficult, if not impossible, to distinguish between an *active hyperemia attended with low metabolism*, and a *late stage of a chronic interstitial nephritis attended with a very slight acute process* and without the presence of waxy casts in the sediment. About five years ago the author examined the urine of a man, aged seventy, in which the urinary picture was quite typical of an active hyperemia. Uremic coma developed two days later and death followed. At the autopsy very small, red, granular kidneys were found, indicative of a marked chronic interstitial nephritis. Of course, in such cases, a knowledge of the clinical history and the physical examination are of the greatest importance.

The usual prominent signs and symptoms of a chronic nephritis will, in most cases, serve to establish the diagnosis.

SENILE INTERSTITIAL NEPHRITIS.

Synonym.—Senile atrophy of the kidneys.

This form of disease usually occurs in persons after the age of from fifty to sixty ; but the disease is not necessarily present in every elderly person. It is usually a part of the general degeneration of the blood-vessels and sometimes a part of a general arteriosclerosis.

In the senile kidney the chief lesions are those due to disease of the vessels. These vascular lesions are accompanied by impairment in the power of regeneration. Previous lesions of the kidney, even though slight in character, may gradually make their influence felt in impairing the resistance of the tissue. The epithelial lesions may consist chiefly in atrophy. Microscopically, the kidney is usually more or less injected and atrophied. On microscopic examination the epithelium of the tubules is degenerated, small, and atrophic. The formation of yellow pigment in the atrophic epithelium is frequently seen. There is some general increase in the connective tissue, but this is chiefly marked close beneath the capsules, and may extend from here in lines into the cortex (Councilman).

Character of the Urine.—The urine does not bear the usual characteristics of the typical chronic interstitial

nephritis, but has more the appearance of a passive hyperemia.

The *quantity* is generally not far from 1500 c.c., and may even be considerably below the normal.

The *albumin* is, ordinarily, from the *slightest possible trace* to a *trace*.

The *normal solids* are absolutely diminished, but no more than would be expected in a person of advanced years when the metabolism is decidedly low. Relatively, they are about normal.

The *sediment* has practically the same appearance as in the early form of chronic interstitial nephritis—an occasional hyaline and granular cast and granular renal cell.

It may be impossible from the urine alone and without a knowledge of the case to make a positive diagnosis of a senile interstitial nephritis.

CHRONIC DIFFUSE NEPHRITIS.

Synonym.—Chronic diffuse nephritis with exudation.

Chronic diffuse nephritis is undoubtedly one of the most common of the chronic diseases of the kidney.

From a clinical point of view, this form of disease partakes essentially of two pathologic conditions : (1) An *interstitial element*, which is generally very prominent and shown by the increased twenty-four-hour quantity, pale color, low specific gravity, increased indoxyl, and relatively and absolutely diminished normal solids ; (2) a *parenchymatous element*, shown by the comparatively high percentage of albumin and the presence of fatty renal elements (fatty casts, fatty renal cells, etc.) in the sediment. Usually, the interstitial element is predominant, hence the characteristic features of the disease in a general way resemble those of a chronic interstitial nephritis.

Pathologically, the morbid processes in the kidney may consist of any one, or a combination of any, of the following conditions : *Chronic glomerular nephritis*, *chronic arteriosclerotic nephritis*, *chronic degenerative and interstitial nephritis*.

In *chronic glomerular nephritis* the essential lesions are in the glomeruli, and consist of extensive hyaline degeneration of tufts and of entire glomeruli, and obliteration of capillaries. Every transition may be seen between these

glomerular lesions and those in the subacute form of nephritis. There may be some increase in the capsular epithelium and connective-tissue formation within the capsule. The tubular epithelium shows extensive degeneration and destruction. Entire tubules are destroyed, often being represented by the thickened irregular membrana propria. There is a general and diffuse increase of the connective tissue affecting almost equally all parts of the kidney. This condition is usually found as an independent affection, or it may be combined with acute infections of various sorts, when there is often a history that points to a previous acute or subacute affection. The kidney may be slightly larger than normal, of normal size, or considerably smaller than normal. The capsule is often adherent, the surface even, not granular, and pale. On section, the cortex varies in width; it may be quite small, opaque, whitish, the markings obscure, the glomeruli not visible nor pale, and the consistence of the tissue greatly increased (Councilman).

(For the pathologic description of chronic arteriosclerotic nephritis and of chronic degenerative and interstitial nephritis, see pp. 307, 308.)

Causes.—The causes of a chronic diffuse nephritis are, in some instances, probably the same as those of chronic interstitial nephritis. The disease sometimes follows an acute nephritis in which the stage of convalescence has been prolonged for many months or years. The author has met with a few cases in which a chronic diffuse nephritis followed an acute nephritis of pregnancy.

Prominent Symptoms.—In the majority of cases of chronic diffuse nephritis the symptoms are, in many respects, the same as in chronic interstitial nephritis. But in this disease there is constantly more or less edema, which is usually slight during the early stages, becoming more marked as the disease advances, when general dropsy may be extreme. There is usually gastric disturbance and frequency of micturition, accompanied by an increase in the daily quantity. Circulatory disturbances are more or less marked, especially when the disease forms a part of a general arteriosclerosis. Anemia, a pasty appearance of the skin, emaciation, and visual disorders are not uncommon. Uremic symptoms are frequently met with, especially in advanced cases, or as the result of acute exacerbations.

The characteristics of the urine of the average advanced case of chronic diffuse nephritis are as follows :

Character of the Urine.—Quantity.—The average quantity is about 2000 c.c. It may be considerably higher—3000 c.c.—or lower,—1500 c.c.,—and it may occasionally be below the normal, but only temporarily. The quantity of urine at night often exceeds that of the day.

Color.—Pale and sometimes greenish.

Specific Gravity.—Average 1010 to 1015. If the twenty-four-hour quantity is unusually high, the specific gravity may be from 1004 to 1008.

Normal Solids.—*Absolutely*, diminished and sometimes to a marked degree; *relatively*, much diminished. The indoxyl is generally normal or increased.

Albumin.—This varies between a *large trace* and ½ of 1 per cent., but the average is usually between ⅛ and ¼ of 1 per cent. The quantity of albumin is much larger than in chronic interstitial nephritis and smaller than in subacute glomerular nephritis.

Sediment.—This is generally slight in quantity, and consists of numerous hyaline and granular casts, mostly with fat adherent; an occasional (or few) fatty cast; numerous renal cells, most of which are fatty, and a few compound granule cells. No blood is seen unless complicated. If the disease is far advanced, a few waxy casts will be found; occasionally, they are present in large numbers. When waxy casts appear in the sediment, the twenty-four-hour quantity of urine will usually be less than normal.

In case the *parenchymatous element* predominates the quantity of urine will be not far from the normal (1500 c.c.), the specific gravity and quantity of albumin will be correspondingly high, and the amount of fat in the sediment will be greater than indicated above. If, on the other hand, the *interstitial element* predominates, the quantity of urine will be large (2500 to 3000 c.c.), the specific gravity and quantity of albumin correspondingly low, and the amount of fat comparatively small.

Differential Diagnosis.—In the diagnosis of chronic diffuse nephritis special attention should be paid to the twenty-four-hour quantity of urine, which, if permanently increased, will usually serve to distinguish it from a *subacute glomerular nephritis*. In some instances of chronic diffuse nephritis, notably following an acute exacerbation while the

dropsy is still marked, the total quantity of urine is often less than normal, the quantity of albumin is very large, and the amount of fat is excessive. Under these circumstances it is usually impossible from the urine alone to distinguish the condition from a subacute glomerular nephritis, without watching the urine for a considerable period. It is often impossible to differentiate between a chronic diffuse nephritis near death, and a subacute glomerular nephritis also near death.

A chronic diffuse nephritis is distinguished from an *uncomplicated chronic interstitial nephritis* by the presence of fat in the sediment, the comparatively high quantity of albumin, and, upon physical examination, the presence of edema in the former disease.

The **duration** of chronic diffuse nephritis will depend largely on whether the interstitial or the parenchymatous element predominates. If the former, the patient may live from ten to fifteen years, providing he has the best of care; on the other hand, if the parenchymatous element is predominant, the duration of life is usually between five and ten years. As in subacute glomerular nephritis, acute exacerbations are very likely to occur, and if they are very numerous, the duration of life may not exceed from five to eight years, and often death occurs within a much shorter period.

The **prognosis** is, in most cases, grave. The appearance of waxy casts in the sediment is an unfavorable sign; death will probably occur within one year.

AMYLOID INFILTRATION.

Synonyms.—Lardaceous kidney; waxy degeneration; chronic depurative disease of the kidneys.

Amyloid infiltration is a disease that is not confined alone to the kidneys. The lesions are usually prominent in other organs of the body as well—notably the liver and spleen.

In amyloid infiltration, as the name implies, the characteristic lesion is the amyloid infiltration about the blood-vessels; consequently, the portion of the kidney that is most seriously affected is the glomerulus. There may be small masses of amyloid along the vascular loops, or the entire glomerulus may be converted into a glassy, homogeneous mass, the result of the deposit of the amyloid material. Usually,

some of the glomeruli are only moderately affected, hence the functions of the kidneys are maintained for some period.

The amyloid material is stained a mahogany-brown color by iodine, whereas the unaffected tissue takes a delicate yellow stain; and a rose-red color by methyl-violet, the undiseased tissue being stained blue.

Causes.—Amyloid infiltration is often an accompaniment of syphilis, phthisis, tubercular disease of the joints, chronic suppuration of the bones, and chronic wasting diseases. The exact reason for amyloid infiltration in these conditions is not known.

Prominent Symptoms.—The features of the urine alone may not definitely indicate the presence of this disease. Usually, the associated conditions (syphilis, tuberculosis, etc.) give hints as to the nature of the process. The liver and spleen are usually enlarged. Diarrhea is a common symptom. Increased arterial tension and cardiac hypertrophy are not usually present, except in those cases in which amyloid infiltration occurs in the secondary contracted kidney. Under these circumstances there may be uremia and retinal changes, which, as a rule, are not met with in uncomplicated amyloid infiltration. Frequency of micturition and the elimination of a large quantity of urine in twenty-four hours are often important and early signs. It is essential that the clinical history, the physical examination, and the urine should receive equal weight in the diagnosis of amyloid infiltration; it rarely happens that the urine alone affords sufficient data for an accurate diagnosis.

Character of the Urine.—The urine of a well-advanced case of amyloid infiltration is as follows:

Quantity.—Usually, above 1500 c.c.; generally, between 2000 and 4000 c.c. The quantity of the day urine usually exceeds that of the night. Like the other chronic affections of the kidneys, the quantity generally falls to normal or below the normal a short time before death.

Color.—Generally, very pale; the urine often has a greenish tint.

Specific Gravity.—This is below the normal; it is usually found to vary between 1012 and 1018.

Normal Solids.—*Absolutely*, normal or slightly diminished, but dependent upon the metabolism. *Relatively*, much diminished, especially if the quantity of urine be very

large. The probable explanation of the normal quantity of solids in the urine is the fact that the parenchyma or secreting structure of the kidney does not become involved until late in the disease, the principal pathologic changes being about the blood-vessels. Absolutely, the indoxyl may be increased, but it is usually diminished.

Albumin.—In an uncomplicated case the quantity of albumin varies between a *trace* and ⅛ of 1 per cent.; only rarely does it exceed ⅛ of 1 per cent. On the other hand it may be less than a trace, particularly if the quantity of urine is in the neighborhood of 4000 c.c.

Sediment.—This is generally very slight in amount, and consists of a few hyaline, granular, and occasional (or few) waxy casts; rarely, a renal cell. No fat nor blood, unless complicated.

The waxy casts appear rather early in this disease, much sooner than in the other chronic diseases of the kidney. The question has often arisen as to whether the waxy casts found in amyloid disease were cylinders of amyloid material or of the same composition as those found near the end of other chronic affections of the kidney? The query still remains unsettled, for the reason that it is very difficult to satisfactorily stain the waxy casts by the stains ordinarily used for the detection of amyloid material. If the suspected sediment is first washed several times by decantation with a dilute solution of glycerine, and methyl-violet added, some of the casts (both waxy and hyaline) will be found to have a slight reddish tint. Further experiments are, however, necessary before any definite conclusions can be drawn from the use of stains.

Amyloid disease of the kidney is very apt to be complicated by parenchymatous degeneration; such changes are probably secondary to the extensive deposit of amyloid material in the glomeruli and the resulting interference with the nutrition of the renal epithelium. Sometimes this parenchymatous change is very marked, so that the urine will have the characteristics of chronic diffuse nephritis; or it may predominate to such an extent that the urine will resemble one of subacute glomerular nephritis, the evidences of amyloid being thereby obscured.

Differential Diagnosis.—In the diagnosis between an *uncomplicated amyloid infiltration* and a *chronic interstitial nephritis* the enlarged liver and spleen, an absence of increased

arterial tension and cardiac hypertrophy, and the history of syphilis, tuberculosis, etc., will usually indicate amyloid disease. From the urine alone it is impossible to distinguish with certainty between these two conditions. It should be said, however, that in amyloid infiltration the total solids and the total quantity of urea are usually higher than in chronic interstitial nephritis, but such a rule is by no means invariable, since amyloid disease is often accompanied by a chronic disease that very much diminishes the metabolism.

As previously stated, in considering the diagnosis of this disease the physical examination and clinical history should always be carefully weighed along with the characteristics of the urine.

The **duration** of this disease is largely dependent on the cause. As a rule, it extends over a period of several years —from ten to fifteen ; sometimes a longer, and occasionally a much shorter, time.

The **prognosis** depends rather on the condition with which this renal affection is associated. As a rule, it is grave.

CHAPTER IX.

DISEASES OF THE KIDNEYS (CONTINUED).

TUBERCULOSIS OF THE KIDNEYS.

Primary tuberculosis of the kidneys is not very rare. It occurs in two distinct forms—viz., *local caseating tuberculosis* and *acute miliary tuberculosis*. The latter form is always associated with tuberculosis in other parts of the body, such as phthisis pulmonalis and tubercular meningitis. This form rarely gives rise to distinct urinary symptoms. Local caseating tuberculosis, on the other hand, usually results in urinary symptoms to a marked degree, and it is this form that deserves special consideration in this connection.

The substance of the kidney may contain only a few, or there may be a large number of, tubercular nodules. The process very soon involves the pelvis of the kidney, and in a majority of the cases not only the pelvis but the ureter as well, and sometimes the bladder and prostate. It may be difficult to say in advanced cases whether the disease has started in the bladder, prostate, or seminal vesicles, and crept up the ureters, or whether it started in the kidneys and proceeded downward. Osler believes that in the majority of cases the latter is true, and the infection is through the blood. One kidney alone may be involved, and the disease creeps down the ureter and may involve the mucous membrane of the bladder to a greater or less extent. The process is common in the middle period of life, but it may occur in the extremes of age. It is more frequent in males than in females.

Prominent Symptoms.—The symptoms are usually those of chronic pyelitis. The urine may be purulent for years, and there may be little or no distress. Even before the bladder becomes involved micturition is often frequent, and many instances are mistaken for cystitis. The condi-

tion may be in progress for many years without marked impairment of health. In cases in which the disease becomes advanced and both organs are affected, constitutional symptoms are more marked. General tuberculosis is common. Intermittent hematuria is of frequent occurrence, denoting ulcerative changes in the mucous membrane of the tubules of the kidney.

Physical examination may detect special tenderness on one side, or the kidney may be palpable in front on deep pressure ; but a tuberculous kidney seldom causes a large tumor. Occasionally, the ureter becomes occluded and pyonephrosis results ; but this is rare in comparison with its frequency in calculous pyelitis.

Character of the Urine.—Early in tuberculosis of the kidney the urine is only slightly altered from the normal. There may be the slightest trace of albumin, and the sediment may contain only a very few leucocytes and an occasional blood globule. When, however, the disease becomes more advanced and ulcerative changes have begun, the urine will usually have the following characteristics :

Quantity.—The total quantity of urine for twenty-four hours is generally increased, although it may be normal or diminished.

Color.—Pale. The urine is usually more or less turbid, due to the pus, blood, etc., in suspension.

Reaction.—Generally acid, except when the urine contains an abundance of blood, when it may be faintly acid or alkaline.

Specific Gravity.—Usually below the normal—1010 to 1015, or thereabouts.

Normal Solids.—Both *relatively* and *absolutely*, diminished. If there is general advanced tuberculosis, the solids will be *absolutely* very low.

Albumin.—The quantity of albumin is dependent, in the first place, on the amount of destruction of the kidney, and, secondly, on the amount of pus and blood present. If the disintegration of the renal tissue is marked, the albumin is usually high, approximating from ¼ to ½ of 1 per cent. If, on the other hand, the tubercular process is localized and not extensive, the amount of albumin may not exceed a *slight trace*, or *trace*.

Sediment.—Abundant. Chiefly pus, which is usually free, but may be more or less clumped ; the pus may be

markedly degenerated. Many small round cells, some of which are usually fatty. Hyaline and granular casts, some of larger diameter, are usually present, but they may be so obscured by the pus as to escape detection. Blood is generally present, but sometimes in small amount; it may, however, be very abundant, intermittent hematuria being a common symptom of this disease. The sediment also contains tubercle bacilli.

To distinguish the condition from a calculous pyelitis is often difficult. Hemorrhage may be present in both conditions, though not nearly so frequently in the tuberculous disease. The diagnosis rests on three points: (1) The detection of some focus of tuberculosis, as in the testes; (2) the presence of tubercle bacilli in the sediment; and (3) the use of tuberculin. In women the kidney involved is now easily determined by catheterizing the ureters after the plan introduced by Kelly, of Baltimore. Dr. Edw. Reynolds, has recently reported a case of early tuberculosis of the kidney,[1] in which the author had the opportunity of making a careful study of the urine, and in which catheterization of the ureters led to the location of the disease.

Detection of Tubercle Bacilli in the Urinary Sediment.

Either centrifugalize the urine or allow the sediment to settle by gravity; decant the supernatant urine, and wash twice by decantation with distilled water. After the second washing, centrifugalize. The sediment is then taken up by means of a pipette and placed on from four to eight cover-glasses, which have been carefully cleansed in nitric acid and then in alcohol. Care should be exercised not to get too much sediment on the cover-glasses, for the layer may, after drying, be too thick, especially if there is much pus in the sediment. These cover-glass preparations are then dried by placing them on an iron or copper plate, under which is placed a very small flame (about ¼ of an inch in height will suffice), the main object being to get very gentle heat so that the specimens will be dried slowly and without being charred. Stain the dried preparations with either carbol-fuchsin (Ziehl-Neelson) or aniline water and fuchsin (Koch-Ehrlich) in the usual manner. Decolorize in 20 per cent. nitric acid, wash in water, and, finally, *still*

[1] "Johns Hopkins Bulletin," Nov., 1898, p. 253.

further decolorize in 70 per cent. alcohol for at least ten minutes. Then stain with an aqueous solution of methylene-blue, mount, and examine.

It is very important that the preparations should be thoroughly decolorized in alcohol in order to be able to distinguish between tubercle bacilli and smegma bacilli; the latter being quite readily decolorized by this means, while the former are not affected. A very close resemblance exists between these two organisms. At times the smegma bacillus appears thicker than the tubercle bacillus, and sometimes the ends have a clubbed appearance, but this is not true in all instances; consequently, the data thus far at hand are of no differential importance. Smegma bacilli are not uncommon in the urine of both male and female, particularly in the urine of those who are not cleanly. It is obvious that special care should be taken in procuring a specimen that is to be examined for tubercle bacilli. Since in those individuals who are not cleanly the smegma collect about the genitalia, it is essential that these parts be thoroughly cleansed before the urine is voided. A still better procedure is to procure a catheter specimen, if possible. Attention to these details contributes materially to a satisfactory result of the examination.

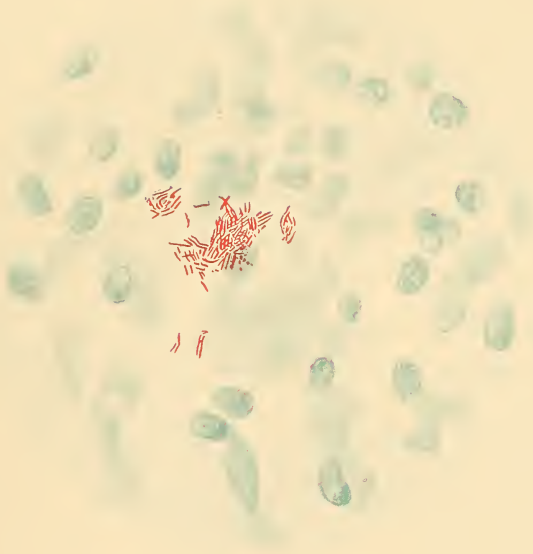
Tubercle bacilli in the urine are usually arranged in groups (Plate 9), although they may occur singly. They may be present in large numbers and easily found; on the other hand, they may be rare and escape detection even after prolonged examination. The fact that tubercle bacilli can not be found in a urinary sediment does not, then, prove their absence. In all suspicious cases a portion of the sediment (½ to 1 c.c.) should be injected into the peritoneal cavity of a guinea-pig. If the bacilli are present, the animal will develop tuberculosis in from six to eight weeks; if not present, the animal will not be affected by the inoculation. This constitutes the safest method for the detection of tubercle bacilli in urine.

RENAL CALCULUS.

Calculi may originate in the secreting structure of the kidney,—usually in the tubules,—forming cavities for their location in the parenchyma of the organ.

Renal calculus is usually unilateral, though there are

Plate 9



Tubercle Bacilli in Urinary Sediment; × 800. (Personal Observation.)

many exceptions to this rule. The calculus, when large, is usually single, the smaller ones being more apt to be multiple.

Renal calculus occurs at all ages, including intra-uterine life. It is, however, most common before fifteen, and after fifty, years of age. In young people and children calculi are most frequent among the poor, while the condition in advancing life is most common in people in comfortable circumstances and of luxurious habits. As a rule, the calculi in infancy are composed of ammonium urate; those in young adults, uric acid; those after fifty years of age are made up of either uric acid or calcium oxalate.

Prominent Symptoms.—These consist of dull aching pain situated deeply in the loin, usually unilateral, and often radiating along the ureter toward the testicle or labia, down the thigh, and sometimes extending as far as the foot. The pain may be sharp and lancinating at times. When a stone enters the ureter, intensely severe paroxysms of pain (renal colic) are usually experienced, lasting a few hours and then suddenly subsiding. The ordinary pain of renal calculus is nearly always increased by exercise—walking or riding. There is often tenderness upon deep pressure anteriorly, especially if the calculus has excited much inflammation. Gastric disturbances are common, including nausea, vomiting, and periods of more or less disordered digestion, hyperacidity, flatulence, etc.

Character of the Urine.—The urine is usually highly concentrated, of high color, high specific gravity, and sharply acid reaction. Sometimes it has a decided smoky color, because of the presence of altered blood pigment. *Relatively*, the solids are generally increased; *absolutely*, about normal, providing the patient is in good general condition; as a rule, the normal solids will depend upon the metabolism.

The amount of albumin depends on the extent of the irritation and the quantity of blood.

The **sediment** is usually that of an active hyperemia or irritation of the kidneys. It is not uncommon to find crystals or microscopic concretions of the same substance as the calculus that is being formed in the kidney. There may be a considerable quantity of blood, which is usually abnormal in character, providing the hemorrhage is not abundant; if profuse, there is generally more or less normal blood. The

sediment may or may not contain pus. It is more common perhaps to find only a few leucocytes rather than an abundance of pus. If much pus is present, it is probable that either an abscess of the kidney or a chronic pyelitis has been produced by the stone.

Renal calculi usually consist of either uric acid or urates, calcium oxalate, or cystin. Occasionally, the calculus is the result of a deposit of phosphates in the kidney. Such a deposition is always secondary to an extension upward from the bladder or pelvis of the kidney. In case of a phosphatic calculus in the kidney the urine is usually pale in color, with an alkaline reaction, and an abundant deposit of phosphates in the urinary sediment.

ABSCESS OF THE KIDNEY.

Abscess of the kidney is usually due either to injury of the organ, to an encysted concretion that sets up a marked irritation in some portion of the kidney, or to tubercular disease of the organ.

The condition is accompanied by the usual symptoms of an abscess in any part of the body—viz., fever, localized pain, cachexia, marked languor, nausea and vomiting, etc. On the affected side there may be a distinct tumor, which, on manipulation, is found to be extremely tender ; again, the condition may exist without tumor.

The abscess usually ruptures into the pelvis of the kidney or into the renal tubules, and the urine that was free from pus will suddenly contain a large amount of it.

Character of the Urine.—The urine generally has the characteristics of a fever urine—high color, high specific gravity, strongly acid reaction, and containing a *very slight trace* or a *trace* of albumin. The *sediment* usually has the appearance of one of active hyperemia, which may be mild or severe, according to the extent of the inflammatory process (circumscribed acute nephritis) about the abscess, and the degree of disturbance that is invariably set up as a result of the elimination of toxines by the healthy kidney. As soon as the abscess evacuates into the urinary tract, the sediment, which is abundant and usually of a *greenish color*, contains an abundance of degenerated pus, many small round cells, usually a few compound granule cells, and more or less blood. There is frequently hematuria fol-

lowing the evacuation of the abscess, especially if any of the renal blood-vessels have been ruptured. This hemorrhage may be slight and of short duration if due to injury of the capillaries, and may be extensive and persistent if one or more of the larger vessels have been ruptured.

The sudden appearance of a large amount of blood and pus in a urine that has previously been clear and free from these elements is strongly suggestive of abscess of the kidney, especially when taken in conjunction with the clinical history and symptoms. A diagnosis of this condition can not be made from the urine alone previous to the rupture of the abscess and without a clinical knowledge of the case.

The **prognosis** is usually grave when the disease is of tubercular origin. When it is due to trauma or to an encysted concretion, the prognosis is often good if an early diagnosis is made. Occasionally, recovery follows drainage of the pus-sac, and in rare instances spontaneous recovery takes place, particularly when the destructive changes are only slight. In most cases of abscess of the kidney surgical interference is necessary.

RENAL EMBOLISM.

Renal embolism consists of an impacted thrombus that has formed in some part of the circulatory system,—usually on the valves of the heart,—and is carried by the blood current to the kidney, where it occludes one of the renal vessels. The anatomic changes resulting from renal embolism are very constant and striking, and the condition is quite commonly found at the autopsy, although only rarely recognized during life.

Prominent Symptoms.—A previous history of endocarditis is generally found. The sudden pain that usually accompanies the occlusion of the renal vessel may be severe, often followed by nausea and vomiting, and sometimes by a state of collapse. On the other hand, the pain may be comparatively slight, although usually persistent for some time. Chills and a more or less irregular temperature are frequent accompaniments of this condition.

Character of the Urine.—From the urine alone the diagnosis of a renal embolism is practically impossible.

The urinary changes usually begin abruptly, and the urine suddenly has the characteristics of one accompanying fever. The urine is usually much diminished in quantity, of high color, and high specific gravity—1025 to 1035. Relatively, the normal solids are increased ; absolutely, normal or slightly diminished. The quantity of albumin depends upon the extent of the disturbance in the neighborhood of the area affected by the embolus. The sediment usually has the characteristics of a more or less severe active hyperemia or a circumscribed acute nephritis, which is in progress around the diseased area.

TUMORS OF THE KIDNEY.

These are benign or malignant. Of the benign tumors, the most common are the *fibromata ; lipomata, lymph-adenomata,* and *angiomata* are constantly met with. *Adenomata* may be congenital. Malignant growths—*sarcoma* or *carcinoma*—may be either primary or secondary. Sarcomata are the more common.

Tumors of the kidney grow rapidly and may attain a very large size—12 to 30 pounds. They are often soft, and hemorrhages frequently occur in them. In sarcomata invasion of the pelvis or of the renal vein is common. In almost all instances tumor is present. An increasing tumor in the anterior lumbar region, between the costal arch and the crest of the ilium, is always suggestive of renal tumor. The tumors are usually fixed, although they may be movable ; they are frequently lobulated.

Prominent Symptoms.—*Hematuria.*—This may be the first indication. The blood is fluid or clotted ; sometimes a blood-clot is passed having the appearance of a cast of the ureter.

Progressive Emaciation.—Loss of flesh is usually marked and advances rapidly.

Pain.—This is generally present, and of a dull aching character, situated in the flank and radiating down the thigh. The pressure of the tumor often causes severe and alarming symptoms, such as edema of the feet and legs, ascites, disturbances of the stomach, various neuroses,—the result of pressure on the large nerve-trunks,—and anemia. There is often frequent micturition, which may be so marked as to indicate a disease of the bladder when only the kidney is involved.

Character of the Urine.—Perhaps the most prominent feature of the urine is the presence of more or less blood—hematuria; occasionally, the amount of fresh blood is very large, but this is not true in every case. The urine usually shows evidence of a circumscribed inflammation or congestion of the kidney in the neighborhood of the new growth: in other words, the urine presents the picture of a more or less severe active hyperemia of the kidney. Pus is generally absent in the sediment, save in advanced cases attended with decided destructive changes in the kidney or changes in the new growth itself. Under such circumstances the quantity of pus is comparatively small, considering the extent of the necrotic changes. Rarely, cancer elements can be recognized in the urinary sediment. Occasionally, the presence of a large number of epithelial cells with large and prominent nuclei and of various shapes is strongly suggestive of new growth, especially if the mucous membrane of the pelvis is involved or has become ulcerated. The presence in the sediment of organized elements, such as renal casts, renal cells, etc., is of little or no diagnostic value in renal cancer.

A **diagnosis** of renal cancer from the urine alone is only of the rarest occurrence, and then only in case particles of the morbid growth with a distinct alveolar structure are discovered in the sediment; but in malignant disease limited to the parenchyma of the kidney the appearance of portions of the growth in the sediment is practically unknown.

CYSTIC DISEASE OF THE KIDNEYS.

Cystic disease of the kidneys is probably the result, in most cases, of some obstruction to the outflow of urine through one or more renal tubules. Three varieties of cysts are met with:

1. *Small cysts*, seen especially in chronic interstitial nephritis, resulting from dilatation of obstructed tubules or Bowman's capsule.

2. *Solitary cysts*, ranging in size from a marble to an orange, or even larger, without evidences of other changes in the kidney.

3. *Congenital cystic kidneys.* In this condition the kidneys are represented by a conglomeration of cysts varying in size from a pea to a marble. The organs are greatly en-

larged, and together may weigh from seven to ten pounds. In the fetus they may attain a size sufficient to impede labor. Little or no renal tissue may be noticeable, although on microscopic examination it is seen that a considerable amount remains in the interspaces.

The *cystic fluid* is usually clear, but it may be turbid, and sometimes reddish-brown or even black in color; occasionally, it is viscid. Specific gravity is usually low. Albumin, blood-corpuscles, and sometimes hematoidin crystals, leucocytes, cholesterin, triple phosphates, and fat globules are found in the contents. Urea and uric acid are present only in traces. The contents of one cyst may have an entirely different character from those of an adjacent cyst.

Character of the Urine.—In general the character of the urine is that of a chronic interstitial nephritis. In some instances the urine is not abnormal, especially in those cases in which there are no other changes in the kidney.

The **diagnosis** of cystic disease of the kidney can not be made with certainty from the urine alone. The condition, especially the congenital form, may exist unsuspected until found at the autopsy, death being the result of some other disease. Great enlargement of both kidneys, with hypertrophy of the left ventricle and increased arterial tension, would suggest cystic disease.

Operative interference is not justifiable. It is important to remember that the conglomerate cystic kidney is almost invariably bilateral. Osler cites an instance in which one kidney was removed and the patient died within twenty-four hours from cystic disease of the other kidney.

CHAPTER X.

DISEASES OF THE URINARY TRACT BELOW THE KIDNEY PROPER.

The diseases of the urinary tract below the kidney proper have received names according to their location and their duration. They are, for the most part, inflammatory in character, and may be either acute or chronic. In a consideration of the urine of all such diseases, the quantity of albumin, the total amount of urea, and the character of the sediment are of special importance for purposes of diagnosis.

PYELITIS.

This is an inflammation of the mucous membrane of the pelvis of the kidney; it may be either acute or chronic.

ACUTE PYELITIS.

An acute inflammation of the pelvis of the kidney may be either mild or severe, and local or general. Primary acute pyelitis is not of common occurrence, but is usually found to exist as an accompaniment or a complication of an acute disease of the kidney proper.

Causes.—The disease is usually produced in one of three ways: (1) By the extension of an inflammatory process downward from the kidney; (2) by the upward extension of disease of the bladder; (3) by irritants confined within the pelvic cavity itself. An acute nephritis is usually accompanied by a more or less severe acute pyelitis (see p. 297)—in other words, the irritant that has set up the nephritis has also had its irritating influence on the mucous membrane of the pelvis by extension downward. Not infrequently an acute pyelitis (together with an acute nephritis) follows exposure to cold and wet, and it may be set up by the irritating action of the

toxines of certain acute infectious diseases, such as typhoid fever, scarlet fever, diphtheria, and septicemia. A gonorrheal infection of the lower urinary tract may, by extension, result in an acute pyelitis, and sometimes, later, an acute nephritis. When an acute pyelitis occurs without an accompanying acute nephritis or disease of the lower urinary passages, it is almost invariably due to the irritating action of crystalline elements or to a small concretion within the pelvic cavity. If due to a concretion, the inflammatory process may be circumscribed. Rarely, the pressure of a new growth, which is located outside of the urinary tract, on the pelvis of the kidney results in an acute pyelitis.

Prominent Symptoms.—There is usually more or less pain referred to the region of the affected kidney or kidneys, and it is often found radiating along the course of the ureter toward the groin. There is frequently some fever, although, as a rule, the temperature is not high. The disease may, however, be ushered in by a chill or a succession of rigors followed by a high temperature for a day or two. Hematuria is an early symptom, and usually continues for several days. The patient may suffer from renal colic, caused by the marked irritation of crystalline elements or by a calculus or blood-clot obstructing the outflow of urine through the ureter. Rarely, a pyonephrosis results from obstruction in the ureter. Micturition is more frequent than normal. The symptoms of an accompanying acute nephritis or a cystitis are often sufficiently prominent to entirely obscure those that are referable to the pelvis itself.

Character of the Urine.—The urine of a simple acute pyelitis, without much involvement of the kidney proper, usually has the characteristics of a fever urine.

Quantity.—Considerably diminished—*i. e.*, from 400 to 800 or 1000 c.c.

Color.—High, and frequently smoky, sometimes a blood-red color, depending upon the amount and character of the blood present.

Specific Gravity.—This is generally higher than normal —1025 to 1030, or as high as 1035.

Normal Solids.—*Absolutely*, diminished; *relatively*, increased.

Albumin.—The quantity of albumin is variable, but in a general way corresponds to the amount of blood and pus present. As a rule, the quantity of albumin is chiefly rela-

tive to the amount of blood rather than to the quantity of pus present. The quantity usually varies between a *slight trace* and ¼ of 1 per cent.

Sediment.—Chiefly normal blood. Numerous small caudate cells from the superficial layer of the pelvis of the kidney. Some pus, both free and in clumps. There are, frequently, clumps of small, medium, or large round cells from the calices of the kidney. Since there is nearly always some extension of the inflammatory process into the straight tubules, a few (or occasional) granular and brown granular casts with adherent renal cells from the straight tubules, and abnormal blood will be found. If the tubular involvement is marked, the number of casts will be much larger, and the general characteristics of the urine will approach those of an acute nephritis complicated by an acute pyelitis. The presence of crystals or crystalline fragments should always be noted, for they may be the cause of the pyelitis, or may lead to the diagnosis of a calculus and the probable composition of the same.

An acute pyelitis as a complication of an acute nephritis or the result of an irritant toxine usually disappears with the subsidence of the primary affection. Sometimes it lasts only a few days and then, quite suddenly, the urine and sediment bear the characteristics of a chronic pyelitis. When the disease is due to the presence of a concretion or to a gonorrheal infection, it very soon becomes chronic, and may continue for months or years as a chronic pyelitis.

CHRONIC PYELITIS.

This is a chronic inflammation of the mucous membrane of the pelvis of the kidney. It may be mild or severe, and local or general.

Causes.—A chronic pyelitis is induced by a variety of causes, among which the following are the most important: (1) The irritation by crystals or calculi—a very common cause. (2) Tuberculosis. (3) The infectious pyelitis that develops in fevers, in which an acute pyelitis precedes the chronic inflammation. (4) Obstruction to the outflow of urine through the ureter, as by an impacted calculus, blood-clot, stricture or twist of the ureter, etc. (5) The presence of decomposing urine, following pressure upon the ureter by tumors located outside the urinary tract. (6) A frequent cause of a chronic pyelitis is the upward extension of an

inflammation of the bladder. (7) Obstruction to the outflow of urine by a tight stricture of the urethra, a very narrow prepuce, or tumor of the bladder. (8) Movable kidney.

Prominent Symptoms.—In the forms of chronic pyelitis associated with the acute febrile diseases symptoms may be wanting. There may be more or less pain in the region of the affected organ. If, at any time, there is retention of the pus as the result of obstruction in the ureter or bladder, chills followed by fever, sweats, and sometimes renal colic ensue. Such symptoms rapidly disappear following an evacuation of the pus, but spontaneous evacuation of the pus cavity (renal pelvis) may not take place; under these circumstances a true pyonephrosis results. Aside from twists of the ureter, perhaps the most common cause of frequent attacks of retention of pus, followed in a few days by evacuation of the pus cavity, is the presence of calculi in the renal pelvis, the obstruction being removed by a change of position or other means. A pyonephrosis with its attending symptoms is not an uncommon outcome of a chronic pyelitis.

Character of the Urine.—The urine has the general characteristics of one of a chronic disease.

Quantity.—Usually, less than normal—about 1200 c.c.

Color.—Pale. The urine is generally very turbid, due to the pus in suspension.

Reaction.—Usually, faintly acid. The urine readily becomes alkaline upon standing.

Specific Gravity.—This is below the normal—1010 to 1015.

Normal Solids.—Both *absolutely* and *relatively*, diminished. The absolute quantity of urea will usually be found to vary between 15 and 25 grams; the extent of the diminution will depend upon the metabolism.

Albumin.—This is relative chiefly to the amount of blood and pus present; if the kidney proper is only slightly involved, the albumin will generally vary between a *very slight trace* and a *large trace*.

Sediment.—Chiefly degenerated pus, both free and in clumps; many small round cells, some in the clumps of pus; a few blood globules. In most cases there is more or less involvement of the straight tubules of the kidney; but renal casts are often difficult of detection in the sediment, owing to the presence of the pus which obscures them.

In a chronic pyelitis the casts present, are usually of large diameter, and they may have leucocytes adherent to them, or there may be true pus casts.

A careful search should always be made for crystals or crystalline fragments, and when present the diagnosis of a calculous pyelitis is rendered probable. On the other hand, a concretion may exist in the renal pelvis without the presence of any formed crystals, or crystalline elements, in the sediment. Great care should be taken not to mistake extraneous particles of dust, pieces of broken glass, etc., for fragments of a calculus.

The urinary sediment should in all doubtful cases be examined for tubercle bacilli, for it is only by this means that a tubercular pyelitis can be eliminated.

The diagnosis of a new growth involving the pelvis of the kidney is very difficult from the urine alone. Rarely, the presence of an unusual number of cellular elements leads to such a diagnosis, but such inferences should be well guarded by clinical signs and symptoms.

Duration and Prognosis.—A chronic pyelitis usually disappears with the removal of the cause, if such is possible. If due to tuberculosis or a new growth of the kidney and its pelvis, surgical interference is usually necessary.

There is constant danger of disease of the healthy kidney, and when it occurs, there is, unfortunately, little that can be done to relieve the condition. The disease in a mild form may continue for years without causing, in itself, much suffering. This is especially the case when the disease is caused by accidental twists of the ureter as in floating kidney, in which instance the urine is retained in the renal pelvis until a time when the pressure of the retained fluid becomes sufficient to force its escape, or until the kidney regains its normal position by a sudden change of position of the patient, or until it is replaced by surgical operation. When the kidney is stitched into position, the chronic pyelitis usually subsides in a short time ; otherwise the disease may continue in a mild form as long as these temporary twists of the ureter occur.

CALCULOUS PYELITIS.

Although this subject has been considered in connection with an acute and chronic pyelitis, it deserves special attention because of its importance.

Calculi that cause pyelitis may be large or small, and may be free in the pelvis or become encysted. They often have projections that extend up into the calices and sometimes into the straight tubules; the tubules thus obstructed become dilated by the purulent urine, and often result in abscesses. When the pressure of the fluid in the abscess sac becomes sufficient to dislodge the obstructing calculus, the urine suddenly contains a large amount of pus, which is almost invariably of a *greenish* color. Sometimes there is a gradual leakage of pus about the seat of the obstruction, and not infrequently the abscess connects with one or more tubules, so that the urine constantly contains pus, and often in enormous quantities. The author has recently seen a case of multiple abscess of the kidney due to a large calculus in the pelvis, in which the pus sacs apparently had a common opening from which an enormous amount of pus was discharged—nearly one-fourth of the twenty-four-hour urine being thick greenish pus.

In calculous pyelitis there may be only slight turbidity of the mucous membrane, such a condition being sometimes called *catarrhal pyelitis*. More commonly, the mucous surface is roughened, grayish in color, and thick. Under these circumstances there are almost always more or less dilatation of the calices and flattening of the papillæ. Following this condition there may be (1) extension of the suppurative process to the kidney itself, forming a pyelonephritis. (2) A gradual dilatation of the calices with atrophy of the kidney substance, and, finally, the production of the condition of pyonephrosis in which the entire organ is represented by a sac of pus with or without a thin shell of renal tissue. (3) After the kidney structure has been destroyed by suppuration, if the obstruction at the orifice of the pelvis persists, the fluid portions may be absorbed, and the pus become inspissated, so that the organ is represented by a series of sacculi containing grayish pap-like masses, which have become impregnated with lime-salts.

Prominent Symptoms.—The symptoms are, for the most part, the same as those in chronic pyelitis. There may be pain in the back or there may be tenderness on deep pressure on the affected side. Before the condition of pyuria is established, besides the attacks of pain, there may be rigors, high fever, and sweats. Pain is often increased by exercise,—walking or riding,—but not in all cases.

Coincident with the retention of pus, a tumor may be felt on the affected side. The general condition of the patient usually indicates prolonged suppuration. Occasionally, nervous symptoms, which may be associated with dyspnea, supervene; or the termination may be by coma. These nervous phenomena have been attributed to the absorption of the decomposed materials from the seat of the disease.

Character of the Urine.—The urine generally has the characteristics of an acute or a chronic pyelitis. The most predominant element in the sediment is the pus, which is often present in large quantity. There is usually more or less blood, and sometimes it is present in considerable quantity. The sediment may, or may not, contain crystalline elements or concretions; the mere absence of crystals would not be sufficient ground for excluding the condition of calculous pyelitis.

Usually, the other (unaffected) kidney is more or less congested as a result of the elimination of toxines from the diseased organ. This is especially the case in chronic pyelitis or abscess of the kidney due to a stone, but it is often very difficult to find renal casts in the presence of so much pus.

Diagnosis. — Between the tuberculous and calculous forms of pyelitis it may be difficult or impossible to distinguish, except by the detection of tubercle bacilli in the urinary sediment. The examination for tubercle bacilli should be made systematically in all suspicious cases, and if not found by the microscope, guinea-pigs should be inoculated with a portion of the sediment.

HYDRONEPHROSIS.

This is a condition due to an obstruction in the ureter and the retention of *nonpurulent urine* in the pelvis of the kidney. If the obstruction continues, the pelvis of the kidney becomes extremely dilated, and as a result of the back pressure there is a marked dilatation of the straight tubules, and then the smaller tubules. Finally, the kidney and its pelvis are converted into a sac, which may be of sufficient size to produce a tumor on the affected side. The kidney soon loses its function after the urine begins to back up into the small tubules, and, finally, the entire work of secretion and excretion is thrown on the other kidney.

About from thirty-five to forty per cent. of these cases are congenital, the remainder may be acquired. The *congenital causes* comprise twists of the ureter upon its axis, undue obliquity of the ureteral opening into the bladder, reduplication, valve-like folds of the mucous membrane of the ureter, and imperforate ureter. The *acquired causes* are (1) an impaction of a calculus; (2) a blood-clot in the ureter; (3) stricture of the ureter, especially following traumatism; (4) twist of the ureter, particularly in case of "floating kidney," and if due to this cause, the condition usually continues until the pressure becomes sufficient to force an opening and allow the fluid to escape (intermittent hydronephrosis); (5) new growth in the pelvis or ureter, or one outside of the urinary tract, causing marked pressure on the ureter.

Prominent Symptoms.—A dull, aching pain is usually present in the renal region. A tumor is present in most cases, gradually encroaching on the median line and downward toward the iliac fossa. A sudden diminution in the size of the tumor coincident with the elimination of an unusual quantity of nonpurulent urine, may be considered diagnostic. Vomiting sometimes occurs during these periods of retention, and occasionally a urinous odor may be observed in the perspiration at such times, especially if both kidneys are involved. Constipation is a frequent result of pressure upon the colon; more rarely, diarrhea may be present from the same cause. As long as the hydronephrosis is single and the remaining kidney healthy, there is usually an absence of uremic symptoms. Enlargement of the unaffected kidney may compensate for the defective elimination. Hypertrophy of the left side of the heart usually follows.

Character of the Urine.—Owing to the virtual loss of function of the affected kidney, the entire work of elimination is thrown on the other kidney and, as a result, it is common to find evidence of more or less active congestion of the unaffected organ. (See Active Hyperemia.) The quantity of urine is generally diminished; the normal solids are *absolutely* diminished, although not to a marked degree; and there is usually albumin, varying between the *slightest possible trace* and a *trace*. The *sediment* usually contains an occasional (or few) hyaline, granular, and brown granular casts, some of which have renal cells and a little abnormal blood adherent; and a few free renal cells and blood globules.

In rare instances the urine may be perfectly normal.

The *fluid in the hydronephrotic sac* is usually of a pale color, of low specific gravity, and contains only small amounts of the normal urinary constituents, notably urea and uric acid. Albumin is generally present, the quantity being in the neighborhood of a *trace*. The *sediment* usually consists of a few blood globules, cells from the pelvis and tubules of the kidney, and a few casts of small diameter from the higher tubules. There is no pus, or, at the most, only an occasional leucocyte.

The outlook in hydronephrosis depends upon the cause. When unilateral, the condition may never produce serious trouble, and the intermittent forms may persist for years and finally disappear. Occasionally, the cyst ruptures into the peritoneum, more rarely through the diaphragm into the pleural cavity and lung. The sac may discharge spontaneously through the ureter and the fluid never reaccumulate, or the condition may change to one of pyonephrosis.

PYONEPHROSIS.

This condition is the result of an obstruction to the outflow of urine through the ureter, and the retention of *purulent* urine in the renal pelvis. It usually follows a preexisting acute or chronic pyelitis, although it may exist primarily as a hydronephrosis, and later become a pyonephrosis as a result of the inflammatory process set up by chemic or mechanical irritants in the pelvis—notably crystalline elements or a calculus.

The destruction of the kidney is sometimes very rapid, because of the retained pus-containing fluid and the extension of the inflammatory process to various parts of the kidney proper. As in hydronephrosis, the back pressure of the retained fluid results, first, in a marked dilatation of the renal pelvis ; next, the straight tubules ; then, the smaller tubes, which become atrophied and lose their function ; and, finally, the disorganized kidney and its pelvis constitute a large pus sac.

Causes.—Any of the causes ascribed to a hydronephrosis may produce a pyonephrosis by partially or entirely occluding the ureter, if a pyogenic organism be present. Of these the most common are impacted calculus, twist of the ureter in case of "floating kidney," and trau-

matic or inflammatory stricture of the ureter. Marked pressure on the ureter or the pelvis of the kidney by new growths that are situated outside of the urinary tract may produce this condition.

Prominent Symptoms.—The most prominent symptoms of pyonephrosis comprise pyuria with constitutional symptoms, such as chills, irregular temperature, emaciation, anemia, and prostration. If there is a tumor, it may be elastic and fluctuating, or hard, and extend both forward and downward. Pain is present, varying with the size of the tumor and degree of fluctuation; it often appears in paroxysms of intensity—*renal colic.* Pressure over the anterior of the tumor greatly increases the pain, or causes it if not present before. On the other hand, lateral pressure may relieve the pain when present. The bowels are usually disturbed, constipation or diarrhea being frequent. The sudden appearance of a purulent urine that has previously been clear and free from pus is often of great diagnostic value.

Character of the Urine.—If the pyonephrosis is unilateral and the occlusion of the ureter on the affected side is complete, the urine usually shows the existence of a more or less severe active hyperemia of the unaffected kidney. This is undoubtedly due partly to the absorption of toxic products from the diseased kidney, and partly to the extra work of elimination. The urine will be free from pus and other evidences of a pyonephrosis, so that the diagnosis of this condition can only be made from the physical examination and the clinical symptoms.

If by any means the obstruction in the ureter be removed, the urine will suddenly become very turbid, and when it settles will contain a very abundant sediment having a *decidedly greenish tint.* On microscopic examination this sediment will be found to consist of a large quantity of degenerated and disintegrated pus, accompanied by an abundance of small round cells. There may be a small amount of blood in this sediment, but usually blood-corpuscles are difficult to find—or, more properly, difficult to recognize—in the presence of so much pus.

The odor of the urine containing the pus is generally very offensive, and sometimes the reaction is alkaline.

The quantity of albumin is usually large,—⅛ to ¼ of 1 per cent. or more,—and very often the albumin is accom-

panied by an abundance of globulin. The author has met with one case in which the quantity of globulin equaled that of the albumin. From a diagnostic point of view the other characteristics of the urine are not especially significant.

It is often necessary to remove the diseased kidney in order to save the life of the patient. The pus sac thus removed usually contains very little, if any, fluid material, but, instead, a thick, putty-like or cheesy mass of inspissated pus, the liquid portion having been previously absorbed. This putty-like substance may contain a deposit of lime-salts.

A pyonephrosis is always attended with danger to life. Perforation into the peritoneal or pleural cavities may occur, or the patient may be worn out by the hectic fever, or amyloid disease may develop.

URETERITIS.

An inflammation of the mucous membrane of the ureter may be acute or chronic. The inflammatory process may be local or general, according to the cause.

A diagnosis of this condition from the urine alone is practically impossible, especially if the urine is voided in the natural way. Since the advent of catheterization of the female ureters, exceptional opportunities have been afforded for studying diseases of this tract, and some instructive observations have been made.

Causes.—This inflammatory condition may be a part of an acute pyelitis or an acute cystitis, by extension. It is probably more frequent in connection with an acute pyelitis, and often due to the same causes. (See p. 333.) Aside from an inflammatory process due to exposure to cold and wet, perhaps the most common cause is the passage of calculi or microscopic crystals of uric acid or calcium oxalate. If the calculus can not be forced through the ureter, it first produces a marked acute ureteritis and later a chronic inflammation at its lodging point, which is frequently at the place where the ureter crosses the brim of the pelvis. The microscopic crystals often produce an irritation or inflammation of the mucous membrane throughout the entire length of the tube. Like an acute pyelitis, the acute process in the ureter soon becomes chronic. The inflammation may have the characteristics of a chronic

ureteritis from the beginning, as in tubercular ulcerations, or a gradual extension upward of a chronic inflammation of the bladder. The pressure on the ureter by new growths located outside of the urinary tract, twists, and strictures of the ureter often produce more or less inflammation.

Symptoms.—The most prominent clinical feature is the paroxysmal sharp pain—renal colic—that starts in the region of the kidney, follows down the line of the ureter into the testicle, and along the inner side of the thigh. During the paroxysm of pain there is usually nausea and vomiting, marked prostration, and sometimes a little fever. (See Renal Calculus.) On bimanual examination the thickened ureter or impacted calculus can, occasionally, be felt through the abdominal wall.

Character of the Urine.—The urine usually has the characteristics of the inflammatory process above or below the ureter—acute or chronic pyelitis, and acute or chronic cystitis. The diagnosis of a simple ureteritis, if such exists without a pyelitis or cystitis, can only rarely be made from the urine alone ; even then it is very difficult to distinguish it from an irritation or acute inflammation of the pelvis of the kidney. In a simple ureteritis due to an impacted calculus the urine usually has a high color, strongly acid reaction, and high specific gravity. The quantity of albumin commonly varies with the amount of blood. The *sediment* frequently contains more or less blood, and sometimes the blood is present in abundance. There are usually small caudate and spindle cells from the ureter, and a few (or numerous) leucocytes.

Catheterization of the ureters may lead to the diagnosis of ureteritis, stricture of the ureter, or the presence of a calculus in the ureter. The history of renal colic, or of more or less continuous pain in the region of the ureter, is of importance in the diagnosis.

CYSTITIS.

This is an inflammation of the mucous membrane of the bladder ; it may be either acute or chronic.

ACUTE CYSTITIS.

Causes.—One of the most common causes of this disease is an infection with micro-organisms, such as the gonococ-

cus in cases of backward extension of a gonorrheal urethritis; with the pyogenic staphylococci and other forms of pyogenic bacteria that have been introduced into the bladder by means of an unclean catheter; and with the tubercle bacillus. It may result from an acute prostatitis; from injury, as with the rough use of sounds; from extensive urethral stricture; from foreign bodies, such as calculi; from drugs, such as cantharides and copaiba; and from new growths. An acute cystitis is not uncommonly seen following exposure to cold and wet, sexual excesses, and simple acute retention of urine. An acute inflammation of the bladder is a frequent complication of acute infectious diseases, notably typhoid fever, in which case it is probably the direct result of the action of the typhoid bacillus.

In the mild cases of acute cystitis the vesical mucous membrane is congested, thickened, and swollen, and the epithelium becomes detached in places, leaving abraded surfaces. In the severe forms the bladder becomes lined with a tough, tenacious layer of mucin (?); there may be ulcerations and sloughing. The submucous connective tissue is, in some cases, infiltrated with pus, and hemorrhagic areas are not uncommon.

Prominent Symptoms.—One of the first symptoms is increased frequency of micturition, which usually becomes more and more prominent, only a very small quantity of urine being voided at each effort at urination. Tenesmus is frequently very severe; the patient will often lean over the vessel or urinal, quivering with the muscular effort, without relief to the distressing and very urgent desire. The pain, which is likewise extreme, may be referred to the neck of the bladder, to the perineum, to the glans penis, or to the hypogastrium, and may radiate into the loins or down the thighs. There is frequently marked constitutional disturbance with more or less elevation of temperature, although in some cases the general disturbance is slight in comparison with the intensity of the local symptoms.

Character of the Urine.—Quantity.—The twenty-four-hour quantity of urine is usually small, varying from 500 to 800 or 1000 c.c.

Color.—Bloody or smoky, depending upon the amount and character of the blood present.

Reaction.—Strongly acid.

Specific Gravity.—Early in the disease the specific gravity is usually high—1025 to 1030; later, it is normal or slightly diminished—1015 to 1022.

Normal Solids.—*Relatively*, increased; but *absolutely*, more or less diminished, depending upon the amount of systemic disturbance set up by the disease.

Albumin.—The quantity of albumin is variable, but in a general way it is relative to the amount of blood and pus in the urine. It is not uncommon for the quantity of albumin to reach or even exceed ¼ of 1 per cent., but usually it is less than this figure.

Sediment.—The sediment, which is generally abundant, consists chiefly of normal blood; considerable pus, some in clumps, and a large amount of squamous epithelium. Numerous small round cells, perhaps some of them fatty, may be found.

CHRONIC CYSTITIS.

Causes.—A chronic cystitis may result from an acute cystitis. In some instances the changes taking place in the mucous membrane of the bladder are so slight and gradual that a chronic process results apparently without a preexisting acute stage. In general, the same causes that have been attributed to an acute inflammation of the bladder may be looked for to explain the presence of a chronic cystitis. Among these causes are to be borne in mind infection by micro-organisms, as following the introduction of insufficiently purified and disinfected catheters or bougies, or when the instrument carries into the bladder pus and bacteria from an ulcerating surface or a pus pocket in the urethra (stricture). A very frequent cause of this form of cystitis is the enlarged prostate. Owing to the inability of the patient to completely empty his bladder, the residual urine sooner or later decomposes by the rapid development of bacteria, and a general cystitis results. In a similar manner many cases of cystitis arise in patients with nervous disease, who have paralysis of the bladder, as in paraplegia; also in persons who are severely ill and stupid from some acute disease, such as typhoid fever. In the acute infectious diseases a chronic cystitis may appear, either as the result of frequent catheterization, or by the action of the bacteria causing the disease.

In cases of vesical calculus, vesical tuberculosis, and new

growths of the bladder, a chronic cystitis is probably more commonly seen than an acute cystitis, since the disturbance by these agencies is at first slight. The subsequent changes, which are often very gradual, become more pronounced, and finally a well-marked chronic inflammatory process is apparent.

In women the agents of inflammation may quite easily enter the bladder from the vagina through the short female urethra; thus arise the frequent cases of cystitis in childbed (usually an acute cystitis). Communications may develop between the bladder and certain neighboring organs, such as vesicorectal or vesicovaginal fistulæ, by which, again, access to the bladder is open to the agents of inflammation.

The pathologic changes in the wall of the bladder may result in atony or atrophy, with thinning of the mucous membrane, fatty degeneration of the muscular fibers almost to the point of disappearance, and great distention of the organ. Again, they may be followed by hypertrophy of the muscular coat, the fibers forming ridges or fasciculi standing out in the interior of the bladder and separated by lozenge-shaped spaces, the organ itself being contracted so that its cavity can contain but a few cubic centimeters of fluid. Sometimes between these muscular bars pouches of mucous membrane protrude, forming distinct sacculi communicating with the interior of the bladder by narrow mouths and remaining permanently; occasionally, they contain calculi. In chronic cystitis of long standing the mucous membrane often takes on a slaty, grayish-black color as a result of hemorrhages. The incrustation of the mucous membrane with urinary salts, especially with ammonio-magnesium phosphate, is also frequently found in the chronic form of this disease.

Prominent Symptoms.—The symptoms of an acute cystitis are present in a modified form. Micturition is not so frequent; tenesmus is much less or is absent (in mild cases); pain is usually very slight, and in mild cases it may be absent; the constitutional symptoms are comparatively slight, and become marked only when renal changes have occurred or when a general toxemia has followed the absorption of the products of urinary decomposition.

Character of the Urine.—Quantity.—The twenty-four-hour quantity of urine is usually only moderately diminished —*i. e.*, 800 to 1400 c.c.

Color.—Generally pale, but it may be normal in color;

it may, however, be tinted with blood to a greater or less extent. The freshly passed urine is generally turbid, due to the presence of pus and epithelium and an abundance of bacteria.

Reaction.—Frequently alkaline, but it may be acid and sometimes it is strongly acid, especially in the early stages of the disease. The reaction varies according to the presence or absence of urea-decomposing organisms.

Specific Gravity.—This varies usually between 1012 and 1020; average about 1015.

Normal Solids.—Both *relatively* and *absolutely*, diminished.

Albumin.—This varies between the *slightest possible trace* (mild cases) and ⅛ of 1 per cent. (severer forms). It is usually directly dependent upon the amount of pus and blood present.

Sediment.—Abundant. If the urine be *acid*, the sediment will consist chiefly of pus and small round cells; considerable squamous epithelium, and generally a small (sometimes a considerable) amount of blood. If the urine be *alkaline*,—ammoniacal,—the sediment will settle in a viscid, sticky mass, which consists mostly of decomposed pus, amorphous phosphates, crystals of triple phosphate, and often crystals of ammonium urate. The pus corpuscles may be so embedded in the mucin-like substance and so changed as to entirely lose their characteristic appearance.

There can be no doubt that decomposing alkaline urine acts as a chemic irritant to the mucous membrane of the bladder; hence, cases of mild cystitis often become intensified by the irritation of the ammonia salts that are formed.

The longer a chronic cystitis continues, the greater the likelihood of the development of a pyelonephritis. In this way a cystitis, especially in chronic diseases of the nervous system and in old age, may become the immediate cause of death.

TUBERCULOSIS OF THE BLADDER.

Tuberculosis of the bladder is not an uncommon condition. The existence of a chronic inflammation of the bladder, in the absence of tangible evidences of infection from gonorrhea, chronic obstruction, or by instrumentation, should always leave a suspicion of the tubercular nature of the affection. The two places in which tuberculosis of the bladder is most likely to commence are the trigone and

ureteral orifices, the latter being the more common. The tubercular process begins with the formation of typical gray nodules in the mucous membrane; these nodules become confluent, caseate, soften, and finally produce ulceration. In more acute cases the disease leads to diffuse cheesy infiltration and general ulceration.

Vesical tuberculosis is found more frequently in males than in females, and is a disease of early and middle life (seventeen and forty years of age). In the male the disease is frequently associated with tuberculosis of the seminal vesicles and of the prostate. The resistance of the mucous membrane of the bladder to tubercle bacilli is quite marked; in some cases of tuberculosis of the kidney the bladder may be irrigated with urine containing tubercle bacilli for years without becoming tubercular.

Prominent Symptoms.—The symptoms of vesical tuberculosis are similar to those of stone in the bladder. The disease is initiated by a frequent desire to urinate, by pain after emptying the bladder, with slight hematuria at longer or shorter intervals. Later in the disease intermittent hemorrhage becomes a conspicuous clinical symptom, but it is never so profuse as in tumor of the bladder. Retention and incontinence of urine are quite common.

Character of the Urine.—Quantity.—The twenty-four-hour quantity is usually diminished, although it may be slightly increased.

Color.—Pale; sometimes bloody. The urine is generally quite turbid from the pus, blood, etc., in suspension.

Reaction.—Nearly always acid, except when the urine contains a large amount of blood, when it may be neutral or alkaline.

Specific Gravity.—Usually, below the normal—1010 to 1015.

Normal Solids.—*Relatively* and *absolutely*, diminished.

Albumin.—The quantity will depend chiefly on the amount of blood and pus present; it usually varies between a *slight trace* and a *large trace*. In case of abundant hematuria the quantity of albumin will, of course, be high—⅛ to ¼ of 1 per cent.

Sediment.—Abundant. Chiefly pus, which is generally free, but may be slightly clumped. Considerable squamous epithelium and many small round cells, some of which are fatty; a few (sometimes numerous) blood globules. The sediment also contains tubercle bacilli.

As in tuberculosis of other parts of the urinary tract, the symptoms are variable and often misleading. Even the presence of tubercle bacilli in the urine, indicating as it does tuberculosis of the urinary system, does not locate the anatomic seat of the disease. The presence of tubercle bacilli and squamous epithelium, which are more or less intimately mixed with the pus, makes the diagnosis of vesical tuberculosis probable.

The **prognosis** in this condition is usually grave. Spontaneous recovery is exceedingly rare. If the disease be mild and limited to the bladder, it may remain in a latent condition for years. There is always danger of an extension of the tubercular process to the kidney, which is soon followed by a suppurative pyelonephritis. There can be but little doubt that appropriate general and local treatment will prolong life and alleviate the distressing symptoms.

In all cases of cystitis in which the cause of the disease is not obvious the urinary sediment should be very carefully searched for tubercle bacilli. In case the organisms can not be found a guinea-pig should be inoculated with a portion of the sediment (½ to 1 c.c.), and the result of this experiment obtained, before eliminating the diagnosis of tuberculosis. (See Detection of Tubercle Bacilli in the Urinary Sediment, p. 325.)

TUMORS OF THE BLADDER.

Tumors of the bladder may be either benign or malignant.

The **benign tumors** include the fibromata, fibromyxomata, and papillomata; of these the latter are by far the most frequent. *Fibromata* and *fibromyxomata* grow from the submucous coat of the bladder; they are either sessile or pedunculated, and are covered by unaltered mucous membrane or by villi. Papillomata grow from the superficial layer of the mucous membrane; they appear as red vascular masses, usually with long pedicles, and occasionally they are sessile. Sometimes the papillæ are long and slender and float in the urine in numerous filaments from a common base; sometimes the mass has a cauliflower appearance, this form of tumor constitutes the so-called *villous growth* of the bladder. (In Fig. 53 the masses represent small portions of very small villi in which characteristic

small caudate cells are arranged about a central cone of fibrous tissue, blood-vessels, etc. The caudate cells have prominent and relatively large nuclei, and are somewhat larger than the average cell from the superficial layer of the pelvis of the kidney. In papillomatous disease of the bladder cells of this kind may be found in the sediment singly or in clumps.) Frequently, they undergo ulceration ;

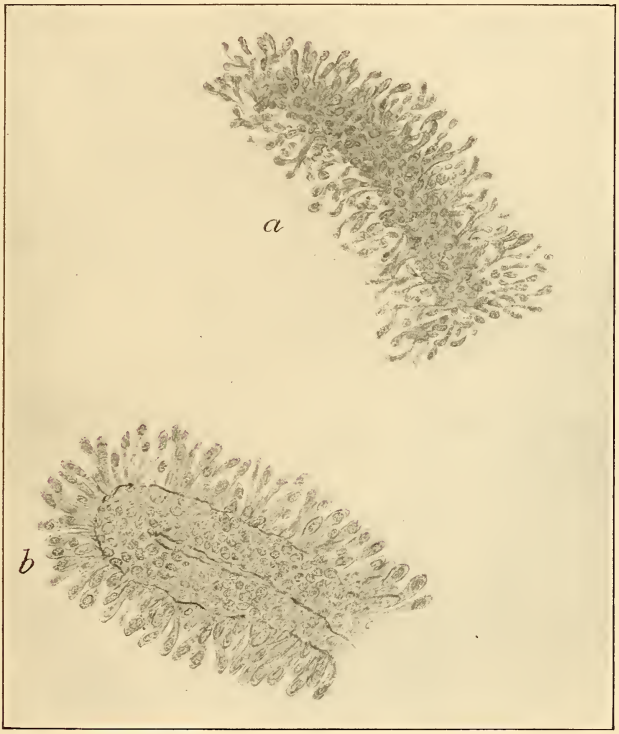


Fig. 53.—Portions of a villous growth of the bladder: *a*, Magnified 190 diameters; *b*, magnified 370 diameters.

they sometimes bleed very freely. Nearly all vesical growths tend to assume a papillomatous character. When the fibrous elements are numerous, the structure is denser ; this constitutes the *fibropapilloma*. There is reason to believe that a growth originally purely papillomatous may become malignant in its later stages ("American Text-book of Surgery").

Malignant tumors of the bladder, although for the most part papillomatous, belong either to the order of sarcomata or to carcinomata. (See Cancer of the Prostate.)

The **prominent symptoms** of tumor of the bladder are those of a chronic cystitis. (See p. 347.) Intermittent hematuria is a common symptom. Pain is usually not so marked as in the average case of chronic cystitis, and it may even be absent, especially if the disease does not invade the trigone (Fenwick). Frequency of micturition is an early and constant symptom.

Character of the Urine.—The urine has much the same characteristics as in chronic cystitis, except that the reaction is generally acid; there is a bloody or smoky color, and on account of the quantity of blood, a comparatively high percentage of albumin. Blood may be present in large amount; in fact, the quantity of blood is often greater than in almost any other disease of the urinary tract. Large blood-clots may partially fill the bladder, and not infrequently they are the cause of retention of urine. The blood is usually not so intimately mixed with the urine as when it comes from the kidney.

After the urine has settled and the blood has been destroyed (see p. 233), shreds are frequently seen floating in the urine. Upon microscopic examination these may be found to consist of pus and cells embedded in mucin, or bits of tissue perhaps resembling the mass represented in figure 53 (villous growth). Inferences as to the nature of these shreds—whether malignant or benign—can not usually be drawn from a microscopic examination of the sediment. Sometimes, as previously stated, the sediment contains caudate cells, single or in clumps, which will lead to the diagnosis of villous growths. Likewise, medium and small round and irregular cells with prominent and relatively large nuclei may be found, suggesting a new growth of the bladder. Usually, the epithelial elements are a predominant feature of the sediment.

Following the introduction of sounds or bougies into the bladder, the urine often contains cells (caudate, large and small round) that have been mechanically detached from the mucous surface. These cells are found both singly and in clumps; and care should be taken not to mistake them for cells of a new growth.

PROSTATITIS.

An inflammation of the prostate gland may be either acute or chronic, and parenchymatous or follicular.

In the *parenchymatous form* the inflammation affects the whole substance of the gland, and constitutes the severer acute forms of prostatitis.

ACUTE PROSTATITIS (PARENCHYMATOUS).

Causes.—Among the causes of this condition may be enumerated gonorrhea, urethral stricture, extreme and prolonged sexual excitement, concentrated and highly acid urine, exposure to cold and wet, violence from instruments, fragments of calculi, trauma, etc. It may also result from the action of chemic irritants, strong urethral injections, the internal administration of cantharides, etc. Gonorrheal inflammation, after the first week, may extend to the prostate, particularly if the patient indulges in liquor, sexual intercourse, or uses strong injections throwing them deep into the urethral canal, or takes violent exercise. Sometimes, during gonorrhea, the prostate becomes inflamed without an exciting cause. The inflammation behind a stricture may extend back and involve the prostate in the same way. Sexual hyperemia, too much prolonged or too often repeated, may lead to an acute prostatitis.

Prominent Symptoms.—The organ swells rapidly, putting the capsule on the stretch, and often reaches the size of a small orange. The exploring finger in the rectum strikes at once against an unevenly enlarged mass that projects into the cavity of the intestine. It is very tense and hot, extremely tender, and can be felt distinctly to pulsate. The lightest touch, even the presence alone of the finger in the rectum, at once excites a marked desire to micturate ; pressure over the pubes has the same result. The patient may have an unnatural desire to defecate ; if he endeavors to do this, he strains ineffectively, causing pain, but getting no relief. There is subjectively a feeling of weight, heat, and throbbing, and sometimes pain in the back and limbs. The stream of urine is usually small, and occasionally there is complete retention of urine as a result of the swelling. Almost invariably there are an associated congestion of the vesical neck and a consequent extreme tenesmus. The urine causes pain in its passage, but the pain is most severe when

the last drops of urine are being expelled. There is generally febrile disturbance, and the patient is usually irritable, despondent, and suspicious.

Character of the Urine.—Quantity.—The twenty-four-hour quantity is small—generally between 500 and 1000 c.c.

Color.—High or bloody.

Reaction.—Strongly acid.

Specific Gravity.—Usually high—1025 to 1035.

Normal Solids. — *Relatively*, increased; *absolutely*, diminished. If the acute process lasts more than two or three days, the solids will be much diminished *absolutely*.

Albumin.—Usually between ⅛ and ¼ of 1 per cent.; but the quantity is dependent chiefly on the amount of blood and pus present.

Sediment.—Chiefly normal blood. Considerable pus, both free and in clumps; many small round cells and a marked excess of cells from the prostatic region (neck of bladder); frequently there are spermatozoa and cells from the seminal passages. Occasionally, casts of the prostatic ducts are present, and with difficulty distinguished from casts of the renal tubules, which may also be present as a result of a coincident renal congestion.

Diagnosis.—The clinical picture of the case is generally sufficient for a diagnosis without an analysis of the urine. In some instances, however, the diagnosis between an acute prostatitis and acute cystitis is not easy, but can often be made by attention to the following points:

Acute Prostatitis.	Acute Cystitis.
Perineal and rectal pain.	Possibly a little tenderness of the perineum on pressure, but little or no rectal pain.
Pain violent and throbbing, aggravated during defecation.	Pain burning, not especially affected by defecation.
Stream of urine diminished in size.	Size of stream not usually affected.
Retention of urine common.	Retention of urine much less common.
Rectal examination shows enlargement and extreme tenderness of the prostate.	No prostatic enlargement or tenderness recognizable on rectal examination.
Urinary sediment contains blood, pus, marked excess of epithelium from prostatic region, spermatozoa, and prostatic casts.	Urinary sediment contains, besides blood and pus, much squamous epithelium, usually no marked excess of cells from prostatic region, and no spermatozoa nor prostatic casts.

A greater or less involvement of the neck of the bladder is often an accompaniment of an acute prostatitis.

PROSTATIC ABSCESS.

An abscess of the prostate is liable to form as the result of a parenchymatous inflammation of the organ. There may be one or more purulent foci, or the whole substance of the prostate contained within its fibrous capsule may suppurate.

The **symptoms** are in many respects similar to those of an acute prostatitis. A sharp chill or a series of rigors announces the beginning of suppuration. As the pus forms it presses upon the already narrowed canal of the urethra; and, finally, unless the abscess is very small, obliterates it entirely, causing retention of urine. There are usually local throbbing and lancinating pain. These abscesses, left alone, discharge into the bladder, urethra, rectum, or through the perineum. When such an abscess opens spontaneously, all pain and discomfort are immediately relieved. A small purulent collection in the prostate may empty itself gradually into the urethra by one or more minute openings; in such cases the diagnosis of a prostatic abscess is not easily made.

Character of the Urine.—This will vary according to circumstances: If the abscess is forming and has not yet opened, the urine will be concentrated, of high color, and high specific gravity, containing a very small amount of albumin; the sediment will consist of a few leucocytes, blood globules, and an excess of cells from the neck of the bladder or prostatic urethra—in other words, a *fever urine*, in which the sediment presents the evidences of an irritation in the prostatic region. On the other hand, if the abscess has ruptured, the urine, with the exception of the sediment, will present the characteristics of that of severe chronic prostatitis. The *sediment*, which is abundant and often *greenish in color*, will consist chiefly of pus, both free and in clumps, that in clumps usually being much degenerated; many small round cells, some fatty, and generally a few compound granule cells; and few or numerous blood globules. There is also an excess of cells from the prostatic region.

CHRONIC PROSTATITIS.

Causes.—A chronic inflammation of the prostate gland may be the result of an acute prostatitis. In some instances, as following sexual excesses, masturbation, etc., the

pathologic process in the organ starts as a slight irritation that gradually increases, finally becoming a well-marked chronic condition without passing through an acute stage. A chronic prostatitis may result from stricture of the urethra, contracted meatus, phimosis, hypertrophy of the prostate in persons past the age of fifty-five, tuberculosis, trauma, irritation by crystalline elements, etc.

Prominent Symptoms.—Perhaps the most prominent symptom of this condition is frequency of micturition. There are usually some pain and a feeling of uneasiness at the neck of the bladder, especially toward the close of urination, and often pain at the end of the penis and along the under surface of the urethra. There may be a mucopurulent discharge from the urethra, but this is not generally the case. Defecation is sometimes painful. Walking causes pain, and crossing the legs decidedly increases it. As the disease advances, the sitting posture becomes painful. Retention of urine is common. Constitutional disturbance may be absent, particularly in mild cases; when the disease is marked, however, there may be more or less fever and mental depression. The finger in the rectum may find slight enlargement and at times detect extra sensibility.

If the disease is the result of *hypertrophied prostate*, not only will the enlargement be apparent to the finger in the rectum, but signs of mechanical obstruction to the outflow of urine will be prominent; the stream will be interrupted and show a lack of force; the patient will be unable to completely empty the bladder, only passing that which is in excess. This "residual" urine may remain stationary in amount, but more often it gradually increases until, in some cases in which both hypertrophy of the prostate and atony of the bladder are marked, only an ounce or two of urine can be evacuated voluntarily, although catheterization will show that the bladder contains possibly a pint or more. The decomposition of the retained urine invariably results in a chronic cystitis; often a pyelonephritis develops; general sepsis occurs; and the patient becoming uremic dies during coma.

Fortunately, a fatal termination is not the outcome of all cases of chronic prostatitis; some are amenable to treatment and entirely recover, especially the milder cases and those

which are not tubercular, or those in which an abscess of the prostate has not developed.

Character of the Urine.—Quantity.—The total quantity for twenty-four hours is usually between 800 c.c. and 1200 c.c.

Color.—Pale. The urine is generally turbid, due to the presence of a large amount of pus in suspension.

Reaction.—Usually acid; if there is an accompanying chronic cystitis, the reaction may be alkaline, especially in cases of hypertrophy of the prostate.

Specific Gravity.—This will generally be found to vary between 1012 and 1018—average about 1015.

Normal Solids.—Both *relatively* and *absolutely*, diminished; the degree of diminution will depend largely on the amount of constitutional disturbance.

Albumin.—The quantity of albumin will depend on the amount of pus and blood; it usually varies between a *very slight trace* and ⅛ of 1 per cent. In case there is an accompanying disturbance or disease of the kidney the amount of albumin will be proportionately higher.

Sediment.—This is abundant, and consists chiefly of pus, both free and in clumps; many small round cells, some of which are fatty; also an excess of cells from the neck of the bladder and prostatic urethra; a few (sometimes numerous) blood globules; and sometimes spermatozoa, and the highly granular cells from the seminal passages. Prostatic plugs (cylinders of long diameter resembling large renal casts or bodies of irregular shapes from dilated ducts or cavities), sometimes with spermatozoa embedded, are of frequent occurrence, especially in the mild (follicular) forms of chronic prostatitis. Frequently, the sediment contains large and small shreds that will be found to consist of pus, small round cells, and dense cells from the prostatic region, which are embedded in mucin (nucleo-albumin). If there is an accompanying chronic cystitis, as is the rule in cases of hypertrophied prostate, the sediment will contain more or less squamous epithelium, and frequently crystals of triple phosphate. A renal disturbance that is probably indirectly due to the chronic prostatitis, and perhaps the result of the absorption of toxines, is not uncommon. An occasional or a few renal casts may be found in the sediment, which are sometimes distinguished with difficulty on account of the abundance of pus.

TUBERCULAR PROSTATITIS.

This disease of the prostate is almost invariably associated with tuberculosis of some other part of the genito-urinary tract. The disease occurs in tubercular, debilitated subjects, its chief feature being cheesy degeneration, situated for the most part in the ducts and follicles of the organ. True miliary tubercle does not seem to occur in the prostate.

The **symptoms** are those of a severe chronic prostatitis. Generally, there is more or less frequency of micturition. The symptoms become spontaneously better or worse, but the general tendency is toward steady aggravation. The cheesy masses ulcerate, form abscesses that break in all directions, leaving open cavities or fistulas. Intermittent hemorrhage from the urethra is quite a constant symptom. The disease is probably more common than has hitherto been supposed.

Character of the Urine.—Quantity.—The twenty-four-hour quantity is usually not far from 1000 c.c.

Color.—Pale. The freshly passed urine is usually turbid, and sometimes it is opaque.

Reaction.—Acid.

Specific Gravity.—Usually, below the average normal, varying between 1012 and 1018.

Normal Solids.—Both *relatively* and *absolutely*, diminished, but dependent largely on the extent of the constitutional disturbance and the appetite.

Albumin.—This varies as the amount of pus and blood present in the urine; it is usually from a *slight trace* to *a large trace.*

Sediment.—This is generally abundant and consists chiefly of pus both free and in clumps; a large number of small round cells, some of which are fatty; often an excess of dense round cells from the neck of the bladder and prostatic urethra; and a few (sometimes numerous) blood globules. When the freshly passed urine is examined, the pus is often found to be ameboid. Large clumps of degenerated and disintegrated pus and cells are occasionally found.

A urine having the above characteristics should always be examined for tubercle bacilli, which, however, are usually difficult to find, but occasionally they are present in

large numbers. (For details concerning the examination for tubercle bacilli, see p. 325.) If the bacilli are not found in the sediment after repeated trials, a guinea-pig should be inoculated with a portion of the sediment in order to determine positively their presence or absence.

CANCER OF THE PROSTATE.

Primary cancer of the prostate is exceedingly rare. It is usually secondary to carcinoma or sarcoma elsewhere, especially in the kidney or testicle. The scirrhous, melanotic, and medullary forms have all been noted; of these the latter is perhaps the most frequent.

The **symptoms** at first are those caused by an increase in the size of the organ, such as obstruction to the outflow of urine, frequency of micturition, and pain. The early symptoms are not pathognomonic. Later in the disease the cancerous cachexia, glandular enlargement, and the evidences of a cancerous affection elsewhere in the body are usually sufficiently prominent to suggest cancer of the prostate. Rectal examination may be of value in determining the form of cancer that exists. Hematuria is common.

Urine.—An analysis of the urine is often of but little value in the diagnosis of cancer of the prostate. The characteristics of the urine are usually those of chronic prostatitis. The urine may, from time to time, contain a large amount of blood. Occasionally, the presence of a large number of medium and small round cells, with relatively large and prominent nuclei, may suggest the presence of malignant disease of the prostate.

The **diagnosis** of cancer of the prostate is very difficult if the disease appears after the organ has from any cause become hypertrophied.

URETHRITIS.

Of all the diseases encountered in genito-urinary surgery urethral inflammation is the most common. Although strictly a local affection, and exerting little or no poisonous action upon the blood, it is the most venereal of all venereal diseases, since it is the commonest malady acquired during the copulative act.

The term *urethritis* signifies simple inflammation of the urethra. The term *gonorrhea*, although etymologically inaccurate, indicating as it does a flow of semen, has been, and is still, universally employed and considered, especially among the laity, to have the same meaning as the term urethritis. But a gonorrhea is in all probability due to a specific organism—the gonococcus. A gonorrhea is a urethritis, but the converse is by no means always true, since urethral inflammation may have a variety of causes other than an infection with the gonococcus. For practical purposes it is better to retain the two terms, calling that gonorrhea that has been unmistakably derived from an individual of the other sex with a gonorrhea, and reserving the term urethritis for all inflammatory urethral discharges having another origin. Or the term *simple urethritis* may be used to indicate those conditions in which the gonococcus is absent, and *specific urethritis* to indicate those in which the gonococcus is present.

Causes.—Simple Urethritis.—Authentic cases are on record of well-marked urethritis following exposure to leucorrheal discharges; to the pus from a healthy abscess, or from a purulent bronchial catarrh; to the secretion from an endocervicitis or endometritis; to the discharge resulting from ulceration or malignant disease of the uterus; to menstrual fluid or acrid vaginal discharges; to powerful injections; to the irritating influences of crystalline elements or the passage of a calculus; to catheterization; to exposure to cold and wet; to a concentrated urine; to the action of certain drugs—cantharides; to the extension of inflammatory diseases from the prostate or bladder; occasionally, to the free use of alcoholic drinks, especially beer—the so-called "beer clap"; and to many other non-specific causes.

Specific Urethritis or Gonorrhea.[1]—There is scarcely a shadow of doubt but that the cause of gonorrhea is the *gonococcus* of Neisser. (See p. 268.) The microscopic detection of this micro-organism is, so far as known, the only safe means of distinguishing between specific urethritis and a simple urethritis.

Prominent Symptoms.—The most constant symptom of a simple urethritis is a urethral discharge. On the first,

[1] For details concerning this disease, see special works on genito-urinary surgery.

second, or third day after having indulged in sexual intercourse, perhaps with a partner having an extensive leucorrhea, the first symptom noticed is a slight, uneasy sensation at the meatus, a little smarting, and a pearly drop of pus at the meatus ; or perhaps the lips of the urethra are glued together in the morning on rising. The inflammation will probably not run high or last long, and upon microscopic examination specific gonococci will not be found. In some instances the discharge is profuse, the inflammation runs high and continues for weeks, and with the exception of the absence of gonococci the disease can not be distinguished from true gonorrhea. There may be pain all along the pendulous urethra, and the canal is sensitive to pressure ; the meatus feels hot and sore, and urination is frequent and painful. Chordee may be as prominent as in a true gonorrheal inflammation. An acute prostatitis or cystitis may follow. General systemic disturbance is sometimes marked. Organic stricture may follow a simple urethritis.

Character of the Urine.—Quantity.—Usually diminished—800 c.c. to 1200 c.c.

Color.—Normal or high. The urine is generally more or less turbid owing to the pus and epithelial cells in suspension.

Specific Gravity.—From 1020 to 1030, but dependent on the concentration of the urine.

Reaction.—Usually, strongly acid.

Normal Solids.—*Relatively*, normal or increased ; *absolutely*, normal. In those cases in which marked constitutional disturbance exists the solids are generally absolutely diminished.

Albumin.—Albumin is invariably present ; the quantity is dependent on the amount of blood and pus present ; it usually varies between the *slightest possible trace* and a *large trace.*

Sediment.—Chiefly dense pus ; many urethral cells and an occasional (or few or numerous) blood globule ; often an excess of mucin (nucleo-albumin). If the inflammatory process is most marked in the prostatic urethra, cells from that region, as well as cells from the neck of the bladder, will be found with the pus. In case of an organic stricture, or gleet, the pus and cells will be found chiefly in shreds of mucin (nucleo-albumin).

The urine should be carefully watched for evidences of

a complicating prostatitis or cystitis, in which case the amount of pus will be larger, and the quantity of blood greater than in a urethritis. There will also be an unusual number of cells from the prostatic region, and, perhaps, casts of the prostatic ducts and spermatozoa; or, in case of cystitis, an abundance of squamous epithelium.

In all cases of urethritis of doubtful origin, a thorough search for gonococci should be made. (For method of staining, see p. 268.)

CHYLURIA.

This is a condition that results from a pathologic communication between the lymphatic system and the urinary

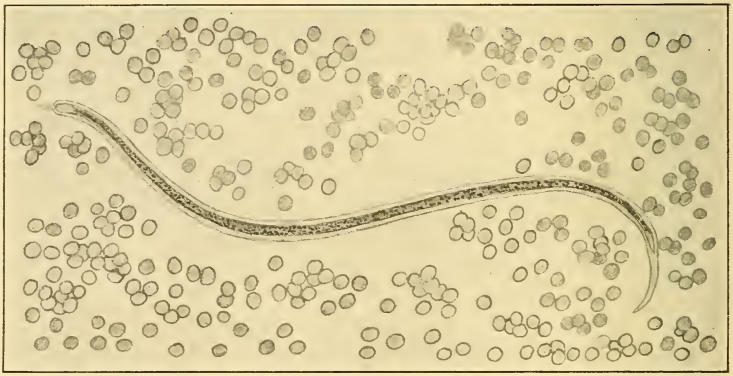


Fig. 54.—The filaria sanguinis hominis. The head can be seen at the left of cut; the tail, at the right. The parasite is inclosed within a hyaline capsule. Magnified 280 diameters.

passages. Under such circumstances the urine has a milky appearance, due to the presence of chyle. The cause of this disease is a parasite—the *filaria sanguinis hominis* (see Fig. 54)—that invades the blood and obstructs the lymphatic channels, finally resulting in the rupture of a lymphatic vessel. The disease appears to be confined chiefly to the tropics (India, China, Bermuda, Brazil, Australia, and the West Indies), or to those individuals who have spent much of their lives there. Guitéras has shown that the disease is not uncommon in the Southern States. It is of rare occurrence in the New England States, the author having met with only five cases; in two of these cases the filaria was readily

found in the blood. Besides the endemic form of this disease, it is very rarely met with following traumatism and disease in which an abnormal communication has formed between the lymphatics and the urinary tract. Osler refers to a nonparasitic form of chyluria. The disease affects alike both males and females, and may occur at any age.

A peculiar feature of the parasite is that it works at night, or while the patient is in the recumbent position, being quiescent while the patient is up and about. In consequence, the night urine is milky, while that passed during the day is clear and usually of normal color; but if the individual sleeps or reclines during the day, the urine passed at that time is milky.

Characteristics of the Urine.—The characteristics of a chylous urine are as follows:

Quantity.—This is usually below the average normal—1500 c.c.; it may, however, be normal or slightly increased.

Color.—Milky. Opaque. Occasionally, the urine is slightly tinged with blood.

Reaction.—Acid.

Specific Gravity.—Usually, normal or slightly diminished; it may be as low as 1010, particularly if the quantity of urine is moderately increased.

Normal Solids.—*Relatively*, normal or slightly diminished. *Absolutely*, slightly diminished, especially the urea and chlorides. The phosphates may be moderately increased.

Albumin.—This will depend chiefly on the amount of blood present in the urine. Usually, the quantity varies between the *slightest possible trace* and a *trace*. Owing to the opacity of the urine, the usual tests for albumin can not be satisfactorily applied. It is necessary to first remove the fat in suspension by shaking with ether; then either the nitric acid or the heat test can be applied to the clear urine in the usual manner.

Sediment.—Slight; often no sediment is visible on inspection. Chiefly fine granular matter, a few leucocytes, and an occasional (or few, and sometimes numerous) blood globule. Perhaps, rarely a hyaline and granular cast and renal cell may be found. Casts are not always present. No fat globules are discernible by the microscope. Often a few uric acid crystals may be seen. The filaria has been found in the urine, but its presence is, by no means, constant.

The fat in a chylous urine is in a complete state of emulsion, and since it can not be seen microscopically, *its presence is determined with certainty only by shaking with ether.* The ether takes up the fat and leaves the urine clear and of normal appearance. The fat does not separate from a freshly passed chylous urine, or one that has been hermetically sealed or is sterile—that is, the fat does not rise to the surface as in the case of milk. Dr. E. S. Wood has in his possession a specimen of chylous urine that he sealed up while it was fresh (sterile) in the year 1874. The fat has not separated and the specimen has its original appearance. When, however, a urine containing chyle is allowed to stand exposed to the air, it undergoes the usual ammoniacal fermentation and the fat rapidly separates, rising to the surface, as in milk.

Sometimes a chylous urine undergoes spontaneous coagulation on standing; occasionally, coagulation takes place in the bladder, and may give rise to most distressing symptoms until it is broken up and removed. The firm, vibrating, jelly-like clots that form after the urine is voided often resemble corn-starch *blanc mange.* This characteristic of a chylous urine is dependent upon the presence of fibrin, the quantity of which varies considerably; usually, it is not present in sufficient amount to cause coagulation.

A chylous urine should always be distinguished from a urine to which milk has been added either accidentally or intentionally. In such a urine the individual globules of fat are readily made out under the microscope, and the fat is not separated from the urine by shaking it with ether.

HEMOGLOBINURIA.

Hemoglobinuria is a condition that is characterized by the presence of *blood coloring-matter in the urine, with very few, if any, of the corpuscular elements of the blood.* This condition should in all instances be distinguished from a hematuria which indicates the presence of both blood pigment and corpuscular elements. (See p. 234.) Hemoglobinuria is the result of the destruction of the red blood-corpuscles within the blood-vessels or tissues; the blood coloring-matter that is then set free finds its way into the urine. The blood pigment, as found in the urine under these circumstances, is generally in the form of oxyhemo-

globin and hematin, although, according to Hoppe-Seyler [1] and Halliburton,[2] in some instances the pigment may be in the form of methemoglobin (spectroscopic examination). Two clinical groups of this condition may be distinguished :

(a) **Toxic Hemoglobinuria.**—This is induced by poisons that cause rapid destruction of the blood-corpuscles, such as carbon monoxide, arseniureted hydrogen, muscarine, potassium chlorate (in large doses) ; also the poisons of scarlet fever, malaria, yellow fever, typhus fever, purpura hemorrhagica, scurvy, and syphilis. It is quite common following extensive burns. Exposure to cold and violent muscular exercise are stated to produce hemoglobinuria, but such instances have not been observed by the author. *Epidemic hemoglobinuria* (Winckel's disease) occurs in the new-born. It begins about the fourth day of life, and is associated with jaundice, cyanosis, and nervous symptoms. This form of disease should be distinguished from simple icterus neonatorum, with which there may be blood and blood coloring-matter. According to Osler, this condition is probably an acute infectious disorder.

(b) **Paroxysmal Hemoglobinuria.**—This form of disease has been found in persons subject to various forms of Raynaud's disease. It is also associated with cold and exertion, and has been brought on in susceptible persons by the use of a cold foot-bath. This form of hemoglobinuria is not infrequent in malaria. According to Bastianelli, it practically never occurs except in infections with the estivo-autumnal parasite. This condition should not be mistaken for malarial hematuria.

The attacks may be preceded by chills and fever ; in other instances the temperature is subnormal. There may be vomiting and diarrhea. Pain in the lumbar region is not uncommon. Jaundice has been present in a number of cases. The paroxysms rarely persist for more than a day or two. Paroxysmal hemoglobinuria is more common in males than in females, and occurs chiefly during adult life.

Character of the Urine.—Quantity.—This is usually below the normal. If much fever, the quantity may not exceed 500 or 800 c.c.

Color.—Smoky or dark brown. In extreme cases the urine may be black.

[1] Hoppe-Seyler, "Physiol. Chemie.," S. 862.

[2] Halliburton, "Chemical Physiology and Pathology," p. 777.

Reaction.—Generally acid; if the urine is highly concentrated, the reaction may be strongly acid.

Specific Gravity.—Usually, normal or high—from 1020 to 1030.

Normal Solids.—*Absolutely*, diminished; the degree of diminution will depend largely on the disease that causes the hemoglobinuria. *Relatively*, increased or normal.

Albumin.—This varies between a trace (mild cases) and ½ of 1 per cent. (severe cases). The quantity of albumin corresponds to the amount of blood pigment present.

Sediment.—Chiefly brown granular matter, colored by the hematin. An occasional, or few, brown and fine granular, and often numerous brown granular, casts. Rarely, an occasional blood globule. The number of blood globules bears no proportion whatever to the intensity of the color of the urine. There are usually, also, a few brown-stained squamous and renal cells.

The **diagnosis** of hemoglobinuria depends upon the dark-brown color, the virtual absence of corpuscular blood elements, the large quantity of albumin, and the detection of blood pigment by means of Teichmann's test (see p. 237) or the spectroscope. Hemoglobinuria should always be distinguished from hematuria; it should not be confounded with the dark-brown urines seen after the external or internal use of carbolic acid, pyrogallic acid, salol, naphthol, and other petroleum compounds, in which the color deepens as the urine stands exposed to the air, and in which the quantity of albumin is small. Hemoglobinuria should not be mistaken for melanuria, or hemotoporphyrinuria. Spectroscopic examination is usually of value in deciding as to the nature of the pigment present.

PNEUMATURIA.

The passage of gas with the urine is not a common condition. Gas may gain entrance to the bladder by the following means: (1) From mechanical causes, as vesical irrigation or cystoscopic examination in the knee-chest position. (2) By developing in the viscus, following the introduction of gas-forming organisms in catheterization or other operations. The yeast fungus, the colon bacillus, and the bacillus aerogenes capsulatus have been found. (3) By

communication with some air-holding viscus, as in cases of vesico-enteric fistula.

Most cases of pneumaturia occur in old men with enlarged prostates, or in case of obstruction from stricture of the urethra. The passage of the gas is usually at the end of micturition, and sometimes may be accompanied by a loud sound. The diagnosis is readily made by causing the patient to urinate while bathing or by plunging the end of the catheter in water.

UREMIA.

A toxemia developing in the course of nephritis or in conditions associated with anuria, usually results in a train of symptoms that have received the name *uremia*. The nature of the poison or poisons that produce these symptoms is as yet unknown.

Many theories as to the cause of uremia have been advanced. The view most widely held is that the condition is due to the accumulation in the blood of waste substances —body poisons—that should be thrown off by the kidneys. As Carter has said, "If, however, from any cause, these organs [the kidneys] make default, or if there be any prolonged obstruction to the outflow of urine, accumulation of some or of all the poisons takes place, and the characteristic symptoms are manifested; but the accumulation may be very slow, and the earlier symptoms, corresponding to the comparatively small dose of poison, may be very slight; yet they are in kind, though not in degree, as indicative of uremia as are the more alarming symptoms, which appear toward the end, and to which alone the name uremia is often given."

Another view is that uremia depends on the products of abnormal metabolism. Hughes and Carter concluded, from a careful study of this question, that the poison is of an albuminous nature; in fact, quite different from anything found in normal urine. Herter and others have shown that the toxicity of the blood-serum in uremic states is much increased. Brown-Séquard suggested that the kidneys have an internal secretion, and it is urged that the symptoms of uremia are due to their disturbance. Traube believed that the symptoms of uremia, particularly coma and convulsions, were due to localized edema of the brain.

It is safe to say that we know practically nothing of the

cause of uremia. Experiments have shown that urea is probably not a causative agent; but how much the other urinary salts and the nitrogenous extractives have to do with the condition has not yet been determined. Bouchard claims to have separated from the urine no less than seven different substances that play a part in uremia:

1. Diuretic substance: fixed, organic, and in reality urea.
2. Narcotic substance: fixed, and of organic nature.
3. Sialogenous substance: organic; chemic nature unknown.

4 and 5. Two substances causing convulsions: one (4) may belong to the group of coloring-matters; it is in reality an alkaloid. The other (5) is the potassium salts.

6. A substance causing contraction of the pupil: fixed, organic, and comparable in many respects to the organic substance that induces convulsions.

7. A substance that reduces heat: fixed and organic.

Bouchard's observations tend strongly to confirm the view now generally held that the symptoms are caused by the retention of excretory products of the body. It must be conceded that the nature of these poisonous ingredients is complex.

Prominent Symptoms.—From a clinical point of view, uremia may be either acute or chronic. The division of the symptoms as given by the French writers is perhaps most practical, and is as follows: (*a*) *cerebral;* (*b*) *dyspneic;* (*c*) *gastro-intestinal.*

Among the **cerebral** manifestations are (1) mania; (2) delusional insanity; (3) convulsions; (4) coma; (5) local palsies; and a variety of nervous phenomena, such as occipital headache, intense itching of the skin, numbness and tingling in the fingers, and cramps in the muscles of the legs.

Dyspnea.—This may be paroxysmal or continuous, and there may be Cheyne-Stokes breathing.

The **gastro-intestinal** manifestations are usually chiefly nausea and vomiting; the latter may be almost uncontrolable. Diarrhea may be present; sometimes it is profuse and associated with an intense catarrhal or even diphtheric inflammation of the colon.

Urine.—An examination of the urine is of the greatest value in the diagnosis of uremia. The *quantity* of urine is usually much diminished; there may be almost complete

suppression. On the other hand, the quantity may be normal or even increased. In a case of chronic interstitial nephritis studied by the author at the Boston City Hospital, uremic symptoms rapidly developed when, for any reason, the quantity fell from 3500 or 4500 c.c. down to 2000 c.c.

The *normal solids* are usually diminished, especially the urea, but they may be normal or only slightly reduced. As a rule, the activity of the symptoms bears an inverse ratio to the quantity of urea excreted. *Albumin* is always present in the urine in this condition. It may vary between the *slightest possible trace* and 3 or 5 per cent., but the quantity will depend upon the nature of the associated lesion. The author has not met with a single instance of uremia in which albumin was not present, at least, in the slightest possible trace. The *sediment* invariably contains abnormally formed elements, particularly renal casts and renal cells. It may contain a variety of other abnormal elements, such as blood, pus, and crystalline elements. Waxy casts are very common in the sediment, especially when the condition accompanies advanced chronic disease of the kidneys.

Uremia may occur during either an acute or chronic kidney disease. An acute exacerbation of a subacute or chronic nephritis is very liable to be followed by uremic symptoms. So far as the author is aware, uremia never occurs during the course of a simple active hyperemia.

Puerperal eclampsia, a common complication arising before, during, or after confinement, in all probability is identical with uremia. It may occur in the course of an extensive passive hyperemia of pregnancy, or as the result of a sudden acute nephritis. A woman who has had a perfectly normal pregnancy may suddenly develop uremia (eclampsia) without previous warning either in the urine or by physical signs. No doubt puerperal eclampsia is the result of a toxemia, and it may have the same cause or causes as uremia.

Diagnosis.—Uremia should, in every instance possible, be distinguished from cerebral lesions, such as hemorrhage, meningitis, and even tumors; also epilepsy, acute alcoholism, opium-poisoning, and diabetic coma. For information regarding the differential diagnosis of uremia, the reader is referred to various works on medicine.

DIABETES MELLITUS.

Diabetes mellitus is a disease in which grape-sugar or glucose is excreted in the urine for a long period,—often for many months or years,—and excreted in large quantity or in sufficient amount to give a reaction with the ordinary clinical tests for sugar. But the term diabetes mellitus can not be applied to all cases in which sugar is detected in the urine. Glucose is occasionally present in the urine for a short period only, as after febrile attacks, acute diseases, and injuries, and as a result of the action of certain toxic substances. These are cases of *temporary glycosuria*, and not true diabetes mellitus. Then, again, after a very large quantity of saccharine food has been taken a small amount of grape-sugar may appear in the urine of many apparently healthy persons, or if the sugar in the diet should exceed a certain limit, a small quantity of it will always be found in the urine; these are instances of *temporary alimentary glycosuria* (Williamson).

Causes.—Hereditary influences are important; instances are on record of its occurrence in many members of the same family. Males are more frequently affected than females, the ratio being about three to two; this is especially true after the age of thirty. In the early period of life, and before the age of thirty, the liability of the two sexes is about equal. The disease may occur in infancy—under one year—or in extreme old age. Hebrews are especially prone to this disease. It is comparatively rare in the colored race (from 8 to 10 per cent., Futcher). In most of the cases of diabetes after thirty years of age the subjects have been excessively *fat* at the beginning of, or prior to, the onset of the disease. The so-called "fat man's diabetes" is not of grave significance, since it is usually the result of excesses of starchy and saccharine diet, and is only occasionally followed by true diabetes. Von Noorden has shown that there may be a "diabetogenous obesity," in which diabetes and obesity develop in early life; such cases are very unfavorable. Gout, syphilis, and malaria have been regarded as predisposing causes. Severe nervous strain and nervous shock precede many cases. In one instance seen by the author a true diabetes followed severe fright at the sight of a snake. The combination of sedentary life, close application to business, and overindulgence in

food and drink seem especially prone to induce the disease. Injury to, or disease of, the brain and spinal cord is not infrequently followed by diabetes. In an investigation of 212 cases of *traumatic glycosuria* by Higgins and Ogden [1] the following results were noted : In cases of scalp wounds and minor head injuries glycosuria was found in 5.95 per cent.; in scalp wounds with exposure of bone, 9.3 per cent.; in concussion, 2.5 per cent.; in fractures of the vault of the skull, 20.8 per cent.; and in fractures of the base, 23.8 per cent. From the examination of these 212 cases the following conclusions were drawn :

1. That sugar may appear in the urine as early as six hours after a head injury, and disappear within twenty-four hours ; the average time for its appearance being from eight to twelve hours ; the average time for its disappearance being from the fifth to the ninth day.

2. That a small proportion of cases exhibit a permanent glycosuria from the date of the injury to the head.

3. That acetone and diacetic acid are rarely, if ever, found in such cases, excepting when the condition becomes a permanent glycosuria, and even then probably only after a number of months or years.

Glycosuria may occur during pregnancy. An irritative lesion of Bernard's diabetic center in the medulla is an occasional cause. Glycosuria sometimes occurs during the course or following acute infectious diseases.

Hibbard and Morrissey [2] found in the observations made on 230 diphtheria cases that glycosuria was present in 25 per cent. of all cases examined ; in 17 per cent. of the fatal cases, and in 19 per cent. of those that recovered. The quantity of sugar in these cases varied between a mere trace and 3⅓ per cent. The time of the appearance of the glucose in the urine varied from the second to the eighteenth day, and the duration varied from one day to several weeks. The authors concluded that, in many instances, antitoxine was the probable cause of the glycosuria.

A glycosuria sometimes makes its appearance just before death in cases of chronic diffuse nephritis and subacute glomerular nephritis. It appears to be in some way connected with the extensive dropsy at this time, and is, perhaps, the result of edema of the brain.

[1] "Boston Medical and Surgical Journal," Feb. 28, 1895.

[2] "Journal of the Boston Society of Medical Sciences," Feb., 1898.

Lesions of the *pancreas* are met with in about 50 per cent. of the cases (Hansemann). Total extirpation of this organ in dogs has been shown by v. Mering and Minkowski to produce diabetes; the same result follows the complete removal of the pancreas in man. In disease of the pancreas diabetes is supposed to be caused by the prevention of the formation of the glycolytic ferment. It is believed that this ferment, which emanates from the pancreas, is taken up by the blood, and that it is by its presence alone that the normal assimilative processes can take place with the glycogen.

The nature of diabetes mellitus is unknown. For a summary of the anatomic changes found in this disease, the reader is referred to Saundby's "Lectures on Diabetes," 1891.

Character of the Urine.—Quantity.—This is usually greatly increased, the increase being generally in direct ratio to the quantity of sugar present. In the average case the quantity varies from 3000 c.c. to 6000 c.c. In very severe cases it may go as high as, or even exceed, 10,000 or 20,000 c.c. in twenty-four hours. Occasionally, the total daily quantity is less than 1500 c.c. This is particularly true in the very mild forms of temporary glycosuria, or near the fatal termination of cases of true diabetes mellitus.

Color.—Usually, very pale. Watery. Sometimes the urine has a normal, or rarely a high, color. On standing diabetic urine speedily becomes opalescent, owing to the rapid development of yeast spores and other fungi.

Reaction.—Generally acid. It is often strongly acid, and the acidity increases at the onset of diabetic coma (Williamson). When a diabetic urine is allowed to stand, it remains acid for many days, and it may even increase in acidity, owing to the development of lactic acid by fermentation.

Specific Gravity.—This is increased; it generally ranges between 1025 and 1050, or it may be higher still. Not infrequently the specific gravity is below 1020. While the density of the urine is raised if a large quantity of sugar be present, we can not conclude, if the specific gravity be low, that sugar will be absent; *the urine should be tested for sugar in every instance, whether it has a high or a low specific gravity.*

Normal Solids.—*Absolutely*, increased, or they may be normal. Occasionally, the total urea goes as high as 60 or

100 grams.[1] Owing to the large quantity of urine, the normal solids are *relatively* diminished. In very mild cases with a small quantity of sugar they may be relatively normal.

Preceding or during diabetic coma the normal solids are usually both relatively and absolutely diminished.

Under ordinary conditions the *total solids* of the urine are high, owing to the presence of the sugar.

Sugar.—The presence of sugar is, of course, the most important abnormality of the urine in diabetes. The percentage varies, according to the nature of the case, from 0.5 up to 8 or 12. The daily quantity of sugar also varies. It is often from 20 to 60 grams in the twenty-four hours, but may rise to 300 or 500 grams. In rare instances the total quantity of glucose may exceed 750 grams.

To estimate the amount of sugar, the total quantity of urine for twenty-four hours must be carefully collected and well mixed, and then a sample submitted to examination. *The twenty-four-hour excretion of sugar should be calculated in all cases, since it is by this means only that definite information regarding the effect of treatment is obtained.*

The twenty-four-hour quantity of urine should always be accompanied by a specimen of the fasting urine (early morning urine); also by a specimen passed after the heartiest meal. A very small amount, or an entire absence, of sugar in the fasting urine constitutes an important element in the diagnosis between a temporary glycosuria and a true diabetes mellitus.

Albumin.—This is usually present, but in very small amount—generally the *slightest possible trace*. In case there is a coexisting chronic interstitial nephritis, which is not very common, the amount of albumin may reach a *trace* or *large trace*.

Sediment.—An occasional hyaline and finely granular cast; rarely a renal cell and blood globule. There is usually, also, a moderate excess of squamous epithelium and sometimes a slight excess of leucocytes. If the urine has been allowed to stand for some period, an abundance of sugar spores (torula cerevisiæ) will be found.

The nature of the renal disturbance in the majority of cases of diabetes mellitus is a renal congestion (active hyperemia), which is probably partly caused by the irritating action of the sugar on the renal epithelium, and possibly by

[1] See p. 56.

the ingestion of an unusual amount of nitrogenous food. But a chronic nephritis (usually the interstitial form) is sometimes met with, especially in those cases of permanent diabetes that have been in progress for several years. Under these circumstances the quantity of albumin is somewhat higher, the number of casts larger, and the normal solids lower than in the average case of diabetes attended with a renal congestion.

Prominent Symptoms.—*In temporary glycosuria* symptoms may be slight or entirely wanting. Usually, polyuria is the most noticeable sign of the condition. A hearty appetite and gastric disorders are not uncommon. A craving for sweets is sometimes present. The patients are, as a rule, obese and past the age of thirty. Occasionally, the symptoms in this form quite closely resemble those associated with true diabetes mellitus, but usually they are milder than in the permanent form of the disease.

In *permanent diabetes* the most prominent symptoms are (1) a constant and seemingly unquenchable thirst, (2) polyuria, (3) hunger, (4) emaciation, (5) general weakness, and (6) a variety of nervous disorders. Although the quantity of water taken is frequently excessive, the tongue and mouth remain dry, parched, and congested. Sometimes the gums are tender and become shrunken so that the teeth loosen; frequently, the saliva is scanty. The skin is dry and harsh. Eczema and erythema, especially about the genital organs, are frequent and annoying symptoms. Boils and carbuncles are among the most common of the skin lesions in diabetes. They often occur at an early stage, and sometimes are the first symptoms noticed by the patient.

The temperature may be normal or subnormal. In advanced cases, and especially preceding or during diabetic coma, the temperature may be as low as 95° or 94° F. As a result of the voracious appetite, the digestion sooner or later becomes disordered. Constipation and attacks of diarrhea are not uncommon; constipation is the rule.

Various nervous manifestations appear, such as neuralgia, neuralgic pains in the chest, pain and tenderness in the calves of the legs (neuritis), sometimes sufficient to interfere with walking. Sensations of abnormal heat of the skin are common. The patient becomes fretful, irritable, and hypochondriacal, and usually there is a marked lessening or a complete loss of sexual power. Gangrene of the

extremities is common, especially in those past the age of from thirty to forty years. Cataract and diabetic retinitis are liable to occur.

The pronounced and persistent polyuria produces frequent micturition, which harasses the patient both day and night. The quantity of urine passed during the day usually exceeds that passed at night. One of the most frequent lung complications is tubercular disease, which is most common in poor, hard-working people. Cardiac weakness and enlargement, sometimes attended by valvular disease or functional disturbances, are not uncommon.

Diagnosis.—An effort should be made in all cases to distinguish between a *permanent diabetes mellitus* and a *temporary glycosuria.* In both forms the sugar eliminated must be glucose (grape-sugar). In the former the sugar is *constantly* present in the urine, while in the latter the fasting urine (early morning urine) is generally free from sugar, or contains only a very slight trace, and the after-meal urine is highly saccharine. A diet free from carbohydrates will often serve to distinguish between these two forms, since in a temporary glycosuria the urine is usually quite readily rendered sugar-free, while in the permanent form the quantity of sugar may be reduced, but the urine is made sugar-free only with great difficulty, or not at all.

Course and Prognosis.—In children the disease is rapidly fatal. It may be stated that the older the patient at the time of the onset, the slower the course. In fleshy elderly individuals, the disease is much more amenable to treatment than in thin persons. Cases without hereditary influences are the most favorable. Persons are met with who have had the disease for fifteen years (Osler). In true diabetes mellitus instances of cure are rare. Not a few of the cases of reputed cures belong to the class of temporary glycosuria. In cases under thirty to forty years of age the outlook is bad.

DIABETIC COMA.

Apart from coma produced by various conditions, such as cerebral hemorrhage, uremia, etc., there is a special group of symptoms ending in coma that is a frequent termination of diabetes. These symptoms are unaccompanied by any gross lesions of the organs, and are apparently due to the toxic condition of the diabetic blood. Generally, the patient

comes under treatment for other symptoms of diabetes before the onset of the coma; occasionally, the patient is first seen during the comatose stage.

Diabetic coma occurs both in the severe and mild forms of diabetes, and rarely, if ever, in a temporary glycosuria. It may occur at any age, but it is very common in young persons and in persons under middle life.

An exciting **cause** is sometimes a long railway journey. A sudden change of diet—from a mixed to a rigid nitrogenous diet—often appears to be an exciting cause of diabetic coma; and it is said that a sudden change from a rigid nitrogenous diet to a mixed nitrogenous and carbohydrate diet has occasionally been immediately followed by coma. The opinion is gradually gaining ground that a highly nitrogenous diet favors the development of coma, especially in the severe cases in which the urine gives a port-wine color with ferric chloride (diacetic acid reaction). In many instances prolonged constipation has appeared to play some part as an exciting cause, but it is not invariably present.

Diabetic coma appears to be occasionally precipitated by intercurrent affections or complications, such as bronchitis, pleurisy, pneumonia, tonsillitis, carbuncles, pharyngeal, ischiorectal, or alveolar abscesses. The administration of anesthetics and the performance of surgical operations have also figured occasionally as exciting causes of coma. Rapid and marked loss of weight sometimes precedes the onset of coma.

The **symptoms** often begin with lassitude, epigastric pain, nausea, and sometimes vomiting. Frequently, dyspnea and headache are early symptoms. The patient becomes anxious, restless, or excited. Speech becomes thick and incoherent, and finally he becomes drowsy, and the drowsiness gradually develops into coma. The pulse is rapid and the tension is low; the heart's action is weak, but cardiac murmurs are not usually heard. The tongue is dry and red, and the face becomes pale and cold; frequently there is slight cyanosis.

Generally, the breath has a peculiar odor; the urine also has the same smell. The latter has been variously described, most frequently perhaps as an odor resembling new-mown hay; it has been termed the *acetone odor*. Convulsions, as a rule, do not occur, and in this respect diabetic coma differs markedly from uremia.

Bremer's blood test with methylene-blue will often serve to distinguish diabetic coma from other forms of coma.

Urine.—The urine is diminished in quantity preceding and during diabetic coma, the color is not so pale and the acidity of the urine is increased. There is frequently a marked diminution in the quantity of sugar before the onset and during the coma. Usually, the quantity of albumin increases. The normal solids become *absolutely* much diminished. The sediment usually contains numerous hyaline and finely granular casts; a few renal cells, which are often quite granular; and an occasional blood globule.

The urine almost invariably gives the reactions for acetone, diacetic acid, and β-oxybutyric acid. (See pp. 175, 177, and 178.)

Importance of Acetone, Diacetic Acid, and β-oxybutyric Acid in Diabetic Urine.—Acetone, diacetic acid, and β-oxybutyric acid are most commonly found in the urine of the advanced cases of true diabetes mellitus. In most instances their presence is an important prognostic element. Although the reactions for acetone, diacetic acid, and β-oxybutyric acid may be obtained in the urine for weeks or months without any comatose symptoms occurring, they certainly indicate the constant danger of coma. The author's experience leads him to believe that when these reactions are obtained, and especially a marked reaction with ferric chloride (diacetic acid), an unfavorable prognosis is warranted, although in rare instances he has known both acetone and diacetic acid to disappear from the urine as the patient improved under treatment. He has never met with these two substances in cases of temporary glycosuria.

DIABETES INSIPIDUS.

This disease is characterized by the elimination of very large quantities of nonsaccharine urine of low specific gravity. Willis, in 1674, first recognized the distinction between the saccharine and nonsaccharine forms of diabetes. The disease is most common in young persons—between five and thirty years of age. Males are more frequently attacked than females. The affection may be congenital, and in a few instances a hereditary tendency has

been noted. Traumatism, such as injury to the head, trunk, or limbs, has occasionally been the exciting cause. The disease has also followed sunstroke, or violent emotion, such as fright; also intracranial growths or other lesions of the nervous system. It has followed rapidly the copious drinking of cold water, or a drinking-bout; or has set in during the convalescence from acute disease. Osler has noted it in several cases of tuberculous peritonitis.

Practically nothing is known of the pathology of this disease. It is, doubtless, of nervous origin.

Prominent Symptoms.—The most prominent symptoms of this disease are the marked and never-satisfied thirst, the elimination of enormous quantities of urine, marked emaciation, and a dry, pinched, and dusky skin. Exceptionally, the disease does not appear to interfere in any way with the general health. The appetite is usually not increased as in diabetes mellitus. Death may take place from some intercurrent affection. Spontaneous cure may take place.

Character of the Urine.—Quantity.—This varies between 5000 c.c. and 20,000 c.c. during the twenty-four hours.

Color.—Very pale. Watery.

Reaction.—Faintly acid or neutral. Upon standing, the urine soon becomes ammoniacal and turbid, and often has a rather offensive, fish-like odor.

Specific Gravity.—This is very low—usually between 1001 and 1005.

Normal Solids.—*Absolutely*, very much increased; the total urea may exceed 100 grams, while the chlorides, phosphates, and sulphates are also very high. *Relatively*, very much diminished.

Albumin.—Usually absent; the urine may, however, contain the *slightest possible trace* of albumin, particularly in cases of long standing.

Sediment.—Very slight. Generally, it is necessary to centrifugalize the urine in order to get any visible sediment. It usually consists chiefly of cellular elements—squamous epithelium and small round cells; sometimes a leucocyte and blood globule are found. In exceptional cases renal casts (pure hyaline) may be found.

Diagnosis.—*Hysteric polyuria* may sometimes simulate this disease very closely. The amount of urine excreted

may be enormous, but there is never a marked increase of the solids, and often only the development of other hysteric manifestations may enable the diagnosis to be made; a polyuria from this cause is, however, always transitory.

In certain cases of *chronic interstitial nephritis* a very large quantity of urine of low specific gravity may be passed, but the usual low total solids, the presence of albumin and of hyaline casts, and the existence of heightened arterial tension, stiff arteries, and hypertrophied left ventricle aid materially in the diagnosis. Occasionally, in chronic interstitial nephritis the normal solids as well as the quantity of urine are very high, as in a case seen by the author about four years ago; a child, age seven; quantity of urine, from 6000 to 7000 c.c.; specific gravity, from 1002 to 1006; urea, 45 grams; chlorine, 13 grams; P_2O_5, 5.5 grams. On account of the absence of the usual signs and symptoms of chronic interstitial nephritis the case was supposed to be one of diabetes insipidus, but at the autopsy very small, red, granular kidneys were found.

The course of diabetes insipidus depends entirely upon the nature of the primary trouble. Sometimes with organic disease, either cerebral or abdominal, the general health is much impaired. In the idiopathic cases the affection has been known to persist for fifty years with a fair degree of health. Death usually results from some intercurrent affection. Recovery may take place.

CHAPTER XI.

THE URINE IN DISEASES OUTSIDE OF THE URINARY TRACT.

FEVER URINE.

In acute febrile conditions the characteristics of the urine become modified from the normal according to the height and character of the fever and the degree of toxemia or altered metabolism. During the early stage of an acute febrile disease the quantity of urine is abnormally small,—from 500 c.c. to 1000 c.c.,—the color is high, there is a high specific gravity, and an intensely acid reaction. There is usually a considerable amount of sediment; often there is an abundant sediment after the urine cools, due to a deposit of amorphous urates. The normal solids are both relatively and absolutely increased, especially the urea, which has been known to be as high as 85 grams in twenty-four hours. Uric acid is also usually increased, although the extent to which it is increased is largely dependent on the disease that causes the fever. The chlorides are always absolutely diminished. The phosphates are absolutely diminished at first, but later they are increased. In a very mild febrile attack albumin may be absent. In the more severe febrile diseases, with high temperature, albumin is always present, varying in amount from the *slightest possible trace* to a *trace.* The sediment usually contains an occasional (or few) granular and brown granular cast, some with blood and renal cells adherent; a few (or numerous) free renal epithelial cells; and a few blood globules.

As the fever begins to abate, the quantity of urine increases, and frequently there is polyuria during the convalescence from the febrile condition. Although during convalescence the patient may be taking more food than in the early stage of the disease, the normal solids for the twenty-four hours will be diminished, owing to the fact that

the food elements are used to build up those tissues that have been diseased. As complete convalescence approaches, the quantity of urine falls to the normal, and the solids gradually rise to their normal quantities. During convalescence the albumin and the other abnormal elements gradually disappear from the urine, and the renal tubules become restored to their normal condition.

In case the acute disease terminates fatally during the acute stage the quantity of urea and other solids, instead of being high, will be found to gradually diminish up to the time of death, and may, on the last day or two of the disease, amount to only 5 or 10 grams in twenty-four hours.

The characteristics of the urine in acute febrile conditions, as a rule, conform to those of an active hyperemia, which may be either mild or severe. Such renal disturbance is no doubt partly due to the irritating action of the concentrated urine itself, but is more directly dependent on the elimination of irritating toxines developed during the disease from which the patient is suffering. Although the renal affection usually begins as an active hyperemia, it often becomes intensified, and may result in an acute nephritis. The extent of the renal involvement is usually in direct proportion to the degree of toxemia.

In acute diseases attended with a serous exudation the characteristics of the urine differ somewhat from the preceding. The chlorides are diminished to a much greater extent than in an ordinary acute affection without exudation, and, indeed, they may be absent. The urea is also not so high (although it may still be above the normal) as in acute disease without serous exudation. In rare instances the total urea may be considerably diminished, apparently as a result of the exudation. (See Pneumonia, p. 385.)

URINE OF CHRONIC DISEASE (NOT RENAL).

In many chronic affections of the body in which fever is absent, such as cancer, tuberculosis, etc., the urine generally has an entirely different appearance from that found in acute febrile diseases.

The quantity is slightly below the normal—1000 c.c. or 1200 c.c.; the color is usually pale, but it may be normal or, rarely, slightly high; the reaction is faintly acid, or it

may be alkaline. The normal solids are both *relatively* and *absolutely* diminished, the amount of diminution being dependent largely upon the appetite, which is generally more or less disturbed. Albumin is usually present, but in very small amount; occasionally, it is absent. The sediment is liable to contain a very few formed renal elements (casts and renal cells), although they, too, may be absent. It is, however, the rule to find, at least, evidences of a renal congestion (active hyperemia), and sometimes coexisting primary kidney disease.

TYPHOID FEVER.

The quantity of urine is diminished—500 c.c. to 800 c.c.; the color is very high (absolute increase of the pigments); the reaction is strongly acid; the specific gravity is usually very high—1030 to 1040; the normal solids are relatively increased. If, on the other hand, the patient has been given a large amount of water or other liquid, the quantity of urine will be nearer the normal and it will have a normal or pale color and a normal or low specific gravity. During the first week of the disease the solids, except the chlorides and phosphates, are absolutely increased, the former being only slightly diminished while the latter are usually much diminished. The quantity of urea may go as high as 60 to 70 grams. The uric acid is also much increased, and the urine not infrequently contains a heavy deposit of amorphous urates. Albumin is almost always present; the quantity varies from the *slightest possible trace* to ⅛ of 1 per cent., the amount being dependent on the height of the fever, the toxemia, and the nature of the resulting renal affection. The sediment is almost certain to contain renal casts, an excess of renal epithelial cells, and a variable quantity of blood—usually a small amount.

An active hyperemia that is more or less severe is the rule in typhoid fever. Sometimes a genuine acute nephritis develops at the onset or during the height of the disease, masking in many instances the true nature of the primary malady; in such cases the prognosis is always to be considered grave. An acute nephritis developing during convalescence from typhoid fever is quite common, but, as a rule, not so serious as when it develops early in the disease; it usually makes its appearance after the fall of the fever. Convalescence from an acute nephritis, which has

developed late in typhoid, is usually slow, but complete recovery is the rule.

Pyuria is a common complication of the disease. The pus is the evidence of a cystitis or a pyelitis, and in the experience of the author the latter is the more common. Under these circumstances the urine invariably has the characteristics of a *chronic* cystitis or *chronic* pyelitis, and it usually contains a large number of typhoid bacilli. (See p. 268.) Orchitis is occasionally met with during convalescence; it is usually associated with a catarrhal urethritis. In pyelitis, cystitis, or urethritis from this cause treatment with the formaldehyde compound known as *urotropin* is usually highly satisfactory.

In the urine of typhoid fever the diazo reaction of Ehrlich is often obtained. (See p. 186.) The clinical value of the reaction is doubtful; it is certain that its value is lessened by its occurrence in acute miliary tuberculosis and various other diseases associated with high fever.

YELLOW FEVER.

The quantity of urine is much diminished from the first. The color is high or dark, depending upon the amount of blood present; rarely, it is bloody. The specific gravity is usually below the normal, but it may be high. The urea is often *relatively* diminished, but it may be normal; *absolutely*, it is much diminished; sometimes it is totally absent (Purdy). Although there is, without doubt, an increased production of urea during the stage of fever, yet, according to Cunnisset, the elimination of urea is always less than normal, the degree of diminution being in direct proportion to the danger of the disease, and affording an important element in prognosis. The chlorides are usually both relatively and absolutely diminished. Albuminuria is regarded by Guitéras as the third characteristic symptom of the disease. In the mild cases the amount of albumin is usually small, but in the severe cases the quantity of albumin is large and there may be numerous tube casts of various kinds, renal epithelium, an abundance of blood, and all the evidences of a severe acute nephritis. Or perhaps complete suppression of the urine may supervene, and death may occur in uremic convulsions or coma within twenty-four or thirty hours. When albumin is present in

the urine on the first day of the disease and continues on the second day, Guitéras states that it indicates a severe case. The urine frequently contains bile.

TYPHUS FEVER.

In this disease the urine is scanty in amount and highly febrile. It is highly colored and strongly acid. Occasionally, it is alkaline, and has a very offensive odor. *Relatively*, the urea is increased; *absolutely*, much diminished; leucin and tyrosin may take the place of the urea, as in acute yellow atrophy of the liver. The uric acid is relatively increased, and it may be absolutely increased, especially during the early stages of the disease. The chlorides are both relatively and absolutely greatly diminished, and may be absent. Albumin is invariably present, but usually in small amount, except in the severe cases attended with acute nephritis. Under such circumstances the urine is bloody and bears the other characteristics of an acute nephritis. (See p. 296.) The proportion of cases in which an acute nephritis occurs varies much in different epidemics; its existence, however, adds decidedly to the gravity of the case. A true hemoglobinuria may be seen in the severe cases. In the mild cases the characteristics of the urine are those of a severe active hyperemia or renal congestion. The sediment contains numerous hyaline and granular casts and renal cells; also a varying amount of blood. At the time of the crisis copious amounts of urine of low specific gravity and pale color are passed. Retention of urine is of frequent occurrence; the region of the bladder should be frequently examined, and the catheter used if required.

RELAPSING FEVER.

In relapsing fever the urinary system is the seat of varying morbid conditions, some of which are of great importance in determining the prognosis. Albuminuria is present in a very large number of the cases, and is not necessarily a cause of very serious alarm. When, however, an abundant excretion of albumin is accompanied by the presence of large numbers of renal casts, renal cells, and much blood, the prognosis is grave. The affection of the kidneys may vary from a simple congestion to an actual acute nephritis, the latter

being sometimes hemorrhagic in character. Complete suppression of urine is sometimes present. Hematuria may be profuse and exhausting; it is a grave complication and is often followed by a fatal issue. Glycosuria has been observed during the course of some cases.

PNEUMONIA.

Early in the disease the urine presents the usual characteristics found in acute febrile conditions attended with exudation. The quantity of urine is very small—often less than 500 c.c.; the specific gravity is high—1030 to 1040; the color is very high, the amount of pigment being both relatively and absolutely increased. The quantity of urea is increased. In some instances the urea is diminished after the first few days of the disease; such cases are usually characterized by delayed convalescence, diarrheal attacks, tuberculosis, pleurisy with effusion, empyema, etc. The uric acid is usually very much increased, especially just after the crisis, and very often the urine contains a very heavy deposit of amorphous urates, and is colored a carmine, deep red, or brown.

The chlorides are very much diminished and may be entirely absent, especially between the third and fifth days of the disease. The reappearance of the chlorine is evidence of beginning convalescence—the beginning of the absorption of the serous exudation from the diseased lung. The chlorine always reappears or commences to increase in quantity before evidences of beginning convalescence can be made out by auscultation and percussion or by a fall in the temperature.

Albumin is invariably present in pneumonia—often only the *slightest possible trace* in mild cases, and a *large trace* to ⅛ of 1 per cent. in the severe cases. Sometimes a large amount of albumin and a bloody or smoky urine indicate the presence of an acute nephritis. In a large proportion of all cases the albumin is evidence of a more or less severe toxic condition. According to v. Jaksch, the appearance of peptone in the urine is indicative of the beginning of resolution.

The sediment usually contains a few (or numerous) hyaline, fine, and brown granular casts, numerous renal cells, and abnormal blood globules. Blood may be present in

abundance, when the sediment usually has the other characteristics of an acute diffuse nephritis. (Compare p. 296.)

The urine may contain bile pigment.

During convalescence from pneumonia the quantity of urine increases and may exceed the normal; the quantity of urea and uric acid return to, and sometimes fall below, the average normal, while the chlorides gradually become increased, finally returning to normal.

PULMONARY TUBERCULOSIS.

In the average uncomplicated case of pulmonary tuberculosis the urine does not present any special peculiarities. The quantity is usually diminished, especially if there is fever; if no fever, the quantity may be increased, even in uncomplicated cases. If amyloid infiltration be present as a complication, the quantity of urine is usually increased. In the average case of pulmonary phthisis with fever the color of the urine is higher than normal, the specific gravity is moderately increased, and the reaction is strongly acid. The normal solids are *relatively* increased; *absolutely*, diminished. The urea is usually diminished, but the extent of the diminution is dependent on the appetite, the general metabolism, and the fever. The uric acid is generally increased, while the sulphates are only moderately diminished. The chlorides are usually somewhat diminished, but the quantity of chlorine is largely dependent on the character of the food taken. If there is marked diarrhea, the chlorides will be found absolutely very much diminished. In some cases of pulmonary tuberculosis the phosphates are absolutely increased, especially when the lung tissue is breaking down rapidly.

Albumin is probably present in the urine of every case of advanced phthisis. As has been stated, subacute glomerular nephritis and amyloid infiltration are frequent complications of pulmonary tuberculosis. (See pp. 303, 320.) Under such circumstances the quantity of albumin is large. If such complications are not present, the quantity of albumin is usually small—*slightest possible trace* to a *trace*.

The sediment usually contains an occasional (or a few) renal cast, renal cell, and a very small amount of blood; in other words, evidence of a more or less marked renal congestion.

Besides the liability of an amyloid infiltration, or a subacute glomerular nephritis as a complication, tubercular ulcerations in the kidney, pelvis of the kidney, or the bladder are very likely to occur. Pyuria is then the most prominent feature of the urine. In all such cases the urinary sediment should be very carefully examined for tubercle bacilli.

MALARIAL FEVER.

During the pyrexia the urine has the usual characteristics of a fever urine. The quantity is small, the color is high, and the specific gravity is increased. After the chill and the fever the urine is often increased in amount and of low specific gravity. There is always an increase in the elimination of urea during a paroxysm, and Jaccoud has noted that this increase commences even before the chill, so that careful quantitative estimations of urea will often foretell the approach of a paroxysm. This increase of the urea excretion he observed two hours before the chill in quotidian, and six or eight hours before in tertian fever. He regards the increased urea as a reliable indication for the proper time for administering quinine in order to anticipate the chill. During the paroxysm the chlorine is eliminated in normal amount. On the days between paroxysms both the urea and chlorine are usually diminished.

The urine usually contains albumin, but generally in small amount—*slightest possible trace.* If an acute nephritis develops, the quantity of albumin is large—⅛ to ½ of 1 per cent. The sediment generally contains renal casts, renal cells, and a few blood globules. The renal disturbance is usually of the nature of a renal congestion or active hyperemia.

An acute nephritis in malaria is not very common in New England. Thayer,[1] who has recently made a study of the urine in malaria at the Johns Hopkins Hospital, draws the following conclusions :

(1) Albuminuria is of frequent occurrence in the malarial fevers of Baltimore, occurring in 46.6 per cent. of the cases studied. (2) It is considerably more frequent in estivo-autumnal infections than in the other forms, occurring in 58.3 per cent. of these instances against 38.6 per cent. in

[1] "Amer. Journ. Med. Sciences," Dec., 1898, p. 646.

the regular intermittent forms. (3) Acute nephritis is not an unusual complication of malarial fever, having occurred in 2.7 per cent. of the cases treated in the wards and between 1 and 2 per cent. of all cases seen at the hospital. (4) The frequency of acute nephritis in estivo-autumnal fever is much greater than in the regular intermittent forms, having been observed in 4.7 per cent. of the cases treated in the wards and in 2.3 per cent. of all cases seen. (5) The frequency of albuminuria and nephritis in malarial fever, while somewhat below that observed in the more severe acute infections, such as typhoid fever, scarlet fever, and diphtheria, is yet considerable. (6) There is reason to believe that malarial infection, especially in the more tropical countries, may play an appreciable part in the etiology of chronic renal disease.

Paroxysmal hemoglobinuria is sometimes a complication of malaria. Like an acute nephritis, this complication is perhaps more common in the Southern States and tropical countries than in New England. Out of several hundred cases of malarial fever at the Boston City Hospital, the author has only once met with hemoglobinuria. The relation of this condition to malaria is not so close as has been thought by many writers. Bastianelli asserts that it is practically proved that malarial hemoglobinuria occurs only in infections with the estivo-autumnal parasite. No doubt it has frequently been confounded with malarial hematuria.

Malarial hematuria of renal origin is sometimes encountered, especially in the estivo-autumnal form of the disease. In such cases the evidences of tubular disturbance of the kidney (casts, renal cells, etc.) is usually very slight.

ERYSIPELAS.

In this disease the urine is scanty in amount, highly colored, and of high specific gravity. *Relatively*, the solids are all increased; *absolutely*, diminished, especially after the first two or three days of the disease. Albuminuria is almost constant; usually, the quantity of albumin is small, varying between a *very slight trace* and a *large trace*. A true acute nephritis is quite common; the quantity of albumin may then reach, or even exceed, 1 per cent. The sediment always contains renal casts, usually an excess of renal epithelium, and a few (or numerous) blood globules,

both free and adherent to casts. The number of casts and cellular elements, and the quantity of blood, may be very large, indicative of an acute nephritis. In the experience of the author an acute pyelonephritis in erysipelas is not uncommon. Chronic pyelitis is sometimes the result of the acute pyelitis; convalescence from this complication is usually slow. In case the erysipelas is complicated by pneumonia, ulcerative endocarditis, or septicemia, a severe acute pyelonephritis is quite sure to follow, and the prognosis is thereby rendered grave.

CHOLERA.

In the first two or three days of this disease—algid or collapse stage—the quantity of urine is very small, or there may be complete suppression; the color is normal or pale, sometimes smoky; the specific gravity is either normal or diminished; and the reaction is faintly acid. The urea is very much diminished; this marked diminution is unusual in most acute diseases, and in cholera it is probably due to the fact that a large proportion of the urea is eliminated with the intestinal discharges. In case of suppression of urine a considerable amount of urea may be eliminated by the sweat glands; indeed, it is sometimes eliminated in sufficient quantity to cause a coating of urea on the skin, especially in the axillæ and groins. The uric acid is also much diminished. The chlorides are very much diminished, or they may be absent. The phosphates are, like the urea, very much reduced.

The indoxyl—indoxyl-potassium sulphate—is much increased, and in rare instances the urine has a blue color and contains a deposit of indigo. In early times, before the recognition of the cholera bacillus, the high indoxyl was considered an important element in the diagnosis of cholera. It should be borne in mind, however, that a large increase in the indoxyl is frequently found in other conditions than cholera, such as peritonitis, intestinal obstruction, etc., so that too much reliance can not be placed on a high indoxyl in the diagnosis of cholera.

During the algid stage the urine invariably contains albumin. The quantity varies, but it may be large and frequently indicates the presence of an acute nephritis. Often the albuminuria disappears with the subsidence of the algid stage.

The sediment contains renal casts, often in large numbers, many renal cells, and a few (or numerous) blood globules. If an acute nephritis, the quantity of blood will be large, and there will be a large number of brown granular, blood, epithelial, and fibrinous casts.

After the third day, in a favorable case, the quantity of urine rapidly increases, the color is pale, and the specific gravity is very low. Coincident with this increase of the urine there is a rise in the urea, chlorides, phosphates, and other solids. The urine may temporarily exceed the normal —for example, it may rise to 60 to 80 grams and then gradually return to the normal. The chlorides and phosphates, however, do not, as a rule, exceed the normal. In case of an acute nephritis during the algid stage a typical convalescent stage of acute nephritis is seen when the patient begins to improve.

But the complication of an acute nephritis during the collapse period may be the direct cause of death by uremic coma. In cholera, after the third day, if the quantity of urine does not increase, the albumin does not diminish, and the urea and chlorine do not begin to rise in quantity, the prognosis can be considered very grave.

SCARLET FEVER.

The urine in this disease is subject to much variation. It is very common, and, indeed, the rule to find evidences in the urine of a severe renal congestion or an acute nephritis (sometimes the acute interstitial form). But in many instances the kidneys escape without greater damage than occurs in other acute febrile affections. An acute nephritis is most common in the second or third week of the disease, and may develop after a very mild attack of scarlet fever. Not infrequently, an acute nephritis makes its first appearance late in the period of desquamation, when it usually exists in a mild form. As a rule, the earlier it develops, the more severe it is.

The renal disturbance varies greatly in intensity, but in all instances during the height of the fever the urine is diminished in quantity and of high specific gravity. It has a high or smoky color, an intensely acid reaction, and the normal solids are *relatively* increased, especially the urea and uric acid ; they are *absolutely* diminished except during

the first day or two of the disease. If there be dropsy, the chlorides and urea are very much reduced, especially the former. Three distinct grades of cases may be recognized.

Mild Cases.—The urine has a high color, and invariably contains albumin—usually the *slightest possible trace* to a *trace*. The sediment contains an occasional (or few) hyaline, granular, and brown granular casts, renal cells, and a few blood globules, free and attached to casts; in other words, there is evidence of a mild renal congestion or active hyperemia. Edema is absent, and the convalescence from the fever is scarcely interrupted.

Severe Cases.—The urine has a smoky color and contains considerable albumin—usually varying in amount between a *large trace* and ¼ of 1 per cent. The sediment contains many hyaline, granular, and brown granular, a few epithelial, blood, and fibrinous casts; also many renal cells and frequently small caudate cells from the superficial layer of the pelvis of the kidney; considerable altered blood, and a few pus-corpuscles—the evidences of an acute pyelonephritis. Edema, especially about the eyelids, is a constant symptom; there may be edema of the feet. The renal symptoms then dominate the entire case. The condition may continue and finally become chronic, but fortunately, in a majority of the cases, the disease yields to judicious treatment, and complete recovery takes place.

Very Severe Cases.—In this class of cases there is usually either complete suppression of urine or the passage of a small quantity of very dark (almost black) urine, which contains a high quantity of albumin—from ½ to 1 ½ per cent. The sediment contains the same elements that are found in the *severe cases*, but in much larger numbers—a very severe acute pyelonephritis. There is marked dropsy, vomiting, and convulsions, and the child dies with the symptoms of acute uremia.

In the favorable cases of acute pyelonephritis the *third or convalescent stage* soon makes its appearance, when the quantity of urine increases, the color is very slightly smoky or pale, and fat appears in the renal cells and is found attached to the casts. As previously stated, with judicious treatment complete recovery usually takes place. Occasionally, convalescence becomes prolonged and a chronic nephritis results. Sometimes a marked chronic pyelitis is the result of the acute pyelitis.

The urine in scarlet fever should in all cases be carefully watched, owing to the fact that renal complications are among the most common.

DIPHTHERIA.

In diphtheria, as in other acute infectious diseases, renal complications are common ; they are, however, less common than in scarlet fever. The quantity of urine is diminished ; the color is high, or, if an acute nephritis, smoky ; the specific gravity is high—1025 to 1035. *Relatively*, the normal solids are increased, but *absolutely*, diminished. Albuminuria is a constant symptom in all severe cases, and, in fact, albumin is present in nearly all of the milder cases. It varies in amount from the *slightest possible trace* to a *large trace*. If an acute nephritis develops, it may exceed ¼ of 1 per cent. The sediment contains renal casts, renal cells, and a small amount of blood both free and on casts—evidences of an active hyperemia.

An acute nephritis is, however, not uncommon. It may appear quite early in the disease. Occasionally, it begins with complete suppression of urine. In comparison with scarlet fever the renal changes lead less frequently to general dropsy. The sediment usually contains, besides brown granular, blood, epithelial, and fibrinous casts, many renal cells, much blood, and numerous small caudate cells from the pelvis of the kidney—evidences of an acute pyelonephritis. The course of the nephritis is usually favorable. Occasionally, there are convulsions, and the patient dies from acute uremia. Sometimes a chronic nephritis follows an acute nephritis. Acute nephritis is a less frequent complication of diphtheria since the advent of the *antitoxine* treatment of this disease.

Hibbard and Morrissey[1] have found that a glycosuria is not uncommon in diphtheria.

SMALLPOX.

In this disease the urine has the usual typical characteristics of fever. The quantity of urine is small, the coloring-matters are increased, and the specific gravity is high. *Relatively* and *absolutely*, the urea is generally increased, but it may, rarely, be *absolutely* much diminished ; under

[1] "Journ. of the Society of Med. Sciences," Feb., 1898.

such circumstances, leucin and tyrosin may appear in the urine instead of urea. The chlorides, sulphates, and phosphates are *absolutely* somewhat diminished. The uric acid is increased, and the urine, on cooling, frequently deposits amorphous urates.

Albumin is invariably present in the urine in all cases of smallpox, and it generally makes its appearance with the onset of the disease. The sediment contains renal casts, renal cells, and a moderate amount of blood both free and adherent to casts. An active hyperemia, which is usually quite severe, is the rule. Occasionally, a true acute nephritis develops, especially in the malignant forms. The urine frequently contains bile pigment. In the hemorrhagic form of the disease hemoglobinuria may be a prominent feature of the urine. Care should be taken not to confound a hemoglobinuria with a hematuria accompanying an acute nephritis.

ACUTE GENERAL PERITONITIS.

In this disease the quantity of urine is very small, the color is high, and the specific gravity is above the normal. A prominent feature of the urine is the very large excess of indoxyl. *Relatively*, the normal solids are increased, except the chlorides, which are very much diminished or absent; *absolutely*, the solids are diminished. Albumin is generally present, and in the sediment will be found renal casts, renal cells, and a variable amount of blood—in other words, evidences of a more or less severe active hyperemia of the kidneys.

In localized peritonitis the chlorides are not, as a rule, much diminished, if at all; the degree of diminution is, however, dependent on the extent of the pathologic process and the amount of serous exudation.

INTESTINAL OBSTRUCTION.

In this condition the urine is small in amount, and there may be almost complete suppression, particularly when the obstruction is high up in the bowel. This is probably due to the excessive vomiting and the small amount of liquid taken. The urine has a high color, and the specific gravity is above the normal—1025 to 1035. *Relatively*, the solids are increased; *absolutely*, diminished. When the obstruc-

tion occurs in the small intestine, the indoxyl is usually very high; in one case the amount of indoxyl reported was as high as 98 milligrams. Albumin is usually present, but in small amount; and the sediment contains renal casts, renal epithelial cells, and a little blood. In the majority of cases of intestinal obstruction the renal disturbance is of the nature of a renal congestion or toxic irritation.

ACUTE YELLOW ATROPHY OF THE LIVER.

The twenty-four-hour quantity of urine is small, the reaction is strongly acid, and the specific gravity is low. The urine contains both bile pigments and the bile acids. *Relatively* and *absolutely*, the normal solids are much diminished. The urea is present in very small amount or it may be absent. Instead of the urea, leucin and tyrosin, one or both, are usually, although not constantly, present in the urine; of 23 recent cases collected by Hunter, in 9 neither was found; in 10, both were present; in 3, tyrosin only; in 1, leucin only. Both leucin and tyrosin have characteristic crystalline shapes (see pp. 227, 228), and are found in the urinary sediment. In the search for these crystals it is advisable to previously render the urine acid with acetic acid and concentrate by evaporation. The phosphates and uric acid are very much reduced. The urine always contains albumin, which may be present in considerable quantity—⅛ to ¼ of 1 per cent. The sediment contains numerous hyaline, granular, and fatty casts, fatty renal cells, and compound granule cells; in other words, the urine indicates a more or less marked fatty degeneration of the kidneys. The casts and renal cells are usually stained yellow by the bile pigment.

Acute yellow atrophy is of rare occurrence and is rapidly fatal. It is characterized by jaundice and marked cerebral symptoms, and anatomically, by extensive necrosis of the liver-cells with reduction in the volume of the organ. The symptoms produced by phosphorus-poisoning closely simulate those of acute yellow atrophy, but it should be borne in mind that the two conditions are not identical.

HYSTERIA.

During and immediately following an attack of hysteria the twenty-four-hour quantity of urine is much increased, not infrequently going as high as 5000 c.c. The color is very pale and watery ; and the specific gravity is low—1002 to 1012 ; the reaction is faintly acid. *Relatively*, the solids are much diminished ; *absolutely*, normal or only slightly diminished, and sometimes they are increased. The urine is frequently free from albumin ; on the other hand, it may be present in very small amount—*slightest possible trace.* The sediment usually contains only a moderate excess of squamous epithelial cells. If the urine contains albumin, after centrifugalizing the sediment will be found to contain an occasional hyaline and finely granular cast, renal cell, and blood globule—in other words, evidences of a very slight active hyperemia, perhaps the result of increased activity of the kidneys. Since hysteria is more common in the female than in the male, the presence in the urine of a profuse vaginal secretion will in many instances account for a very slight albuminuria, without necessarily having any evidence of a renal disturbance.

Charcot has called attention to the fact that in hysteria the quantity of urine may be very small. He records a case in which the patient suffered from vomiting and diarrhea, and in which there was complete suppression of urine for eleven days. Deception was not possible, as the patient was closely watched.

CEREBROSPINAL MENINGITIS.

In this disease the urine has the characteristics of a fever urine accompanied by exudation. The quantity of urine is small ; the color is normal or pale, and sometimes it is high ; the specific gravity is usually somewhat above the normal ; and the reaction is only faintly acid or it may be alkaline. The total quantity of urea is high, the increase usually amounting to 25 per cent. or more (Purdy). The phosphates are much increased in the early part of the disease, so that upon performing the heat test for albumin without the customary addition of acetic acid, an abundant precipitate is thrown down by the test ; later in the disease the phosphates become diminished. The chlorides are

greatly diminished from the first and may, in rare instances, be absent. Albumin, which is invariably present, varies in quantity from the *slightest possible trace* to ⅛ or ¼ of 1 per cent., but is dependent on the amount of renal involvement and the quantity of blood present. Glycosuria has been noted in some instances. The sediment contains hyaline, granular, and brown granular casts, renal epithelial cells, and more or less blood.

The renal disturbance is usually an active hyperemia, which may be quite severe. Rarely, an acute nephritis with marked hematuria develops, especially in the malignant types.

In certain cases there is sometimes doubt as to the diagnosis between typhoid fever and an acute cerebrospinal meningitis. Aside from a bacteriologic investigation, an examination of the urine is sometimes of assistance in arriving at a conclusion. The principal differences in the urine in the two diseases are as follows:

Meningitis.	Typhoid Fever.
Fever Urine with Exudation.	*Fever Urine without Exudation.*
Color.—Normal or pale.	*Color.*—Very high.
Reaction.—Faintly acid, neutral, or alkaline.	*Reaction.*—Strongly acid.
Chlorine.—Much diminished or absent.	*Chlorine.*—Slightly diminished.
Phosphates.—Much increased.	*Phosphates.*—Diminished.

MELANCHOLIA.

In this disease the total quantity of urine is usually much diminished, no doubt in part due to the ingestion of very little liquid. The specific gravity is high, and the coloring-matters and normal solids are *relatively* increased. The urine is frequently heavily loaded with urates and oxalates. The indoxyl is generally increased. The irritating action of the concentrated urine, and in some instances the mechanic irritation by the crystals of uric acid or calcium oxalate, may be the cause of slight albuminuria and a renal congestion (active hyperemia).

ACUTE MYELITIS.

Owing to an involvement of the sphincters in this disease retention or incontinence of urine is an early symptom. An acute or chronic cystitis may rapidly develop, when the

urine becomes faintly acid or alkaline, bloody, and purulent. In such cases the danger of a pyelonephritis by extension is very great; not infrequently, death occurs during uremic coma. One very prominent feature of the urine in acute myelitis is a marked increase in the indoxyl.

EPILEPSY.

Temporary albuminuria accompanied by more or less renal disturbance is of frequent occurrence, especially in those cases of epilepsy in which the convulsive seizures succeed each other very rapidly. Immediately following the attacks the quantity of urine is often much increased, the color pale, the specific gravity low, and the reaction faintly acid. At this time the urea, phosphates, and uric acid are said to be increased.

As suggested by Taylor,[1] the question of auto-intoxication is to be considered as a possible cause of albuminuria and the renal disturbances in cases of severe nervous affection. It is quite probable that the nervous disease itself may give rise to certain products that are later excreted by the kidneys. This is, however, contrary to the view, as generally held, that the effete products normally excreted by the urine are sometimes retained in the body, and that they are the direct cause of various nervous disturbances.

ACUTE ARTICULAR RHEUMATISM.

In acute rheumatism the urine has the characteristics of that of an acute disease. It is small in quantity, has a high color, and a high specific gravity—1025 to 1030. *Relatively*, the quantity of urea is increased, *absolutely*, usually diminished. The uric acid is often both *relatively* and *absolutely* increased, sometimes to a much larger extent than in most of the other acute diseases. The urine, upon cooling, may contain an abundant deposit of amorphous urates. The chlorides and phosphates are only moderately diminished in an uncomplicated case; the sulphates are often increased. If a pericarditis develops, the chlorides and phosphates become very much diminished, and may temporarily entirely disappear from the urine. A sudden fall in the

[1] "Boston Med. and Surg. Journ.," Sept. 22, 1898.

amounts of these two constituents of the urine is, therefore, indicative of a serious complication.

Albumin is usually present, but in very small amount—*slightest possible trace.* Rarely, it occurs in large quantity attended by an acute nephritis, of which the urinary sediment bears abundant evidence. In the average case of acute rheumatism the sediment contains only a very few renal casts, renal cells, and an occasional blood globule, free and adherent to casts; in other words, the sediment is characteristic of an active hyperemia.

GOUT.

During an attack of gout the volume of urine is generally diminished, the color is high, and the specific gravity is above the normal. The uric acid is diminished during the paroxysm; although it is probably formed in unusual quantities in this disease, the deposit of urates in the joints and tissues accounts for the deficient elimination by the kidneys. Usually, the quantity of urea is not materially altered during the paroxysm of gout. The phosphates are generally much diminished. Albumin is nearly always present, but usually in very small amount. The sediment contains hyaline, granular, and brown granular casts, renal cells, and altered blood free and adherent to casts—the evidences of a secondary active hyperemia of the kidney.

Between the attacks or paroxysms, the quantity of urine is normal or even increased. The normal solids are usually about normal, except the uric acid, which is now eliminated in increased amount; this is especially marked immediately following the paroxysm. Evidence of a more or less marked renal irritation persists between the attacks.

It should be borne in mind that in chronic gout a chronic interstitial nephritis is not uncommon. Under such circumstances the quantity of urine is increased; *absolutely*, the urea is much diminished, albumin is present, but usually in minute quantity, and the casts in the sediment are generally of the small, narrow, hyaline, and finely granular order.

Sugar may be found intermittently in the urine of gouty persons—gouty glycosuria. The condition may pass into true diabetes, but it is usually very amenable to treatment. Oxaluria may also be present. Calculi are not uncommon in gouty subjects.

ANEMIA.

In the various forms of anemia the urine presents certain characteristics that are common to all. The twenty-four-hour quantity is generally diminished—1000 c.c. to 1200 c.c.; the color is pale; the specific gravity is below the normal—about 1015; and the reaction is acid. *Relatively* and *absolutely* the normal solids are diminished, but the degree of diminution is dependent largely on the appetite and general metabolism.

In *simple anemia* and *chlorosis* the urine occasionally contains the *slightest possible trace* of albumin and formed renal elements in the sediment; on the other hand, albumin and renal casts may be absent.

In *leukemia* the presence of a minute trace of albumin and renal casts is perhaps more common than in simple anemia. Fatty cells and fat adherent to the casts are not uncommon. The indoxyl is frequently increased. *Absolutely*, the urea is diminished. The uric acid excreted is always in excess, and, perhaps, as suggested by Salkowski, stands in direct relation to the splenic tumor or to the abundant leucocytes. The proportion of uric acid to urea may be as high as 1 to 15.

In *pernicious anemia* the urine, although usually pale, may be highly colored from the excess of so-called *pathologic urobilin* (Hunter and Mott). The uric acid is increased. Albumin, varying in quantity from the *slightest possible trace* to a *trace*, is usually present in the late stages of the disease, and the sediment usually contains renal casts, granular renal cells, and a small quantity of blood. Von Jaksch has noted the presence of peptonuria in this disease, but so far as known it has little or no significance.

SCURVY.

In this disease the quantity of urine is reduced, the coloring-matters are increased, and the urine may contain a large amount of blood pigment—hemoglobinuria. *Absolutely*, the normal solids are diminished, especially the chlorine. The urine is generally albuminous, and sometimes albumin is present in large amount, especially if there be hemoglobinuria or an acute nephritis. The sediment usually contains renal casts, renal cells, and in case of

hemoglobinuria an abundance of brown granular matter. Hematuria is sometimes present, and under all circumstances should be distinguished from a hemoglobinuria. The author has occasionally met with a genuine acute nephritis in this disease. A more or less marked renal congestion is not uncommon.

CARBOLIC ACID POISONING.

In this condition the urine is diminished in quantity; the color is variable, being usually pale or normal when freshly voided, but upon standing exposed to the air becomes smoky and finally very dark; occasionally, the urine is dark when it is passed. This characteristic change of color, following the external or internal use of carbolic acid and other phenol compounds, is due to an oxidation of the decomposition products of the phenol or phenol compounds. (See Color of the Urine, p. 25.) The specific gravity is usually normal or diminished; it may be above the normal. The reaction is acid. *Relatively*, the normal solids are normal or diminished, depending upon the severity, and occasionally they are relatively increased; *absolutely*, diminished, especially the ordinary sulphates, while the conjugate sulphates are much increased. (See Phenol-potassium Sulphate, p. 89.)

The urine contains albumin; usually a *very slight* trace, but in the severe cases it may be as high as ⅛ of 1 per cent. The sediment contains hyaline, granular, and brown granular, and sometimes epithelial casts, renal cells, and abnormal blood free and adherent to the casts. A more or less marked renal congestion is the rule, but occasionally a true acute nephritis is present.

Care should be taken not to confound a dark urine following the use of phenol compounds with a urine containing melanin, in which case the urine is often pale when passed, but upon exposure to the air becomes dark. (See Melanin, p. 194.)

POISONING BY PHOSPHORUS AND ARSENIURETED HYDROGEN.

The characteristics of the urine in cases of poisoning by arseniureted hydrogen and phosphorus are, for the most part, identical. Hemoglobinuria is the principal symptom.

The quantity of urine is diminished. The normal solids are greatly diminished, especially the urea. In severe cases leucin and tyrosin may appear in the urine. Albuminuria is invariably present; usually, the amount of albumin is large, although the quantity will depend on the severity of the case. The sediment will contain numerous brown granular and fatty casts, fatty and brown granular renal and compound granule cells, a variable but usually small amount of blood, and sometimes crystals of leucin and tyrosin—evidences of extensive fatty degenerative changes in the kidney *plus* a hemoglobinuria.

APPENDIX A.

METHOD OF RECORDING URINARY EXAMINATIONS.

The advisability of making and preserving urinary records is obvious, since it is only by this means that the progress of disturbances or diseases of the kidney (favorable or unfavorable) can be followed from week to week, or month to month, or year to year. Such records should be made on separate sheets of paper provided for the purpose and incorporated with the clinical history and physical examination of the patient, or be kept in a book by themselves with cross-references to the volume containing the clinical history, etc. For ordinary use printed urine blanks (see p. 403) can be obtained, and as each test is made the result, indicated by abbreviations, should be affixed to the spaces left for the purpose.

The abbreviations used upon the blank forms have the following meanings: *Uph.* = urophæine; *Ind.* = indoxyl; *Cl.* = chlorine; $\overset{+}{U}$. = urea; $\overset{-}{U}$. = uric acid; *Sf.* = sulphatès; *E. P.* = earthy phosphates; *A. P.* = alkaline phosphates; *Sp. Gr.* = specific gravity; *Sed.* = sediment; *Alb.* = albumin, etc.

The common abbreviations used in recording the results of analysis are: + = increased; — = diminished; n = normal. For much increased or much diminished: m + and m —, respectively; similarly, sl. + and sl. — for a slight increase and slight decrease. Other abbreviations, according to the habit and convenience of the recorder, may equally well be adopted.

The plan of incorporating the urinary records into book form is to be encouraged, especially for those who make a large number of analyses. Such a book properly indexed can be prepared by any competent printer at a moderate cost. A record of this kind is far more serviceable and convenient than the separate sheets.

ANALYSIS OF URINE.

Date .....

Name.....

Amt. in twenty-four hours = *Sp. Gr.* =

Color = *Sed.* =

Odor =

Reaction =

Uph. = $\overset{+}{U}$. (%) = *Cl.* = *E. P.* =

Ind. = $\overline{U}$. = *Sf.* = *A. P.* =

Albumin =

Bile Pigments =

Sugar =

Sediment =

Quant. $\overset{+}{U}$. = *grams.* P_2O_5 = *grams.*

Cl. = " *Sugar* = "

Diagnosis =

Tabular Arrangement of Heller's Tests (modified).

Physical Properties.

COLOR.—Pale, normal, high, or dark.

ODOR.—

REACTION.—Acid, neutral, or alkaline.

SP. GR.—By urinometer.

SEDIMENT.—Slight, considerable, or much.

Normal Constituents.

UROPHÆINE (Uph.).—7 c.c. H_2SO_4 + double quantity of Ur. = immediate garnet-red color.

INDOXYL (Ind.).—15 c.c. HCl (+ 2 gtt. HNO_3) + 30 gtt. Ur. = amethyst color, developing in from five to twenty minutes.

UREA ($\overset{+}{U}$.).—With NaOBr. (Squibb's apparatus.)

URIC ACID ($\bar{U}$.).—½ tt. Ur. + HCl = $\bar{U}$ cryst. in 24 hours.

CHLORINE (Cl.).—Ur. + HNO_3 + $AgNO_3$ (1 : 8) = solid ball of AgCl, if normal.

SULPHATES (Sf.).—½ tt. Ur. + $BaCl_2$ sol. (1 : 4 sol. + HCl) = ppt. ½ concavity of tt. in from eighteen to twenty-four hours, if normal.

EARTHY PHOSPHATES (E. P.).—½ tt. Ur. + NH_4OH = ppt. ¼ to ½ in. in tt., in from eighteen to twenty-four hours, if normal.

ALKALINE PHOSPHATES (A. P.).—Filtrate from E. P. + $MgSO_4$ sol. ($MgSO_4$ + NH_4Cl + NH_4OH) = ppt. ½ to ¾ in. in tt., in from eighteen to twenty-four hours, if normal.

Abnormal Constituents.

ALBUMIN (Alb.).—Heat or HNO_3 = coagulum or zone.

BILE PIGMENTS.—Marechalt's test (iodine).

SUGAR.—Fehling's solution. Phenylhydrazin test. Fermentation test.

SEDIMENT.—Let settle or centrifugalize, and examine by microscope.

ORDER OF APPLYING TESTS.

In the routine analysis of a urine it is advisable first to note the twenty-four-hour quantity, the color, the odor if at all peculiar, the reaction, and the specific gravity. The next in order should be the tests for urophæine and indoxyl, and then the test for albumin. If more than a *trace* of albumin be present, it must be removed before testing for chlorides, sulphates, or sugar. Having removed the albumin by heat from one-third or one-half of a test-tube of the urine after the addition of one drop of acetic acid (see p. 131) the test for chlorides, sulphates, and sugar should then be performed. If in the test for albumin a zone of acid urates appears, it should be noted. Such a zone indicates a relative excess of uric acid and urates. The tests for earthy and alkaline phosphates are next in order, and then the test for bile pigments.

The quantitative test for urea should be performed in every instance, and this is most conveniently done by means of the Squibb or the Doremus apparatus. The percentage should be noted, and the total number of grams of urea calculated. If sugar be present, it should also always be quantitated, and the total quantity reported in grams.

The amount of sediment that a urine contains can only be determined after the urine has completely settled. The degree of opacity of the urine can not always be considered a criterion of the amount of sediment present. A urine may be very turbid, for example, by bacteria, and yet contain very little sediment. As soon as the sediment has completely settled, it should be carefully examined by means of the microscope for casts, renal cells, fatty cells, fat adherent to the casts, blood, pus, crystalline elements, etc.

METHOD OF MAKING DIAGNOSES OF DISEASES OF THE KIDNEYS FROM THE URINE.

The diagnoses of the different diseases of the kidneys are made chiefly by exclusion.

It has been shown that, even in a single affection of the kidneys, the characteristics of the urine vary with the severity of the process and the extent of the diseased condition; furthermore, that diseases of the kidneys are very liable to become complicated by other pathologic conditions of these

organs. Thus, the urine becomes modified to a greater or less extent from what one would find if the original disease were uncomplicated. For example, a subacute or chronic disease of the kidneys is very liable to be complicated by a more or less severe acute process; under such circumstances, the underlying subacute or chronic process may be partially or entirely obscured by the acute complication. *Obviously, an absolute standard of disease, to which an unknown specimen of urine should conform, is entirely out of the question.* In other words, a urinary disease is not invariably accompanied by a urine of specific character, but by characteristics subject to more or less variation.

In the foregoing pages of this work the author has endeavored to outline a fairly typical urine of each disease. Having made an accurate examination of an unknown specimen of urine, it will be found that the characteristics of such a urine harmonize in a general way with those known to be associated with this or that disease.

In the consideration of a given urine that shows evidence of a renal disturbance or disease (presence of renal casts) the first and most important feature from the standpoint of diagnosis is the total quantity of urine.

A *diminished quantity* (less than 1500 c.c.) is, as a rule, indicative of any of the following conditions:

1. Active hyperemia.
2. Passive hyperemia.
3. Acute nephritis (first and second stages).
4. Subacute glomerular nephritis (all stages).
5. Chronic renal diseases toward death.

An *increased quantity* (more than 1500 c.c.) is strongly suggestive of any of the following conditions:

(*a*) Convalescence from severe active hyperemia.
(*b*) Convalescence from acute nephritis.
(*c*) Chronic interstitial nephritis.
(*d*) Chronic diffuse nephritis.
(*e*) Amyloid infiltration.

Having limited the probable renal disturbance or disease to the class characterized by a small or a large quantity of urine, the next step is to distinguish between the different renal conditions of that class by means of the quantities of *normal solids*, the amount of albumin, and the peculiarities of the sediment—*i. e.*, the presence or absence of blood on casts, the presence or absence of fat from the kidney, the

size and character of the renal casts, etc. In this way the most probable disturbance or disease of the kidneys can usually be narrowed down to one or, perhaps, two of the conditions under consideration.

Having arrived at the most probable renal affection, the next step is to determine the location and nature of any complications that may be present, whether in the kidneys or in some other portion of the urinary tract.

In the application of this plan of urinary diagnosis it is obvious that the student must thoroughly familiarize himself with the characteristics of the urine of each disease of the kidneys, as well as of those of other portions of the urinary tract.

APPENDIX B.

REAGENTS AND APPARATUS FOR QUALITATIVE AND QUANTITATIVE ANALYSIS OF URINE.

The reagent bottles should be made of pure, clear glass, free from lead and other impurities. Those for liquid reagents should have a capacity of about 250 c.c., while those for solid reagents need not have a capacity over 120 c.c. All bottles should be fitted with ground-glass stoppers, and should have labels upon them in raised glass letters, or a ground-glass label with black letters, and the chemic symbol of the reagent below and separate from the lettering.

Many of the reagents given below are not really necessary for the ordinary routine analysis of urine, but for efficient laboratory work all of those given will be found necessary.

LIQUID REAGENTS.

Sulphuric acid, C. P. (H_2SO_4).
Hydrochloric acid, C. P. (HCl).
Nitric acid, C. P. (HNO_3).
Acetic acid ($HC_2H_3O_2$).
Ammonic hydrate (NH_4OH).
Sodic hydrate (NaOH), U. S. P.
Magnesia mixture. (See p. 109.)
Sol. potassium ferrocyanide (1 : 10).
Tinct. iodine, U. S. P.
Sol. lead acetate (1 : 5).
Sol. basic lead acetate (1 : 5).
Alcohol, 95 per cent.
Sodic hydrate for urea. (See p. 52.)
Bromine (modified) for urea. (See p. 52.)
Fehling's solution. (See p. 149.)
A. Cupric sulphate solution.
B. Alkaline tartrate solution.

Sol. barium chloride. (See p. 113.)
Sol. ferric chloride—aqueous (1 : 10).
Millon's reagent. (See p. 170.)
Esbach's reagent. (See p. 133.)
Sol. silver nitrate (1 : 8).
Phenylhydrazin (pure).
Chloroform.
Formaline.
Sol. boric acid (saturated).
Standard sol. silver nitrate. (See p. 103.)
Standard sol. uranium nitrate. (See p. 110.)
Distilled water.

SOLID REAGENTS.

(*All reagents should be chemically pure.*)

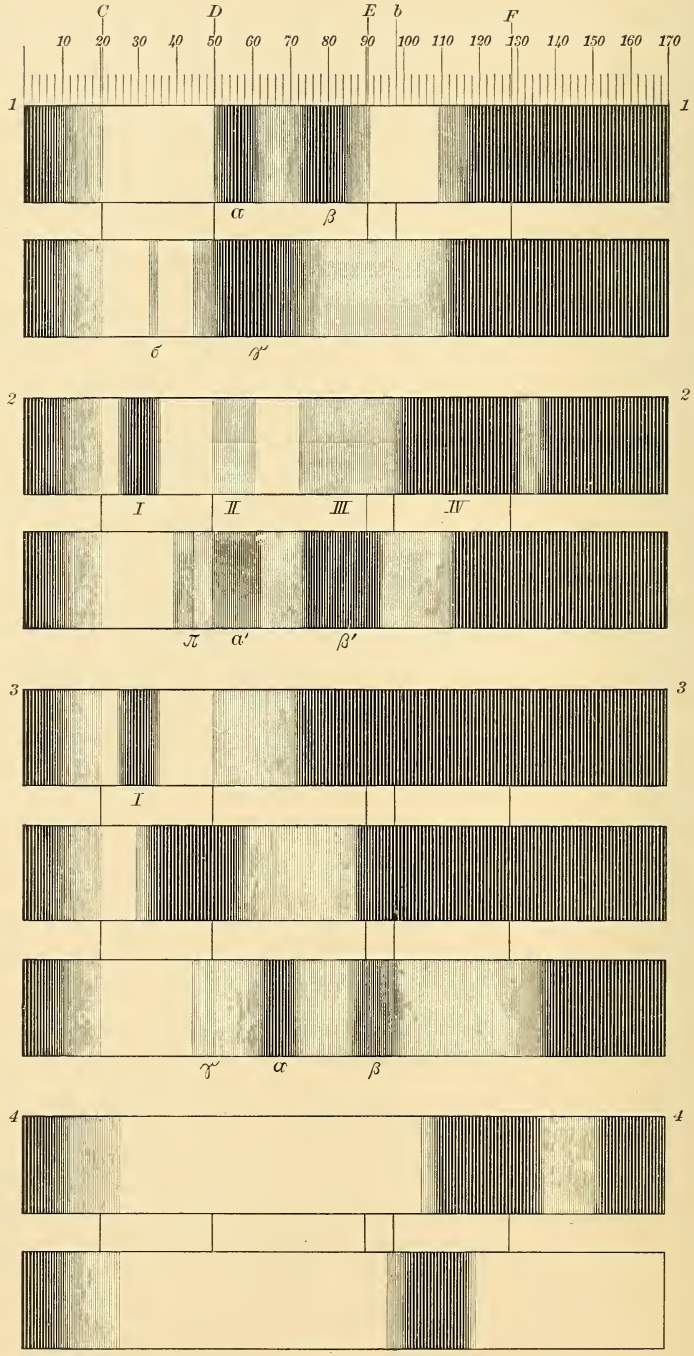
Cupric sulphate.
Caustic soda.
Sodium chloride.
Potassium iodide.
Potassium chromate.
Ammonium sulphate.
Magnesium sulphate.
Ammonium chloride.
Sodium acetate.
Potassium ferrocyanide.
Potassium chlorate.
Picric acid.
Citric acid.
Lead acetate.
Sulphanilic acid.
Sodium nitrite.
Sodium carbonate.
Mercuric chloride.
Potassium bromide.
Sodium nitroprusside.

APPARATUS.

Test-tubes.
Test-tube brush.
Test-tube rack.
Bunsen burner with two feet rubber tubing, or a spirit lamp.
Urinometer (Squibb or other of reliable make).
Urinometer glass with foot and parallel sides. (See Fig. 2.)
Wine-glasses. (See Fig. 13.)
Urea apparatus (preferably Squibb's).
Urine glasses. (See Fig. 24.)
Funnels, large and small.
Filter papers (cut) 4, 6, and 8 inches in diameter.
Glass tubing for pipettes.
Glass rods (assorted sizes).
Litmus paper (red and blue).
Graduates (100, 500, and 1000 c.c.).
Evaporating dishes (assorted sizes up to one liter).
Crucibles.
Porcelain spatula.

Platinum wire inserted in glass rod.
Platinum foil.
Burettes (50 c.c., graduated in tenths of a cubic centimeter).
Retort stand with burette clamp attached.
Tripod with copper-wire gauze to cover.
Triangles.
Water-bath (preferably copper with rings).
Crucible tongs.
Beakers (nests of six).
Wash bottle (500 c.c.).
Flask (250 c.c.).
Liter flask (graduated on neck).
Graduated pipettes (5, 10, and 50 c.c.).
Dropping bottle, bulb stopper.
Esbach's albuminometer.
Accurate thermometer.
Accurate balances, turning at 1 milligram.
Microscope—Zeiss, Leitz, or Bausch and Lomb, with nose-piece; objectives corresponding to 3, 5, and 7 of Leitz make, and 1 and 3 eye-pieces, Leitz make; Abbey condenser; and $\frac{1}{12}$ oil immersion lens.
Glass slides, cover-glasses, cedar oil, and Canada balsam (in solution).
Centrifuge capable of 2000 revolutions per minute.

Plate 10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Spectra (after Neubauer and Vogel).

1. *a*, Oxyhemoglobin; *b*, hemoglobin, free from oxygen.

2. Methemoglobin: *a*, in neutral solution; *b*, in alkaline solution.

3. *a*, Hematin in acid alcoholic solution; *b*, in ammoniacal solution; *c*, reduced hematin.

4. *a*, Urobilin in acid solution; *b*, zinc salt in ammoniacal solution.

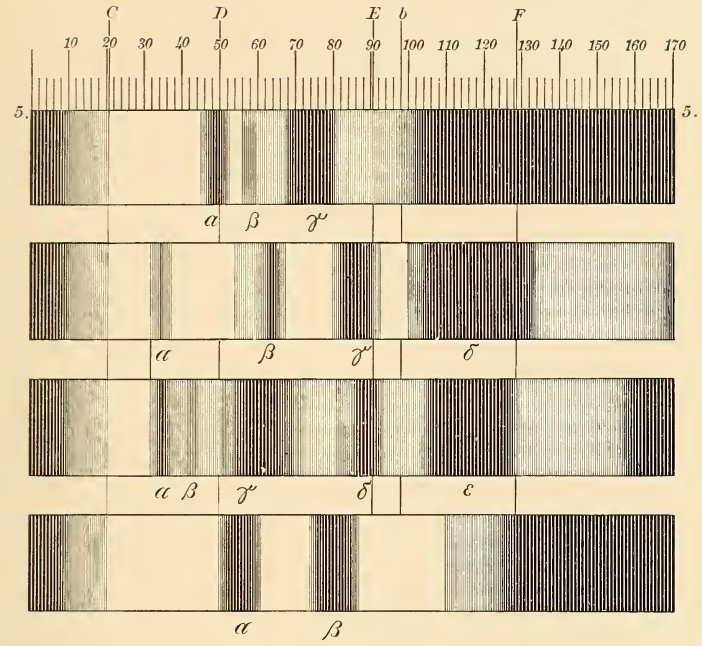
SPECTRA, CONTINUED (AFTER NEUBAUER AND VOGEL).

5. Hematoporphyrin: *a*, acid; *b*, alkaline; *c*, neutral; *d*, metallic spectra.

6. Bilicyanin: *a*, in acid solution; *b*, in alkaline solution.

7. Uroerythrin.

Plate II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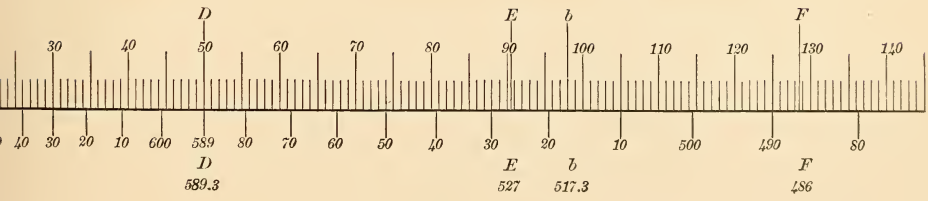
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