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A MANUAL

OF

CLINICAL DIAGNOSIS

BY MEANS OF MICROSCOPIC AND CHEMICAL METHODS,

FOR

STUDENTS, HOSPITAL PHYSICIANS, AND PRACTITIONERS.

BY

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FELLOW OF THE AMERICAN ACADEMY OF MEDICINE.

SECOND EDITION, REVISED AND ENLARGED.

With 133 Illustrations on Wood and 14 Colored Plates.

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TO

HIS WIFE,

WHO HAS SO FAITHFULLY AIDED IN ITS PREPARATION,

THIS VOLUME IS AFFECTIONATELY DEDICATED

BY THE

AUTHOR.

PREFACE TO THE SECOND EDITION.

In the present edition the endeavor has been made to bring the volume thoroughly up to date. The parasitology and bacteriology of the blood, saliva, feces, urine, and vaginal discharge have been almost entirely rewritten. New methods of chemical examination which have appeared since the publication of the first edition have been embodied in the work, and some of the older and complicated ones omitted. Throughout the text numerous additions have been made, so that the size of the volume has been increased by about fifty pages. The examination of the cerebro-spinal fluid and its clinical significance have been carefully considered. Some of the illustrations have been replaced by more accurate ones, and others entirely new have been added where they appeared to be of value to the student.

In conclusion, the writer wishes to thank the medical profession for the kind manner in which the first edition has been received.

CHARLES E. SIMON.

1302 Madison Avenue, Baltimore, Md., 1897.

PREFACE TO THE FIRST EDITION.

It is curious to note that, notwithstanding the great importance of clinical chemistry and microscopy, but little attention is paid to these subjects, either by hospital physicians or by those engaged in general practice. This lack of interest is referable primarily to the fact that a systematic study of these branches has hitherto been greatly neglected, not only in American medical schools, but also in those of Europe.

It is no rarity to hear physicians in general practice claim that they are too busy to conduct careful examinations of the urine, sputum, blood, gastric juice, etc. Would it not be reasonable to suppose, however, that a physician who is overwhelmed with work to such an extent that he cannot find the time to make use of aids in diagnosis which are quite as important as the stethoscope, the laryngoscope, or the ophthalmoscope, would be in a position to employ an assistant in his laboratory? The younger practitioner is certainly not placed in such a dilemma, and it is a fair assumption that he could successfully compete with his more experienced colleague, in matters of diagnosis at least, were he to familiarize himself sufficiently with laboratory methods of diagnosis.

The time is at hand when the practice of medicine is becoming what it was long ago, but then unjustly, called, a true science and art. No continuing success can be built on empiricism or upon the proportion of guesswork which is inseparable from dependence upon "the experienced eye." "Diagnosis" is now the password in medical science. A knowledge of electro-diagnosis, of ophthalmoscopy, of laryngoscopy, etc., is at the present day a *sine qua non* for accurate diagnosis. Equally important at all times, and frequently even more important, is a knowledge of clinical chemistry and microscopy. It is inconceivable that a physician can rationally diagnose and treat diseases of the stomach, intestines, kidneys, and liver, etc., without laboratory facilities.

It has been the author's aim to present to students and physicians

those facts in clinical chemistry and microscopy which are of practical importance. With the hope of exciting interest in these unjustly neglected subjects, he has not confined himself to bare statements of facts, which must in themselves be dry and uninteresting, but he has attempted to point out the reasons which have led up to the conclusions reached.

Chemical and microscopic methods are described in detail, so that the student and practitioner who has not had special training in such manipulations will be enabled to obtain satisfactory results.

The subject-matter covers the examination of the blood, the secretions of the mouth, the gastric juice, feces, nasal secretion, sputum, urine, transudates, exudates, cystic contents, semen, vaginal discharges, and milk. In every case a description of normal material precedes the pathologic considerations, which latter in turn are followed by an account of the methods used in examination. A glance at the table of contents will furnish an idea of the various subjects considered under each heading.

It was not deemed advisable to burden the volume with a complete enumeration of the various literary sources consulted by the author in its preparation, and the names of the various investigators mentioned in the text have been largely introduced as a matter of historical interest.

In conclusion it is the agreeable duty of the author to express his sincerest thanks to his wife for assistance without which this volume could not have been written, and likewise for those illustrations which are original; to Dr. William H. Welch for his kindness in placing the former Hygienic Laboratory of the Johns Hopkins Hospital at his disposal during the years 1892 and 1893; to Dr. W. Milton Lewis for much valuable aid in the correction of the manuscript and proof-sheets; and to Messrs. Lea Brothers & Co. for the typographical excellence of the work, the extremely satisfactory reproduction of the drawings, and for many acts of courtesy.

CHARLES E. SIMON.

BALTIMORE, MD., 1896.

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CLINICAL DIAGNOSIS.

CHAPTER I.

THE BLOOD.

GENERAL CONSIDERATIONS.

If blood be allowed to flow directly from an artery into a vessel surrounded by a freezing-mixture, and containing one-seventh of its own volume of a saturated solution of sodium sulphate, or a 25 per cent. solution of magnesium sulphate (one volume to four volumes of blood), it will be observed that after some time a sediment, presenting the ordinary color of arterial blood, has formed at the bottom, which is covered by a layer of clear, straw-colored fluid, the blood-plasma.

Upon microscopic examination the sediment will be seen to contain:

a. Numerous homogeneous, non-nucleated, circular, biconcave disks. These measure on an average 7.5 μ in diameter, and are of a faint greenish-yellow color when viewed through the microscope, while *en masse* they present the color of arterial blood: the erythrocytes or red corpuscles of the blood.

b. Roundish or irregularly shaped nucleated cells. These are far less numerous than the red corpuscles, and devoid of coloring-matter: the leucocytes, colorless or white corpuscles of the blood.

c. Minute colorless disks, measuring less than one-half of the diameter of a red corpuscle: the so-called plaques, or blood-plates of Bizzozero.

GENERAL CHARACTERISTICS OF THE BLOOD.

The Color.

Chemical examination of the blood has shown that its color is referable to the presence of an albuminous, iron-containing sub-

stance, hæmoglobin, contained in the bodies of the red corpuscles, which is characterized by its great avidity for oxygen, and forms a compound therewith, known as oxyhæmoglobin. The relatively larger amount of the latter encountered in the arteries, as compared with the veins, causes the difference in the appearance of arterial and venous blood, the former presenting a bright scarlet-red, the latter a dark-bluish color. A bright cherry-red color of the blood is noted in cases of poisoning with carbon monoxide, while a brownish-red or chocolate color is observed in cases of poisoning with potassium chlorate, aniline, hydrocyanic acid, and nitrobenzol. A somewhat milky appearance is frequently seen in cases of well-marked leukæmia, and the author recalls an instance in which attention was first directed to the existence of this disease by the peculiarly milky appearance of a drop of blood obtained for the purpose of a hæmoglobin estimation. In chlorosis and hydræmic conditions, as would be expected, the blood looks pale and watery.

The Odor.

The peculiar odor of the blood, which differs greatly in different animals, the *halitus sanguinis* of the ancients, is dependent upon the presence of certain volatile, fatty acids, and may be rendered more distinct by the addition of concentrated sulphuric acid.

The Specific Gravity.

The specific gravity of the blood in healthy adults varies between 1.046 and 1.067, being higher on an average in men, 1.055, than in women, 1.054, and children—boys 1.052, girls 1.050. It is diminished to a certain extent by fasting, the ingestion of solids and liquids, gentle exercise, pregnancy, etc. The specific gravity, moreover, depends upon the bloodvessel from which the specimen is taken, being higher, generally speaking, in venous than in arterial blood.

Under pathologic conditions the specific gravity may vary between 1.025 and 1.068. In nephritis, chlorosis, the anæmias in general, as also in cachectic conditions (pulmonary phthisis, carcinoma of the stomach, etc.), it may diminish to 1.031. An increased specific gravity is met with in febrile diseases (typhoid fever 1.057 to 1.063), conditions associated with pronounced cyanosis (emphysema, fatty

heart, uncompensated valvular disease, 1.054 to 1.068), and obstructive jaundice, 1.062.

Methods of Determining the Specific Gravity of the Blood.

Roy's Method. A number of test-tubes are filled with a mixture of glycerine and water in different proportions, so that the specific gravity in the different tubes shall vary between 1.025 and 1.068. Blood is then drawn from the tip of a finger, or the lobe of the ear, into a capillary tube connected with an ordinary hypodermic syringe, pressure being carefully avoided. A drop of blood is placed in each tube, in which it will sink as long as the specific gravity of the glycerine mixture is lower than that of the blood, while it will remain suspended in a mixture the specific gravity of which is equivalent to its own.

Roy states that it is important for the purpose of comparison to make such examinations in every case at the same hour, as the specific gravity of the blood has been shown to undergo diurnal variations.

Hammerschlag's Method. A cylinder, measuring about 10 cm. in height, is partly filled with a mixture of chloroform (sp. gr. 1.526) and benzol (sp. gr. 0.889), presenting a specific gravity of 1.050 to 1.060. Into this solution a drop of blood is allowed to fall directly from the finger, pressure being avoided, and care being taken that it does not come in contact with the walls of the vessel. The drop, moreover, should not be too large, as it will otherwise separate into several droplets, giving rise to inaccurate results. Should the drop sink to the bottom, it is apparent that the specific gravity of the mixture is lower than that of the blood, necessitating the addition of more chloroform. This should be added, drop by drop, while the mixture is thoroughly stirred. If, on the other hand, the drop of blood should tend toward the surface, it is best to add an amount of benzol sufficient to cause the blood to sink to the bottom, and then to bring it to the proper degree of suspension by the subsequent addition of chloroform. As soon as the drop remains suspended the mixture is filtered, and its specific gravity ascertained by means of an accurate areometer, registered to the fourth decimal. The figure obtained will express the specific gravity of the blood.

The chloroform-benzol mixture may be kept indefinitely.

With a little practice, results sufficiently accurate for clinical

purposes may thus be obtained with an expenditure of but very little time.

Schmaltz and Peiper's Method. Where delicate scales are available the method of Schmaltz and Peiper may be employed, being the most accurate: A capillary tube, measuring about 12 cm. in length and 1.5 mm. in width, with its ends tapering to a diameter of 0.75 mm., is filled with blood and carefully weighed, when the weight of the blood, divided by the weight of an equivalent volume of distilled water, will indicate the specific gravity.

Siegl and Schmaltz have shown that with the exception of hydræmic conditions the specific gravity of the blood varies with the amount of hæmoglobin. A simple method is thus given, by means of which hæmoglobin estimations can be made in the absence of more expensive instruments, in the majority of cases. Cabot even prefers this method to the use of Fleischl's hæmometer. In the following tables, which are taken from his work,[1] the varying degrees of specific gravity, as obtained with Hammerschlag's method, and that of Schmaltz and Peiper, are given with the corresponding amounts of hæmoglobin. The figures, however, are in all probability not quite accurate:

Specific gravity according to Hammerschlag.	Hæmoglobin.	Specific gravity according to Schmaltz and Peiper.	Hæmoglobin.
1.033–1.035	25–30 per ct.	1.030	20 per ct.
1.035–1.038	30–35 "	1.035	30 "
1.038–1.040	35–40 "	1.038	35 "
1.040–1.045	40–45 "	1.041	40 "
1.045–1.048	45–55 "	1.0425	45 "
1.048–1.050	55–65 "	1.0455	50 "
1.050–1.053	65–70 "	1.048	55 "
1.053–1.055	70–75 "	1.049	60 "
1.055–1.057	75–85 "	1.051	65 "
1.057–1.060	85–95 "	1.052	70 "
		1.0535	75 "
		1.056	80 "
		1.0575	90 "
		1.059	100 "

Direct Estimation of the Solids of the Blood. Five drops of blood (0.2 to 0.3 gramme), obtained by means of a fairly deep incision, or puncture, into the tip of a finger, moderate pressure being made upon the middle phalanx, if necessary, are collected

[1] Clinical Examination of the Blood. Wm. Wood & Co.

in a watch-crystal. This is at once covered with its fellow, the two being held together by means of a spring, and weighed. The specimen (open) is then dried at a temperature of from 60° to 70° C. for twenty-four hours, and again weighed, the weight of the solids being thus ascertained.

In healthy adults the following values were obtained by Stintzing and Gumprecht:

	Average.	Maximum.	Minimum.	Average water.
In men . . .	21.6	23.1	19 6	78.4 per cent.
In women . .	19.8	21.5	18.4	80.2 "

In conditions associated with chronic anæmia the solids, as would be expected, are always considerably diminished. In leukæmia, on the other hand, owing to the large number of leucocytes present, a relative increase is observed.

The Reaction.

The reaction of the blood during life, owing to the presence of disodium phosphate, Na_2HPO_4, and sodium bicarbonate, $NaHCO_3$, is alkaline, the degree of alkalinity in terms of sodium hydrate under normal conditions corresponding to 182 to 218 mgrms. for every 100 c.c. of blood. v. Jaksch gives 260 to 300 mgrms. as the normal, and Canard 203 to 276 mgrms.

The alkaline reaction of the blood may be demonstrated by repeatedly drawing a strip of red litmus-paper, thoroughly moistened with a concentrated solution of common salt, through the blood, and rapidly washing off the corpuscles with the same solution, when, as a general rule, the alkaline reaction can be clearly made out.

Small plates of plaster-of-Paris or clay, stained with neutral litmus-solution, may be similarly employed, the blood in this case being washed off with water.

Generally speaking, the alkalinity of the blood is lower in women and children than in men, and is, furthermore, influenced by the process of digestion, exercise, etc. At the beginning of digestion, when hydrochloric acid is being secreted in large amounts, the alkalinity of the blood increases; while later on, when both hydrochloric acid and peptones are reabsorbed, the alkalinity in turn diminishes.

A decrease is observed following violent muscular exercise, such as forced marches in the case of soldiers, owing in all probability to an excessive production of acids in the muscles.

Under pathologic conditions a diminished alkalinity of the blood is frequently observed, which is particularly marked in cases of pronounced anæmia (108 to 145 mgrms. of NaOH), increasing as the number of red corpuscles and the amount of hæmoglobin diminish. In cases of chlorosis, however, the diminution in the number of red corpuscles is accompanied by a normal, or but slightly diminished alkalinity of the blood, as a whole. In leukæmia, pernicious anæmia, nephritis when accompanied by uræmia, various hepatic diseases, diabetes, carcinoma, the various profound cachexiæ, pseudo-leukæmia, poisoning with carbon monoxide, and acids, and finally in high fever, as in typhoid fever, and toxic processes in general, the alkalinity of the blood is diminished, the lowest value found corresponding to 108 mgrms. of NaOH. A similar decrease follows the prolonged use of acids, while an increase is brought about by the ingestion of alkalies. An increase in the alkalinity of the blood occurs after a cold bath, and it is interesting to note that this is apparently associated with an increase in the bactericidal power of the blood. Possibly the beneficial effect of the cold baths in fever may be explained upon this basis.

v. Jaksch employs the following method, a modification of that originally devised by Landois: Eighteen watch-crystals are prepared, each containing a mixture of a concentrated solution of sodium sulphate and a $\frac{1}{100}$ and a $\frac{1}{1000}$ normal solution of tartaric acid in varying proportions, so that crystal

No.	C.c.		C.c.
I.	Shall contain	0.9 of the $^1/_{100}$ norm. sol. of the acid, and	0.1 of the conc. Na_2SO_4 sol.
II.	" "	0.8 " " " " "	0.2 " " " "
III.	" "	0.7 " " " " "	0.3 " " " "
IV.	" "	0.6 " " " " "	0.4 " " " "
V.	" "	0.5 " " " " "	0.5 " " " "
VI.	" "	0.4 " " " " "	0.6 " " " "
VII.	" "	0.3 " " " " "	0.7 " " " "
VIII.	" "	0.2 " " " " "	0.8 " " " "
IX.	" "	0.1 " " " " "	0.9 " " " "
X.	" "	0.9 " $^1/_{1000}$ " " "	0.1 " " " "
XI.	" "	0.8 " " " " "	0.2 " " " "

etc., for every c.c. of the mixture.

Blood is taken, preferably from the back, by means of cupping-glasses, and, before it coagulates, 0.1 c.c. is added to every c.c. of the mixture described, when the reaction is determined in every crystal by means of very sensitive litmus-paper. The amount of acid contained in the specimen exhibiting a neutral reaction in terms of NaOH will then indicate the degree of alkalinity of the blood.

As 150 (molecular weight) parts by weight of tartaric acid ($C_4H_6O_6$) combine with 80 (molecular weight) parts by weight of NaOH, or 75 with 40, according to the equation:

$$C_2H_2(OH)_2\begin{matrix}COOH\\COOH\end{matrix} + 2NaOH = C_2H_2(OH)_2\begin{matrix}COONa\\COONa\end{matrix} + 2H_2O$$

a normal solution would contain 75 grammes of pure tartaric acid to the liter and a $\frac{1}{100}$ and a $\frac{1}{1000}$ normal solution, respectively, 0.75 and 0.075 gramme. As 1000 c.c. of a $\frac{1}{100}$ normal solution would correspond to 0.4 gramme of NaOH, and 1000 c.c. of a $\frac{1}{1000}$ normal solution to 0.04 gramme, 1 c.c. of the $\frac{1}{100}$ normal solution will represent 0.0004, and 1 c.c. of the $\frac{1}{1000}$ normal solution 0.00004 gramme of NaOH.

Supposing, then, a neutral reaction to have been obtained in the crystal containing 0.6 c.c. of the $\frac{1}{100}$ normal solution, the alkalinity of the 0.1 c.c. of blood in terms of NaOH would correspond to 0.00024 gramme of NaOH, or 0.24 gramme to 100 c.c. of blood

As the alkalinity of the blood rapidly diminishes after being drawn, owing, in all probability, to the formation of an acid caused by the decomposition of the hæmoglobin, it is apparent that the experiment must be performed as rapidly as possible, not more than one minute and a half being allowed to elapse between the taking of the blood and the conclusion of the experiment.

This method has hitherto been the only one which was available for clinical purposes, and the results detailed above have been obtained by its aid. It is open to numerous objections, however, and still too complicated for routine work. Of late a new method, suggested by Löwy, has attracted much attention, and, to judge from the literature before us, is destined soon to replace the one described. It is both simpler and more accurate. The results, however, differ considerably from those given above, and a careful revision of all the work thus far accomplished with the old method will be necessary before definite conclusions can be reached. For the convenience of future investigators a table is here appended containing some of the results which have already been obtained in some of the more important diseases. In healthy adults, while fasting, the alkalinity of the blood, according to Löwy's method, corresponds to about 300 to 325 mgrms. of sodium hydrate for every 100 c.c. of blood. Variations amounting to 75 mgrms. plus or minus, are,

however, not uncommon, and, according to Strauss, the unavoidable errors may correspond to 30 mgrms.:

Carcinoma œsophagi	227–643
Carcinoma ventriculi	256–635
Ulcus ventriculi	302–460
Anadeny of the stomach	354–360
Alcoholic gastritis	343–379
Chronic enteritis	212–272
Phthisis pulmonalis	450–468
Bronchitis	239–343
Neurasthenia	225–426
Arterio-sclerosis	208–344
Chronic arthritis	368–465
Erysipelas	498
Typhoid fever	270–640
Pneumonia	263–464
Septicæmia	443
Leukæmia	368–835
Pernicious anæmia	429
Diabetes mellitus	362–457
Chronic interstitial nephritis	310–409
Chronic parenchymatous nephritis	312–490
Cirrhosis of the liver	272–345

Löwy's Method. Five c.c. of blood obtained from one of the superficial veins of the arm (preferably the median cephalic) are allowed to flow into a small flask provided with a long and partially graduated neck and containing 45 c.c. of a 0.25 per cent. solution of ammonium oxalate. Coagulation is thus prevented and the blood made lake-colored—*i. e.*, the hæmoglobin is dissolved from the stroma of the red corpuscles. The mixture is then titrated with a $\frac{1}{25}$ normal solution of tartaric acid with lacmoid paper soaked in a concentrated solution of magnesium sulphate, as an indicator. The lacmoid paper is prepared as follows:

A mixture of 100 grammes of resorcin, 5 grammes of sodium nitrite, and 5 c.c. of distilled water are heated on an oil-bath to a temperature of 110° C. A violent reaction occurs at this point, and the flame should be removed before this is reached. The substance is then heated to a temperature of 115°–120° C. until all the ammonia which is evolved during the process has been driven off. The residue, which should be of a pure blue color, is dissolved in water and precipitated with hydrochloric acid. Upon cooling the coloring-matter is filtered off by the aid of a suction-pump, and

washed with a little water. It is then dissolved in absolute alcohol, filtered, and the solution allowed to evaporate in an atmosphere free from ammonia. One gramme of the pigment, which crystallizes out in reddish-brown, glistening platelets, is dissolved in 1000 c.c. of 45 per cent. alcohol, when strips of fine Swedish filter-paper are soaked in the solution and allowed to dry.

As a normal solution of tartaric acid contains 75 grammes in the litre (see page 23), a $\frac{1}{25}$ normal solution will contain 3 grammes, and 1 c.c. of the $\frac{1}{25}$ normal solution will correspond to 0.0016 gramme of sodium hydrate.

Supposing, then, that 10 c.c. of the $\frac{1}{25}$ normal solution were necessary to neutralize the 5 c.c. of blood, the alkalinity of these 5 c.c. in terms of sodium hydrate would correspond to 0.016 gramme, and the alkalinity of 100 c.c. of blood to $0.016 \times 20 = 0.320$ gramme —*i. e.*, to 320 mgrms.

CHEMICAL EXAMINATION OF THE BLOOD.

General Chemistry of the Blood.

A general idea of the chemical composition of the blood may be formed from the accompanying table of C. Schmidt, calculated for 1000 parts:

	Man.	Woman.
Corpuscles	513.0[1]	369.2
Water	349.7	272.6
Hæmoglobin and globulins	159.6	120.1
Mineral salts	3.7	3.55
Plasma	486.9	603.8
Water	439.0	552.0
Fibrin	3.9	1.91
Albumins and extractives	39.9	44.79
Mineral salts	4.14	5.07

If blood be allowed to flow into a vessel and set aside, it will be observed that at the expiration of a few minutes the entire mass has become transformed into a semi-solid, gelatinous material, which is spoken of as the blood-clot or the *placenta sanguinis*. Still later it will be seen that a small amount of straw-colored fluid has appeared on top of the clot, which gradually increases in amount, while the clot itself undergoes shrinkage, until finally the latter, greatly

[1] This figure is too high ; in man it varies between 420 and 470 for 1000 parts of blood.

diminished in size, floats in the surrounding fluid. The straw-colored fluid which has thus been obtained during the process of coagulation is spoken of as the blood-serum.

If, furthermore, a bit of the clot be examined microscopically, this will be seen to consist of a more or less dense network of fibres, the meshes of which are filled with blood-corpuscles, which may be washed out, leaving the fibrous network, fibrin, behind.

Chemically speaking, fibrin belongs to the class of the so-called coagulated albumins, and probably does not occur in the circulating blood, but is formed only during the process of coagulation.

The albumins which are found in plasma are fibrinogen, serum-globulin, and serum-albumin, and while serum-globulin and serum-albumin are likewise encountered in the serum, the fibrinogen has disappeared, and traces of a new albuminous body, fibrino-globulin, are found. There appears to be no doubt that fibrin results from the fibrinogen by a process of dissociation, traces of a soluble albumin, fibrino-globulin, being formed at the same time. Modern researches, furthermore, have shown that the transformation of fibrinogen into fibrin is dependent upon the action of a ferment, the fibrin-ferment, derived in all probability from the leucocytes of the blood by a process of plasmoschisis. The presence of serum-globulin apparently hastens coagulation in an indirect manner, as is done by calcium chloride and the calcium salts in general.

Under normal conditions blood clots in from two to six minutes after being shed, while in disease, notably in hæmophilia, coagulation may be greatly delayed, or even not occur at all, so that fatal hemorrhage may follow the infliction of trifling wounds. Whether or not this condition is referable to certain abnormalities in the chemical composition of the blood is as yet undetermined.

A tendency to hemorrhage is also observed in scurvy, purpura, in some infectious diseases, such as typhoid fever, yellow fever, in poisoning with phosphorus, etc.

Since the formation of fibrin begins as soon as the blood has left its natural channels, it is apparent that absolutely accurate analyses of blood-plasma can hardly be expected. The appended analyses of the plasma of the horse's blood are taken from Hoppe-Seyler and Hammarsten, the figures having reference to 1000 parts :

Water	908.4	917.6
Solids	91.6	82.4
Total albumins	77.6	69.5
Fibrin	10.1	6.5
Globulin	....	38.4
Serum-albumin	....	26.4
Fat	1.2	12.9
Extractives	4.0	
Soluble salts	6.4	
Insoluble salts	1.7	

The chief points of difference existing between plasma and serum are the absence of fibrinogen and the presence of traces of fibrino-globulin, as well as of large quantities of fibrin-ferment, in the latter.

From the following table it will be seen that a marked difference exists in the nature of the mineral ingredients between serum and red corpuscles, the latter being relatively rich in potassium salts and phosphorus, and poor in sodium salts and chlorine.

The figures have reference to 1000 parts of blood:

	Man.		Woman.	
	Red corpuscles.	Serum.	Red corpuscles.	Serum.
K_2O	1.586	0.153	1.412	0.200
Na_2O	0.241	1.661	0.648	1.916
CaO	.....	.....	.....	.....
MgO	.....	.....	.....	.....
Fe_2O_5	.....	.....	.....	.....
Cl	0.898	1.722	0.362	1.44
P_2O_5	0.695	0.071	0.643	2.202

It is noteworthy that the amount of sodium chloride in the serum, 6 to 7 p. m., remains fairly constant whether large amounts of sodium chloride are ingested or none given at all. It is quite probable that the sodium chloride of the plasma serves the purpose of preventing the hæmoglobin of the corpuscles from being dissolved by the water of the blood. The term "isotonia" has been applied by Hamburger to a salt solution which is just strong enough to prevent the solvent action of the water upon the hæmoglobin of the red corpuscles. In the case of the serum, however, we meet with a condition of hyperisotonia—*i. e.*, an amount of salt in excess of that actually required in order to prevent the destruction of the red corpuscles, the advantage of which is, of course, apparent, if the variations to which the amount of water in the blood is subject be borne in mind.

In addition to the substances mentioned, the following are also found in the blood:

Fat occurs in an amount varying from 1 to 7 p. m. in fasting animals, while following the ingestion of a meal rich in fats as much as 12.5 p. m. has been encountered.

Soaps, cholesterin, and lecithin have likewise been found.

Sugar, probably glucose, appears to form a normal constituent of the plasma, amounting to 1 to 1.5 p. m. in man. While it is possible to increase this amount to a certain degree by the ingestion of large quantities of sugar, this appears in the urine, according to Claude Bernard, as soon as 3 p. m. has been exceeded. In addition to glucose another reducing-substance has been found in the blood, which differs from the former in not being fermentable.

Among the extractives which have been found there may be mentioned: urea, uric acid, kreatin, carbamic acid, sarco-lactic acid, glycogen, and hippuric acid, and under pathologic conditions xanthin, hypoxanthin, paraxanthin, adenine, guanine, leucin, tyrosin, lactic acid, cellulose, β-oxybutyric acid, acetone, and biliary constituents.

It has been pointed out that the color of the blood is referable to the presence of hæmoglobin contained in the red corpuscles, and also that the color varies from a bright scarlet-red in the arteries to a dark bluish-red in the veins, the exact shade depending upon the amount of oxygen present in combination with hæmoglobin as oxyhæmoglobin. Upon chemical examination two other gases may be demonstrated under physiologic conditions, viz., carbon dioxide and nitrogen. Of these the latter appears to play no part in the body-economy, and the amount present merely corresponds to that which would be absorbed by an equal volume of distilled water, viz., 1.8 vol. p. c., calculated at 0° C. and 760 Hgmm. pressure.

The amount of oxygen and carbon dioxide, on the other hand, undergoes considerable variation, depending upon the particular bloodvessel from which the specimen is taken—*i. e.*, whether this be an artery or a vein, and, furthermore, upon the velocity of the blood-current, the temperature of the body, rest, exercise, etc.

The relation existing between the amounts of these gases in arteries and veins may be seen from the following table:

	Arterial blood.	Venous blood.
Oxygen	21.6 per cent.	6.8 per cent.
Carbon dioxide	40.3 "	48.0 "
Nitrogen	1.8 "	1.8 "

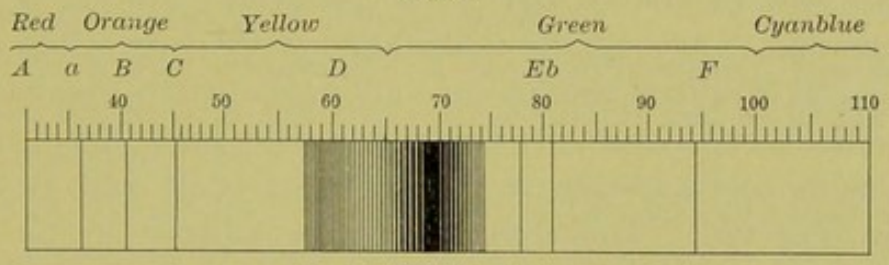
Oxygen, as already pointed out, occurs principally in chemical combination with hæmoglobin (oxyhæmoglobin), only 0.26 per cent. being present in solution in the plasma.

Of the carbon dioxide which may be obtained from the blood, only one-tenth is held in solution, while the remaining portion is found in the red corpuscles, in the form of a loose compound with the alkalies of the corpuscles, and possibly also in combination with hæmoglobin. This portion amounts to about one-third of the total quantity, while the remaining two-thirds are probably held in chemical combination by the alkalies of the plasma and certain albuminous bodies.

Blood-pigments.

Hæmoglobin. Hæmoglobin as such is found in only relatively small amounts in the circulating blood, occurring essentially in combination with oxygen as oxyhæmoglobin, which predominates in arterial blood, while a mixture of oxyhæmoglobin and hæmoglobin is met with in venous blood, and hæmoglobin almost exclusively in the blood of asphyxia.

FIG. 1.



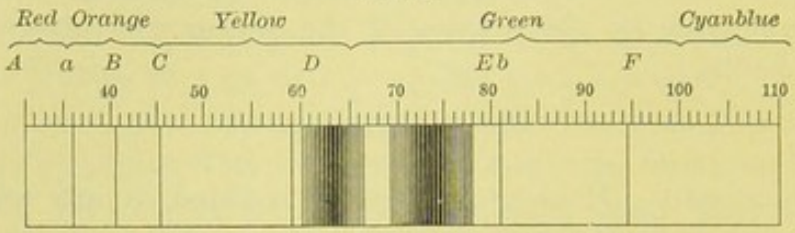
Spectrum of reduced hæmoglobin. (v. JAKSCH.)

The spectrum of hæmoglobin, in suitable dilution, shows one single band of absorption between *D* and *E*, which, however, does not lie midway between these lines, but extends slightly beyond *D* toward the left (Fig. 1). The substance is characterized by the ease with which it forms compounds with certain gases, and notably so with oxygen. As has been stated above, carbon dioxide also, to a certain extent at least, occurs in combination with hæmoglobin. In cases of poisoning compounds of hæmoglobin with carbon monoxide, with nitric oxide, and possibly also with sulphuretted hydrogen, cyanogen, and acetylene have been observed.

Oxyhæmoglobin. Oxyhæmoglobin is the most important constituent of the blood. In sufficiently dilute solution it shows two

bands of absorption between *D* and *E;* one band, *α*, which is not so wide as the second, *β*, but darker and more sharply defined, borders upon *D*, while the second, which is wider, but less sharply defined, lies at *E* (Fig. 2). This spectrum can be readily transformed into that of hæmoglobin by the addition of a reducing agent, such as an ammoniacal solution of ferrous tartrate (Stokes' fluid), ammonium sulphide, and cuprous salts.

FIG. 2.



Spectrum of oxyhæmoglobin. (V. JAKSCH.)

Under normal conditions the amount of oxyhæmoglobin is fairly constant, but varies somewhat in different countries, in accordance with the habits of the people. As a result of sixty-one estimations Leichtenstern found 14.16 per cent. as the average in healthy men, 13.10 per cent. in women, and in old age about 95 to 115 per cent. of the normal. Among the inhabitants of the large cities of our country such excellent results are only exceptionally obtained, and in the writer's experience it is rare to find more than 13.01 per cent. As a general rule amounts varying between 10.96 and 12.33 per cent. are observed. This difference is undoubtedly owing to the fact that the average German spends very much more of his time outside the city-limits than the average American. Larger amounts are thus also found among the French and the English.

While the ingestion of large amounts of water does not call forth a dilution of the blood and a diminution in the amount of oxyhæmoglobin, an increase occurs upon the withdrawal of liquids. Fat persons, furthermore, show a smaller amount of oxyhæmoglobin than corresponds to their age.

A great diminution in the amount of oxyhæmoglobin may be encountered under pathologic conditions, and especially in chlorosis, while a relative increase is not infrequently met with in diabetes mellitus, owing to the excretion of abnormally large quantities of water. In nephritis with pronounced œdema it falls considerably below the normal.

In a series of observations Quincke found the following amounts in the diseases indicated:

		Fleischl.[1]
Angina pectoris	14.4 per cent.	107.0
Cerebral apoplexy	14.1 "	104.9
Scurvy	14.6 "	108.6
Hepatic cirrhosis	10.1 "	75.1
Chlorosis	5.32–9.92 "	39.5–73.9
Splenic leukæmia	5.8 "	43.1
Nephritis	8.5–10.7 "	63.2– 79.6
Diabetes	14.4–15.9 "	107.1–118.3
Typhoid fever	12.7–14.6 "	94.4–108.6
Recurrens	14.4 "	107.0
Meningitis	15.0 "	111.6
Pyæmia	11.3 "	84.0
Phosphorus-poisoning	14.9 "	110.8

In an analysis of 63 cases of chlorosis, observed at the Johns Hopkins Hospital, an average amount of 5.68 per cent. (42.3, Fleischl), with a minimum of 2.35 per cent. (17.5), was observed. Similar results were obtained by the writer in an analysis of 31 cases. The average amount was 6.46 per cent. (42.8, Fleischl), and the lowest amount 2.46 per cent. (18, Fleischl). Chlorosis thus occupies the foremost position among the various pathologic conditions associated with oligochromæmia.

Very low figures are also seen in cases of pernicious anæmia and leukæmia, where 2.68 per cent. (20, Fleischl) and 4.36 per cent. (32.5), respectively, were obtained.

While in typhoid fever the amount of oxyhæmoglobin is always reduced, according to Osler, and usually in a greater relative proportion than the number of red corpuscles, the most severe grades of anæmia may here be encountered during convalescence, when the amount of oxyhæmoglobin may fall as low as 2.68 per cent. (20, Fleischl).

In the early stages of carcinoma of the stomach the cachexia is not well pronounced, and Schüle states that in his analysis of 198 cases it only occurred in 30 per cent. This agrees entirely with the writer's experience, who repeatedly found amounts of hæmoglobin exceeding 60 per cent. Later in the disease a most pronounced oligochromæmia is, however, invariably encountered. At this place the writer wishes to insist upon the importance of systematically repeated examinations of the blood in all cases of suspected

[1] See estimation of hæmoglobin with Fleischl's hæmometer, p. 32.

carcinoma of the stomach. A steady decline from week to week, when taken in conjunction with the other symptoms, and occurring in patients who have passed the fourth decade, is certainly very suspicious.

A notable diminution in the amount of hæmoglobin is further observed in tuberculosis, syphilis, chronic lead and mercurial poisoning, chronic nephritis, chronic enteritis, etc.

As the oxyhæmoglobin is contained in the bodies of the red corpuscles, it might be inferred that the amount of the former will directly depend upon the number of the latter, so that the degree of an anæmia could be determined by an enumeration of the red corpuscles as well as by a direct estimation of the amount of oxyhæmoglobin.

While this rule holds good generally, there are numerous exceptions which go to show that a diminution in the amount of oxyhæmoglobin, viz., an *oligochromæmia*, is not necessarily accompanied by a corresponding diminution in the number of red corpuscles—*i. e.*, an *oligocythæmia*. In chlorosis, for example, the red corpuscles may be present in normal numbers, while the amount of oxyhæmoglobin is greatly diminished. Here, it is true, a well-defined oligocythæmia simultaneously occurs in all severe cases, but even then the oligochromæmia exceeds the oligocythæmia. Conversely, in pernicious anæmia the oligocythæmia, while accompanied by an oligochromæmia, quite constantly exceeds the latter.

It is thus clear that definite inferences regarding the amount of hæmoglobin cannot be drawn from an enumeration of the red corpuscles, and *vice versa*.

While it is generally possible to form a fairly clear idea of the degree of an anæmia by inspection—*i. e.*, by noting the "color" of a patient—it is a well-known fact that not every pale face denotes an anæmic condition. Whenever special accuracy in examination or results for comparison are desired, recourse should hence be had to instruments especially devised for the purpose of determining the amount of hæmoglobin, known as hæmoglobinometers or hæmometers.

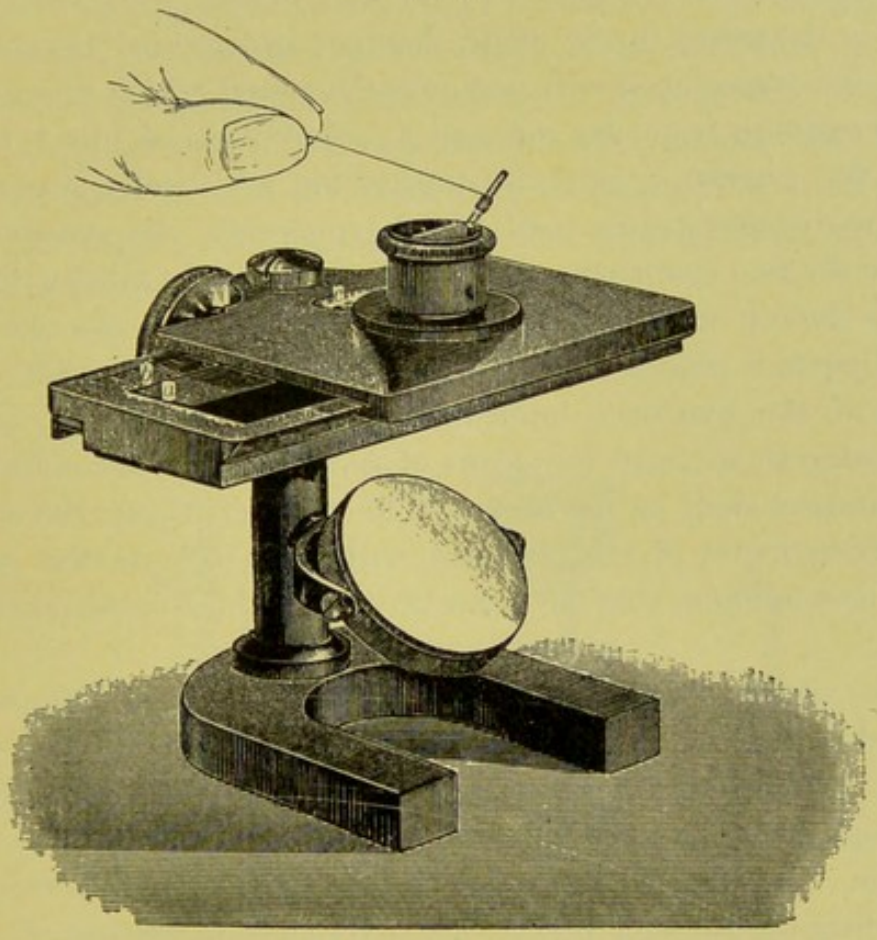
Among these instruments that devised by Fleischl is undoubtedly the most convenient and has already largely replaced the older forms of Gowers, Malassez, and Hayem.

Estimation of Hæmoglobin with Fleischl's Hæmometer. The principle of the method depends upon the comparison of the

color of the blood, diluted with water, with that of a glass wedge stained with the golden purple of Cassius or a similar pigment.

The instrument (Fig. 3) essentially consists of the glass wedge, *a*, just mentioned, to which a scale, *b*, is attached, ranging from 0 to 120, 0 being placed at the thinnest, 120 at the thickest portion of the wedge. This, by means of a rack and pinion, can be made to slide from side to side beneath a platform corresponding to the stage of the microscope. In the centre of the platform there is a circular

FIG. 3.



v. Fleischl's hæmometer.

opening into which artificial light (daylight is not permissible) is projected from a circular plate of plaster-of-Paris, mounted beneath in the position of the mirror of a microscope. Into the circular opening a metallic tube, 1.5 cm. in height, closed at the bottom with a plate of glass, and divided into two equal compartments by a metal partition, is fixed. One compartment receives the light through the glass wedge, the red chamber, the other directly from the plaster-of-Paris reflector, the white chamber.

Capillary pipettes accompany the instrument and are of such a capacity that, if the blood of a perfectly normal individual be used, the mixture of blood and water, placed in the compartment receiving light directly from the white plate, shall correspond in color to that derived from the colored wedge at the mark 100. The two compartments are partially filled with water, when the required amount of blood is obtained by placing one end of a capillary pipette in contact with a drop of blood obtained from the tip of a finger, or, still better, from the lobe of the ear that has been carefully cleansed with water, alcohol, and finally with ether. The pipette is immersed in the white chamber and rotated between two fingers, when the blood will pass into the water, which dissolves out the hæmoglobin from the corpuscles. Any trace of blood remaining in the pipette is carefully washed out with water, an ordinary medicine-dropper being used for the purpose. By means of the dropper the two compartments are then completely filled with water until a convex meniscus is obtained over the two chambers. A slip of paper is placed over the visible portion of the scale on the surface of the platform, immediately behind the well, *c*, and the glass wedge so adjusted by means of the screw that the color in the two chambers shall be the same. The number facing the notch in the scale-aperture of the platform will then indicate the percentage of hæmoglobin, that of a healthy individual corresponding to 100.

As the normal amount of hæmoglobin contained in 100 grammes of blood is a little less than 14 grammes, the number 100 on the scale of Fleischl's instrument corresponding to 13.7 per cent., the percentage in a given specimen may be calculated according to the equation: $100 : 13.7 :: p : x$, and $x = 0.137\ p$, where p represents the reading on the scale and x the corresponding amount of hæmoglobin contained in 100 grammes of blood.

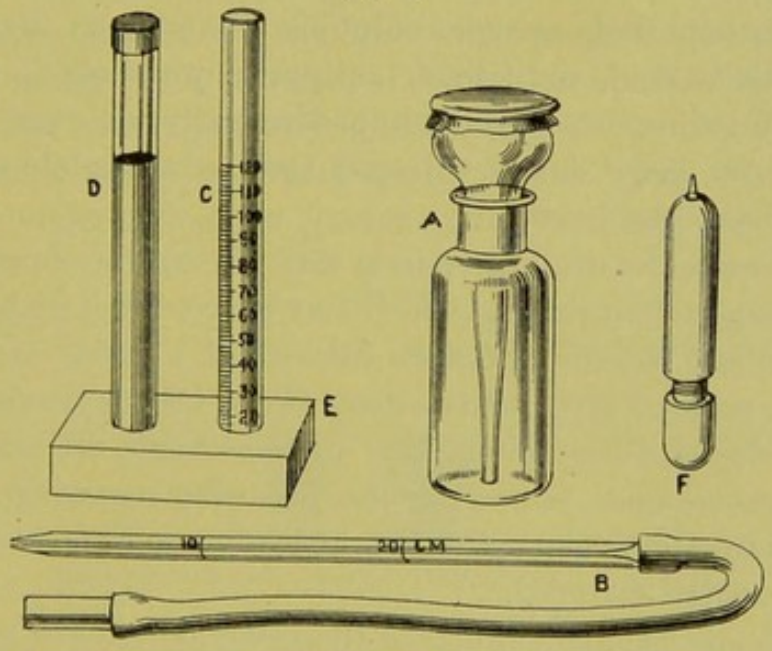
According to Dehio, certain errors are incurred in the estimation of hæmoglobin by means of Fleischl's hæmometer, which become the more marked the smaller the percentage. These may be obviated, however, and accurate results obtained, as far as such is possible, with the employment of colorimetric methods, if the instrument be previously tested with a solution of blood the color of which accurately coincides with that of the wedge at the 100 mark. To this end the standard solution is diluted with from 10 to 90 volumes of water, and any difference that may exist in the read-

ings of the instrument, as compared with the known percentages, noted.

If the number of red corpuscles be known, the amount of hæmoglobin contained in each, "la valeur globulaire" of Lepine, can now be readily determined, which is a point of considerable importance in differential diagnosis.

Estimation of Hæmoglobin with Gowers' Hæmoglobinometer. Gowers' hæmoglobinometer is much cheaper than that of Fleischl and yields results which compare favorably with those obtained with that instrument. The apparatus (Fig. 4) consists of: a closed tube (D), containing a solution of picrocarmine-glycerine, the color of which corresponds to a 1 per cent. solution of normal blood; a similar tube (C), about 11 cm. in height, provided with an ascending scale of 134 divisions, each corresponding to 20 cbmm.; a capillary pipette (B), marked at 20 cbmm.; a guarded lancet (F); and a dropping-bottle with rubber top (A).

Fig. 4.



Gowers' hæmoglobinometer.

In order to estimate the relative amount of hæmoglobin in a given case the tip of a finger, or, still better, the lobe of the ear, is freely punctured, after having been carefully cleansed as described above, and the pipette filled with blood to the 20 cbmm. mark by suction. Any trace of blood that may adhere to the outer surface of the pipette is carefully wiped off, and the contents at once mixed with a few drops of distilled water, previously placed in the graduated

tube, so as to guard against the blood coagulating on its walls. In order to make the error incurred, when this method is employed, as small as possible, care should be had to remove completely every trace of blood from the interior of the pipette by refilling it with distilled water and blowing the contents into the graduated tube. The two tubes are then held side by side, directly against the light, or against a sheet of white paper, when water is added drop by drop, until the shade of color is the same in the two tubes. The division on the scale ultimately reached will express the relative percentage of hæmoglobin.

The method of estimating the amount of hæmoglobin from the specific gravity of the blood has been described on page 20.

Hæmoglobinæmia. The term hæmoglobinæmia has been applied to a condition in which, as the result of abnormal influences, the hæmoglobin is dissolved out from the red corpuscles, and, appearing in the plasma as such, leads at first to a very decided choluria and in extreme cases to hæmoglobinuria.

Various poisons, such as potassium chlorate, carbolic acid, pyrogallic acid, naphthol, arsenic, sulphide of antimony, hydrochloric acid, sulphuric acid, antifebrin, antipyrin, phenacetin, sulphonal, tincture of iodine, when given hypodermically, or even internally in sufficiently large doses, will call forth a hæmoglobinæmia, followed by hæmoglobinuria.

Fresh morels also contain a poison which is capable of producing an intense hæmoglobinuria, and which may be extracted with hot water.

In acute and chronic infectious diseases of a severe type, such as scarlatina, typhoid fever, intermittent fever, icterus gravis, syphilis, as also in diseases depending upon a hemorrhagic diathesis, such as variola hemorrhagica, scurvy, as also following insolation, extensive burns, and frostbite, hæmoglobinæmia, leading to hæmoglobinuria, is not infrequently observed.

An epidemic hæmoglobinuria of the newly born and a paroxysmal or intermittent hæmoglobinuria, both of unknown origin, have likewise been described.

In a case of Raynaud's disease which the author had occasion to observe in the clinic of Dr. H. M. Thomas, at the Johns Hopkins Hospital, hæmoglobinuria at times followed epileptiform seizures.

Finally, hæmoglobinæmia followed by hæmoglobinuria is observed after transfusion of the blood of one mammal into the circulation of another.

In some cases, and particularly in those following poisoning with chlorates, etc., the hæmoglobinæmia ultimately leads to a well-pronounced methæmoglobinæmia (see below).

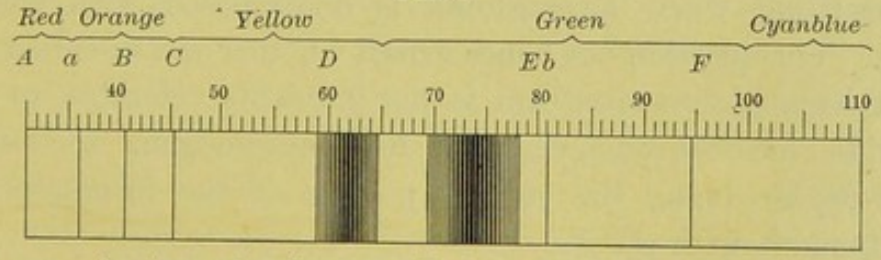
A hæmoglobinæmia, aside from the urinary examination, may be readily recognized by a spectroscopic examination of the serum, when the two bands of absorption of oxyhæmoglobin will be observed.

A very simple method which may be employed for the same purpose is the following: A small amount of blood is drawn from the patient by means of cupping-glasses and immediately placed on ice, where it is allowed to remain for from twenty to twenty-four hours. At the expiration of this time the clot will have shrunk, floating, if the blood be normal, in the clear, straw-colored serum, while a beautiful ruby-red color is obtained in cases of hæmoglobinæmia. If, furthermore, some of this serum be heated to a temperature of from 70° to 80° C., the coagulum in the presence of hæmoglobin will present a more or less deep brown color.

Carbon Monoxide Hæmoglobin. In cases of coal-gas poisoning the blood, both of arteries and veins, presents a bright cherry-red color, owing to the presence of carbon monoxide hæmoglobin.

Such blood when properly diluted, like oxyhæmoglobin, shows two bands of absorption between *D* and *E* (Fig. 5), which are nearer the violet end of the spectrum, however, and may be readily

FIG. 5.



Spectrum of carbon monoxide hæmoglobin. (V. JAKSCH.)

distinguished from those referable to oxyhæmoglobin by the addition of a reducing agent. This will not affect the spectrum of carbon monoxide hæmoglobin, while that of oxyhæmoglobin is transformed into the spectrum of reduced hæmoglobin.

For medico-legal purposes a number of additional tests have been devised, among which that suggested by Hoppe-Seyler is one of the simplest and at the same time most reliable. The blood is treated with double its own volume of a solution of sodium hydrate (sp. gr. 1.3.). Normal blood is thus changed into a dirty-brownish mass,

which, when spread out upon a porcelain plate, exhibits a trace of green, while carbon monoxide blood yields a beautiful red under the same conditions.

Nitric Oxide Hæmoglobin. The blood in cases of poisoning with nitric oxide, owing to the presence of nitric oxide hæmoglobin, yields a spectrum which is similar to that of carbon monoxide hæmoglobin, the bands, however, being less sharply defined and paler than those of the latter, and which, like these, do not disappear upon the addition of a reducing substance.

Sulphuretted Hydrogen Hæmoglobin (Methæmoglobin Sulphide). In cases of poisoning with sulphuretted hydrogen, notwithstanding the researches of Hoppe-Seyler, which go to show that hæmoglobin will enter into combination with this gas, no definite changes can be discovered in the blood upon spectroscopic examination. It is stated, however, that in such cases the blood becomes dark and of a dull greenish tint, the distinction between arterial and venous blood being at the same time lost.

Carbon Dioxide Hæmoglobin. With carbon dioxide, as mentioned above, hæmoglobin is also thought to enter into combination, the spectrum being similar to that of reduced hæmoglobin. The latter, in fact, is formed artificially when carbon dioxide is passed through a solution of oxyhæmoglobin. If this process be carried further, hæmoglobin is decomposed, a precipitate of globulin being thrown down, and an absorption-band obtained which is similar to that resulting when hæmoglobin is decomposed with acids (see below). The question has hence arisen whether the so-called carbon dioxide hæmoglobin spectrum is not in reality referable to carbon monoxide hæmochromogen, the hæmochromogen, according to Hoppe-Seyler, being the colored portion of the hæmoglobin and its compounds with gases.

The blood-changes occurring in cases of poisoning with *hydrocyanic acid* and *acetylene* are as yet but little known, and the reader is referred to special works upon toxicology for their consideration.

Hæmatin. If hæmoglobin in aqueous solution be heated to a temperature of from 60° to 70° C., it is decomposed into an albuminous body, belonging, in all probability, to the class of globulins, and hæmatin. The same result is also reached by treating the aqueous solution with acids, alkalies, or the salts of various heavy metals.

Hæmatin is an amorphous, blackish-brown or bluish-black sub-

PLATE I.

FIG. 1.



Crystals of **Hæmin.** (Highly magnified.)

FIG. 2.



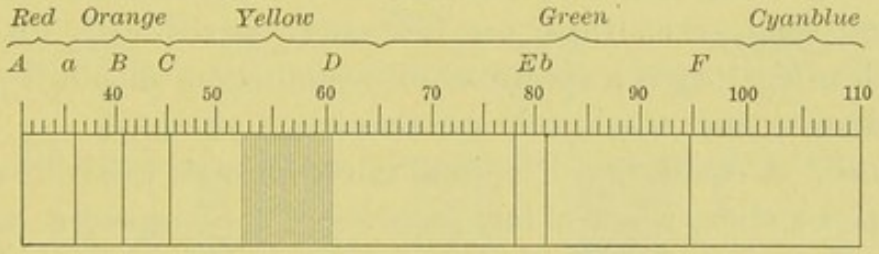
Crystals of Hæmatoidin from an Acholic Stool.
(v. Jaksch.)

stance which is frequently encountered in old transudates, in the stools after hemorrhages, and after meals rich in meats—*i. e.*, blood. It is said to occur in the urine in cases of poisoning with arsenic, and in the blood of animals poisoned with nitrobenzol the presence of this body is likewise said to be demonstrable with the spectroscope.

In acid solutions it shows a well-defined spectral band between *C* and *D* (Fig. 8). Between *D* and *F* a second band is seen, which is much wider, but less sharply defined than the first, and may be resolved into two bands by dilution, one between *b* and *F*, near *F*, and another between *D* and *E*, near *E*; a fourth faint band, finally, may be obtained between *D* and *E*, near *D*. As a rule, only the band between *C* and *D*, and the broad band, viz., the two bands between *D* and *F*, are seen.

In alkaline solutions, on the other hand, it shows but one broad band, the greater portion of which lies between *C* and *D*, extending slightly beyond *D* (Fig. 6).

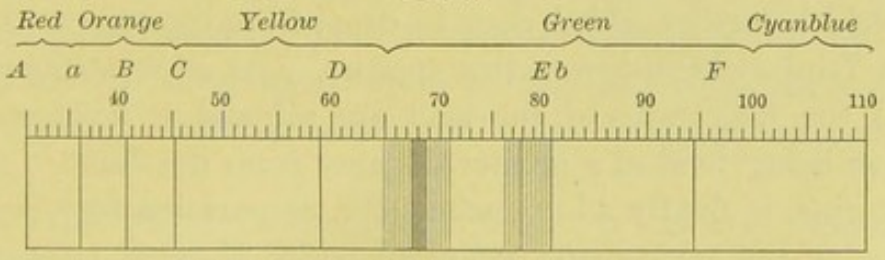
FIG. 6.



Spectrum of hæmatin in alkaline solution. (v. JAKSCH.)

If an alkaline solution of hæmatin is treated with a reducing substance, reduced hæmatin results, which gives rise to two bands of absorption between *D* and *E* (Fig. 7).

FIG. 7.



Spectrum of reduced hæmatin. (v. JAKSCH.)

Hæmin. Hæmatin readily combines with one molecule of hydrochloric acid to form hæmin. This substance crystallizes in light or dark brown rhombic plates or columns, which are highly characteristic (Plate I., Fig. 1). They bear the name of their discoverer,

Teichmann. The size of these crystals varies with the manner in which they are produced, the largest specimens being encountered when the glacial acetic acid (see below) is allowed to evaporate as slowly as possible. Specimens measuring from 15 μ to 18 μ in length may then be seen. Smaller crystals will be present at the same time, occurring either singly or gathered in stars, rosettes, and crosses.

As these crystals may be obtained from mere traces of blood, their formation must be regarded as conclusive evidence in medico-legal examinations. Lewin and Rosenstein have pointed out, however, that under certain conditions a negative result may be reached, even if the coloring-matter is derived from the blood. This is the case especially when the hæmoglobin has been transformed into hæmochromogen or hæmatoporphyrin, or when substances have been mixed with the blood which are either capable of altering its general composition or which, through their mere presence, interfere with the reaction itself. Such substances are certain salts of iron (rust), lead, mercury, and silver; further, lime, animal charcoal, and sand, when these are intimately mixed with the blood. In medico-legal cases a spectroscopic examination should hence also be made whenever the hæmin reaction is not obtained.

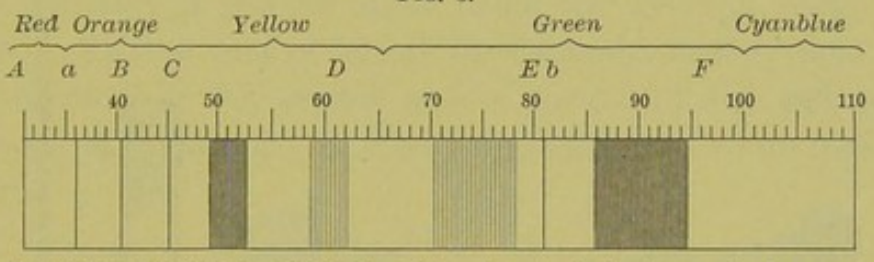
Method. A small drop of normal salt-solution is carefully evaporated upon a slide, when a few particles of the suspected material, powdered or teased as finely as possible, are placed upon the delicate layer of crystallized salt. The preparation is covered with a cover-glass, and glacial acetic acid allowed just to fill the space between the two glasses. The specimen is then carefully heated (three-quarters to one minute) until bubbles of gas begin to form beneath the cover. While evaporation is being continued glacial acetic acid is further added, drop by drop, from the edge of the slip, until a faint reddish-brown tint appears. As soon as this point is reached the last traces of the acid are allowed to evaporate, the specimen being held at a greater distance from the flame. A drop of glycerine is finally added, when the preparation may be examined under the microscope, attention being directed especially to any reddish-brown streaks or specks, which, in the presence of blood, can usually be made out with the naked eye.

Methæmoglobin. Methæmoglobin is a pigment closely related to oxyhæmoglobin, and is frequently encountered in sanguinous transudates, cystic fluids, and in the urine in cases of hæmaturia

and hæmoglobinuria. In the circulating blood methæmoglobin is found after the ingestion of large quantities of potassium chlorate, notably so in children, as also after the inhalation of nitrite of amyl, the use of kairin, thallin, hydrochinon, pyrocatechin, iodine, bromine, turpentine, ether, perosmic acid, permanganate of potassium, and antifebrin. (See Hæmoglobinæmia, p. 36.)

The spectrum of an aqueous or slightly acidified solution of methæmoglobin (Fig. 8) closely resembles that of an acid solution of hæmatin, but differs from the latter by the ease with which it is transformed into that of hæmoglobin upon the addition of an alkali and a reducing substance. The spectrum of hæmatin under the same conditions is transformed into that of an alkaline solution of hæmochromogen. In alkaline solutions, on the other hand, two bands of absorption are observed, which are similar to those of oxyhæmoglobin, but differ from these by the fact that the band nearer *E*, β, is more pronounced than the one at *D*, *a*. A third, but very faint, band may further be observed between *C* and *D*, near *D*.

FIG. 8.



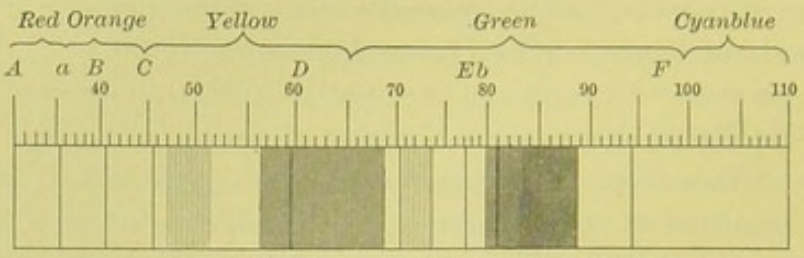
Spectrum of methæmoglobin in acid and neutral solutions. (V. JAKSCH.)

Hæmatoidin. Small amorphous particles of an orange or ruby-red color, or crystals belonging to the rhombic system (Plate I., Fig. 2), occurring either singly or in groups, are frequently met with in the sputum, the urine, and the feces, as well as in old extravasations of blood. They were first discovered by Virchow, who applied the term hæmatoidin to this particular pigment, the hæmic origin of which is undoubted, being probably derived from hæmatin.

Hæmatoporphyrin. Hæmatoporphyrin is likewise a derivative of hæmatin, and, according to Nencki and Sieber, isomeric with bilirubin. In dilute solution with sodium carbonate it shows four bands of absorption, one between *C* and *D*, a second one, broader than the first, about *D*, especially marked between *D* and *E*, a third one, not so broad and less sharply defined between *D* and *E*, and a fourth one, broad and dark, between *b* and *F* (Fig. 9).

The clinical significance of this body, which also appears in the urine, as well as the causes giving rise to its formation, is as yet unknown. (See Hæmatoporphyrinuria.)

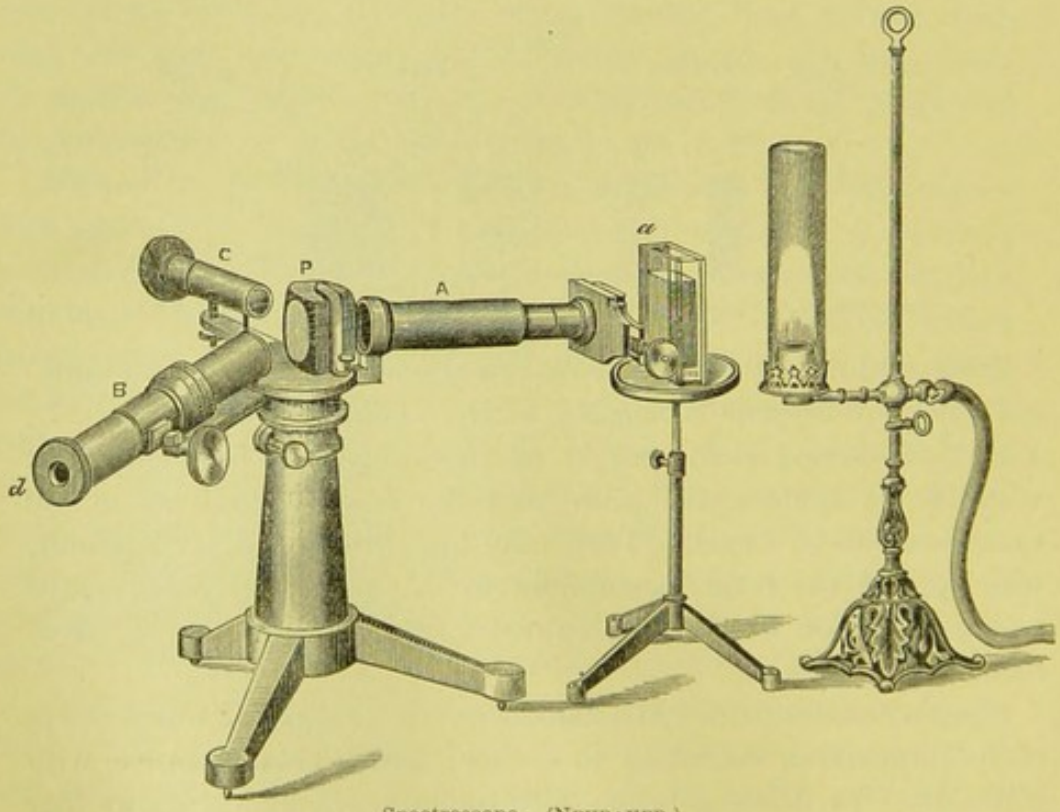
Fig. 9.



Spectrum of hæmatoporphyrin in alkaline solution.

While it is usually possible, as pointed out above, to recognize definitely the presence of blood by the hæmin-test, recourse should always be had to a spectroscopic examination whenever the exact nature of the pigment under consideration is to be determined.

Fig. 10.



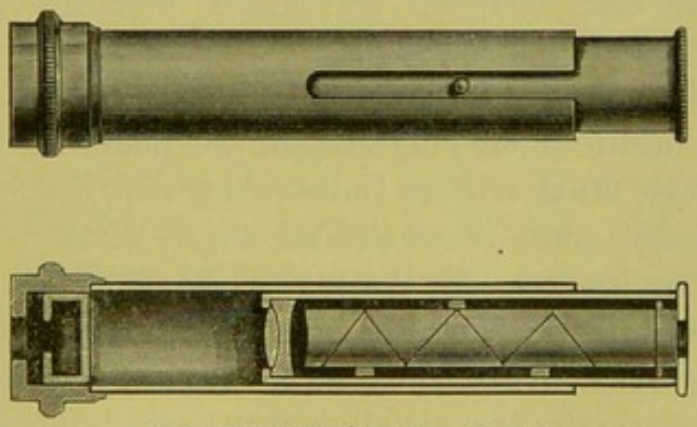
Spectroscope. (Neubauer.)

The Spectroscope. The spectroscope (Fig. 10) essentially consists of a tube (A), provided with a slit at its distal end which may be narrowed or widened, and a collecting-lens at its proximal end.

Through the latter rays of sunlight or of artificial light are thrown upon a prism (P), where they are decomposed into a colored spectrum which is viewed through an astronomical telescope (B). Through a third tube (C) a fine scale, illuminated by artificial light, is reflected by the prism to the eye of the observer, appearing immediately above the colored spectrum, the left end of which is red, passing into yellow, this into green, then into blue, indigo, and finally into violet, which occupies the right end. These colors, however, are not continuous, but are interrupted by a large number of vertically placed dark lines, named after Frauenhofer. The most marked of these he designated by the letters: *A*, *a*, *B*, *C*, *D*, *E*, *b*, *F*, *G*, and *H*. Of these, *A* is found at the left end and *B* in the middle of the red portion of the spectrum, *C* at the boundary of the red and the orange, *D* in the yellow, *E* in the green, *F* in the blue, *G* in the indigo, and *H* in the violet portion; *a* is situated in the red between *A* and *B*, nearer *A*, and *b* in the green between *E* and *F*, nearer *E*. (See Fig. 1.)

If now a colored medium be placed between the slit and the light, not all the rays of colored light reach the eye, but some become absorbed. In the case of blood, for example, it may thus be seen that a portion of the yellow and a portion of the red rays are absorbed, a spectrum of this kind being spoken of as an absorption-spectrum.

FIG. 11.



Browning's spectroscope. (ZEISS.)

For clinical purposes various instruments, modifications of the one described, have been devised, among which those of Desego of Heidelberg, Zeiss of Jena (Fig. 11), and Hoffmann of Paris, as well as Hering's lensless spectroscope, and Henocque's instrument, the latter two, owing to their cheapness particularly, deserve especial mention.

THE PROTEIDS OF THE BLOOD.

In considering the proteids of the blood from a clinical point of view, it is necessary to distinguish between an increase and a diminution in their normal amount, constituting the conditions of *hyperalbuminosis* and *hypalbuminosis*, respectively. As may be expected, the former is met with whenever water is more rapidly withdrawn from the system than it can be supplied, and is hence observed in cases of cholera, acute diarrhœa, following the use of purgatives, etc. This increase in the amount of proteids is only a relative increase, however. The occurrence of an absolute increase has not as yet been satisfactorily demonstrated. An absolute hypalbuminosis, on the other hand, is observed following a direct loss of proteids from the blood, as in hemorrhage, dysentery, albuminuria of high degree, the formation of large collections of pus, etc. This is generally associated with a relative increase in the amount of water —*i. e.*, a hydræmia, which is particularly noticeable after hemorrhages, and referable to a diminished secretion and excretion of water, as well as to a direct absorption from the tissues.

The term *hyperinosis* has been applied to a condition in which the amount of fibrin is increased. This is said to occur in various inflammatory diseases, such as pneumonia, pleurisy, acute articular rheumatism, and erysipelas, while a diminished amount of fibrin, *hypinosis*, has been observed in malaria, nephritis, pyæmia, and pernicious anæmia.

In order to determine the amount of fibrin, 30 to 40 c.c. of blood, obtained by means of cupping-glasses, are placed in a previously weighed beaker, fitted with an India-rubber cap, through the centre of which passes a piece of whalebone, firmly fixed. The blood is defibrinated by beating with the whalebone, when the beaker with its contents is weighed, the difference indicating the weight of the blood. The beaker is then filled with water and the mixture again beaten, whereupon the fibrin is allowed to settle; after being washed with normal salt-solution it is filtered through a filter of known weight, further washed with normal salt-solution until free from coloring-matter, then boiled in alcohol to dissolve out the fat, cholesterin, and lecithin, dried at 110° to 120° C., and weighed upon cooling over sulphuric acid.

In leukæmic blood v. Jaksch was able to demonstrate peptones in considerable quantities, and especially so after death, when the amount

progressively increased as decomposition advanced. Matthes, on the other hand, could detect no true peptones, but found that the blood contained a deuteroalbumose. In one case the serum contained an abundance of nucleoalbumin, derived in all probability from degenerated leucocytes.

In order to test for peptones, all other proteids should first be removed, when a positive biuret-reaction in the filtrate will indicate their presence.

Carbohydrates.

Sugar. Sugar, as indicated above, occurs normally in the blood, its quantity varying between 1 and 1.5 p. m. Under pathologic conditions this amount may be exceeded by far, and notably so in diabetes, in which Hoppe-Seyler found as much as 9 p. m. in a certain case.

In addition to sugar a non-fermentable reducing substance has been encountered in the blood, the exact nature of which is still unknown.

Large quantities of a reducing substance, the greater portion of which consisted of sugar, have been met with by Trinkler in carcinoma; it was observed at the same time that carcinoma of the internal organs was associated with far greater amounts of sugar than cancerous diseases of the skin and the mucous membranes. It is also interesting to note in this connection that an increase in the degree of the cachexia was not accompanied by an increase in the percentage of sugar.

The results reached by Trinkler apparently also bear out the correctness of the conclusions formed by Freund, who claimed that a differential diagnosis between carcinoma and sarcoma, in which latter condition no increase in the amount of sugar was noted, can always be effected upon the basis of an examination of the blood in this direction.

In the following table the percentages found in the different diseases investigated are given, from which it is apparent that next to carcinoma the largest quantities of sugar are met with in the infectious diseases and the lowest figures in diseases of the kidneys:

	Average. Per cent.	Minimum. Per cent.	Maximum. Per cent.
Carcinoma . . .	0.1819	0.1023	0.3030
Typhoid fever . .	0.0950	0.0875	0.1022
Pneumonia . . .	0.0943	0.0813	0.1092
Dysentery . . .	0.0838	0.0796	0.0915
Vitium cordis . .	0.0737	0.0664	0.0897
Peritonitis . . .	0.0701	0.0450	0.0917
Tuberculosis . . .	0.0653	0.0450	0.0817
Syphilis. . . .	0.0553	0.0449	0.0748
Nephritis and uræmia .	0.0489	0.0321	0.0559

In order to demonstrate sugar in the blood, 15 to 30 grammes, obtained by venesection or cupping-glasses, are placed in an evaporating-dish and treated with an equal weight of finely powdered sodium sulphate and a few drops of acetic acid. The mixture is brought to the boiling-point and passed through a muslin filter as soon as the coagulum has become black and spongy, water having been previously added to the original volume. The filtrate is passed through Swedish paper. In the final filtrate the sugar is then estimated as pointed out elsewhere. (See Urine.)

Or the blood is treated with four to five times its volume of strong alcohol (94 to 96 per cent.), slightly acidified with acetic acid. The mixture is allowed to stand for several hours, no heat being applied. It is then filtered and evaporated on the water-bath until all the alcohol has been driven off. Should any albumin separate out during this process, the residue is again extracted with alcohol. The final residue is dissolved in water. In this solution the sugar is then estimated according to Knapp's method.

Of late Cavazzani has drawn attention to another method of freeing the blood from proteids which is said to be entirely satisfactory and less expensive. To this end 20 to 30 c.c. of blood are added to 200 c.c. of distilled water in a porcelain dish and treated with five or six drops of a solution consisting of 10 parts of acetic acid (sp. gr. 1:040) and 1 part of lactic acid. The mixture is boiled for eight to ten minutes, filtered, and the coagulum washed repeatedly with hot water and finally pressed out in a piece of muslin. The resulting filtrates, which are practically colorless, are then concentrated to a small volume, and any traces of albumin which may still separate out filtered off. If too much of the acid solution has been added, it may happen that the mixture does not clear up on boiling. It is then only necessary to add a few crystals of sodium carbonate, when coagulation will occur at once. On the other hand, it may

at times be necessary to add a few more drops of the acetic acid solution.

Glycogen. There appears to be no doubt that glycogen normally occurs in the blood of various animals. Huppert, in fact, succeeded in demonstrating its presence in all animals examined, the amount varying between 0.114 and 1.560 grammes for one hundred parts of blood. Czerny, on the other hand, was not able to confirm these results in the case of healthy adults, while in sick children an examination of the leucocytes furnished positive results, glycogen being met with—in chronic gastro-intestinal diseases, pneumonia, anæmia, furunculosis, cachectic conditions the result of tubercular disease, asphyxia, etc. In diabetes and leukæmia also the glycogen-reaction is said to be quite pronounced.

Livierato, who recently investigated this question with great care, arrived at the following conclusions: 1. Glycogen is constantly present in the blood of healthy individuals; its presence, however, is confined to the blood-plasma. When present in increased amounts it also occurs in the leucocytes. 2. It is absent in cases of acute articular rheumatism and in inflammatory conditions of the serous membranes. 3. Increased amounts are found in acute croupous pneumonia, in typhoid fever, in phthisis, in the various exanthemata, etc. 4. In hepatic and cardiac diseases associated with effusion it is either absent or present only in traces. 5. An endoglobular reaction only may be obtained during the second half of the ninth month of pregnancy and during the first four or five days of the puerperal period. 6. The increase in the amount of glycogen is dependent upon the existence of an active local process, associated with fever, upon the formation of exudates containing peptonizable material, or upon the existence of a more or less pronounced hyperleucocytosis.

In order to test for glycogen a drop of blood is carefully spread out between two cover-slips and dried at an ordinary temperature, when a drop of a solution composed of 1 gramme of iodine and 3 grammes of potassium iodide in 100 grammes of concentrated mucilage is allowed to flow between the two glasses. In the presence of glycogen brown-colored granules will be observed occurring either free in the blood or contained in the so-called neutrophilic leucocytes.

Cellulose. Cellulose has occasionally been found in the blood of tubercular patients.

Urea.

Urea normally occurs in the blood in traces—0.016 to 0.020 per cent.—larger amounts being encountered whenever, for any reason, as in nephritis, various diseases of the urinary organs, cholera Asiatica, cholera infantum, eclampsia, etc., its elimination is *impeded*, or whenever, as in fever, owing to increased albuminous decomposition, urea is *formed* in abnormally large quantities.

In this connection it is interesting to note that a smaller amount of urea is found in fatal cases of eclampsia than in those ending in recovery, an observation which has been explained by the assumption that in this condition not only the kidneys, but also the liver, loses its functional activity.

The methods which are available for the detection of urea in the blood are still too complicated for clinical purposes, and the value of the information derived so small as hardly to repay for the labor involved. Hoppe-Seyler's method should be employed whenever an examination in this direction is deemed advisable.[1]

Uræmia. Formerly it was thought that the complex of symptoms generally spoken of as uræmia was referable to the retention in the blood of urea or ammonium carbonate. This view has since been disproved, however, although it must be admitted that in uræmia an increased amount of urea is frequently noted. Other views, according to which uræmia is referable to an accumulation of potassium salts, of extractives, and especially of kreatinin, or of ptomaïnes in the blood, must still be regarded as being *sub judice*. There is no reason, however, to ascribe the uræmic condition to the retention in the blood of one particular constituent of the urine, and it is not at all improbable that a retention of all may be responsible for the symptoms observed.

Uric Acid and the Xanthin-bases.

Uric Acid. Formerly, the presence of appreciable amounts of uric acid in the blood was regarded as pathognomonic of gout.

Since that time a definite lithæmia has been observed in a variety of disorders, however, such as pneumonia, acute and chronic nephritis, chronic gastritis, catarrhal angina, conditions associated with

[1] See Hoppe-Seyler: Handbuch der physiologisch- und pathologisch-chemischen Analyse. Vierte Auflage, p. 363.

an insufficient aëration of the blood, as in various diseases of the heart, pleurisy with exudation, emphysema when accompanied by cyanosis, the severer forms of anæmia, etc. v. Jaksch claims to have found uric acid in the blood in 88.88 per cent. of his cases of nephritis. Fever in itself does not appear to lead to an increased production of uric acid, as negative results were obtained in nine cases of typhoid fever out of eleven, in five cases of acute articular rheumatism out of six, etc. The conclusion is thus forced upon us that the diminished alkalinity of the blood observed in nephritis and anæmia is, to some extent at least, dependent upon the presence of a nitrogenous acid, while the diminished alkalinity of the blood observed in fevers is not referable to this cause.

From a survey of the literature upon the subject it would appear that an increased elimination of uric acid in the urine is not necessarily accompanied by an increase in the amount of uric acid in the blood. Further researches in this direction are, however, highly desirable, and particularly so in connection with the various forms of gastric disease, in which an increased elimination of uric acid, according to the author's experience, is so frequently observed.

In order to test for uric acid in the blood the following method may be employed: 100 to 300 c.c. of blood, obtained by means of cupping-glasses, are at once diluted with three to four times their own volume of water and placed upon a water-bath. As soon as coagulation sets in a few drops of a 0.3 to 0.5 per cent. solution of acetic acid are added until a feebly acid reaction is obtained. After having been kept upon the boiling-water bath for from fifteen to twenty minutes longer, until the albumin has separated out and settled in brownish flakes, the mixture is filtered while hot and the precipitate washed repeatedly with hot water. Filtrate and washings, which usually present a slightly yellow or brownish color, are again brought to the boiling-point after the addition of 0.3 to 0.5 per cent. of acetic acid, decanted, filtered, and after the addition of a small amount of disodic phosphate further treated according to the Ludwig-Salkowsky method (see Urine). The first filtrate is then treated with hydrochloric acid, evaporated to about 10 c.c., and allowed to stand for twenty-four hours, when the uric acid that has separated out is filtered off through asbestos or glass-wool. The filtrate may then be examined for xanthin-bases according to the same method. If no uric acid crystallizes out, as not

infrequently occurs, the acid fluid is directly examined for uric acid by means of the murexide-test (which see). If, upon the addition of ammonia, no distinct red color develops, the residue, after thorough desiccation, is dissolved in water, when a reddish color may be regarded as indicating the presence of uric acid, while a yellow or brown color is referable to certain xanthin-bases. Hopkins' method may also be employed.

Garrod's Test: This test may be advantageously employed if it be merely desired to determine whether or not large amounts of uric acid are present in the blood. A few c.c. of blood-serum (5–10) or of serous fluid, obtained by means of a blister, are placed in a watch-crystal and treated with from 6 to 10 drops of a 30 per cent. solution of acetic acid. A thread of linen is immersed in the fluid, which is then kept at a low temperature for from twelve to twenty-four hours. At the expiration of this time a few uric-acid crystals will have separated out upon the thread if the substance be present in large amounts. The true nature of these crystals may then be further determined by the microscope and the murexide-test. (See Uric Acid in the Urine.)

Xanthin-bases. Xanthin-bases, as pointed out before, do not occur in normal blood, but have been encountered under pathologic conditions, as in typhoid fever, lymphatic tuberculosis, emphysema, phthisis pulmonalis, pleurisy, and chronic nephritis.

The method above indicated for the demonstration of uric acid in the blood should also be employed when it is found desirable to test for these bodies. (See Urine.)

Fat and Fatty Acids.

An increase in the amount of fat normally present in the blood, aside from that arising after the ingestion of large amounts of fatty food, is met with in cases of obesity, chronic alcoholism, injuries affecting the long bones, as also in severe cases of diabetes, various hepatic diseases, chronic nephritis, tuberculosis, malaria, cholera, etc. This increase constitutes the condition spoken of as *lipæmia*. The term *lipacidæmia* has been applied to the occurrence of volatile fatty acids in the blood, noted by v. Jaksch in various febrile diseases, leukæmia, and at times in diabetes, in which this condition is supposed to stand in a causative relation to the coma. β-oxybutyric acid has been found post mortem in the blood in diabetes.

To test for fat in the blood it is only necessary to examine a drop microscopically for the presence of minute, highly refractive globules which are readily soluble in ether.

To test for fatty acids 20 to 30 c.c. of blood, obtained by means of cupping-glasses, are treated with an equivalent weight of sodium sulphate and boiled. The filtrate is then evaporated to dryness and extracted with absolute alcohol. Upon evaporation of this solution fatty acid crystals will be obtained, which can be readily recognized with the microscope. (See Feces.)

Lactic Acid.

There appears to be some doubt whether or not lactic acid normally occurs in the blood of man during life, while after death its presence appears to be constant, the amount determined as zinc lactate varying between 0.233 and 6.575 p. m. In the series of cases studied by Irisawa it was impossible to account for the great variations observed in the amount of lactic acid by the character of the disease causing the fatal termination, and it is possible that the cause therefore lies in the fact that in some cases the blood was obtained shortly after death, while in others many hours had elapsed, as Irisawa himself suggests.

The method employed by him is the following: 100 to 300 c.c. of blood are extracted with three times their own volume of alcohol, filtered, and the filtrate evaporated to a syrupy consistence. This is then made strongly alkaline with barium hydrate and shaken with large quantities of ether, in order to remove the fats present. The residue is acidified with phosphoric acid and again shaken with ether for twenty minutes at a time, until the process has been repeated five or six times, the lactic acid passing over into the ether. The ether is distilled off from the extract, the residue taken up with water, and the solution carefully evaporated in order to drive off any ether still remaining, as well as the fatty acids. Carbonate of zinc is now added and the solution heated to 100° C. and filtered. The filtrate is evaporated on a water-bath until crystallization begins, when it is allowed to cool and treated with a few drops of absolute alcohol, in order to effect a complete separation of the lactate of zinc. The solution is allowed to stand exposed to the air until a constant weight is obtained.

From the blood of living dogs Irisawa was able to obtain lactic

acid in every case, and it was observed, moreover, that the amount found stood in direct relation to the degree of anæmia produced.

Biliary Constituents.

Biliary constituents—*i. e.*, bile-pigment and biliary acids—are not encountered in the blood under normal conditions, but are found whenever they are present in the urine (which see). It is noteworthy, furthermore, that bilirubin may frequently be demonstrated in the blood when a urinary examination in this direction yields negative results, and, according to v. Jaksch, bilirubin occurs in the blood in nearly every case in which urobilin exists in the urine, showing that bile-pigment circulating in the blood is, in all probability, transformed into urobilin in the kidneys.

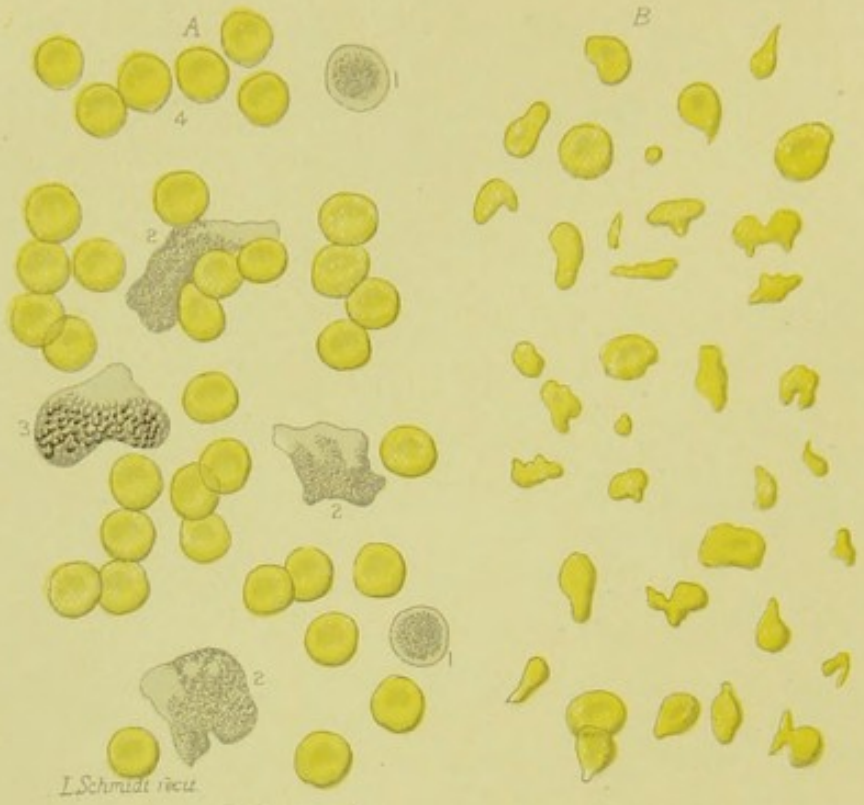
A *cholæmia* is encountered in various pathologic conditions associated with a resorption of bile from the biliary passages, as in obstructive jaundice, an excessive elimination of bile into the intestinal canal, as well as with an increased destruction of red corpuscles.

In order to test for biliary acids in the blood, the presence of which leads to destruction of the red corpuscles, as well as to the circulatory disturbances so constantly encountered, the blood is first treated with alcohol, in order to remove the proteids. The biliary acids which are present in the filtrate are next transformed into their lead salts by means of acetate of lead and ammonia, and thus precipitated. After washing with water the precipitate is boiled with alcohol and filtered. The lead salts are decomposed by means of sodium carbonate, the solution is again filtered, the filtrate evaporated to dryness, and the residue extracted with absolute alcohol. The alcohol is distilled off, when the biliary salts of sodium will crystallize out or remain behind as an amorphous mass, which may be tested directly according to Pettenkofer's method. To this end some of the residue is dissolved in water and treated with two-thirds of its volume of concentrated sulphuric acid, care being taken that the temperature does not rise beyond 60° C. To this mixture a few drops of a 20 per cent. solution of cane-sugar are added, when in the presence of biliary acids a beautiful violet color is obtained, which is referable to the action of furfurol, formed from the cane-sugar and the acid, upon the biliary acids.

Bilirubin can be demonstrated in the blood most readily in the

PLATE II.

FIG. 1.



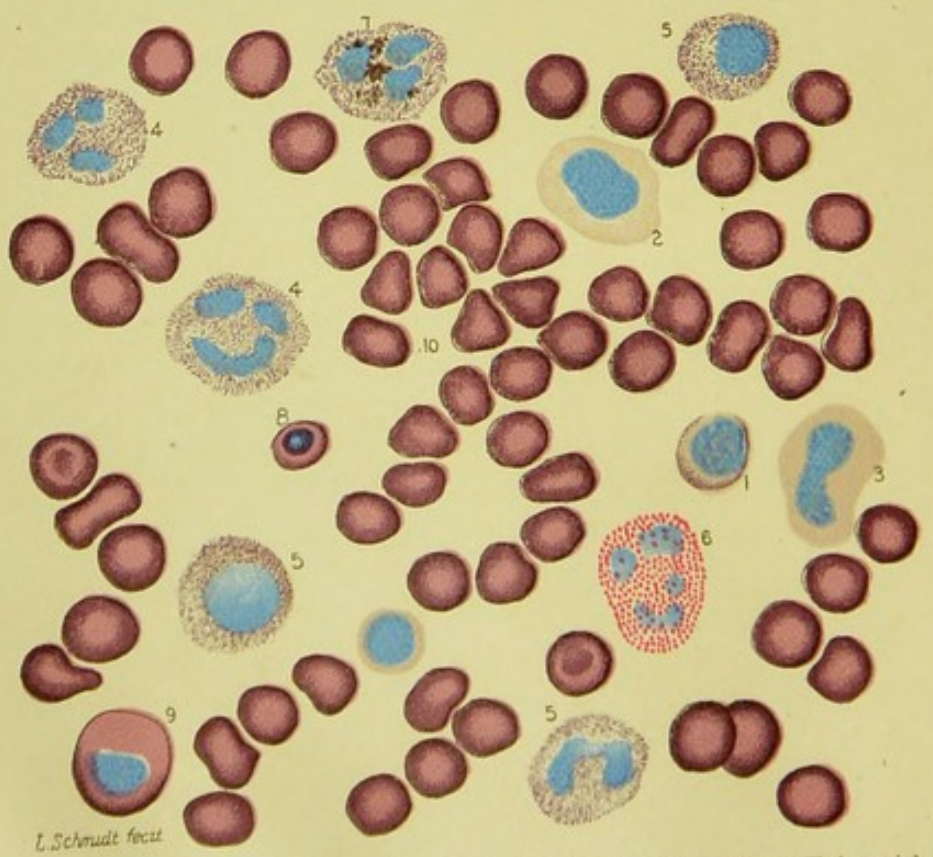
Elements of Normal Blood.

1, Small Mononuclear Leucocyte; 2, Neutrophilic Leucocytes; 3, Eosinophilic Leucocyte; 4, Normal Red Blood Corpuscles. Unstained Specimen.

Poikilocytosis.

Unstained Specimen taken from a Case of Pernicious Anæmia. (Personal Observations.)

FIG. 2.



The Various Elements of the Blood Stained with Ehrlich's Tri-acid Stain.

1, Small Mononuclear Leucocytes; 2, Large Mononuclear Leucocytes; 3, Transition Form; 4, Neutrophilic Leucocytes; 5, Myelocyte; 6, Eosinophilic Leucocyte; 7, Melaniferous Leucocyte; 8, Normoblast; 9, Megaloblast; 10, Normal Red Corpuscles. (Personal Observation.)

following manner: 10 to 15 c.c. of blood, obtained by means of cupping-glasses, are allowed to coagulate, when the serum is removed by means of a pipette, filtered through asbestos, and coagulated in as thin a layer as possible, at a temperature of 80° C. Under such conditions normal serum will present a light straw color, while in the presence of biliary coloring-matter a light-greenish color is obtained, which becomes grass-green on standing. Should the serum contain hæmoglobin, as in cases of hæmoglobinæmia, a brownish color results.

Acetone.

Acetone has been found in considerable amounts in the blood under various pathologic conditions, and especially in fevers.

In order to demonstrate the presence of acetone in the blood this is first extracted with ether and subsequently distilled, when the distillate is tested as indicated elsewhere. (See Acetonuria.)

MICROSCOPIC EXAMINATION OF THE BLOOD.

The Red Corpuscles.

Variations in the Size of the Red Corpuscles. If a drop of blood, most readily obtained from the tip of a finger or the lobe of the ear, be examined with the microscope, a large number of faintly yellow, non-nucleated, circular, biconcave disks will be observed: the red corpuscles, or erythrocytes of the blood (Plate II., Fig. 1, *a*).

Under normal conditions variations in the size of the red corpuscles are observed, and Hayem distinguishes between corpuscles of average size, measuring from 7.2 μ to 7.8 μ in diameter, small corpuscles, presenting an average diameter of from 6 μ to 6.5 μ, and large corpuscles, measuring from 8.5 μ to 9 μ.

In certain diseases which are accompanied by a marked oligocythæmia both abnormally small and large corpuscles are encountered, which have been termed microcytes and macrocytes, respectively. The former measure from 3.5 μ to 6 μ, the latter from 9.5 μ to 12 μ in diameter. Still larger forms, the megalocytes, or giant corpuscles of Hayem, are also at times seen in which the diameter measures from 10 μ to 16 μ. These latter are of consid-

erable importance, as their presence in large numbers appears to be confined almost entirely to the blood of pernicious anæmia. In chlorosis they are far less common.

The terms *microcythæmia* and *macrocythæmia* have been applied to conditions in which the smaller or the larger forms, respectively, predominate in the blood. While there appears to be no doubt that a true macrocythæmia exists in the circulating blood in various forms of anæmia, and while microcytes also may occur, as such, in the circulating blood, the latter are only exceptionally met with, the ordinary microcythæmic condition, according to Hayem, being artificially produced during the preparation of the specimen, so that this term really conveys a wrong impression, and should be discarded. Although admitting the correctness of Hayem's view to a certain degree, there can be no doubt that, under pathologic conditions, abnormally small red corpuscles are quite constantly met with in large numbers, be they pre-existent, as such, in the circulating blood, or produced artificially during the preparation of the specimen. They are thus seen accompanying the condition of macrocythæmia, in pernicious anæmia, leukæmia, the pseudo-leukæmic condition of children, the various severe anæmias in general, and even in chlorosis.

Variations in the Form of the Red Corpuscles. Going hand in hand with variations in the size of the red corpuscles there are variations in form, and both microcytes and macrocytes, particularly the latter, generally do not present the normal circular appearance, but abnormalities in form, noted in connection with those of normal size (Plate II., Fig. 1, *b*). Corpuscles are thus seen which resemble a flask, a kidney, a biscuit, an anvil, etc., while others, again, present such irregularities in form that it is impossible to compare them with any known object.

The term *poikilocytosis* has been applied to alterations both in the size and in the form of the red corpuscles. This condition may be observed in the various forms of anæmia, and is especially pronounced in pernicious anæmia, of which disease it was once thought to be pathognomonic. In chlorosis, poikilocytosis is usually only seen in the most severe cases, and particularly in those manifesting a tendency toward thrombosis and embolism.

Variations in the Number of the Red Corpuscles. The number of red corpuscles in the blood of healthy individuals is fairly constant, and the statement generally found in text-books

that 5,000,000 to 5,500,000 are contained in every cbmm. of blood in the adult male and 4,500,000 in the adult female is fairly accurate.

An increase in the number of red corpuscles is noted almost exclusively in conditions associated with a loss of large quantities of fluid from the body. It is thus especially encountered in the so-called algid state of cholera Asiatica, where from 6,200,000 to 6,500,000 may be found in the cbmm. In the ordinary forms of severe diarrhœa an increase of 1,500,000 is also by no means rare. An increase is further observed in diabetes, but is not dependent upon a concentration of the blood, as it may also be seen following an increased ingestion of fluids as well as while fasting. While there can thus be no doubt that a polycythæmia does occur, experiments have demonstrated almost exclusively that such a condition does not exist in what is generally spoken of as true plethora, and that the various symptoms of plethora, formerly attributed to an increase in the total amount of blood or of the red corpuscles, are referable, more likely, to vasomotor disturbances.

A diminution in the number of red corpuscles, on the other hand, is frequently observed; it may be temporary, when following hemorrhages, for example, or permanent. An oligocythæmia is observed in various forms of anæmia, of whatever origin, and the number may fall to 360,000, and even lower in fatal cases. In pernicious anæmia the lowest figures have been noted, and Quincke cites a case in which just before death only 143,000 red corpuscles were counted in the cbmm.

When the anæmia is progressive the body apparently becomes habituated to the diminution in the number of red corpuscles, and it is surprising to find individuals attending to the duties of every-day life with a blood-count of only 2,000,000, or even less. It is not uncommon even to meet with cases of pernicious anæmia in hospitals in which the patients with only 500,000 corpuscles are not obliged to go to bed. Nevertheless it must be admitted that, whenever the number falls beneath this figure, recovery is probably out of the question. A sudden reduction in their number to 1,000,000, moreover, is usually followed by a fatal result.

Very important is the fact that in acute gastritis and usually in chronic gastritis also the number of red corpuscles is not diminished, while in cases of carcinoma a marked oligocythæmia exists. In the severer forms of chronic gastritis a diminution is fairly con-

stant, but rarely so marked as in carcinoma, if we except those cases of gastric anadeny which present the clinical picture of a pernicious anæmia. In ulcer of the stomach normal values are found unless hæmatemesis has recently occurred or unless the disease is associated with profound chlorosis.

Nucleated Red Corpuscles. Two varieties of nucleated red corpuscles may be seen:

1. Normoblasts: These are nucleated red corpuscles of the size of an ordinary erythrocyte, and appear to be identical with those normally found in the bone-marrow of adults. The nucleus of normoblasts, which frequently shows signs of undergoing division, is usually situated centrally, although an eccentric position also is not infrequently observed. These forms are further characterized by the great avidity with which their nuclei take up stains (Plate II., Fig. 2).

Free nuclei, undoubtedly derived from the normoblasts, may also be met with in the blood.

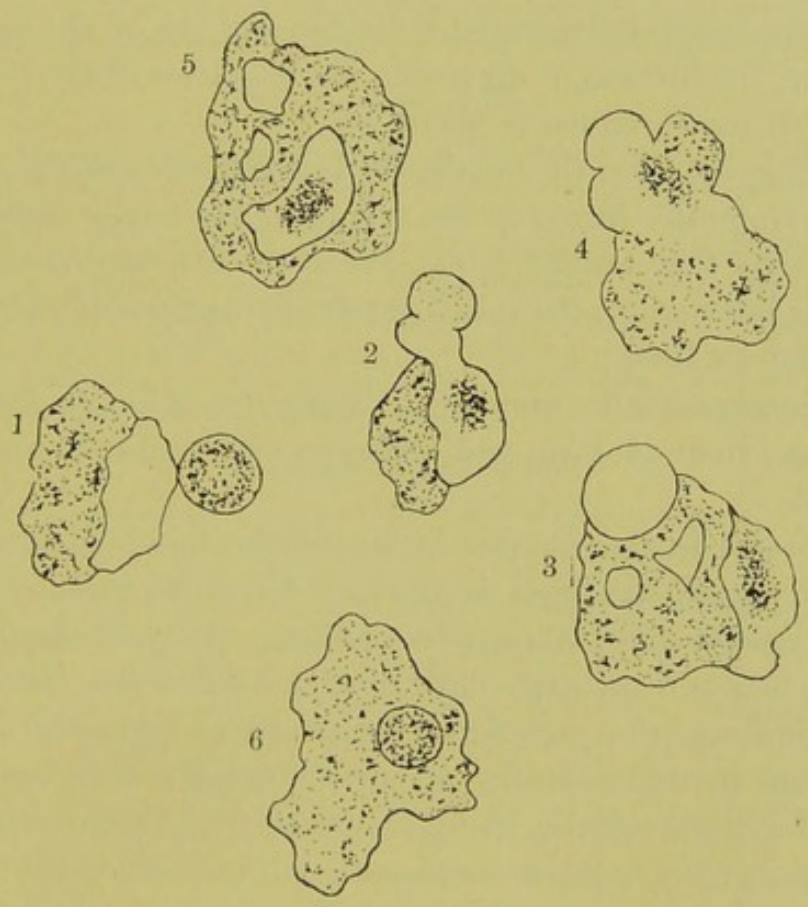
2. Megaloblasts, or gigantoblasts of Ehrlich: These elements are from three to five times as large as a normal erythrocyte, and are provided with a large nucleus, which, according to Ehrlich, never manifests signs of undergoing division, however, and is rarely stained as deeply as the normoblastic nucleus (Plate II., Fig. 2). As the megaloblasts are normally met with only in fœtal bone-marrow, Ehrlich views their presence in the blood of adults as a symptom of degenerative metamorphosis. Their presence in the blood in the absence of normoblasts he furthermore regards as a very grave symptom. Recently, however, Askanazy has reported a case of bothriocephalus anæmia in which megaloblasts in large numbers, but scarcely any normoblasts, could be discovered, and in which the patient recovered completely after the expulsion of sixty-seven parasites. The same observer also noted that the nuclei of megaloblasts may undergo indirect division, and that the nuclei of normoblasts frequently present the picture of karyorhexis. He concludes that a material difference does not exist between normoblasts and megaloblasts, and that the former develop from the latter.

Megaloblasts are especially numerous in pernicious anæmia and leukæmia, while in the so-called secondary anæmias they occur in only small numbers and are at the same time much degenerated. As a rule, nucleated red corpuscles cannot be made out in fresh preparations, and it is generally necessary to stain the blood according to special methods (see p. 66).

The Leucocytes.

The leucocytes, or colorless corpuscles of the blood, as seen in freshly prepared specimens, are roundish or irregularly shaped cells, being mostly larger than the red corpuscles; they are nucleated, and many are distinctly granular in appearance, so much so, in fact, that the nuclei are often entirely hidden from view (Plate II., Fig. 1, *a*). In a carefully prepared specimen some leucocytes will be met with which are endowed with the power of locomotion, creeping over the field of the microscope by throwing out pseudopodia in a manner

FIG. 12.



Phagocytosis.

analogous to that seen in amœbæ. In their general mode of living these motile leucocytes, moreover, closely resemble the latter organisms, and it is most interesting to observe the manner in which these little bodies take up cellular débris, and even obnoxious organisms that may be present in the blood. In malarial blood, for example, in which, as will be shown more particularly later on, certain amœbic parasites are present, one is not infrequently able to

observe leucocytes approach these bodies and take them up by flowing around them, as it were (Fig. 12). Metschnikoff even regards this function of the leucocytes as their most important one. Those leucocytes which possess this power of removing foreign matter from the blood have been termed phagocytes by this observer; and, according to his views, the outcome of a bacterial invasion of the body, figuratively speaking, will depend upon the superiority of the organisms engaged in warfare. The term *phagocytosis* has been applied to the destruction of bacteria by leucocytes.

Variations in the Number of the Leucocytes. While the number of red corpuscles is subject to very slight variations under physiologic conditions, that of the leucocytes varies within fairly wide limits, being influenced by the age and sex of the individual, pregnancy, the process of digestion, the character of the bloodvessel from which the specimen is taken, etc.

According to Osler, the number of leucocytes per cbmm. of blood, obtained from the finger or the ear, normally varies between 5000 and 7000, so that taking 5,000,000 as the average number of red corpuscles per cbmm., the ratio between the two would vary between 1 : 714 and 1 : 1000.

In women a smaller number of leucocytes is found, according to Moleschott, than in men, while Hayem was unable to observe any difference.

An increase in the number of leucocytes, to which condition the term *leucocytosis* has been applied by Virchow, is met with under both physiologic and pathologic conditions. As Goldscheider rightly suggests, it would be better, however, to restrict the term leucocytosis to indicate the number of leucocytes in a general way, while an increase in their number should be spoken of as *hyperleucocytosis*, and a diminution in their number as *hypoleucocytosis*.

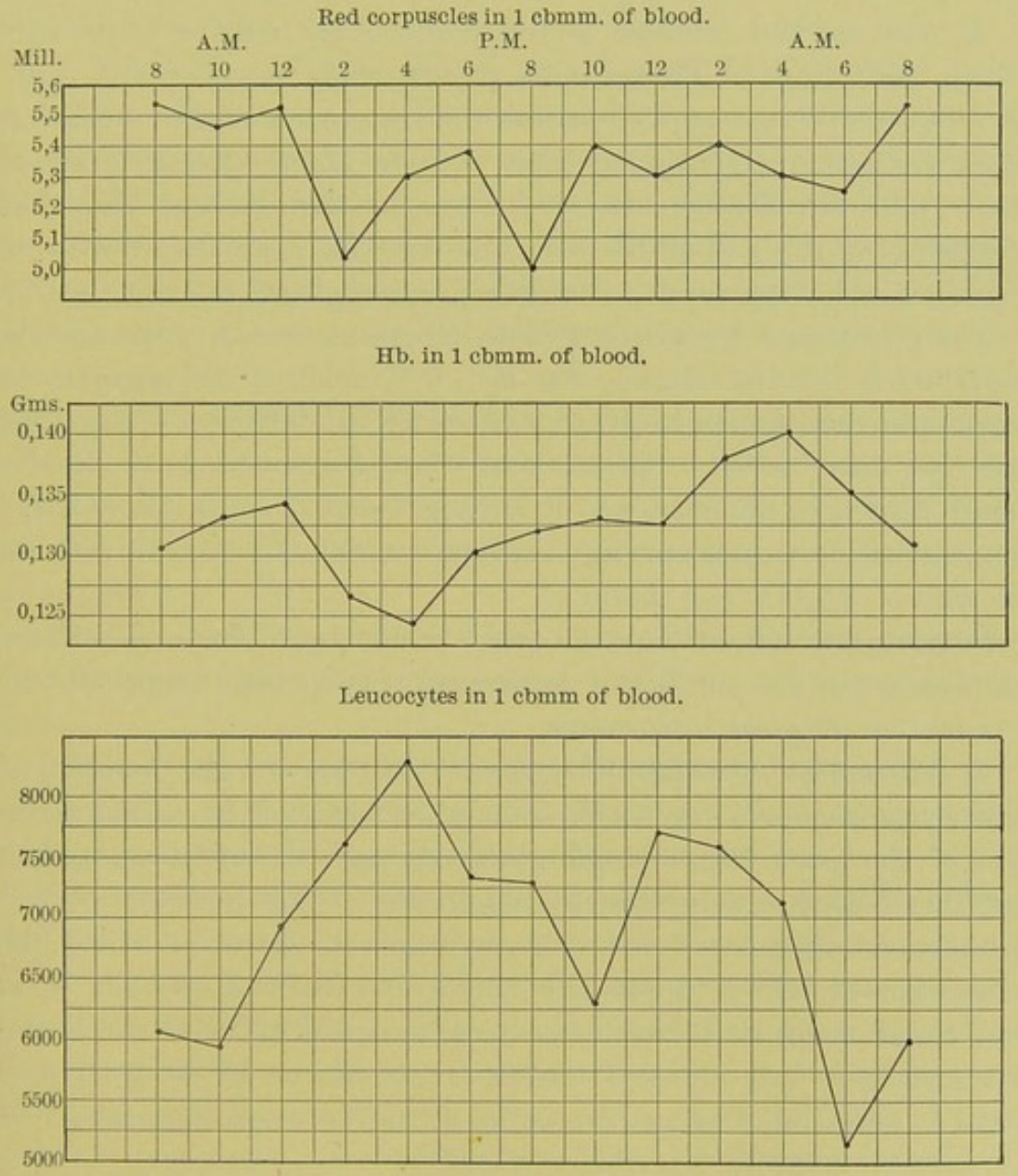
Physiologic Hyperleucocytosis. An increase in the number of leucocytes occurring in health is noted especially in children, during the process of digestion, in pregnancy, following the use of cold baths, etc.

According to Hayem, about 18,000 leucocytes are found in the blood of infants during the first eighty hours of life, 8000 during the first month, while in children aged from several months up to the fourth year 6000, and in adults and old age only 5000 are counted on an average, according to the same observer.

An idea of the marked increase occurring during the process of

digestion, constituting the physiologic "digestive leucocytosis" of Virchow, may be formed from the accompanying diagram, to which two charts have been added, illustrating the diurnal variations in the amount of hæmoglobin and the number of red corpuscles (Fig. 13).

FIG. 13.



Showing the diurnal variations in the number of red corpuscles, the amount of hæmoglobin, and the number of leucocytes. (Taken from REINERT.)

This form of hyperleucocytosis appears to be more marked in health than in disease, and notably in gastro-intestinal diseases. Schneyer was thus able to note the absence of a digestive hyperleucocytosis in every one of his eighteen cases of carcinoma of the stomach, and records five similar cases described by Müller. In

almost all cases of ulcer of the stomach and of benign stenoses of the pylorus, on the other hand, the usual increase in the number of leucocytes could be established. Should further investigations confirm these results, it is apparent that an examination of the blood in this direction would be of the greatest importance in the differential diagnosis between carcinoma and ulcer of the stomach.

A very marked increase is frequently noted after a cold bath, which, according to Thayer, may even amount to 284.6 per cent. In his own person on one occasion the leucocytes, which numbered 3250 per cbmm. before the bath, rose to 12,500 twenty minutes later. As the observer reports, however, that he was blue and shivering at the end of his bath, the stimulus given can hardly be regarded as having produced only a physiologic effect.

The physiologic hyperleucocytosis observed during pregnancy is particularly marked during the last five months, and appears to occur quite constantly in primiparæ, while in multiparæ exceptions are frequently noted. In an analysis of thirty-one cases Rieder could thus note the existence of a hyperleucocytosis in twenty, the number of leucocytes varying between 10,000 and 16,000, with an average of 13,000 per cbmm.

Pathologic Hyperleucocytosis. Under pathologic conditions an increase in the number of leucocytes is frequently observed and is a matter of great importance.

A leukæmia, in which the greatest increase in the number of leucocytes is noted, may thus be diagnosed at once by an enumeration of the leucocytes, a single glance through the microscope often being sufficient to determine the diagnosis. This increase is most pronounced in cases of the lieno-myelogenous form, in which the proportion of white to red cells may be 1 : 10, 1 : 5, or even 1 : 1; and Osler states that cases have been recorded in which the leucocytes actually outnumbered the red corpuscles. In the lymphatic form of leukæmia the increase is not so marked, and the proportion of 1 : 10 but rarely exceeded.

Aside from leukæmia a hyperleucocytosis is observed in all acute inflammatory diseases, and it may be said that the increase in the number of the leucocytes is directly proportionate to the degree of the local reaction, so that it is possible to predict in a given case whether or not a hyperleucocytosis will occur. In typhoid fever, for example, in which the local reaction is slight, no hyperleucocytosis, or one of only mild degree, will be observed, while with a compli-

cating pneumonia or pleurisy, in which the local reaction is well pronounced, a correspondingly marked hyperleucocytosis will be found. This is most important, as complications in this disease may thus often be discovered by an examination of the blood, and in conjunction with the clinical symptoms a correct, or, at least, a probable, diagnosis may often be reached, which would have been out of the question otherwise.

To cite only one example: A convalescent from typhoid fever suddenly complained of pains in the abdomen, particularly marked in the right iliac fossa, which increased within a few hours to such a degree that full doses of morphine and chloroform inhalations became imperative. Four hours later the patient was comatose, with a pulse ranging from 160 to 200 and a temperature of 105.5° F. At this stage an examination of the blood showed an approximately normal number of leucocytes. Within the next twenty-four hours icterus, accompanied by the passage of bile-colored urine and clay-colored feces, developed, and the next day a biliary calculus was found in the stool. The diagnosis of cholelithiasis was based upon the result of the blood-examination in conjunction with the clinical symptoms.

An osteomyelitis may be similarly recognized at a time when the clinical symptoms in themselves alone would not warrant the diagnosis.

In pneumonia the degree of hyperleucocytosis may serve as a direct index of the amount of lung-tissue involved, disappearing during the crisis or even a few hours before it sets in.

The hyperleucocytosis here is quite constant, excepting, according to Tschistovitch and v. Jaksch, certain cases in which it is absent, or but slightly marked, and which, according to the same authorities, are invariably fatal. The results reached at the Johns Hopkins Hospital, however, do not appear to bear out the correctness of this view, as fatal cases were observed in which 45,000 and even 114,000 leucocytes were counted per cbmm. Further investigations in this direction are urgently needed, and, should the general results obtained by Tschistovitch and v. Jaksch be confirmed, a blood-examination in pneumonia would be of the greatest prognostic value. As in pneumonia, so also in erysipelas, the hyperleucocytosis terminates by crisis.

In phthisis hyperleucocytosis apparently only occurs when the disease has led to the formation of cavities.

A cachectic hyperleucocytosis, often of great intensity, is noted in cases of malignant disease; but it is still an open question whether or not this is dependent upon the local reaction in the neighborhood of the growth. To judge from personal observations, the existence of a hyperleucocytosis in the differential diagnosis between malignant and benign diseases of the stomach invariably points to the former.

General Differentiation of the Various Forms of Leucocytes. Upon ordinary microscopic examination three varieties of leucocytes can be distinguished. (Plate II., Fig. 1, *a*.) Some are round, smaller than a red corpuscle, and provided with a large, round nucleus, which is surrounded by a very narrow rim of non-granular protoplasm. Others are met with which are likewise round, of the size of an ordinary red corpuscle, the large single nucleus being surrounded by a narrow zone of non-granular protoplasm. The large cells, the bodies of which are filled with granular material, often hiding the nucleus from sight, are representatives of the third variety.

Upon further examination differences may also be demonstrated in the character of the granulations. Some leucocytes will thus be observed in which these are very fine, giving the entire body of the cell a cloudy appearance, and usually obscuring the nucleus, which may be brought into view, however, together with its nucleoli, by treating the preparation with a drop or two of a 1 per cent. solution of acetic acid. On the other hand, very coarse granulations may be observed in certain leucocytes, while still others, as already pointed out, are apparently non-granular.

Within late years Ehrlich has studied these various granulations in their behavior toward aniline-dyes, the results obtained being most interesting, and, as will be shown, of decided value from a clinical standpoint. He was able to demonstrate the existence of different chemical affinities between these minute particles of protoplasm and the reagents employed. Some are thus only colored by acid stains, others again only by those of a basic nature, while still others are stained only by neutral stains.

The Aniline-stains. Ehrlich divides the acid stains derived from coal-tar into two large groups: *i. e.*, into stains which will color the granulations (see below) even when employed in concentrated solutions of glycerine, and into those which can only be employed in aqueous solutions.

The first group contains:

(1) The highly acid bodies belonging to the fluorescin series, viz., eosin, methyl-eosin, coccin, pyrosin J and R; (2) the highly acid nitro-bodies, such as aurantia; (3) the two groups of sulpho-acids—*i. e.*, indulin, bengalin, and nigrosin, on the one hand, and the azo-stains, tropæolin, Bordeaux, and Ponceau, on the other.

The second group contains:

(1) Fluorescin and chrysolin; (2) ammonium picrate and naphthylamin-yellow; (3) orange and true yellow.

Representatives of the basic stains are: fuchsin (rosanilin), the methyl derivatives of rosanilin, viz., methyl-violet, methyl-green, etc., the phenyl derivatives of rosanilin (triphenyl-rosanilin), roso-naphthylamin, cyanin, safranin, etc.

As an example of a neutral stain there may be mentioned the picrate of rosanilin.

Differentiation of the Leucocytes according to their Behavior toward Aniline-stains. According to their behavior toward these various pigments, Ehrlich has divided the granular leucocytes found in the blood into eosinophiles, basophiles, and neutrophiles. By the aid of his methods the following forms of leucocytes, the study of which is especially important in the differential diagnosis of leukæmia, may be made out in the blood. (Plate II., Fig. 2.)

1. Small mononuclear leucocytes. These are mostly smaller than the red corpuscles or of equal size. They are devoid of granular matter, each cell being provided with a large, deeply-staining nucleus, surrounded by a narrow rim of non-granular protoplasm. As they appear to be formed, to a large extent at least, in the lymphatic glands, they are also spoken of as *lymphogenic leucocytes* or *lymphocytes*.

The increase in the number of leucocytes observed in the lymphatic form of leukæmia occurs in this variety only, while the large mononuclear elements, as well as the polynuclear leucocytes, are at the same time relatively diminished to a considerable extent. In the lieno-myelogenous form, on the other hand, the lymphocytes are relatively diminished. A relative increase in the number of lymphocytes is observed in healthy infants, in various diseases of infancy, in chlorosis, pernicious anæmia, secondary syphilis, in the late stages of typhoid fever, in certain cases of Basedow's disease, hæmophilia, goitre, etc.

2. Large mononuclear leucocytes. These are larger than the red

corpuscles, their nuclei oval or elliptical in form, and surrounded with a somewhat wider zone of protoplasm, which, as in the first variety, is apparently non-granular. They probably represent a later stage in the development of the small mononuclear form. Some writers, however, still maintain that they are formed in the spleen and in the bone-marrow. They occur in increased numbers, in cases of chronic malaria, in measles, at the end of scarlet fever, etc.

3. Cells which are of the same size as those belonging to the second variety, or a little smaller, and filled with very fine neutrophilic granules, the ε-granulations of Ehrlich. The nucleus is a long body, which is twisted upon itself into irregular forms, often presenting a broken appearance, and conveying the impression as though several nuclei were present. Such leucocytes are hence spoken of as *polynuclear neutrophilic leucocytes*. As Ehrlich has suggested, the polynuclear appearance, however, is probably referable to post-mortem changes, the condition of the nuclei being in reality polymorphous. In accord with this view they have hence also been termed *polymorphonuclear leucocytes*. They also are supposed to represent a later stage in the development of the small and large mononuclear cells. While basophilic and eosinophilic granules have been found in all animals examined in this direction, it is interesting to note that neutrophilic granules occur only in man, an observation which may be of considerable importance in the medico-legal examination of the blood. The ordinary forms of hyperleucocytosis are referable to an increase in the number of these elements. All pus-corpuscles, moreover, according to Ehrlich, belong to this class.

4. Cells are encountered in every specimen of blood, which appear to be *transition forms* between the second and third varieties. These are mononuclear, the nuclei, however, presenting a constricted appearance, indicating that they are beginning to become polymorphous. As a general rule, no granulations are found, but exceptionally they do occur, when they are neutrophilic in character.

5. Cells which are of the size of the third variety, provided with a polymorphous nucleus, and large, ovoid or roundish, highly refractive, fat-like granulations, the α-granulations of Ehrlich. These only take up acid stains, such as eosin, and the leucocytes are therefore spoken of as *eosinophilic leucocytes*. According to Ehrlich, they are derived from the bone-marrow only, and have hence also

been termed *myelogenic leucocytes*. There appears to be some doubt, however, as to the correctness of this view, as marked differences can be shown to exist between the eosinophilic leucocytes that are found in the circulating blood and those encountered in the bone-marrow. The latter are essentially myelocytes (see below), viz., mononuclear leucocytes, in which eosinophilic granules are found. Their presence in the blood, according to recent researches, appears to be confined to leukæmia. Formerly an increase in the number of the ordinary eosinophilic leucocytes, which possibly represent the senile stage in the development of the small mononuclear variety, was regarded as almost pathognomonic of the lieno-myelogenous form of leukæmia. While an increase, both relative and absolute, in their number is observed in most cases of this disease, it does not occur invariably, and careful examinations have shown, moreover, that a similar increase may be noted in other diseases, and notably in true bronchial asthma, in certain diseases of the bones, the skin, the nervous system, in trichinosis, and at times even in health. In diminished numbers they are found during the process of digestion, in pneumonia, typhoid fever, diphtheria, influenza, after castration, etc. The phagocytes of the blood are essentially of this variety.

6. Basophilic leucocytes are accidentally met with in the blood in various conditions, and especially in leukæmia, but are as yet of no diagnostic significance. The granulations, the γ and δ granulations of Ehrlich, appear to be the same as those observed in the so-called Mastzellen, found in connective tissue especially; the same term has hence been applied to this particular variety.

Of late Neusser has drawn attention to the fact that basophilic granules are not infrequently seen arranged about the nuclei of the mononuclear and polynuclear leucocytes, and he regards their presence as characteristic of the so-called uric acid diathesis. As tubercular disease, moreover, is usually not seen in such cases, Neusser believes that their presence in cases of phthisis may be regarded as a favorable symptom. Futcher, on the other hand, was unable to confirm Neusser's results. Further researches, however, are necessary before definite conclusions can be reached.

7. Still another form is found in the blood under pathologic conditions, notably in leukæmia, to which the term *myelocytes* has been applied, as they appear to originate only in the marrow of bone. These cells apparently represent an arrest or perverted form of

development, being essentially large mononuclear leucocytes, the bodies of which are filled with neutrophilic granules. At times they acquire a very large size, exceeding that of all other elements occurring in the blood, but never become amœboid.

The presence of large numbers of this variety, which is rarely seen in the blood under normal conditions and particularly when associated with an increased number of the ordinary leucocytes and the presence of so-called eosinophilic myelocytes, may be regarded as highly suggestive of the lieno-myelogenous form of leukæmia, while they are usually absent in the lymphatic form.

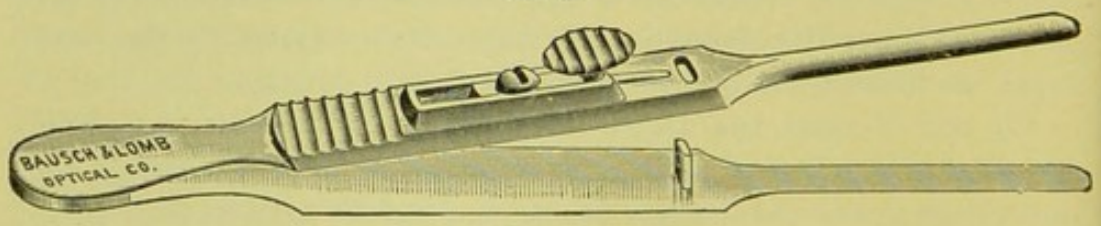
8. Certain polynuclear leucocytes may also be encountered in the blood under pathologic conditions, in which no granulations can be demonstrated with Ehrlich's triple stain. Nothing is known of their significance.

The leucocytes normally present in the blood occur in definite proportions, which are quite constant, as shown in the following table:

Polynuclear neutrophilic leucocytes	60–75	per cent.
Lymphocytes	20–30	"
Large mononuclear leucocytes and transition-forms	6	"
Eosinophilic leucocytes	2–4	"
Mastzellen, less than	1.0	"

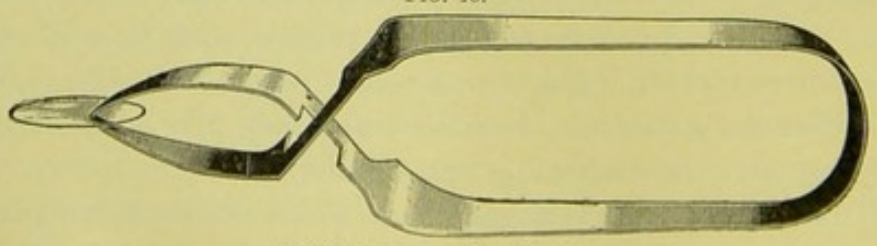
The Drying and Staining of Blood. In order to obtain specimens of value cover-slips of the finest grade, carefully cleansed with

FIG. 14.



Ehrlich's cover-glass forceps.

FIG. 15.



Linsley's cover-glass forceps.

absolute alcohol or with dilute nitric acid, are indispensable. Care should also be taken to *handle the cover-glasses with forceps only*, as

the warmth of the fingers in itself is sufficient to cause post-mortem changes in the red corpuscles. For this purpose specially constructed forceps, such as those suggested by Ehrlich, will be found of great assistance. (Figs. 14 and 15.) The tip of a finger, or preferably the lobe of the ear, should be cleansed with soap and water, alcohol and ether. A small drop of blood is then received upon a cover-glass and spread out in such a manner that the layer shall not be thicker than the diameter of a red corpuscle. To this end it is most convenient to cover the drop of blood with a second cover-glass, pressure being avoided, and to draw the glasses apart in a horizontal direction. The same result may also be reached by spreading out the blood with the edge of a second cover-slip, a fine camel's-hair brush, or a specially devised mica spatula. This step in the preparation of dried specimens is the most difficult, and requires a certain amount of experience as well as care.

A number of specimens are thus prepared, and when dried at an ordinary temperature will keep almost indefinitely.

If it is desired to make an early examination, the specimens are further fixed by exposure to a temperature of from 110°–115° C. for from 5–30 minutes. Immersion in absolute alcohol, or a mixture of equal parts of absolute alcohol and ether for half an hour, also answers the purpose. Very convenient is the use of formol, a mixture of 40 per cent. formic aldehyde in methyl alcohol and water. One part of formol is diluted with nine times its volume of water, and one part of the mixture thus obtained with nine times its volume of alcohol. The immersion of the specimen in this solution for but one minute is said to furnish admirable results. The continued exposure of the blood to a temperature of from 100°–120° C. for from one to two hours can thus usually be dispensed with, although it may be advantageously employed in special cases. For the purpose of fixing specimens by heat the use of a small coal-oil stove, upon which a copper plate measuring 40 x 10 cm. is placed, will be found most convenient. Upon the plate the line corresponding to the desired temperature is ascertained by means of a series of drops of water extending from the middle toward either end, and noting the line at which bubbles will appear in the water. The specimens are then placed just inside of this line. When once properly regulated the apparatus, which may very advantageously be placed in a box so as to guard against currents of air, will be found to furnish a fairly constant tempera-

ture. A drying-oven may, of course, be used for the same purpose.

When fixed according to one of the methods indicated, the dried specimen is ready to be stained. For this purpose a number of solutions may be employed, the selection of the special mixture depending upon the particular points to be elicited.

Staining with Eosin. A 0.1–0.5 per cent. aqueous solution or a 0.25–0.5 per cent. alcoholic solution is used, upon which the dried specimen is allowed to float for from ten to twenty minutes if the former is used, while one-half or one minute only is necessary in the case of the latter. It is then rinsed with water, dried between layers of filter-paper, and mounted in xylol-balsam.

The red corpuscles are stained a bright red, the protoplasm of the leucocytes a faint red, while the eosinophilic granules are deeply colored.

Staining with Ehrlich's Tri-glycerine Mixture. This is composed of 2 grammes each of eosin, aurantia, and nigrosin in 30 grammes of glycerine. The specimens are allowed to remain upon the stain for from sixteen to twenty-four hours, when they are rinsed in water, dried, and mounted as described.

The red corpuscles are colored orange, the bodies of the leucocytes a dirty gray with dark nuclei, and the eosinophilic granules a bright red.

Staining with Ehrlich's Hæmatoxylin-eosin. The solution is prepared by dissolving 4–5 grammes of hæmatoxylin in a mixture of 100 grammes each of distilled water, alcohol, and glycerine. To this solution 20 grammes of glacial acetic acid and an excess of alum are added. After exposure to the sun for four to six weeks about 1 per cent. of eosin is finally added. The specimen is left in the stain exposed to the sun in a covered beaker for twenty-four hours, when it is rinsed in water, dried, and mounted.

The red corpuscles are colored a bright red, the nuclei of the normoblasts and megaloblasts a deep black, the bodies of the leucocytes a light lilac, their nuclei a dark lilac, the eosinophilic granules a bright red, while the bodies of the lymphocytes are scarcely stained at all, and their nuclei appear only a shade lighter than those of the nucleated red corpuscles.

Staining with Ehrlich's Tri-acid Stain. This is the differential stain mostly used at the Johns Hopkins Hospital, and one which usually furnishes excellent results. It has the advantage also that an exposure of the specimen to the stain for six to eight

minutes only is necessary. Its preparation requires some care, and it is important, furthermore, that the mixture should stand for one to two weeks before being used. Saturated aqueous solutions of acid fuchsin, orange G, and methyl-green are first prepared and allowed to stand until clear, when they are gradually mixed in the proportions indicated below:

Fuchsin solution	9 c.c.
Distilled water	6 "
Orange solution	18 "
Methyl-green solution	20 "
Alcohol (94 per cent.)	15 "
Distilled water	30 "
Glycerine	5 "

After staining for from six to eight minutes the specimen is rinsed in water, dried, and mounted.

The nuclei of the leucocytes are stained a greenish-blue, those of the red corpuscles nearly black, the red corpuscles orange, the eosinophilic granules red, and the neutrophilic granules a violet or a lilac color. (Plate II., Fig. 2.)

Staining with Aronsohn and Philips' Modified Tri-acid Stain. Saturated aqueous solutions of orange G, acid rubin, and methyl-green are prepared, and the various ingredients mixed in the following proportions:

Orange solution	55 c.c.
Acid rubin solution	50 "
Distilled water	100 "
Alcohol	50 "

To this mixture are added :

Methyl-green solution	65 c.c.
Distilled water	50 "
Alcohol	12 "

The mixture should stand for from one to two weeks before being used.

A drop of the solution added to a Petri-dishful of water is employed for staining-purposes, an exposure of the specimen for twenty-four hours being required. The specimen is then rinsed off in water, absolute alcohol, cleared in origanum oil, and mounted.

The various elements of the blood are colored as with Ehrlich's stain.

Staining with Chenzinsky-Plehn's Mixture. This consists of 40 grammes of a concentrated alcoholic solution of methylene-

blue, 20 grammes of a 0.5 per cent. solution of eosin in 70 per cent. alcohol, and 40 grammes of distilled water. The specimen is stained for twenty-four hours.

The red corpuscles assume the color of eosin, while the eosinophilic granules are bright red and the nuclei of the leucocytes blue.

Staining with Ehrlich's Neutral Mixture. This consists of five volumes of a saturated aqueous solution of acid fuchsin, to which one volume of a concentrated aqueous solution of methylene-blue is added slowly, while shaking. The mixture is treated with five volumes of distilled water and filtered after having stood for several days. The specimens are stained for from five to twenty minutes.

The red corpuscles present the color of fuchsin, their nuclei as well as those of the leucocytes are black or a light lilac, the eosinophilic granules red, and the neutrophilic granules violet.

Special Staining of Basophilic Leucocytes. The staining-fluid consists of 100 c.c. of distilled water, to which 50 c.c. of a saturated alcoholic (absolute) solution of dahlia are added. Upon clearing, 10–12.5 c.c. of glacial acetic acid are added. The specimen is stained for from five to ten minutes. A saturated aqueous solution of methylene-blue may be employed for the same purpose and in the same manner.

With the exception of bacteria, only the basophilic leucocytes are stained (red), while pus-corpuscles are but faintly tinged.

In order to stain the perinuclear basophilic granules of Neusser the following modified mixture of Ehrlich should be employed:

Saturated aqueous solution of acid fuchsin	50 c.c.
Saturated aqueous solution of orange G.	70 "
Saturated aqueous solution of methyl-green	80 "
Distilled water	150 "
Absolute alcohol	80 "
Glycerine	20 "

A differential enumeration of the various forms of leucocytes can only be carried out in stained specimens, Ehrlich's tri-acid stain being the most useful for this purpose. From 1000–1200 leucocytes at least should be counted in order to obtain reliable results. The use of Zeiss's net-micrometer will be found of great value.

As will be described, moreover, the actual number of leucocytes contained in one cbmm. of blood may be readily ascertained in an indirect manner by counting the number of leucocytes and red corpuscles in stained specimens (see page 75).

The Plaques.

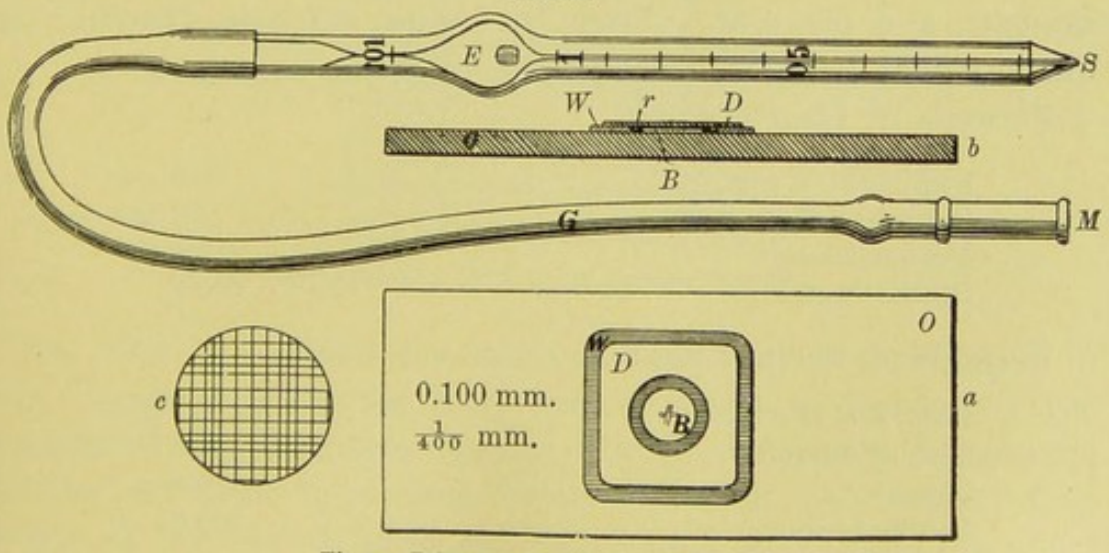
In addition to the leucocytes and erythrocytes large numbers of small, roundish elements are encountered in the blood, which are free from coloring-matter and may be frequently observed collected into small heaps, resembling bunches of grapes. These are the blood-plates or plaques of Bizzozero. According to Hayem, they represent ordinary red corpuscles in an early stage of development, and have hence been termed *hæmatoblasts*. This opinion, however, is not shared by many hæmatologists.

According to Osler, they number from 200,000 to 500,000 per cbmm. under normal conditions, and are said by Hayem to occur in greatly diminished numbers in the blood in pernicious anæmia. This observation, however, lacks confirmation. In order to demonstrate their presence the drop of blood should at once be mixed with Hayem's fluid (see p. 72).

The Enumeration of the Corpuscles of the Blood by the Method of Thoma-Zeiss.

Of the various instruments employed for the enumeration of blood-corpuscles, that of Thoma-Zeiss appears to be the most satisfactory. (Fig. 16.)

FIG. 16.



Thoma-Zeiss blood-counting apparatus.

It consists of a capillary pipette (*S*) having a bulb in its upper third, the lower end being graduated in parts numbered from 0.1 to 1, while above the bulb a mark bearing the number 101 is

placed. With this goes a counting-chamber (*B*) measuring exactly 0.1 mm. in depth, the floor of which is ruled into sets of 16 small squares, each small square underlying a space of $\frac{1}{4000}$ cbmm.

Enumeration of the Red Corpuscles. In order to count the red corpuscles with this instrument the tip of a finger, or, better still, the lobe of the ear, is punctured with a sharp-pointed scalpel, after having been carefully cleansed with soap and water, alcohol, and finally with ether. The exuding blood is drawn into the capillary tube to a given mark, generally to 1 or 0.5, according to the degree of dilution desired, care being taken that no pressure is exerted upon the finger and that the tip of the instrument comes in contact with the blood only. The point of the tube is then rapidly and carefully wiped, and the blood diluted, as a rule, with a 3 per cent. solution of common salt, which is drawn into the pipette until the 101 mark is reached.

Toison's fluid is still more convenient as a diluent, as the leucocytes are stained by the methyl-violet, and thus rendered more easily visible. Its composition is the following:

Distilled water	160 parts.
Glycerine	30 "
Sodium sulphate	8 "
Sodium chloride	1 part.
Methyl-violet	0.025 part.

Other solutions, such as a 15–20 per cent. solution of magnesium sulphate, a 5 per cent. solution of sodium sulphate, Hayem's or Pacini's fluid, may also be employed for the same purpose.

Formula of Hayem's fluid:

Bichloride of mercury	0.5 grm.
Sodium sulphate	5.0 grms.
Sodium chloride	2.0 "
Distilled water	200.0 "

Formula of Pacini's fluid:

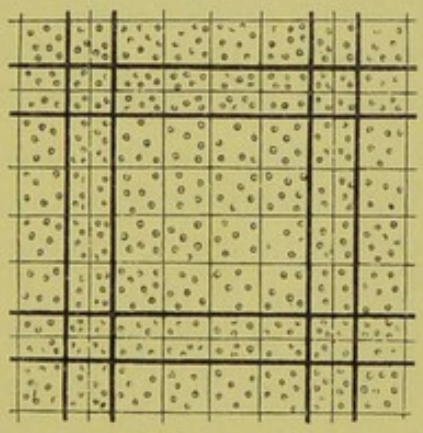
Bichloride of mercury	2.0 grms.
Sodium chloride	4.0 "
Glycerine	26.0 "
Distilled water	226.0 "

The contents of the bulb are now thoroughly mixed by shaking, in which the glass bead (*E*) contained in the bulb aids very materially. The contents of the capillary tube are then cautiously expelled, as this practically contains only the diluting-fluid; a

drop of the mixture is placed in the counting-chamber, and the cover-slip (*r*) adjusted, bubbles of air being carefully excluded. When properly prepared, Newton's colored rings should be seen at the margin of the drop. After allowing the corpuscles to settle —from three to five minutes are generally sufficient—they are counted. At least one whole field, or, if special accuracy be required, two whole fields, should be gone over—*i. e.*, 200 or 400 small squares, respectively, when counting the red, and at least four whole fields when counting the white.

It is convenient to count the red corpuscles in sets of four small squares, lying side by side in a horizontal direction, note being taken of every corpuscle that touches the boundary-lines of the large squares, no matter whether the body of the cell lies inside or outside of these lines. It will be noted that every large square is separated from its neighbor, both horizontally and vertically, by a row of small squares traversed by a mesially placed line, which serves as a guide to the next large square. (Fig. 17.) As a general rule, it will be found most convenient to ignore these intermediary squares, account being taken only of the large ones.

FIG. 17.



Appearance of blood in the Thoma-Zeiss cell.

In order to calculate the number of red corpuscles contained in one cbmm. of blood the total number noted is divided by the number of small squares counted, the result giving the average number contained in one small square—*i. e.*, in $\frac{1}{400}$ cbmm. One cbmm. of the diluted blood will then contain 4000 times this number, and one cbmm. of undiluted blood the product of this figure and the degree of the dilution.

Example: Supposing that 1200 red corpuscles were counted in 400 small squares, the average number contained in one—*i. e.*, in

$\frac{1}{4000}$ cbmm. of diluted blood—would be 3, corresponding to 12,000 corpuscles for each cbmm.; supposing, further, that the blood was diluted 200 times, there would be 2,400,000 in one cbmm. of the undiluted blood.

Enumeration of the White Corpuscles. With this instrument the leucocytes, when present in increased numbers, may also be counted, at least four whole fields, as indicated above, being taken into account.

With an approximately normal number of leucocytes, however, it is necessary to resort to special pipettes, which are constructed so as to permit of obtaining a mixture of 1 : 10 or 1 : 20. With the diluting-fluids mentioned above it would be impossible, however, to count the leucocytes in a mixture of this proportion, as a large number would be concealed by the red corpuscles. A 0.3–0.5 per cent. solution of acetic acid is therefore used, which destroys the red corpuscles and renders the nuclei of the white more distinct. In the absence of a special instrument, an ordinary 1 cbmm. pipette accurately graduated in tenths may be employed. 0.9 c.c. of the acetic acid solution is placed in a watch-crystal and there mixed with 0.1 c.c. of blood, when the counting-chamber is filled and covered as described. In order to obtain greater accuracy the entire field of the microscope is now counted, a lower power being employed with which the rulings are just visible. The cubic contents of the field are now determined according to the formula $Q = \pi r^2 \times 0.1$. Q represents the cubic contents to be determined; r, the radius, which is readily ascertained by noting the number of vertical lines which cross the field, bearing in mind that the distance between two of these is equivalent to $\frac{1}{20}$ mm. (the area of each small square being $\frac{1}{400}$ mm.), and dividing the transverse distance by 2; the value, π, is constant, 3.1416; 0.1 represents the depth of the chamber.

If n represents the number of white corpuscles contained in the field, the cubic contents of which are Q, the number of corpuscles, N, contained in one cbmm. of the diluted blood is ascertained according to the equation:

$$Q : n :: 1 : N \text{ and } N = \frac{n}{Q}.$$

As the blood has been diluted ten times, the value of N for the non-diluted blood will be $\frac{10.n}{f.Q.}$, where n represents the total number of leucocytes and f the number of fields counted.

Example: Supposing the number of leucocytes found in 50 fields to have been 600, and the cubic contents of each field 0.03925 cbmm., the total number of leucocytes contained in one cbmm. of undiluted blood, according to the equation:

$$N = \frac{10.n}{f.Q} = \frac{10 \times 600}{50 \times 0.03925} \text{ would be } 3057.$$

Special care should be taken to keep the pipette in clean condition. After use it should be rinsed with (1) the diluting-fluid, (2) distilled water, (3) absolute alcohol, and (4) ether. If dust or coagulated blood adhere to the pipette, it should be removed by repeated rinsings with strong acids or alkalies, assisted if necessary by a bristle.

Indirect Enumeration of the Leucocytes.

The number of leucocytes may also be ascertained in an indirect manner by accurately counting the number of red corpuscles and leucocytes in dried and stained specimens with a Zeiss net-micrometer, the ratio between the two varieties being thus ascertained. With the Thoma-Zeiss apparatus the number of red corpuscles contained in one cbmm. of blood is then determined, when the corresponding number of leucocytes is found according to the equation:

$$l : r :: L : R, \text{ and } L = \frac{lR}{r} = 7142,$$

where l and r represent the number of leucocytes and erythrocytes, respectively, counted in the dried specimens, and where L indicates the unknown number of leucocytes and R the number of red corpuscles contained in one cbmm. of blood, as determined with the Thoma-Zeiss instrument.

Example: Supposing that 700 red corpuscles and only one leucocyte were counted in the dried specimen, and that an estimation of the erythrocytes with the Zeiss apparatus indicated the presence of 5,000,000 in one cbmm. of blood, the corresponding number of leucocytes would be 7142, as is apparent from the calculation:

$$L = \frac{lR}{r} = \frac{1.5000000}{700} = 7142.$$

Notwithstanding the apparent simplicity of the process of blood-counting, considerable experience is required in order to obtain

results that are free from unavoidable errors. In using the Thoma-Zeiss apparatus errors of more than 2–3 per cent. should not occur.

The Hæmatokrit.

Within late years the centrifugal machine has also been applied to blood-counting, and it may be safely asserted that should the

FIG. 18.

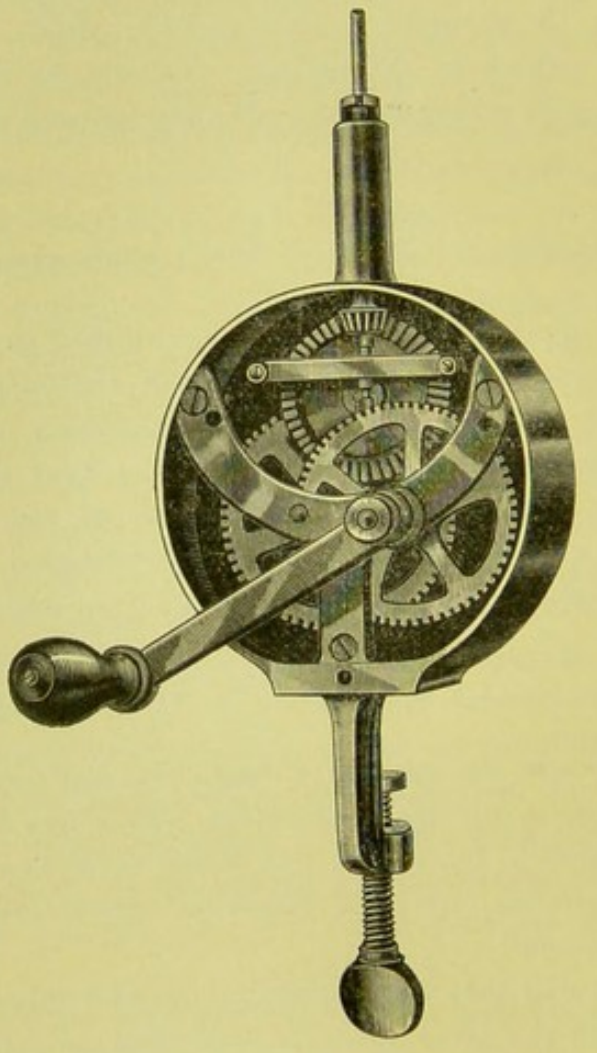
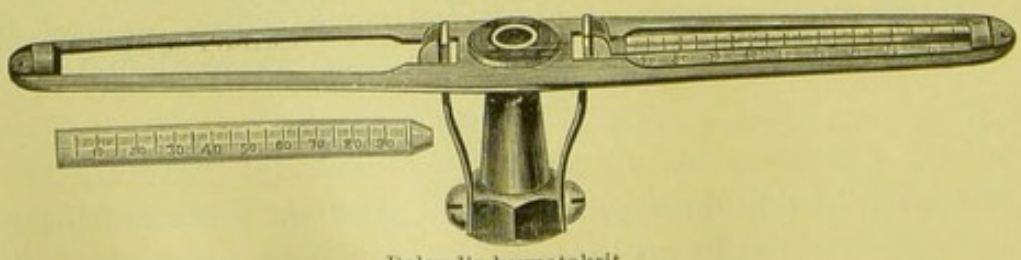


FIG. 19.



Daland's hæmatokrit.

claims set forth for the hæmatokrit, as the instrument is termed, be borne out by actual experience, the use of cytometers, which is both tedious and fatiguing, will soon be abandoned.

Daland's latest modification of this instrument, originally devised by Hedin, is represented in the accompanying illustrations (Figs. 18, 19, 20, 21), and can be strongly recommended to both hospital

FIG. 20.

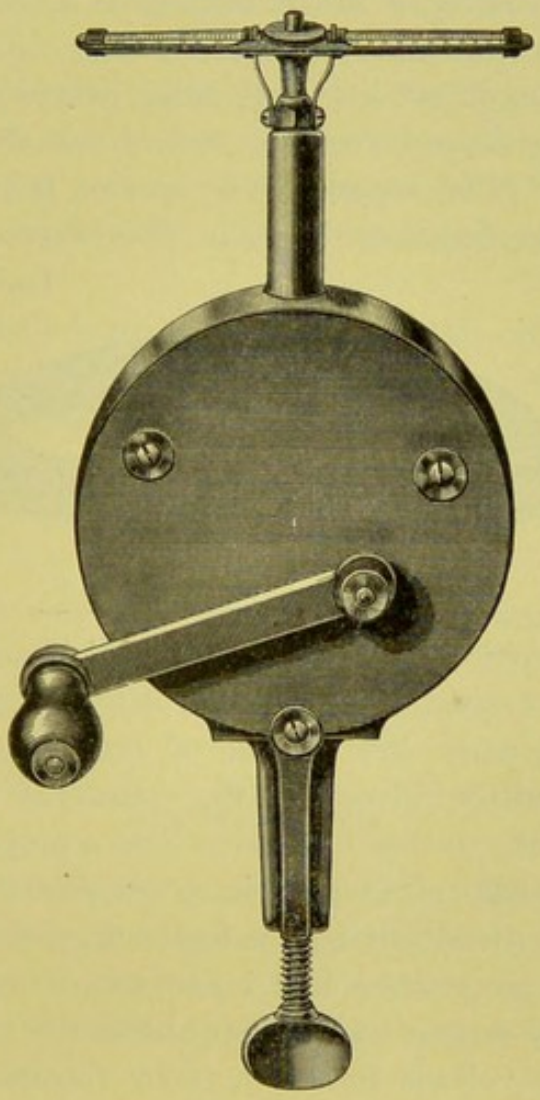
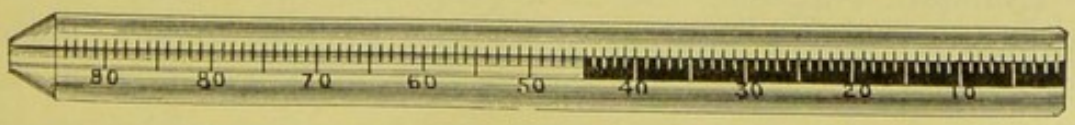


FIG. 21.



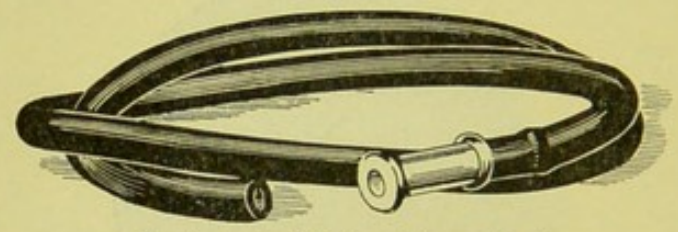
Daland's hæmatokrit.

physicians and those engaged in general practice. It consists essentially of a metallic frame (Fig. 19), supported upon a spindle which can be rotated at high speed, one single revolution of the large

handle causing 134 revolutions of the frame. Two glass tubes 50 mm. in length and having a diameter of 0.5 mm. accompany the instrument. Each tube (Fig. 21) bears a scale ranging from 0 to 100, the individual divisions of which are rendered easily visible by a lens-front. The outer ends of the tube fit into small, cup-like depressions, the bottoms of which are covered with thin rubber. The inner extremities are held in position by springs. The instrument should be firmly secured to a solid table and oiled daily when in use.

To examine the blood, a rubber tube, provided with a mouth-piece (Fig. 22), is slipped over the end of one of the glass tubes, when the latter is filled completely by suction from a drop of blood obtained from the finger or the ear. The blunt point of the tube

FIG. 22.



Suction-tube of Daland's hæmatokrit.

is then quickly covered with the finger and the tube fixed in the frame. This is rotated at a speed of 10,000 revolutions for two or three minutes, when the volume of red corpuscles is directly read off. In healthy individuals the volume of red corpuscles is about 50 per cent., so that in a given case a proportionate expression of the percentage of corpuscles, as compared with the normal, can be obtained by multiplying the figure upon the scale by two.

As it has been ascertained that 1 per cent. by volume represents about 100,000 red corpuscles, it is only necessary to add five ciphers to the percentage-volume found in order to obtain the number of red corpuscles in one cbmm. of blood.

Example: Supposing that in a given case the reading was 35; by multiplying this figure by 100,000, 3,500,000 would represent the number of red corpuscles contained in one cbmm. of blood.

The amount of hæmoglobin contained in each corpuscle is ascertained approximately by dividing the amount of hæmoglobin determined by means of Fleischl's instrument by the number of corpuscles found with the hæmatokrit.

If normal blood be examined with the hæmatokrit, the leucocytes

will be seen to form a narrow white band at the central end of the column of red corpuscles. If a hyperleucocytosis exist, it is readily recognized.

BACTERIOLOGY AND PARASITOLOGY OF THE BLOOD.

It is generally admitted that micro-organisms do not normally occur in the blood; in conditions which may be said to stand midway between health and disease, however, they are at times met with. In patients suffering from furuncles, for example, bacteria may be found in the skin, in the lymphatic glands, and even in the blood of neighboring tissues, other symptoms of disease being absent. To this condition the term "latent microbism" has been applied by Verneuil.

Under truly pathologic conditions, on the other hand, micro-organisms are not infrequently found, and an examination with this view will often lead to a correct diagnosis.

Physicians who, in our latitudes at least, do not resort to the microscope in fever cases, certainly ignore a most important aid to diagnosis.

For ease of reference the various organisms that are met with in the blood in disease will be described under the headings of the respective diseases in which they are found.

Typhoid Fever.

In typhoid fever Eberth's bacillus (Plate VIII., Fig. 3) may at times, though rarely, be demonstrated in the blood, particularly, it is claimed, when taken from the roseolar spots. As an aid to diagnosis, however, no reliance should be placed upon the results of such an examination.

Widal's Serum-test.

Very much more important is the fact that the blood-serum of patients afflicted with typhoid fever possesses the property of causing arrest of motility and the agglutination of the specific bacilli. This observation, originally made by Pfeiffer, was first utilized for diagnostic purposes by Widal. The method which bears his name has now been quite generally adopted in the clinical laboratory, and must be regarded as a most valuable aid in the diagnosis of typhoid

fever. Whether or not the *serum-test* is of greater value than the diazo-reaction of Ehrlich still remains to be seen. Like this, it is open to several objections. The principal ones are the following: 1. It may be altogether absent in true cases of typhoid fever. This, however, is rarely the case. 2. The reaction may not be obtained before the end of the third week or may even be delayed until a relapse occurs, as the writer was able to observe in a recent case. 3. A positive result may be reached even after months and years following an attack of typhoid fever. 4. There are cases in which immunity against the disease apparently exists and in which distinct agglutination and loss of motility are observed in healthy individuals who have never passed through any serious illness. 5. The reaction has also been observed in various other diseases, such as acute miliary tuberculosis, tubercular peritonitis, phthisis, heart-disease, etc. The number of such cases, however, which have thus far been reported is very small, and it is quite likely that future investigations will show that the positive results obtained are referable to some error of technique, as the method has scarcely reached its highest degree of perfection. The majority of observers are quite unanimous in affirming that the reaction is only observed in connection with typhoid fever. Only a positive result, however, is of value.

Three methods of examination are available, of which the first is probably the most reliable.

1. After careful disinfection of the arm 5 or 6 c.c. of blood are withdrawn from one of the superficial veins by means of a sterilized hypodermic syringe and placed in a sterilized test-tube measuring from 10 to 12 cm. in length. The blood is allowed to stand until the serum has separated from the clot, which may be hastened by loosening the coagulum from the walls of the tube with a platinum needle. Eight drops of the serum are added to 4 c.c. of nutrient bouillon, which should be as nearly neutral as possible, when the mixture is inoculated with one oese (platinum loopful) of a fresh bouillon-culture of the typhoid bacillus, not more than twenty-four hours old. The tube is kept at a temperature of 37° C. for twenty-four hours. At the end of this time and frequently earlier already the bouillon will be absolutely clear, or very nearly so, while little flakes, composed of the bacilli, will be seen at the bottom and adhering to the sides of the tube, if the case under observation is one of typhoid fever; otherwise the bouillon has become uniformly cloudy,

and a true sediment does not occur. A pseudo-reaction may also occur at times, which should not be confounded with the one just described. Innumerable macroscopic, dust-like particles will then be seen scattered throughout the fluid, which can be readily distinguished from the cloudy appearance of non-typhoidal specimens. It has been suggested that this result is obtained in cases of intense infection with the bacillus coli communis. Should any doubt arise it is only necessary to keep such tubes for a few hours longer at a temperature of 37° C., when it will be noticed that the dust-like aspect has given place to the ordinary cloudy appearance observed in cases which are not typhoid fever.

2. A small amount of blood, obtained by puncturing the ear, is received in a suitable receptacle, which can be sterilized in a spirit flame. A drop of the serum is mixed with 25 drops of a fresh bouillon-culture (sixteen to twenty-four hours old), and one drop of the mixture directly examined upon a cupped slide with a $\frac{1}{12}$ oil-immersion lens. If the case in question be one of typhoid fever, rather large conglomerations of agglutinated, motionless bacilli will then be found evenly scattered throughout the field of vision, while the interspaces are either entirely free from bacilli or very nearly so. If necessary, the observation should be continued for two hours; but, as a rule, a positive result is already obtained within thirty minutes if the case be one of typhoid fever.

3. Two or three drops of blood are received upon a slide or a piece of paper and allowed to dry, care being taken that the specimen is not exposed to dust. A drop of distilled water is then placed upon the blood and allowed to remain for several minutes, when it is washed off with five or ten drops of the bouillon-culture and examined as just described. It is interesting to note that the dried blood retains its agglutinative properties for weeks and even months.

This method is, of course, the simplest for the general practitioner, and is the one generally employed in municipal bacteriologic laboratories. The results, however, are less reliable than those obtained with the second, and particularly with the first.

Pneumonia.

Recent researches have brought to light the interesting fact that in fatal cases of acute croupous pneumonia the specific diplococcus

is quite commonly present in the blood, while in cases ending in recovery it is only exceptionally encountered. The writer found, as a matter of fact, that a positive result is obtained in more than 89 per cent. of the fatal cases. The invasion of the blood usually occurs twenty-four to forty-eight hours ante mortem, but may also take place at an earlier date or be delayed. From the standpoint of prognosis a bacteriologic examination of the blood may thus be of considerable importance. It should be remembered, however, that while a positive result is always a symptom *mali ominis*, there are cases on record in which recovery occurred notwithstanding the presence of diplococci in the blood. In such cases a metastatic infection has probably occurred.

The examination, which should be repeated every day, is conducted as follows: After disinfection of the arm one of the superficial veins is compressed with a finger and punctured with an ordinary hypodermic syringe, which has been previously sterilized in boiling water. Five c.c. of blood are aspirated and agar-tubes —liquefied at 40° C.—inoculated, each with 1 c.c. of the blood. Plates are then prepared and kept at a temperature of from 35°–37° C. The colonies number from 2 to 200, and appear as small, round, grayish, jelly-like drops, which are quite characteristic. During their growth they cause a greenish discoloration of the blood-agar. Other bacteria possess the same property, but in a less marked degree than the diplococcus pneumoniæ.

The individual organism (Plate IX., Fig. 2) is capsulated and usually occurs in pairs, arranged end-to-end or in short chains. At times, however, the chains are quite long, and it may then be difficult to distinguish it from certain streptococci. It is easily stained with the usual aniline-dyes. In order to differentiate the capsule the following method, suggested by Welch, is best employed: Spread and dried cover-glass preparations are treated first with glacial acetic acid, which is allowed to drain off, and is replaced (without washing in water) with aniline gentian-violet solution. The staining-solution is repeatedly added until all the acid is displaced. The specimen is now washed in a weak salt-solution (about 2 per cent.), and examined in this, and not in balsam. The capsule and coccus can then be differentiated.

The organism also grows on gelatin without causing its liquefaction.

Sepsis.

The importance of a careful bacteriologic examination of the blood in cases of septic infection has now been definitely established. Large quantities of blood are, however, necessary, and reliance should never be placed upon a microscopic examination of a single drop. In doubtful cases it is best to cup the patient and to inoculate agar-plates and bouillon-tubes with the serum. The animal experiment, viz., the injection of 0.5 to 2.0 c.c. into the peritoneal cavity of white mice will also be found most valuable. Petruschky has shown that in severe cases of septic infection it is almost always possible to find streptococci in the blood, while in the milder cases a negative result is reached. He has found, moreover, that while as a general rule the presence of streptococci will justify a grave prognosis *quoad vitam*, death does not necessarily occur in every case. His results are tabulated below:

Negative Results.

	Deaths.
5 cases of puerperal fever	1
2 " phlegmonous abscess associated with erysipelas	0
3 " simple erysipelas	0
8 " erysipelas (convalescing)	0
1 " endocarditis	0
1 " pleurisy with effusion	0
1 " " with pericarditis	0
2 " pneumonia	1
2 " acute articular rheumatism	0
1 " scarlatina	0
5 " typhoid fever	0
7 " phthisis (in 3 of which a general pyogenic infection was found post mortem; 2 streptococci)	4

Positive Results.

	Deaths.	Recoveries.
5 cases of sepsis following phlegmonous abscesses or pulmonic infection (4 streptococci, 1 staphylococci)	3	2
9 " puerperal infection (8 streptococci, 1 staphylococci)	3	6
1 case of ulcerative endocarditis (streptococci)	1	0
2 cases of mixed infection (streptococci)	1	1

Streptococci are frequently met with in the blood after death from diphtheria, while the staphylococcus aureus and Loeffler's bacillus

are more rarely seen. In scarlatinal sepsis streptococci have likewise been found.

Of the other micro-organisms which may be met with in septic conditions the diplococcus pneumoniæ is the most common. It has been found in peritonitis, associated with carcinoma of the uterus, in cases of suppurative oöphoritis, following childbirth, and in cases of biliary abscess at the time of the chill. Friedländer's bacillus was also found in the latter disease. In a case of gonorrhœal septicæmia reported by Thayer and Blumer the gonococcus was found in the blood during life. Proteus vulgaris has been found in a few instances.

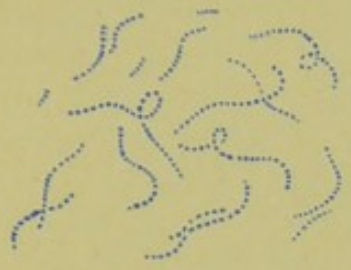
Staphylococcus pyogenes aureus occurs in the form of minute spherical bodies, averaging about 0.8 μ in diameter, which readily stain with the basic aniline-dyes, as also with Gram's method. They usually occur in clumps, but may also be seen in pairs and in short chains. The organism grows on all culture-media, and in the presence of oxygen gives rise to the formation of an orange-yellow pigment. Gelatin is rapidly liquefied; it coagulates milk and clouds bouillon. The *staphylococcus pyogenes albus* and *citreus* differ from the aureus by the absence of pigment in the first and by the formation of a lemon-yellow pigment in the second.

Streptococcus pyogenes (Plate III., Fig. 1) occurs in chains of spherical cocci which usually vary from four to twenty in number. The size of the individual organism is somewhat greater than that of the staphylococcus, but may vary even in one and the same chain. It is readily stained with the basic aniline-dyes and also with Gram's method. It grows on all culture-media at the temperature of the room, forming small gray, granular colonies on agar and gelatin. As a rule, it does not liquefy gelatin, and it may or may not coagulate milk and cloud bouillon. Several varieties are recognized, viz., *streptococcus brevis*, which forms short chains; *streptococcus longus*, which occurs in long chains; streptococci which render bouillon cloudy, and those which do not; streptococci which form flocculent or sandy or scaly or viscous sediments.

The *streptococcus conglomeratus* grows without clouding the bouillon, in the form of dense, separate particles, scales, or thin membranes at the bottom and sides of the tube, and on shaking the sediment it breaks up into little specks, without producing uniform, diffuse cloudiness. The chains are long and interwoven in conglomerate masses. (Welch.)

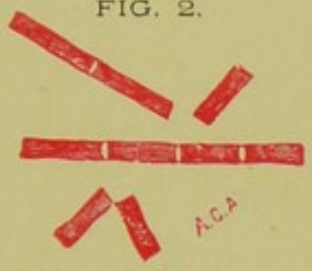
PLATE III.

FIG. 1.



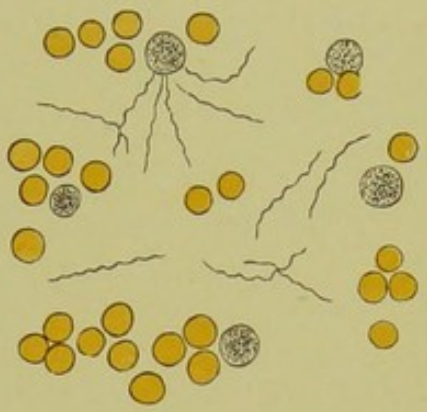
Streptococcus Pyogenes. (Abbott)

FIG. 2.



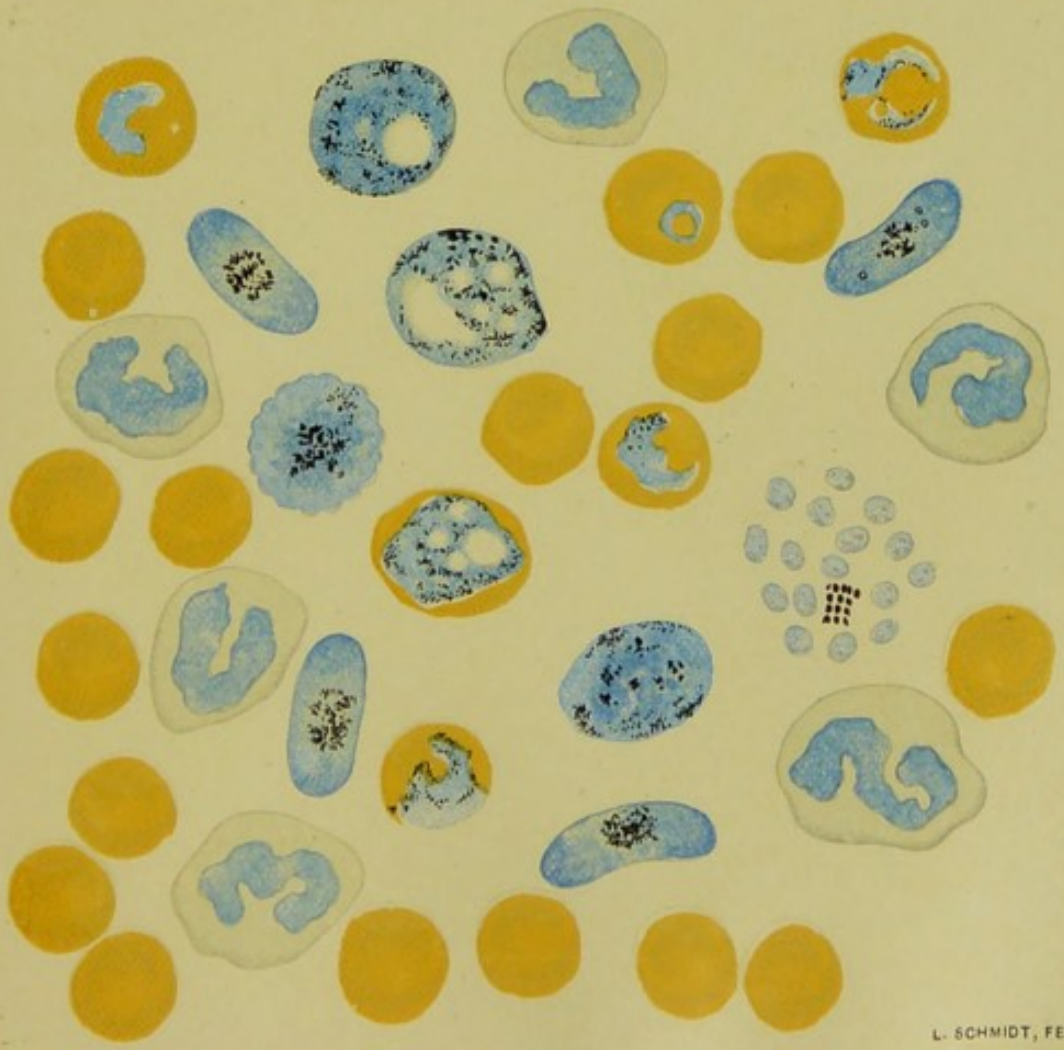
Bacillus Anthracis, highly magnified to show Swellings and Concavities at Extremities of the Single Cells.

FIG. 3.



Spirilla of Relapsing Fever. (v. Jaksch.)

FIG. 4.



Malarial Blood Stained with Chenzinsky-Plehn's Solution. (Personal Observation.)

Anthrax.

The bacillus of anthrax, as first pointed out by Pollender, Brouell, and Davaine, is frequently met with in the blood, where it should be sought for in doubtful cases by staining according to Loeffler's method. To this end cover-glass preparations are floated for five to ten minutes upon a mixture of 30 c.c. of a concentrated alcoholic solution of methylene-blue and 100 c.c. of a 1 : 10,000 solution of potassium hydrate; they are then washed for five to ten seconds in a 0.5 per cent. solution of acetic acid, treated with alcohol, dried, and mounted in balsam. Thus stained, the bacilli appear as rods measuring from 5 μ to 12 μ in length by 1 μ in breadth, usually presenting a segmented appearance, the extremities being slightly thickened. Spores are not found, as the organism multiplies by fission. When present in large numbers it is not even necessary to stain, as the organisms can then be seen without difficulty in fresh specimens. (Plate III., Fig. 2.)

In doubtful cases in which a microscopic examination of the blood yields negative results a few c.c. of the blood may be injected into a mouse or a guinea-pig, in the blood of which the bacilli will soon be found in enormous numbers if the disease be anthrax.

Acute Miliary Tuberculosis.

In acute miliary tuberculosis tubercle-bacilli have repeatedly been observed in the blood, but while their presence may be regarded as pathognomonic of the disease, the search for them is most tedious and often in vain. Nevertheless a careful examination of the blood is indicated in doubtful cases, but the fact should ever be borne in mind that only a positive result is of value.

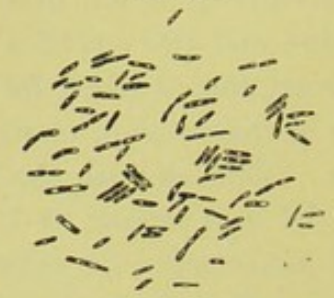
For methods of staining and a description of the tubercle-bacillus the reader is referred to the chapter on Sputum.

Glanders.

In glanders the specific bacillus is constantly present in the blood, and may be demonstrated by staining the dried preparations on a cover-glass for five minutes with a concentrated alcoholic solution of methylene-blue, mixed just before using with its own volume of a 1 : 10,000 solution of potassium hydrate. From this mixture the

specimen is passed for a second or two into a 1 per cent. solution of acetic acid which has been tinged a faint yellow by the addition of a little tropæolin 00 solution; it is then decolorized by washing in water containing two drops of concentrated sulphuric acid and one drop of a 5 per cent. solution of oxalic acid for every 10 c.c.

FIG. 23.



Bacillus of glanders. (ABBOTT.)

In specimens thus stained the bacilli appear as short rods, measuring 2 μ to 3 μ in length by 0.3 μ to 0.4 μ in breadth, often containing a spore at one end. (Fig. 23.)

Influenza.

In influenza a specific organism has been described by Pfeiffer and Kitasato as occurring in the sputum; it is also constantly present in the blood of such patients. The organism in question appears in the form of minute rods measuring 0.1 μ in breadth by 0.5 μ in length, occurring either singly or in chains of threes or fours. In suitably prepared specimens, owing to the fact that their poles take up the stain more readily than the middle portion, they convey the impression of diplococci.

Canon advises the following method for demonstrating their presence in the blood: Cover-glass preparations that have been allowed to dry at an ordinary temperature are placed in absolute alcohol for five minutes and then stained at a temperature of 37° C. for from three to six hours with Chenzinsky-Plehn's solution (see p. 69). The specimens are then washed in water, dried between layers of filter-paper, and mounted in balsam. Stained in this manner the red corpuscles are colored red, and the leucocytes, as well as the bacilli, blue. As a rule, only from four to twenty of these are found in one preparation, usually occurring singly, but also in groups. Owing to the fact that they are found in the

blood only during the acme of the disease, Canon recommends the examination of the sputum for diagnostic purposes, a view with which personal observations are entirely in accord.

Relapsing Fever.

Relapsing fever is characterized by the presence in the blood, and here only, of spirilla or spirochætæ which bear the name of their discoverer, Obermeier. In order to search for these organisms no special precautions are necessary. After having carefully cleansed the finger as described, a drop of blood is mounted upon a very thin cover-glass. This is directly inverted upon the slide, when the specimen is ready for examination; an oil-immersion lens is not required. Attention is drawn to the presence of these organisms by certain disturbances noticeable among the red corpuscles, and upon careful examination it will be seen that these are caused by the wriggling movements of the spirilla. The spirochætæ Obermeieri are long, slender filaments, measuring from 36 μ to 40 μ in length by 0.3 μ to 0.5 μ in breadth, and present from eight to twelve incurvations of equal size with tapering extremities. (Plate III., Fig. 3.) These last two characteristics serve to distinguish this species from that described by Ehrenberg, in which the radius of the incurvations is not the same in all, and in which the extremities do not taper.

The number of spirilla that may be found in a drop of blood varies, being greater during the access of the fever, when twenty, or even more, may be observed in the field of the microscope. They occur either singly or in bunches of from four to twenty, specimens such as those figured in the table being frequently seen. In the quiescent stage they are sometimes arranged in the form of rings or of the figure 8. After the crisis they seem to disappear entirely, and their presence during an afebrile period may therefore always be regarded as indicating a pseudocrisis. During the afebrile periods small, bright, round bodies have been described as occurring in the blood, which according to some are spores, but according to others merely represent débris of the spirilla.

Culture-experiments have not been very satisfactory, although Koch, at a temperature of from 10° to 11° C., observed an increase in their number.

That confusion should ever arise in distinguishing the spirilla of

relapsing fever from the free flagella observed at times in malarial fever appears very improbable to the writer.

Malaria.

The discovery of a specific micro-organism belonging to the class of protozoa, the *plasmodium malariæ of Laveran*, in the blood of malarial patients, and of its invariable presence in the different forms of this disease, must be regarded as one of the most important in clinical medicine. This is not the place to point out how frequently a diagnosis of malarial fever based upon clinical symptoms alone has proved false, how often a tuberculous, a syphilitic, or a septic infection has been overlooked, and termed malaria. It will suffice to say that errors of this kind, in view of our present knowledge and the ease with which they can be avoided by every physician, should no longer occur. The diagnosis of malaria should in every case be based upon a microscopic examination of the blood.

The search for the specific organism, it is true, may be very tedious at times, but it will always be crowned with success if the disease in question be malaria. Again and again the author has seen cases in which the clinical symptoms alone would not have warranted the diagnosis of malaria, and in which the true nature of the disease was cleared up only by a careful examination of the blood; and cases have often been seen in which the diagnosis of malaria based upon clinical symptoms alone was disproved by the absence of plasmodia from the blood and the post-mortem examination.

While it is true that the life-history of the organism is as yet only imperfectly understood, it being still an open question whether or not the various forms observed represent different stages in the development of one and the same species, this is of no importance from a clinical standpoint, and the demonstration in the blood of any one of the forms to be presently described will always warrant the diagnosis of malaria.

The parasite in question, as stated above, is a protozoon, and belongs to the class of hæmatozoa, representatives of which are found in the blood of various animals, such as the rat, frog, tortoise, carp, various birds, etc.

Method of Examination. The necessary amount of blood is best obtained by puncture of the lobe of the ear after this has

been thoroughly cleansed with soap and water and dried. The first few drops are wiped away. A small drop of blood is then received upon a cover-glass held with a pair of forceps, care being taken that the tip of the drop only is touched, when the specimen is immediately transferred to a slide. Cover-glasses and slides must be absolutely clean, and it is best to keep both in bottles filled with alcohol or a mixture of alcohol and ether. If these precautions be taken and the drop is not too large, the corpuscles will spread out in an even layer between the two glasses and retain their principal features. Pressure should always be avoided. For the examination of the specimens an oil-immersion lens is almost indispensable, unless, indeed, the observer has been thoroughly trained in hæmatologic research.

Whenever the specimens can be examined within one hour after their preparation, it is probably always best to use fresh blood. If, however, a longer time must elapse, or if it is desired to preserve the specimens, dry cover-glass preparations must be employed. These are best fixed by immersion for thirty minutes in absolute alcohol or a mixture of equal parts of absolute alcohol and ether, when they may be stained with Chenzinsky-Plehn's solution (which see). The specimens should be floated on the solution, and allowed to remain for several hours. They are then washed in water, dried between filter-paper, and mounted in a drop of balsam. The red corpuscles will be colored a light red, the leucocytes blue, the eosinophilic granules a deep red, and the parasites blue (Plate III., Fig. 4).

This method, as well as the one presently to be described, may also be advantageously employed by the beginner, who may experience some difficulty in the recognition of the hyaline forms of the organism.

A drop of a concentrated solution of methylene-blue in 0.6 per cent. salt-solution is placed upon the finger and a drop of blood allowed to flow directly into this, when it is mounted in the usual manner, care being taken that as small a drop as possible, both of the staining-fluid and of the blood, be employed. The organisms are colored a light blue, while the red corpuscles present their normal color. Should any of the latter be also stained, as happens at times, the color will be uniform throughout, so that no confusion can possibly arise between these and the plasmodia.

The following forms may be found in the blood :

1. *Hyaline non-pigmented intracellular bodies.* These apparently represent the earliest stage in the development of the parasite, and are found in all forms of malarial fever, being especially abundant during the latter part of the paroxysm or immediately thereafter. At first sight they may be mistaken for vacuoles, but upon closer investigation it will be found that they exhibit distinct movements of an amœboid character, and may thus be easily recognized with a little experience.

The rapidity with which these changes in the form of the organism occur in the tertian type of ague is most astonishing, and sketches of any one phase can often, indeed, be made only from memory, while in quartan fever the movements are much slower and far less extensive.

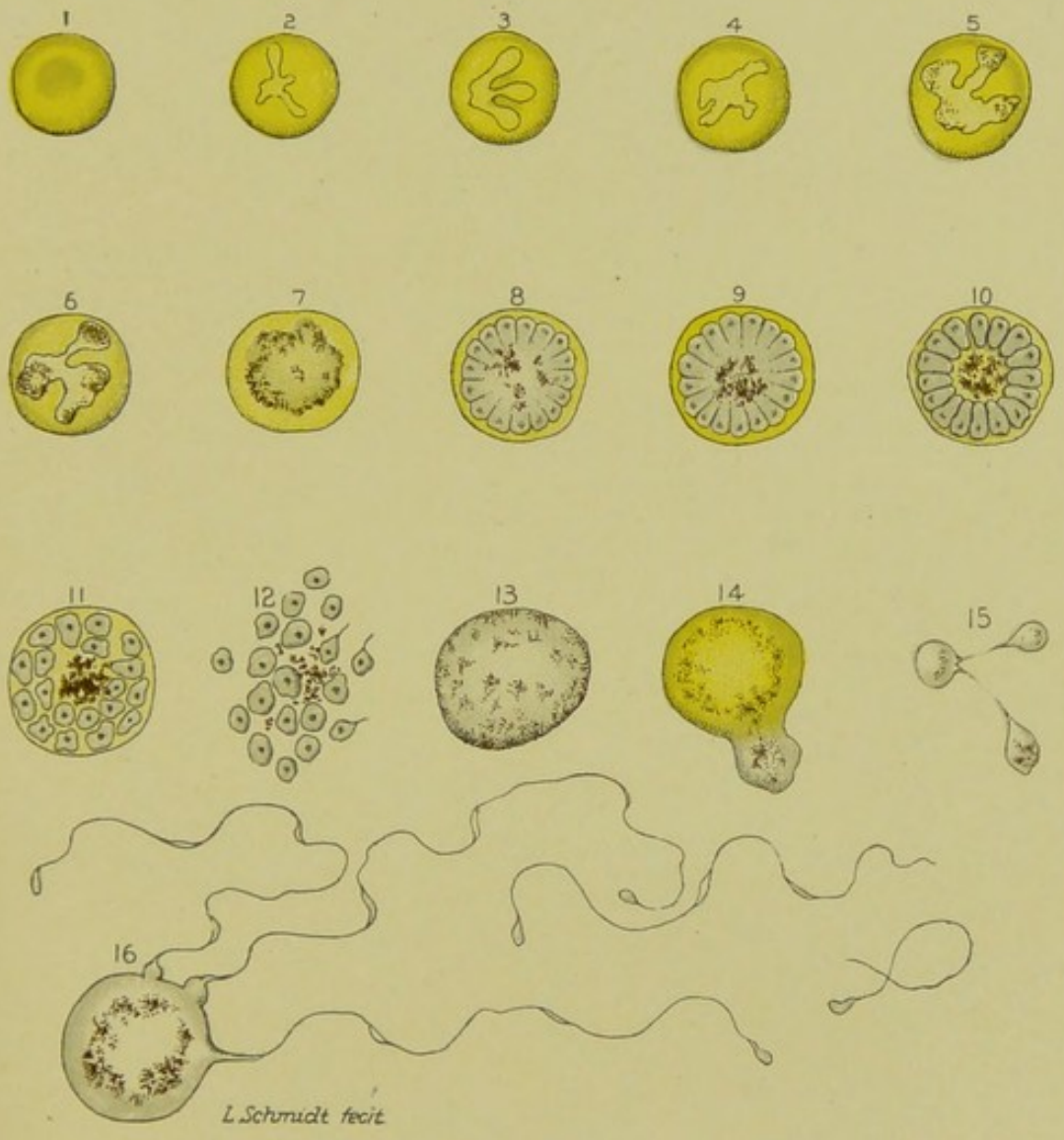
In the irregular fever of the æstivo-autumnal form amœboid movements may likewise be observed, but more commonly the parasite assumes a ring-like appearance, and does not throw out distinct pseudopodia. If these forms be carefully observed, it will be found that they are not absolutely quiescent, but alternately expand and contract.

In tertian fever the organism (Plate IV.) is pale and indistinct, while in quartan fever it is sharply outlined and somewhat refractive (Plate V., Fig. 2). In the æstivo-autumnal form the organism is usually much smaller than in the tertian type, and the ring-like bodies just described frequently present a distinctly shaded aspect at some point in their interior which closely resembles the darker portion in the centre of a normal corpuscle (Plate V., Fig. 1). It is thus possible, even at this stage in the development of the parasite, to distinguish between fever of the tertian, quartan, and æstivo-autumnal type.

The numbers in which these small, non-pigmented intracellular organisms may at times be met with is most astonishing. In a case of pernicious malarial fever of the algid type, which the writer had occasion to examine, and in which a history of only one week's illness without chills was obtained, normal red corpuscles were indeed only exceptionally found. The case was one of the æstivo-autumnal form of fever.

2. *Pigmented intracellular organisms.* These represent a later stage in the development of the parasite, and, like the non-pigmented intracellular bodies, are met with in all types of malarial fever. Their appearance, however, differs considerably

PLATE IV.

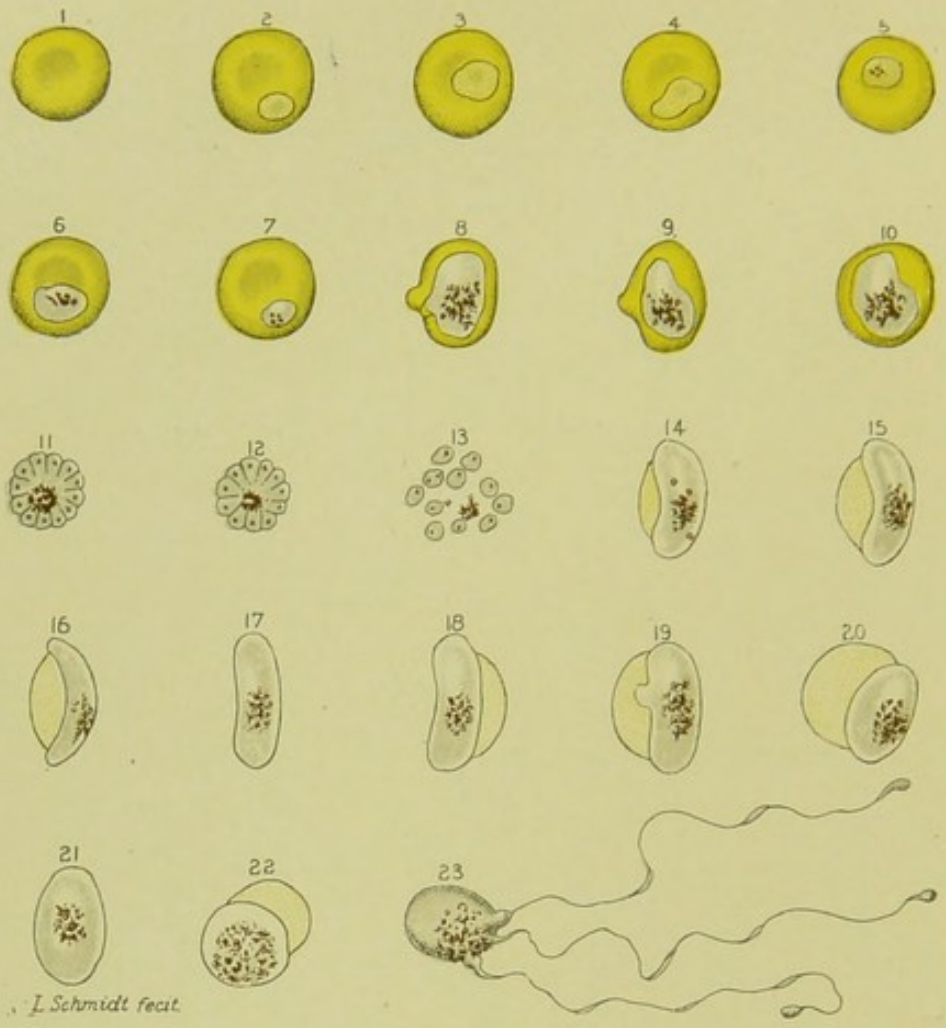


The Parasite of Tertian Fever.

1, Normal Red Corpuscle; 2-4, Non-pigmented Stage of the Organism, showing Amœboid Movements; 5-7, Progressive Pigmentation and Growth; 8-11, the Process of Segmentation; 12, Young Forms; 13, Large Extra-cellular Organism; 14, Mode of Formation of Extra-cellular Body; 15, Small Fragmented Extra-cellular Organism; 16, Flagellate Body and Free Flagella. Unstained Specimen. (Personal Observation.)

PLATE V.

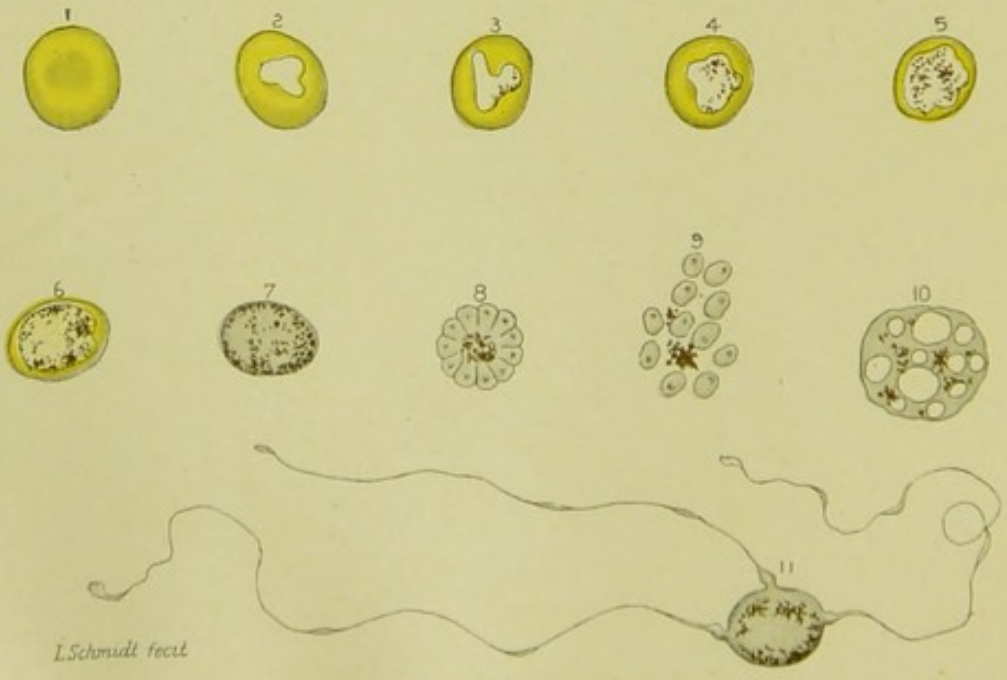
FIG. 1.



The Parasite of Aestivo-Autumnal Fever.

1, Normal Red Corpuscle; 2-10, Gradual Growth of the Organism; 11 and 12, Segmenting Bodies; 13, Young Forms; 14-22, Crescents, Ovoids and Spherical Bodies, with and without Bib; 23, Flagellate Body. Unstained Specimen. (Personal Observation.)

FIG. 2.



The Parasite of Quartan Fever.

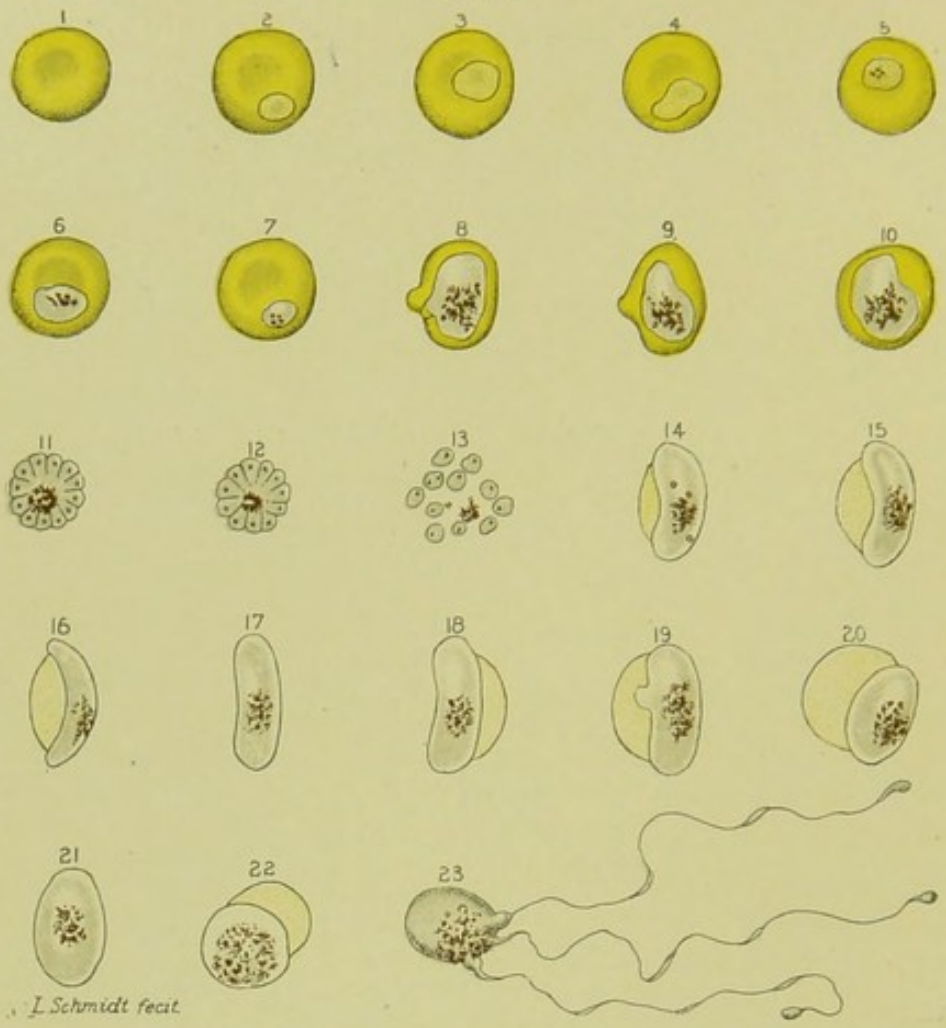
1, Normal Red Corpuscle; 2-6, Gradual Growth of the Organism; 7, Pigmented Extra-cellular Body; 8, Segmenting Body; 9, Young Forms; 10, Vacuolated Extra-cellular Body; 11, Flagellate Form. Unstained Specimen. (Personal Observation.)

in the various forms. In tertian fever minute granules of a reddish-brown color appear in the bodies of the organism very soon after the paroxysm. These gradually increase in number, while the invaded corpuscles proportionately become paler and paler, until finally only an indistinct shell-like outline can be discerned. In fresh specimens the granules, which often assume the form of little rods, resembling bacteria, exhibit most active molecular movements, attracting attention at once. The body of the parasite, which during its development has gradually increased in size, is probably hyaline, and may still be seen to undergo amœboid movements. These are not nearly so active, however, as in the non-pigmented stage. The movements, moreover, cannot be followed so readily, owing to the presence of the granules. At first sight these appear to be scattered in small collections throughout the red corpuscle, and the impression may be gained that several organisms are present at the same time. Upon closer investigation, however, it will be seen that this is only apparently the case, and that the granules are confined to the bulbous extremities of the pseudopodia of a single parasite. Before the end of forty-eight hours the organism has filled out the entire red corpuscle, which at the same time has also attained a larger size than normal. The amœboid movements become less and less marked, and the pigment-granules, which may still be quite active, tend to collect about the periphery. (Plate IV.)

In quartan fever pigmented intracellular bodies likewise appear very soon after the paroxysm. The individual granules, however, are somewhat larger, of more irregular size, and darker in color than those seen in the tertian type. (Plate V., Fig. 2.) Instead of exhibiting active molecular movements, moreover, they are almost entirely quiescent, being usually grouped along the periphery of the organism. While amœboid movements can at first be observed, these become less and less marked, until finally, at the end of from sixty-four to seventy-two hours, they have ceased entirely. The organism then presents a round or ovoid form, but does not fill the red corpuscle entirely. It is curious to note that in this form of ague the red corpuscles do not become decolorized, but rather darker than normally, and at times specimens may be seen which present a distinctly greenish or brassy appearance. When the parasite has become fully developed the corpuscle is smaller than normally, and upon staining it may be seen that the

PLATE V.

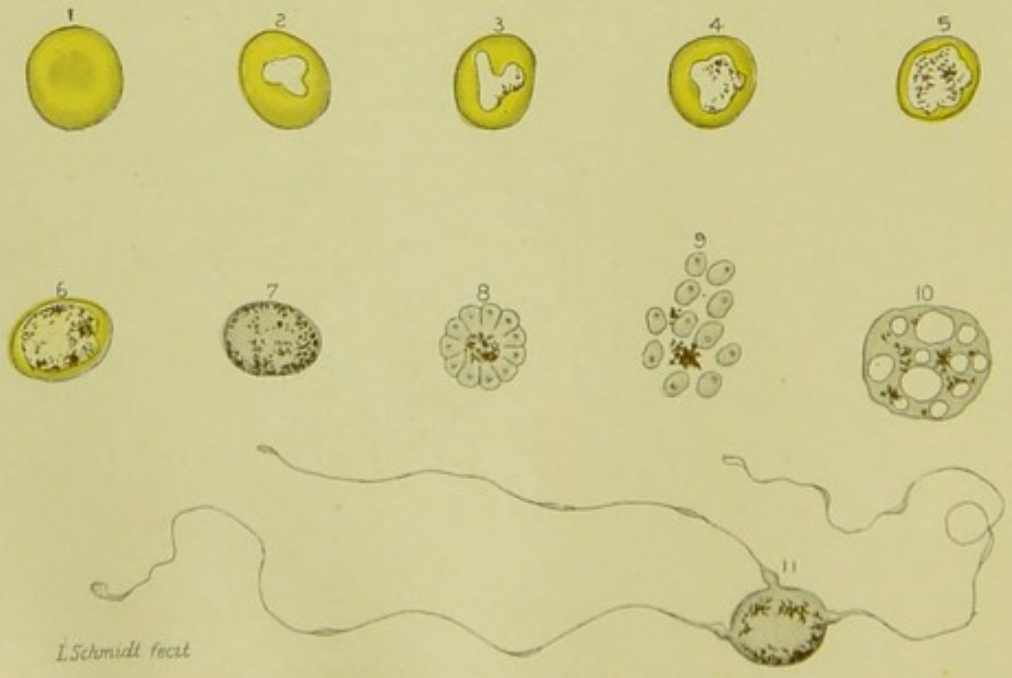
FIG. 1.



The Parasite of Aestivo-Autumnal Fever.

1, Normal Red Corpuscle; 2-10, Gradual Growth of the Organism; 11 and 12, Segmenting Bodies; 13, Young Forms; 14-22, Crescents, Ovoids and Spherical Bodies, with and without Bib; 23, Flagellate Body. Unstained Specimen. (Personal Observation.)

FIG. 2.



The Parasite of Quartan Fever.

1, Normal Red Corpuscle; 2-6, Gradual Growth of the Organism; 7, Pigmented Extra-cellular Body; 8, Segmenting Body; 9, Young Forms; 10, Vacuolated Extra-cellular Body; 11, Flagellate Form. Unstained Specimen. (Personal Observation.)

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organism is still surrounded by a narrow zone of corpuscular protoplasm, even when this is not apparent in unstained preparations.

The pigmented intracellular bodies which may be found in æstivo-autumnal fever (Plate V., Fig. 1) can be readily distinguished from those observed in tertian and quartan ague, as in these forms pigment-granules also appear after the paroxysm. They are never numerous, however, and often only one or two minute, dark granules can be detected near the periphery of the organism. The latter, even in the later stages of its development, scarcely ever occupies much more than one-third of the corpuscle. Usually the granules exhibit scarcely any movements. As in the quartan type of ague, decolorization of the red corpuscles does not occur, and here, as there, a greenish, brassy appearance is often observed. At times the red corpuscles are shrunken, crenated, or spiculated.

At the beginning and during the paroxysm forms are at times seen in which the few pigment-granules that may be present have gathered in the centre of the parasite and formed a solid clump. From the fact that these are only observed during the paroxysm, and that central blocks of pigment are only found during the stage of segmentation (see below) in tertian and quartan ague, and from the fact that pigment-bearing leucocytes are observed at the same time and are likewise only found during the same stage in other types of the fever, Thayer and others conclude that these bodies are pre-segmenting forms of the parasite. The gradual evolution of the non-pigmented intracellular body in æstivo-autumnal fever is, however, but imperfectly understood, as the principal changes apparently occur in the spleen. In a fatal case of undoubted æstivo-autumnal fever, however, a large, pigmented intracellular organism, much resembling those seen in cases of tertian fever, was found by the writer in the spleen. Possibly its presence may be explained by assuming the existence of a mixed infection. In the peripheral blood only the small, non-pigmented and pigmented intracellular organisms described above were found during life, although numerous examinations of the blood were made. Just before death a crescent was obtained from the blood of the finger.

3. *Segmenting bodies.* In cases of tertian and quartan fever the progress of segmentation may be directly observed under the microscope if specimens of blood be obtained just prior to or during the chill. In tertian fever organisms will then be seen in which the destruction of the red corpuscle has advanced to a stage

where it is only possible to make out a pale contour of the original host. The parasite itself has gradually assumed a granular appearance, and the pigment-granules, which until then have exhibited pronounced molecular movements, now become quiescent, larger and rounder, and show a distinct tendency to collect in the centre of the body, where they form a roundish mass in which the individual components can scarcely be made out. While this change in the position of the pigment is taking place, beginning segmentation of the surrounding granular protoplasm will be observed. This at first is most marked at the periphery, from which delicate striæ will gradually be seen to extend toward the central mass, dividing up the protoplasm into a number of oval bodies which closely resemble the petals of a flower. (Plate IV.) Still later these bodies, which in reality are the sporules of the parasite, will be found scattered in an irregular manner throughout the interior of the organism. The apparent envelope then disappears, and the sporules, which in tertian fever usually number from fifteen to twenty, lie free in the blood. Quite frequently, also, a sudden expulsion of the little bodies is observed and the impression gained as though the envelope had been burst asunder. Upon close inspection, even at the petal stage, it will be seen that almost every sporule presents a tiny dot in its interior, which may at first sight be mistaken for a pigment-granule, but which in all probability is a nucleus. In two cases the writer thinks that he could also make out a little cilium at one end of a sporule, but it is possible that this was only an accidental appearance. After the expulsion of the sporules these are frequently seen to move about in an active manner, but sooner or later they come to a rest.

While the progress of segmentation is very frequently observed to proceed in the manner described above, this is not invariably the case. It may thus happen that segmentation occurs before the pigment-granules have had time to gather at the centre, or that the parasitic protoplasm breaks up into sporules directly without the intervention of the petal stage. In every case, however, the formation of sporules is directly associated with the occurrence of a paroxysm, and represents the process of reproduction of the parasite.

The ultimate fate of the sporules is as yet unknown, but it is likely that they in turn invade new corpuscles, cause their destruction, and become segmented, thus giving rise to a new generation. As the process of segmentation, moreover, coincides in time with

the occurrence of the chill, it would appear that the interval elapsing between two consecutive chills—*i. e.*, the type of the ague—depends upon the rapidity with which the non-pigmented forms arrive at maturity.

In quartan ague the manner in which segmentation takes place differs somewhat from that observed in the tertian form. It will here be observed that the pigment-granules, which, as has been pointed out above, have gathered along the periphery of the organism, as the parasite approaches maturity become arranged in a stellate manner, and apparently reach the centre through certain definite protoplasmic channels. Here they finally form a dense clump, and while the protoplasm assumes a finely granular appearance segmentation proper begins and proceeds as in the tertian form. In quartan ague, however, the number of segments is, as a rule, smaller, varying between six and twelve. The entire segmenting body, moreover, is smaller than in the tertian form, and the segments are arranged in a more symmetrical manner. Here, indeed, the most perfect rosettes are observed. (Plate V., Fig. 2.)

In æstivo-autumnal fever segmenting bodies are only exceptionally seen in the peripheral blood, and it appears that the process of reproduction occurs principally in the spleen. The pre-segmenting forms, described above, here undergo segmentation in a manner closely resembling that observed in tertian fever. The number of segments, moreover, is about the same, varying, as a rule, between ten and twenty. The segmenting body itself, however, is much smaller than in either the tertian or quartan form, and it is not possible to distinguish any remains of the original host.

4. *Crescentic, ovoid, and spherical bodies.* (Plate V., Fig. 1.) These are only observed in cases of æstivo-autumnal fever when this has persisted for at least one week. At first sight they apparently bear no relation to the other forms which have already been described, and it has long been an open question whether or not these bodies actually represent a stage in the life-history of the common malarial parasite. Grassi and Feletti have applied the name *Laveriana malariæ* to this form. More recent investigations have rendered it probable that they are directly derived from the pigmented intracellular forms. Specimens may thus be met with in which crescentic bodies are found in the interior of red corpuscles that have lost but little of their original color. Such observations, however, are not common. The

typical crescents which are usually seen are highly refractive bodies, somewhat larger than a red corpuscle, measuring from 7 μ to 9 μ in length by 2 μ in breadth. Their extremities are usually rounded off and joined by a delicate, curved line bridging over their concave border. This is supposed to represent the remains of the original host. At other times this hood-like appendage is found along the convex border. The little pigment-granules and rods, which are always found in the interior of the crescents, are generally collected about the centre of the body, although they are occasionally also seen in one of the horns. While usually quiescent, a migration of some of the granules toward one extremity and back to the central mass may at times be observed. The ovoid and spherical bodies, which are usually much smaller than the crescents, exhibit the same general features, however, and are often likewise provided with a little hood. It is supposed by some that the spherical bodies develop from the ovoids, and these again from the crescents. Like the crescents, the ovoid and spherical forms may be found in the interior of red corpuscles.

5. *Extracellular pigmented bodies.* In tertian and quartan ague some of the pigmented intracellular bodies, instead of undergoing segmentation when they have arrived at maturity, may be seen to leave their hosts and to appear as such in the blood. At the same time they increase considerably in size, and in the tertian form may indeed become as large as a polynuclear leucocyte. (Plate IV.) The pigment-granules, moreover, exhibit an activity in their movements which is most astonishing, and never observed under other conditions. The outline of the parasite is then usually irregular and quite indistinct. Upon careful observation it will be seen that in some of these bodies the movements of the granules after awhile become less and less marked, and finally cease, while the body of the parasite itself becomes still more irregular in outline. This appearance undoubtedly is referable to the death of the organism. In others a gradual fragmentation is observed, small particles of the pigmented mother-substance being cut off from the parent-form. It is thus quite common to see the original parasite break up into four or five smaller bodies in which the movements of the pigment-granules persist for some time. Sooner or later, however, these cease, the outlines of the bodies become more and more indistinct, and death occurs. In still others the formation of vacuoles may be observed, the pigment-granules at the same time becoming quiescent. This process is likewise

regarded as one of degeneration. Most interesting, however, is the fact that *flagellation* may occur in some of these extracellular forms. It will then be observed that the pigment-granules which exhibit a most surprising activity in their movements tend to collect near the centre of the organism, while at the same time curious undulating movements may be made out along its contours. Suddenly one or more (one to six) extremely slender filaments will be seen to be protruded from as many points on the periphery, presenting minute enlargements here and there in their course. (Plate IV.) The length of these filaments, or flagella, as they are termed, varies considerably. As a rule, it does not exceed the diameter of from five to eight red corpuscles, but much larger specimens are at times observed, and it appears to the writer that in most illustrations they are represented too short. With these flagella the organism exerts most active whipping movements, scattering the red corpuscles to the right and left. Attention is, indeed, usually first drawn to the presence of these bodies by the disturbance which they cause in the field of vision. Occasionally one of the flagella may be seen to become detached from the body of the parasite and to move about among the corpuscles in a rapid, snake-like manner. In microscopic specimens they gradually come to a rest and often curl into a spiral. Their ultimate fate is not known.

That an error should ever happen in distinguishing such detached flagella from the spirilla of relapsing fever seems very improbable, as the true nature of these formations is shown by the presence or absence of other forms of the malarial organism.

Beyond the fact that the flagellate organisms in tertian fever are larger than in the quartan form, no special points of difference exist. (Plate V., Fig. 2.) In æstivo-autumnal fever similar changes may be observed in the crescents, ovoids, and spherical forms. In crescents it is thus not at all uncommon to observe a small hyaline protrusion from the surface of the organism, which may later become detached. This process was formerly regarded as one of regeneration, but it is questionable whether this is actually the case. In other specimens, again, true fragmentation, or vacuolization, may occur, and flagellate bodies are met with in this type of fever as well as in tertian and quartan ague. The flagellates, as in quartan fever, are smaller than those observed in the tertian form, but other points of difference do not exist. (Plate V., Fig. 1.)

From the above description it will be seen that three forms of

the malarial parasite may be found in the blood, viz., the parasite of tertian, quartan, and æstivo-autumnal fever, and it has been shown that these three forms may be readily distinguished from each other. It should be mentioned, however, that in tertian and quartan fever several groups of the same organism may be present at one time, and as the process of segmentation coincides with the occurrence of a paroxysm, it will be readily seen that the number of paroxysms within a given time depends directly upon the number of groups which may be present in the blood. If a double infection with the tertian parasite has occurred, one group of organisms may thus have just reached the segmenting stage, while the second group has only attained a twenty-four hours' growth, the result being that maturity is reached by the two groups on successive days. Quotidian fever is then the result. Should still more groups be present, the clinical picture will accordingly become more complicated. In quartan ague, similarly, double quartan fever will occur if two groups be present, and triple quartan fever if three groups be present at one time.

In conclusion, it may not be out of place to refer to the presence of pigment-bearing leucocytes in the blood of malarial patients. These are quite constantly met with during the paroxysm, and it is indeed often possible to observe the process of *phagocytosis* directly under the microscope (See Fig. 12.) The forms which are taken up are the central pigment-clumps of organisms that have undergone sporulation, the small, fragmented extracellular forms, the flagellate bodies, and even the segmenting bodies. In every case where pigment-bearing leucocytes—which are probably always of the neutrophilic, polynuclear variety—are observed malarial fever should be suspected and a careful examination made, as a melanæmia has so far only been observed in this disease, in relapsing fever, and in connection with the rare melanotic tumors, in which not only leucocytes containing melanin occur in large numbers, but also masses of this pigment float free in the blood.

FILARIASIS.

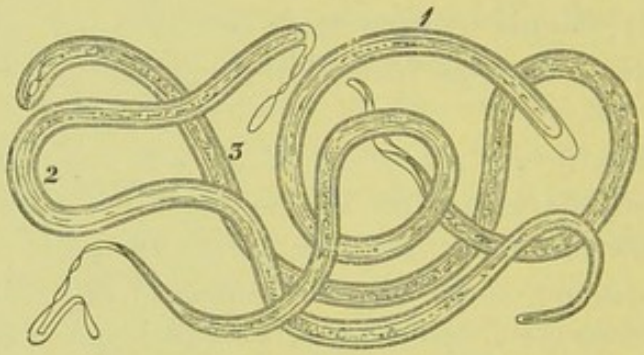
Filaria sanguinis hominis (Lewis), *syn.*, filaria Wuchereri (da Silva Lima); filaria Bancrofti (Cobbold); filaria Mansoni; trichina cystica (Salisbury); trichina sanguinis hominis nocturna (Manson).

Several varieties of the parasite (Fig. 24), which belongs to the

class of nematodes, have been observed in the blood of man. Among these are filaria sanguinis hominis nocturna, filaria sanguinis hominis diurna, or filaria sanguinis hominis, *var.* major, and filaria sanguinis hominis, *var.* minor.

The female of filaria nocturna, according to Manson's description, is "a long, slender, hair-like animal, quite three inches in length, but only one one-hundredth inch in breadth, of an opaline appearance, looking as it lies in the tissues like a delicate thread of catgut, animated and wriggling. A narrow alimentary canal runs from the simple club-like head to within a short distance of the tail, the remainder of the body being almost entirely occupied by the reproductive organs. The vagina appears about one twenty-fifth of an inch from the head; it is very short and bifurcates into two uterine

FIG. 24.



Filaria sanguinis hominis. (After LEWIS.)

horns, which, stuffed with embryos in all stages of development, run backward nearly to the tail." (Osler.) The male worm is rarely seen, and is much smaller than the female. While the adult parasite has its habitat in the lymphatics, the embryos, which are set free in enormous numbers, invade the blood-current, in which they may readily be found at night; during the day an examination of the blood will usually yield negative results. This periodicity may, however, be reversed by having the patient sleep in the daytime and be about at night. Each embryo has an envelope of its own, which is hyaline in appearance and within which the young worm, measuring 0.34 mm. in length by 0.0075 mm. in breadth, is able to extend and contract itself. In fresh preparations these organisms are readily detected by the disturbance which their movements create among the corpuscles, when they are apparently transparent and homogeneous, but after some time, when the worm

has come to rest, it will be seen that they are granular and transversely striated.

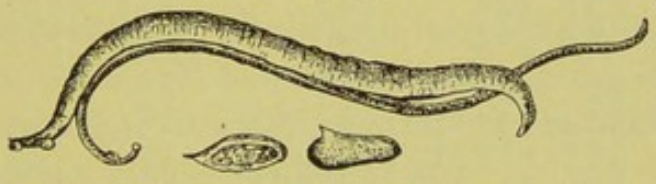
As the mere presence of these parasites usually does not produce symptoms, and as an examination of the blood made in daytime, as already stated, generally yields negative results, attention is only drawn to their presence when symptoms pointing to an occlusion somewhere in the course of the lymphatic channels exist, as evidenced by chyluria (which see), elephantiasis, or lymph scrotum.

DISTOMIASIS.

Bilharzia hæmatobia (Cobbold), *syn.*, gynæcophorus (Diesing); distomum hæmotobium (Bilharz); schistosoma (Weinland); distoma capense (Harley); thecosoma (Maguin-Tandon.)

The Bilharzia hæmatobia belongs to the class of trematode plâtodes, and has never been met with in the United States or in Europe. According to Bilharz, the greater portion of the Fellah and Coptic population of Egypt is infected by it, giving rise to

FIG. 25.



Bilharzia hæmatobia. Male and female, with eggs. (V. JAKSCH.)

diarrhœa, hæmaturia, and ulceration of the mucous surfaces. The male is smaller but thicker than the female, measuring from 12 to 14 mm. in length; on its abdominal surface a deep groove is found with overlapping edges, which serves for the reception of the female (Fig. 25).

While the adult parasite is but rarely seen in the blood, its ova are frequently detected. These are slender bodies, measuring 0.12 mm. in length by 0.04 mm. in breadth, and provided with a distinct little spike-like projection, issuing from one extremity or the side.

Differential Table of the More Important Diseases of the Blood.

	Disease.	Hæmoglobin.	Red blood-corpuscles. Number.	Form.	Valeur globulaire.	Nucleated red corpuscles.	Leucocytes. Number.	W. : R.	Neutrophiles.	Eosinophiles.	Basophiles.	Myelocytes.	Lymphocytes.	Large mononuclear forms.	Plaques.
The essential anæmias.	Chlorosis,	A relatively great diminution.	Usually normal; in severe cases greatly diminished.	Numerous poikilocytes in the severer cases.	Not increased; generally diminished.	Normoblasts occasionally found.	Only slightly increased.	1 : 408 as an average.	.....	.....	.....	.....	.....	.....	.....
	Pernicious anæmia	The diminution is not proportionate to the degree of oligocythæmia.	The oligocythæmia is always marked and usually extreme.	Pronounced poikilocytosis.	Increased.	Normoblasts and megaloblasts always present, particularly the latter.	No increase, rather a decrease.	.....	.....	.....	.....	.....	.....	Slight increase	Absent or few in numbers.
Leukæmia.	Myelogenous form.	The oligochromæmia corresponds to the degree of oligocythæmia or is somewhat more marked.	The oligocythæmia is moderate.	.....	Normal or diminished.	Nucleated forms in large numbers, normoblasts especially.	Enormous hyperleucocytosis.	1 : 10 to 1 : 1	Increased.	Increase	Occasionally seen.	Always present, may amount to 25 per ct.	Relatively diminished; may be less than 1 per ct.	.....	.....
	Lymphatic form,	.....	.....	.....	.....	Nucleated forms are rare.	Leucocytosis not so extreme as in the myelogenous form.	The ratio 1 : 10 is rarely exceeded.	There is a relatively great diminution.	Rarely increased	.....	Usually absent, unless the bone-marrow is involved.	Increase	Relatively much diminished.	Often abundant.
	The simple secondary anæmias.	The oligochromæmia is directly proportionate to the oligocythæmia.	There is oligocythæmia of variable intensity.	No change in mild cases; well-marked poikilocytosis in severe cases	Usually no change; never increased; at times diminished.	Always present, especially normoblasts	Always a relative and usually an absolute increase.	.....	The increase in leucocytes is usually referable to an increase in the number of neutrophiles.	.....	.....	.....	.....	.....	.....
	Pseudo-leukæmia.	....	There is no marked oligocythæmia.	The poikilocytosis is never extreme.	.....	Normoblasts are occasionally seen.	Leucocytosis never marked.	.....	.....	.....	.....	.....	Relative increase	.....	.....

CHAPTER II.

THE SECRETIONS OF THE MOUTH.

SALIVA.

NORMAL saliva is a mixture of secretions derived from the submaxillary, sublingual, parotid, and mucous glands of the mouth. It is a colorless, inodorous, tasteless, somewhat stringy and frothy liquid, and serves the purpose of aiding in the acts of mastication, deglutition, and digestion. Its amount per diem varies from 600 to 1200 grammes.

General Characteristics.

Normal saliva has a specific gravity of from 1.002 to 1.009, corresponding to the presence of from 4 to 10 grammes of solids. Its reaction is usually slightly alkaline; it may, however, become acid at times, when lactic acid fermentation takes place in the mouth. This acid, according to Magittot, corrodes the enamel of the teeth, and may ultimately produce dental caries.

Chemistry of the Saliva.

In order to give an idea of the general composition of the saliva the following analyses are appended, the figures corresponding to 1000 parts by weight:

Water	995.2	994.20	988.1
Ptyalin[1]	1.34	1.30	1.3
Mucin, Epithelium	1.62	2.20	2.6
Fatty matter	...	...	0.5
Sulphocyanides	0.06	0.04	0.09
Alkaline chlorides	0.84	...	...
Disodium phosphate	0.94	2.20	3.4
Magnesium and calcium salts	0.04	...	...
Alkaline carbonates	...	...	...

[1] These figures are too high, as they refer to the total precipitate obtained with alcohol.

In order to demonstrate the presence of the sulphocyanides it is usually only necessary to heat a few c.c. of the pure saliva, faintly acidified with hydrochloric acid, with a dilute solution of perchloride of iron, when a red color will be seen to develop. If necessary, larger quantities, such as 100 c.c., are evaporated, and the test applied to the concentrated fluid. Of organic matter a little albumin, mixed with mucin, and about 1 gramme of urea pro litre are found. Of all these substances, the ptyalin is especially interesting from a physiologic point of view. It may be prepared in a pure state, according to Gautier's method:

To a large quantity of saliva alcohol (98 per cent.) is added as long as a flocculent precipitate is seen to form. This is collected upon a small filter and dissolved in a little distilled water. The solution thus obtained is treated with several drops of a solution of bichloride of mercury, in order to remove albuminous material, which is filtered off. The excess of mercury is removed by means of sulphuretted hydrogen, when the remaining liquid is evaporated at a temperature of from 35° to 40° C., and taken up with strong alcohol. The insoluble residue is dissolved in a little water, filtered, dialyzed in order to remove inorganic salts, and finally precipitated with strong alcohol, when ptyalin will separate out in light flakes. Obtained in this manner ptyalin is a white, amorphous substance, soluble in water, dilute alcohol, and glycerine. In neutral or even slightly alkaline solutions, but not in acid solutions, ptyalin rapidly transforms boiled starch into dextrin and sugar at a temperature of from 35° to 40° C. This transformation takes place according to the equation:

$$\underset{\text{Starch.}}{10C_6H_{10}O_5} + 4H_2O = \underset{\text{Maltose.}}{4C_{12}H_{22}O_{11}} + \underset{\text{Achroödextrin.}}{C_6H_{10}O_5} + \underset{\text{Erythrodextrin.}}{C_6H_{10}O_5}$$

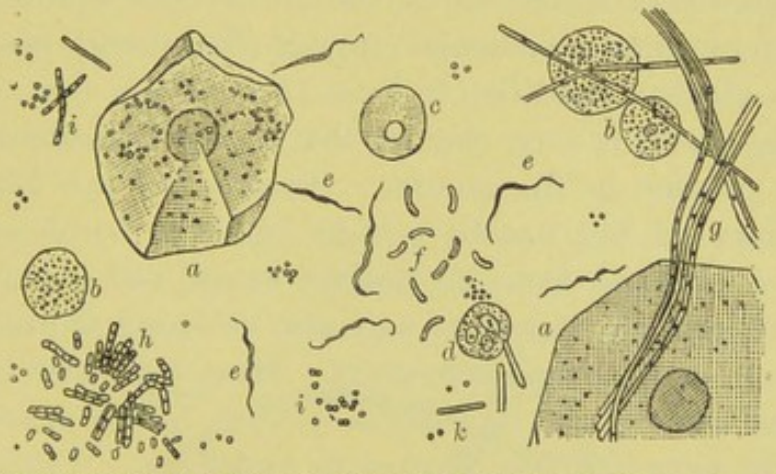
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The test for nitrites, which may likewise be present in the saliva, is conducted in the following manner: About 10 c.c. of saliva are treated with a few drops of *Ilasvay's reagent* and heated to a temperature of 80° C., when a red color will develop in the presence of nitrites. The reagent is prepared as follows: 0.5 gramme of sulphanilic acid in 150 c.c. of dilute acetic acid, and 0.1 gramme of naphtylamin are dissolved in 20 c.c. of boiling water. After standing for some time the supernatent fluid is poured off from the blue sediment, treated with 150 c.c. of dilute acetic acid and kept in a *sealed* bottle.

Microscopic Examination of the Saliva.

If normal saliva be allowed to stand, two layers will be seen to form, viz., an upper clear and a lower cloudy layer, which latter contains certain morphologic elements. Among these salivary corpuscles, pavement epithelial cells, and micro-organisms are found. (Fig. 26.)

FIG. 26.



Buccal secretion (eye-piece III., obj. Reichert, 1/15. homogeneous immersion; Abbe's mirror, open condensers). Friedländer's and Günther's method (v. JAKSCH). *a*, epithelial cells; *b*, salivary corpuscles; *c*, fat-drops; *d*, leucocytes, *e*, spirochæta buccalis; *f*, comma-bacillus of mouth; *g*, leptothrix buccalis; *h*, *i*, *k*, various fungi.

The salivary corpuscles resemble white corpuscles very closely, but differ in their greater size and coarser appearance. The epithelial cells found in the saliva are large, irregular, polygonal cells, provided with well-defined nuclei and nucleoli; they exhibit certain irregularities in size according to their origin, and belong to the class of pavement or stratified epithelium.

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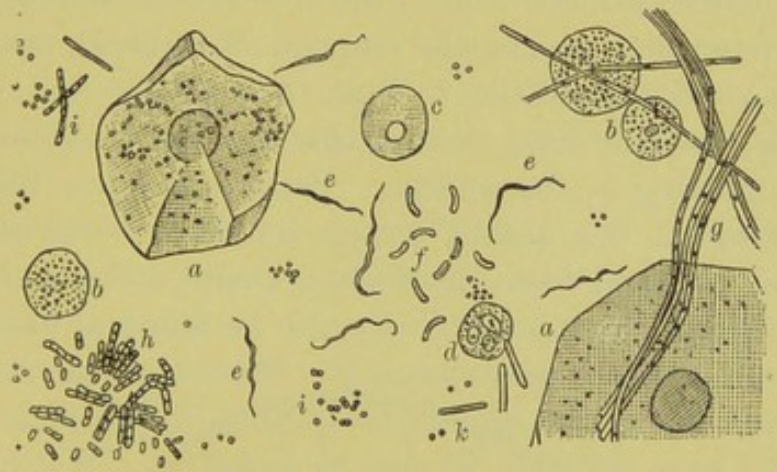
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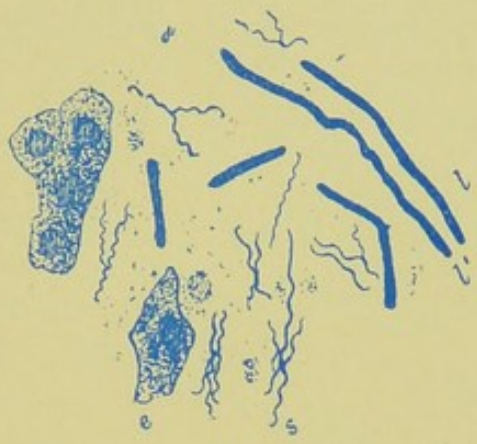
then undoubtedly derived from ingested food, bacteria are always present in large numbers, and it cannot be surprising that all forms which are found in the air, food, and drink may here be encountered. (Plate VI., Fig. 1.) Some of these, such as leptothrix buccalis innominata, bacillus buccalis maximus, leptothrix buccalis maxima, iodococcus vaginatus, spirillum sputigenum, and spirochæte dentium, are always present. Together with other bacteria these have been found in carious teeth, in abscesses communicating with the mouth and pharynx, and in exudates on the mucous membranes of these parts. In all probability, however, they are non-pathogenic. In this connection it is interesting to note that in contradistinction to the bacteria which are only temporarily found in the mouth the majority of those which are constantly present cannot be cultivated on artificial media.

Important from a practical standpoint is the fact that a number of pathogenic micro-organisms may at times be found under normal conditions. The diplococcus pneumoniæ, also known as the pneumococcus of Fraenkel and Weichselbaum, the diplococcus lanceolatus, the micrococcus lanceolatus, the micrococcus septicæmiæ sputi, and the micrococcus pneumoniæ cruposæ (Sternberg), has thus been found in a virulent condition in from 15 to 20 per cent. of healthy individuals, and it is even claimed that in a non-virulent state it is *constantly* present in the mouth. Streptococci are likewise frequently observed, but usually possess but little virulence or none at all when obtained from the healthy mouth and tested upon animals. Pyogenic staphylococci may also be found at times, but are far less common than the streptococci. Most important is the occasional occurrence of the diphtheria bacillus in the mouth in individuals who have not been exposed to contagion. Welch[1] mentions that virulent organisms were found by Park and Beebe in the healthy throats of eight out of 330 persons in New York, who gave no history of direct contact with cases of diphtheria. Two of these eight persons later developed the disease. Non-virulent bacilli were found in twenty-four individuals of the same series, and the pseudo-diphtheria bacillus in twenty-seven. Other pathogenic bacteria which may be found in normal mouths are the micrococcus tetragenus, the bacillus pneumoniæ of Friedländer, the bacillus crassus sputigenus, and the bacillus coli communis.

[1] Dennis' System of Surgery: Surgical Bacteriology.

PLATE VI.

FIG. 1.



Bacteria of the Mouth. (Cornil Babes.)

FIG. 2.



Leptothrix Buccalis. (v. Jaksch.)

It is interesting to note that the secretions of the mouth and throat, as most secretions of the body, possess a certain degree of germicidal power. The staphylococcus aureus, the streptococcus pyogenes, the micrococcus tetragenus, the typhoid bacillus, and the cholera spirillum, when present in moderate numbers, are thus killed by the saliva. The diphtheria bacillus, however, is far more resistent, and may survive for twenty-four to forty days. It has been found as a matter of fact that the organism may be demonstrated in the throats of some individuals who have passed through an attack of diphtheria, during several weeks after all the clinical symptoms have disappeared. The diplococcus pneumoniæ is even said to grow well in saliva, although it rapidly loses its virulence. By then cultivating it upon pneumonic sputum, however, the virulence of the organism is again restored. The individual bacteria will be considered in detail later on.

Pathologic Alterations.

It has been mentioned that from 600 to 1200 c.c. of saliva are secreted in the twenty-four hours. This quantity varies under certain conditions. An increase is thus frequently noted in pregnancy, in various neurotic conditions, in inflammatory diseases of the mouth, in dental caries following the administration of pilocarpin, in poisoning with mercury, acids, and alkalies. The quantity is diminished in all febrile diseases, in diabetes, and often in nephritis. The effect of psychic emotions upon the secretion of saliva as well as of other glands is well known, an increase or decrease in the flow being produced under various conditions.

In determining whether or not salivation actually exists the physician should not only be guided by the statements of his patient, but an actual estimation of the amount secreted within a definite period of time should be made. Hysterical individuals not infrequently complain of "salivation," when a direct estimation will show that the amount of saliva is not only not increased, but actually diminished.

Among qualitative changes may be mentioned an increase in the amount of urea, which has been repeatedly observed, especially in nephritis.

Urea may be demonstrated as follows: The saliva is extracted with alcohol, the filtrate evaporated, and the residue dissolved in

amyl alcohol. This is allowed to evaporate spontaneously, when crystals of urea will separate out, and may then be examined microscopically and chemically. (See Urine.)

Bile-pigment and sugar have thus far never been found in the saliva.

Of drugs, potassium iodide and potassium bromide rapidly pass into the saliva. Upon this property the indirect examination of the gastric juice as to its digestive power—*i. e.*, the presence or absence of free hydrochloric acid—by means of the potassium iodide and fibrin packages of Günzburg, is partly based.

In order to test for potassium iodide strips of filter-paper moistened with starch solution are immersed in the saliva acidified with nitric acid: in the presence of potassium iodide the starch-paper will turn blue.

The Saliva in Special Diseases of the Mouth.

Catarrhal Stomatitis. In this affection the quantity of saliva is increased. Microscopically an increased number of epithelial cells and many leucocytes are noted, their number depending upon the intensity of the morbid process.

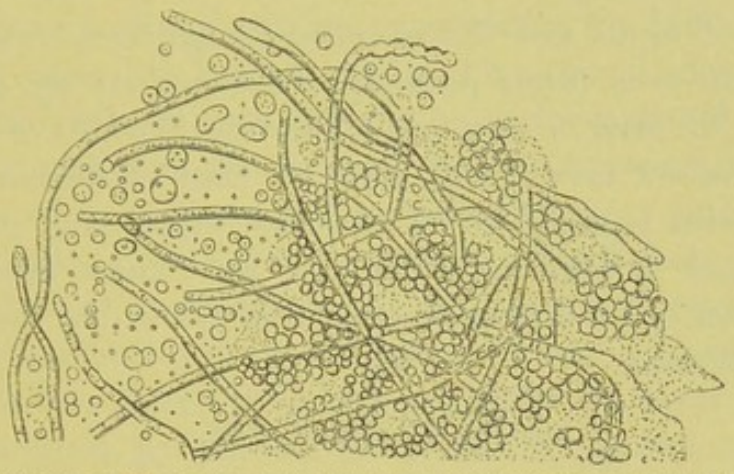
Ulcerative Stomatitis. In this condition, following mercurial poisoning or scurvy, the same appearance is noted microscopically as in simple stomatitis. In addition there may be observed necrotic tissue, red blood-corpuscles, and innumerable leucocytes. The reaction of the saliva is intensely alkaline, its color markedly brown, and its odor fetid.

Gonorrhœal Stomatitis. The number of cases of gonorrhœal stomatitis that have thus far been observed is small. The disease, however, has as yet received but little attention, and is probably more common than is generally supposed. In the adult it may be contracted through coitus *contra naturam*, while in the newborn the infection is undoubtedly brought about in the same manner as the corresponding disease of the conjunctiva. In suspected cases the exudate which forms upon the gums, the tongue, and the palate should be examined for the presence of gonococci. In adults the organism has thus far not always been found; in the newborn, however, Rosinski has succeeded in demonstrating its presence in all cases examined.

Thrush. Oïdium albicans (Fig. 27) is mostly observed in chil-

dren, but may also occur in adults, and especially in phthisical individuals, sometimes lining the whole mouth. If in such a case a bit of the membrane be pulled off and examined microscopically, it will be found to consist of epithelial cells, leucocytes, and granular detritus, with a network of branching, band-like formations, which

FIG. 27.



Oïdium albicans, the vegetable parasite of muguet or thrush.
(Reduced from CH. ROBIN.)

present distinct segments. The contents of the segments are clear, and usually contain two highly refractive granules—the spores, one of which is situated at each pole. These segments diminish in size toward the end of each band, their contents at the same time becoming slightly granular.

TARTAR.

In a bit of tartar scraped from the teeth actively moving spirochætæ are seen, as well as long, usually segmented bacilli, frequently forming bands which are colored a bluish-red by a solution of iodo-potassic iodide. Leptothrix buccalis, shorter bacilli which are not colored by the above reagent, micrococci, and a large number of leucocytes and epithelial cells which have undergone fatty degeneration are also found.

COATING OF THE TONGUE.

A brown coating of the tongue is often observed in severe infectious diseases, consisting of remnants of food and incrustated blood. Microscopically, in addition to a large number of epithelial cells, enormous numbers of micro-organisms and a large number of dark,

cell-like structures, probably derived from desquamated epithelial cells, are found. The white coating of the tongue contains epithelial cells in large numbers, many micro-organisms, and a few salivary corpuscles.

TUBERCULOSIS OF THE MOUTH.

In cases of lupus and the so-called benign form of tuberculosis of the mouth it is rarely possible to demonstrate the presence of tubercle bacilli, even in scrapings taken from the base of the ulcers, or in the diseased tissue itself, while in cases of ulcerative disease associated with phthisis in its advanced stages they may be frequently found in large numbers. In some cases, however, their demonstration is by no means easy. In the saliva they are only exceptionally seen.

ACTINOMYCOSIS.

In cases of actinomycosis it is occasionally possible to demonstrate the presence of the specific organism in or about carious teeth. More commonly, however, the patients are not seen until the primary symptoms of the disease have disappeared, when the typical kernels can no longer be found at the *original* points of entry or have become unrecognizable owing to calcification and retrogressive changes.

Usually the disease has already progressed to the formation of a distinct tumor or abscess, and it may then be necessary to make an exploratory incision and to examine the scrapings which are brought away. The number of kernels which may be found is at times very small, but a careful examination will probably always lead to their detection if the disease in question be actinomycosis.

COATING OF THE TONSILS.

Pharyngomycosis Leptothrica.

In the props met with in the crypts of the tonsils in cases of follicular tonsillitis, as also in persons who have had frequent attacks of tonsillitis, according to Chiari, epithelial cells and long, segmented fungi—the leptothrix buccalis (Plate VI., Fig. 2)—which are colored bluish-red with a solution of iodo-potassic iodide, are seen. At times patches composed of these fungi extend over a con-

siderable area of the tonsils, so that it may be doubtful whether or not the disease be a beginning diphtheria. A microscopic examination, however, will in such cases settle all doubts.

Diphtheria.

Recognizing the great importance of an early diagnosis in such a dreaded disease as diphtheria, an examination for Löffler's bacillus in doubtful cases has become just as important to-day as that for the bacillus of tuberculosis, and every physician should make himself familiar with the methods employed for its recognition.

By means of a sterilized, stout platinum loop, a pair of forceps, or a cotton swab, a piece of membrane is scraped from the tonsils, the soft palate, or the pharynx and at once transferred to a sterilized test-tube, closed with a pledget of cotton. A particle of the membrane is then spread in as thin and uniform a layer as possible, upon a cover-glass, by means of the platinum loop or forceps, which have been previously passed through the flame of a Bunsen burner. When dry the specimen is fixed by being passed through the flame three or four times, when it is ready for staining. For this purpose Löffler's alkaline solution of methylene-blue, which consists of 30 c.c. of a concentrated alcoholic solution of methylene-blue in 100 c.c. of an aqueous solution of potassium hydrate (1 : 10,000), may be advantageously employed, the specimen being stained for from five to ten minutes. It is then rinsed in water, placed on a slide, the excess of water removed with filter-paper, and examined with a one-twelfth oil-immersion lens.

A dahlia methyl-green solution may likewise be employed. This consists of 10 grammes of a 1 per cent. aqueous solution of dahlia-violet and 30 grammes of a 1 per cent. aqueous solution of methyl-green. The specimen is stained for from one to two minutes.

If it is desired to employ Gram's method, the specimen is most conveniently stained for three minutes with a freshly prepared concentrated alcoholic solution of gentian-aniline water. This is prepared by adding aniline oil to 10 c.c. of distilled water, drop by drop, thoroughly shaking after the addition of each drop, until the solution becomes opaque. It is then filtered and treated with 10 c.c. of absolute alcohol and 11 c.c. of a concentrated alcoholic solution of gentian-violet. The specimen is decolorized in a solution composed of 1 gramme of iodine and 2 grammes of potassium

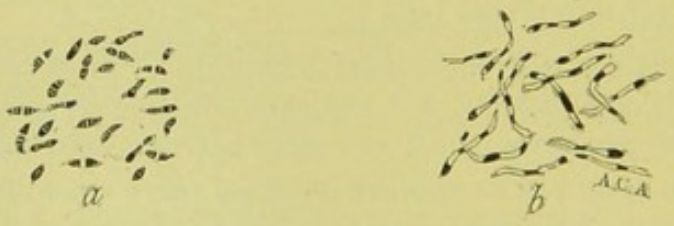
iodide, dissolved in 300 c.c. of water. After remaining in this solution for five minutes the specimen is rinsed in alcohol and the process repeated until the violet color disappears. It is then transferred to absolute alcohol, oil of cloves, and mounted in balsam.

Cultures should also be made, preferably upon a mixture of blood-serum and bouillon, as recommended by Löffler. This is composed of three parts of blood-serum and one part of bouillon, containing 10 per cent. of peptone, 3 per cent. of grape-sugar, and 0.5 per cent. of sodium chloride, the mixture being solidified in the usual manner. Upon this medium Löffler's bacillus grows so much more rapidly than other organisms usually present in the secretions of the mouth and throat that at the end of twenty-four hours they often form the only colonies that attract attention. Should other colonies of similar size be present these are generally quite different in appearance. In this manner a diagnosis can be made upon the day following the inoculation of the tube.

In the absence of blood-serum bouillon, alkaline bouillon, nutrient gelatin, nutrient agar, glycerine-agar, and potato may be employed. Coagulated egg-albumin, as pointed out by Booker, and milk are also good soils.

The colonies are large, round, elevated, and grayish-white in color, with a centre that is more opaque than the slightly irregular periphery. The surface of the colony is at first moist, but after a day or two assumes a dry appearance.

FIG. 28.



Bacillus of diphtheria. (ABBOTT.)

a. Its morphology when cultivated on glycerine agar-agar. *b*. Its morphology as seen in cultures on Löffler's blood-serum.

The bacillus (Fig. 28) is non-motile and varies in size and shape, its average length being from 2.5 μ to 3 μ, its breadth from 0.5 μ to 0.8 μ. Its morphologic characteristics are so peculiar as to render its identification upon cover-slip preparations and in sections of the diphtheritic membrane an easy matter in most cases.

Sometimes the organism appears as a straight or slightly curved rod; especially characteristic, however, are irregular and often bizarre forms, such as rods with one or both ends terminating in a little knob, and rods broken at intervals, in which short, well-defined round, oval, or straight segments can be made out.

Some forms stain uniformly, others in an irregular manner; the most common present the appearance of deeply stained granules in faintly stained bacilli.

Streptococci are also seen, as a rule, and it may be said that the gravity of a case is directly proportionate to the number of streptococci present.

It is important to note that diphtheria bacilli may still be found in the throat for weeks after all clinical symptoms have disappeared. Patients should hence be isolated until a bacteriologic examination has demonstrated the absence of the organism.

CHAPTER III.

THE GASTRIC JUICE AND GASTRIC CONTENTS.

THE SECRETION OF GASTRIC JUICE.

The gastric juice is the result of the glandular activity of the stomach, and the only secretion of the digestive tract which presents an acid reaction.

As is well known, the mucous membrane of the stomach is covered throughout its entire extent by a single layer of cylindrical epithelium, which dips down in places to line the orifices and larger ducts of the numerous tubular glands with which it is beset. Of these latter, two kinds have been described, viz., the fundus and pyloric glands, so named from the location at which they are principally found. In the secretory portion of a fundus gland two different sets of cells can be distinguished, one being small, granular, and polyhedral or columnar, bordering upon the narrow lumen of the tube, termed chief or principal cells by Heidenhain; they are also known as central or adelomorphous cells. These stain with aniline-dyes to only a slight extent. The others, known as parietal, delomorphous, or oxyntic cells, are variously situated between the adelomorphous cells and the membrana propria, being most numerous in the necks of the glands. They are larger than the chief cells, oval or angular and finely granular in structure, possessing a strong affinity for the aniline-dyes. The pyloric glands, which are found only in the region of the pylorus, on the other hand, are characterized by the greater length of their ducts, which are also lined by the cylindrical epithelium of the mucous membrane proper. The secretory portion of these glands is represented by a single layer of short and finely granular, columnar cells, which closely resemble the chief cells of the fundus glands. In addition to these a few isolated cells, the cells of Nussbaum, are found, which in structure and in their behavior to aniline-dyes resemble the parietal cells.

Upon chemical examination the gastric juice is seen to consist

essentially of water, free hydrochloric acid, pepsin, rennet (a milk-curdling ferment), mucus, and certain mineral salts.

Of these constituents free hydrochloric acid is secreted by the parietal cells, pepsin and the milk-curdling ferment by the chief cells of the fundus and the pyloric glands, while the mucus is the product of the cylindrical goblet-cells lining the stomach and the wider portions of its glandular ducts.

It must be borne in mind, however, that the ferments mentioned do not exist in the cells as such, but as zymogens, which are transformed into the ferments through the activity of the free hydrochloric acid. According to modern investigations, moreover, the zymogens only are *secreted* by the cells.

Until recently it was supposed that the gastric juice is only secreted upon appropriate stimulation of the nervous mechanism of the stomach, either directly or indirectly, and that the stomach in its quiescent state—*i. e.*, when not digesting—is empty. The researches of Schreiber and Martius, however, have rendered the correctness of this view very doubtful, as they were able to obtain quantities of gastric juice, varying from 1 to 60 c.c., from the non-digesting stomach of every normal person examined; and the writer, likewise, has never failed to obtain a few c.c. under the same conditions.

TEST-MEALS.

Although the secretion of gastric juice takes place continuously, the amount that can usually be obtained from the non-digesting organ is not sufficient for analytical purposes. It is, therefore, necessary to stimulate the glandular apparatus of the stomach to increased activity. This may be accomplished with thermic, chemical, electric, and digestive stimuli, among which the last named are the most convenient and the most effective, furnishing a picture not only of the chemical, but also of the motor and resorptive activity of the organ. The analytical results will, however, depend to a large extent upon the character of the food ingested, starches and fats exerting but a slight stimulating effect, while proteids cause a copious secretion of gastric juice. The ingestion of fluids at the same time will likewise influence the results obtained, owing to the dilution of the gastric juice. The time of the height of digestion, moreover, varies with the kind and quantity of food taken. In order to obtain uniform results it is, therefore, neces-

sary to withdraw the gastric contents at a certain period after the ingestion of a meal of known composition and bulk.

Numerous test-meals have been proposed. The following are the most important:

The Test-breakfast of Ewald and Boas.

This consists of from 35 to 70 grammes of wheat-bread and from 300 to 400 c.c. of water or weak tea without sugar. It is best to give this meal to the patient early in the morning when the stomach is empty—*i. e.*, as a breakfast. The gastric contents are obtained one hour later.

The Test-dinner of Riegel.

This consists of a plate of soup (400 c.c.), a beefsteak (200 grammes), a slice or two of wheat-bread (50 grammes), and a glassful of water (200 c.c.). The contents of the stomach are obtained after four hours. The disadvantage of this method lies in the fact that the lumen of the stomach-tube is frequently occluded by large pieces of undigested meat, a source of annoyance which may be guarded against, however, by making use of finely chopped meat.

The Double Test-meal of Salzer.

For breakfast the patient receives 30 grammes of lean, cold roast, hashed or cut into strips sufficiently small as not to obstruct the stomach-tube, 250 c.c. of milk, 60 grammes of rice, and one soft-boiled egg. Exactly four hours later the second meal is taken, consisting of 35–70 grammes of stale wheat-bread and 300–400 c.c. of water. The gastric contents are withdrawn one hour later. In his manner the gastric juice is not only obtained at the height of digestion, but an idea may at the same time be formed of the motor power of the stomach. Under normal conditions the organ should contain no remnants of the first meal at the time of examination.

The Test-breakfast of Boas.

This consists of a plateful of oatmeal-soup, prepared by boiling down to one pint a quart of water to which one tablespoonful of rolled oats has been added. A little salt may be used if desired, but nothing more. The contents of the stomach are obtained one

hour later. This test-meal was devised by Boas in order to guard against the introduction from without of lactic acid, which is present in all kinds of bread. The meal is employed in doubtful cases of cancer of the stomach in which a quantitative estimation of lactic acid is to be made, the stomach being washed out completely the night before.

Still other test-meals have been suggested, but they do not possess any material advantage over those described.

THE STOMACH-TUBE.

The stomach-tubes which are now generally in use are essentially large Nélaton catheters. They should measure at least from 72 to 75 cm. in length, and be provided with three fenestra, of which one is placed at the end of the tube and two laterally, as near the end as possible. For the purpose of washing out the stomach the tube is connected with a glass funnel by means of ordinary rubber tubing, which can be detached from the stomach-tube proper. There is no advantage in rubber funnels or in having a continuous tube.

It is important that the tubes should be thoroughly cleansed in hot water as soon after use as possible. The advice of Boas, moreover, to have special marked tubes for tuberculous, syphilitic, and carcinomatous patients should be borne in mind. Patients in whom lavage is to be practised for any length of time should provide their own instruments.

Contraindications to the Use of the Tube.

Of direct contraindications to the use of the tube there should be mentioned the existence of the various forms of valvular disease when in a state of imperfect compensation, angina pectoris, arteriosclerosis of high degree, aneurism of the large arteries, recent hemorrhages from whatever cause, marked emphysema with intense bronchitis, acute febrile diseases, etc.

The Introduction of the Tube.

The technique of the introduction of the tube should be as simple as possible; the exhibition of complicated bottle-arrangements for

the purpose of obtaining the gastric juice only adds to the excitement of a nervous patient, and should be avoided. The patient's clothing and floor of the room should be protected from being soiled by material that may be vomited along the sides of the tube, the dribbling of saliva, etc. For this purpose Turck's rubber bib with pouch may be advantageously employed. "It is so arranged as to form a pouch in front to catch the saliva or stomach-contents that may be thrown off from the mouth or stomach. A detachable tube passes from the bottom of the pouch and is conducted into a basin or any vessel."[1]

FIG. 29.



Boas' bulbed tube.

Cocainization of the pharynx is *rarely* necessary, but may be resorted to in hyperæsthetic individuals, a 10 per cent. solution being employed.

The tube, held like a pen, is introduced to the posterior wall of the pharynx, the patient bending his head *forward, and not backward*, as is usually advised. The patient is then told to swallow, but this is not absolutely necessary. The tube is pushed on until resistance is felt when it meets with the floor of the stomach. The entire process does not occupy ten seconds. At the least sign of cyanosis, or of marked pallor, the tube should be withdrawn at once and the patient observed for a day or two before a second attempt is made.

If the gastric juice does not flow at once, the patient is instructed to bear down with his abdominal muscles, and, if this be insufficient, to cough a little. Repeated attempts of this kind will usually bring about the desired result, unless the tube has not been introduced far enough or too far; in the latter case it will double upon itself, so that its end may actually stand above the level of the liquid. (Method of expression.)[2]

Aspiration must at times be employed. For this purpose Boas' bulbed tube (Fig. 29) is most convenient. The manner in which it

[1] Manufactured by G. Tiemann & Co., New York.

[2] Pressing upon the abdomen with the hands is of no object.

is used is the following: The proximal end of the tube, after having been introduced into the stomach, is compressed and the bulb squeezed, when the distal end is clamped and the bulb allowed to expand. When this is repeated several times a partial vacuum is produced in the tube, which usually causes a flow of gastric juice. In the absence of such an instrument the stomach-tube may be connected with a bottle in which a partial vacuum has been established by aspiration (Fig. 30). Unless the patient is accustomed to the introduction of the tube these more complicated apparatus should be avoided as much as possible. (Method of aspiration.)

The writer has found that in cases in which gastric juice cannot be obtained by expression the flow may often be started by suction with the mouth, and he regards this method as preferable to the one just described. With due precautions, viz., holding the tube between the fingers near the mouth of the patient, so as to be informed at once, by the sense of touch, when the stomach contents have reached this point, unpleasant results will be obviated. If only a very small amount of gastric juice is present in the stomach —*i. e.*, when a definite flow cannot be established—it is best to suck lightly with the mouth, to compress the tube firmly, to remove it as rapidly as possible, and empty it into a little dish. A few drops sufficient to test for free hydrochloric acid can thus always be obtained, even from the non-digesting organ.

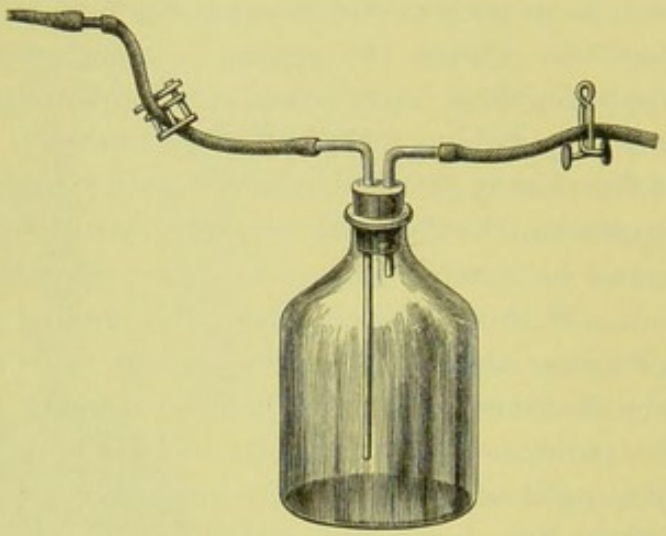
Einhorn's bucket-method is of little value, as the amount of gastric juice which can be obtained is entirely insufficient for analytical purposes. It may be employed, however, in patients who are particularly nervous and object to the use of the tube, and possibly, also, when its use is contraindicated. The test for hydrochloric acid can be made, but the amount of information which can thus be obtained is in itself of comparatively little importance.[1]

In order to *wash out the stomach* the funnel-tube is attached, the funnel filled with lukewarm water or any desired medicated solution, elevated to a height somewhat above the head of the patient, and the water allowed to flow. From 500 to 1000 c.c. may be introduced at one time. By suddenly depressing and inverting the funnel, over a suitable vessel, before all water has left the funnel, a siphon arrangement is established and the stomach emptied. It is well to measure the returning water as well as the

[1] For a description of this method the reader is referred to Einhorn's article in the Twentieth Century Practice, vol. viii. Wm. Wood & Co.

amount introduced. Should the flow diminish or cease before all the water has been removed, the end of the tube probably stands above the level of the liquid, and the flow can be started again by pushing the tube on further or by withdrawing it a little, as the case may be.

FIG. 30.



Arrangement of bottle for the aspiration of the gastric contents.

Washing out the stomach soon after the ingestion of a full meal is always very tedious and annoying if not an impossible procedure, as the fenestra readily become obstructed. Should this occur, the funnel, filled with water, is elevated as high as possible, with a view to overcome the obstruction by hydrostatic pressure, or, if this prove insufficient, the funnel-tube is detached and the obstruction dislodged by means of air, for which purpose a Politzer-bag or the bulb of a Boas' tube is very convenient.

GENERAL CHARACTERISTICS OF THE GASTRIC JUICE.

Pure gastric juice is an almost clear, faintly yellowish fluid, of a sour taste and a peculiar, characteristic odor. Its specific gravity varies between 1.002 and 1.003, corresponding to the presence of but 0.5 per cent. of solids. Its reaction, owing to the presence of hydrochloric acid, is acid.

AMOUNT.

Very little is known of the total quantity of gastric juice secreted in the twenty-four hours. The figure given by Beaumont, viz., 180 grammes *pro die*, based upon observations made upon the often-quoted Canadian hunter, Alexis St. Martin, is undoubtedly too low. The amount given by Bidder and Schmidt, viz., that corresponding to about one-tenth of the body-weight, is probably more correct.[1] It may be stated *a priori*, however, that the quantity secreted varies within wide limits, being influenced by numerous factors and notably by the degree of the appetite and the amount and character of the food taken, especially that of the proteids. The age and sex of the individual, the time of day, notably in its relation to the ingestion of food, the emotions, etc., undoubtedly influence the glandular activity of the stomach.

From the non-digesting organ, as has been pointed out, from 1 to 60 c.c. of gastric juice may be obtained at one time. The amount which can be procured during the process of digestion, on the other hand, varies with the amount of liquid ingested, the time of expression, the size and motor power of the stomach, and the degree of transudation; the process of resorption probably does not play any part, as it has been ascertained that very little water, if any, is absorbed by the stomach.

According to Boas, from 20 to 50 c.c. of filtrate can be obtained exactly one hour after the ingestion of Ewald's test-breakfast under physiologic conditions.

Abnormally large quantities of gastric juice are practically only found in cases of so-called *hypersecretion*, the "Magensaftfluss" of the Germans, which may occur periodically or continuously. Formerly the presence of gastric juice in appreciable quantities in the non-digesting stomach was regarded as conclusively proving the existence of this disease, but in the light of Schreiber's researches this position can no longer be maintained. The diagnosis should, hence, only be made when in conjunction with the clinical symptoms of hypersecretion from 100 to 1000 c.c. of pure *gastric juice* can be obtained from the non-digesting organ. To this end the stomach should be emptied completely by the tube before retiring,

[1] Grünewald's figure—*i. e.*, 1580 grammes—the author likewise regards as too low. The daily secretion appears to vary between 2000 and 3000 c. c.

and an examination made upon the following morning, no food or liquids being allowed in the meantime.

In various pathologic conditions abnormally large quantities of liquid may be obtained, which cannot, however, be regarded as gastric juice. Attention will be drawn to these conditions at another place.

CHEMICAL EXAMINATION OF THE GASTRIC JUICE.

Chemical Composition of the Gastric Juice.

As has been briefly shown above the gastric juice consists of water, free hydrochloric acid, certain ferments, their zymogens, and mineral salts. Analyses giving the exact chemical composition of pure, uncontaminated gastric juice in man are still wanting, owing to the difficulty of excluding the saliva. In patients the subjects of gastric fistula analytical studies have, however, repeatedly been made, and from the table below, taken from Schmidt, an idea may be formed of the various amounts of solid constituents contained in 1000 parts of gastric juice uncontaminated by food or the products of digestion, but not free from saliva:

Water	994.40
Solids	5.60
Organic material	3.19
Sodium chloride	1.46
Calcium chloride	0.06
Potassium chloride	0.55
Ammonium chloride	...
Hydrochloric acid	0.20
Calcium phosphate, Magnesium phosphate, Iron phosphate	0.12

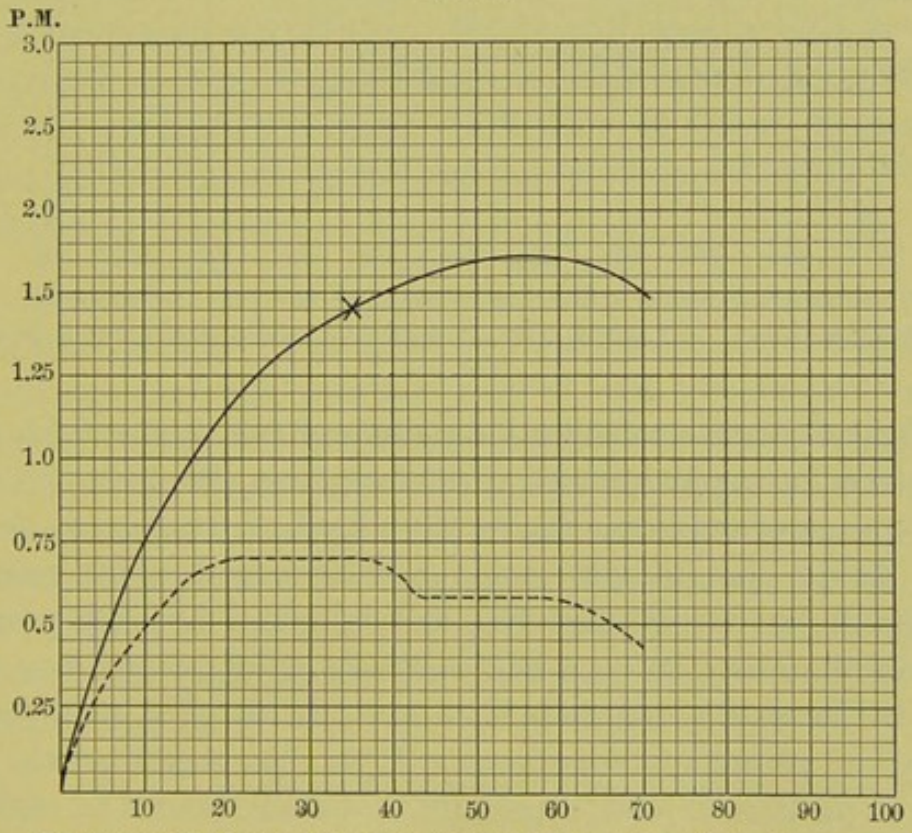
The Acidity of the Gastric Juice is Referable to the Presence of Free Hydrochloric Acid.

It has been conclusively demonstrated by Schmidt that the acidity of the gastric juice is due to the presence of free hydrochloric acid. After accurately determining the amount of chlorine and all basic substances present, it was found that after all of the latter had been saturated a quantity of hydrochloric acid still remained, which in the dog varied between 0.25 and 0.42 per cent., with an average

of 0.33 per cent. The amount of free acid was also determined by titration and the same results reached as by gravimetric analysis.

While the acidity of pure gastric juice—*i. e.*, gastric juice not contaminated by saliva or food in its various stages of digestion—is thus solely due to the presence of free hydrochloric acid, other factors enter into consideration in the examination of the gastric contents during the process of digestion. Acid salts and varying amounts of lactic acid derived from the carbohydrates of the food are also found. At the beginning of digestion the acidity, according to Ewald, is due to a certain extent to the presence of lactic acid.[1] Hydrochloric acid, it is true, is present at the same time, but is held in combination by albuminous material. Later on, when the albuminous affinities have become saturated, it appears as such, with the result that the formation of lactic acid progressively

FIG. 31.



Illustrating the curve of acidity after Ewald's test-breakfast. (ROSENHEIM.)

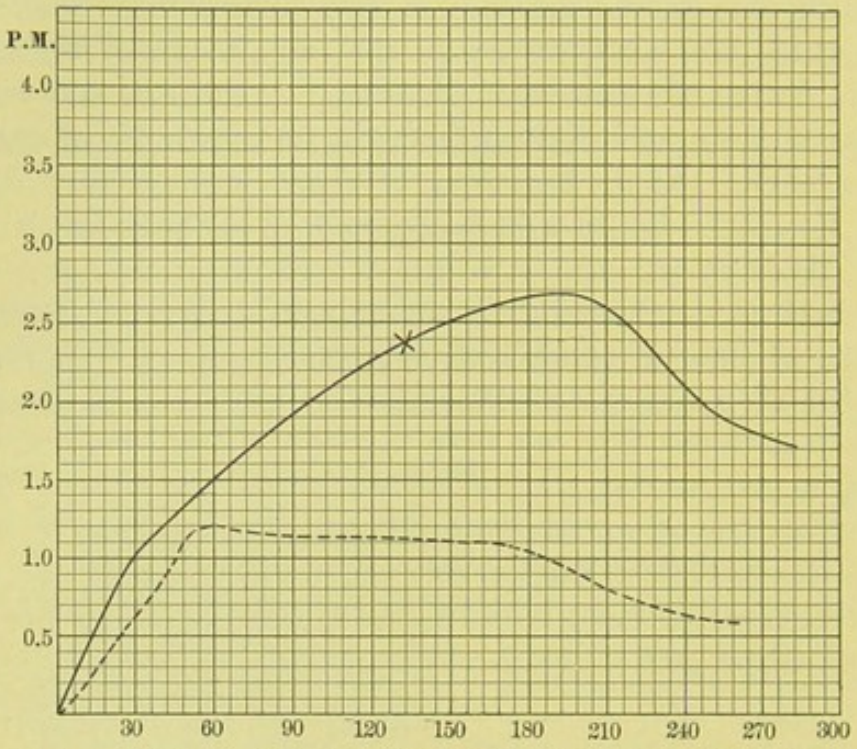
—— Hydrochloric acid. - - - - - Lactic acid. × Beginning of the stage of free hydrochloric acid. P M. Pro mille. The numbers upon the abscissa indicate the minutes.

diminishes, owing to the inhibitory action on the part of the hydrochloric acid upon the lactic-acid-producing organisms. The varying degrees of acidity after such test-meals as those of Ewald and

[1] See Lactic Acid, p. 153.

Riegel, at different periods of digestion, and the amount of the two acids present, may be seen from the accompanying diagrams (Figs. 31 and 32).

FIG. 32.



Illustrating the curve of acidity after Riegel's test-breakfast. (ROSENHEIM.)

—— Hydrochloric acid. - - - - - Lactic acid. × Beginning of the stage of free hydrochloric acid.

Under pathologic conditions the amount of free hydrochloric acid, as will be shown, may undergo great variations, diminishing on the one hand to zero, and increasing on the other to 0.5 per cent., or even more. At the same time the amount of lactic acid, which normally is present in very small amounts, and is absent altogether at the height of digestion, may greatly increase. Fatty acids, moreover, which are normally not present in the gastric juice, may also be observed in pathologic conditions. It is thus seen that the total acidity of the gastric juice, especially in disease, cannot be regarded as indicating the amount of one single acid, unless the absence of abnormal acids, lactic acid, and acid salts is insured.

Method of Determining the Total Acidity of the Gastric Contents.

To this end a known quantity of gastric juice is titrated with a one-tenth normal solution of sodium hydrate, using phenolphthalein as an

indicator, when the number of c.c. of the one-tenth normal solution employed, multiplied by the equivalent of 1 c.c. of this solution in terms of hydrochloric acid, will indicate the amount of acid present in terms of the latter, from which the percentage-acidity is readily calculated.

A normal solution of sodium hydrate is one containing the equivalent of its molecular weight in grammes—*i. e.*, 40 grammes, in 1000 c.c. of distilled water; a decinormal solution will, therefore, contain 4 grammes in the same volume of water. This quantity is dissolved in less than 1000 c.c. and the solution brought to the proper strength by titrating it with a solution of oxalic acid of known strength.

From the equation,

$$2NaOH + C_2H_2O_4 = C_2Na_2O_4 + 2H_2O,$$

it is seen that two molecules of NaOH (mol. weight 40) combine with one molecule of $C_2H_2O_4 + 2H_2O$ (mol. weight 126), or 4 parts by weight of the former with 6.3 of the latter. One-tenth gramme of oxalic acid would, hence, require 15.873 c.c. of the one-tenth normal solution of NaOH for its neutralization, as is apparent from the equations:

$$6.3 : 1000 :: 0.1 : x; \quad 6.3x = 100 \text{ and } x = \frac{100}{6.3} = 15.873$$

One-tenth gramme of pure, crystallized oxalic acid is dissolved in distilled water, and the solution titrated with the one-tenth normal solution of sodium hydrate which is to be corrected, using two or three drops of a 1 per cent. alcoholic solution of phenolphthalein as an indicator, until the rose color of the solution has entirely disappeared; 15.9 c.c. should bring about this result. As the NaOH solution, however, has been purposely made too strong, less will be required. The amount of water that must then be added in order to bring the solution to its proper strength is determined by the formula $C = \frac{Nd}{n}$, in which C represents the number of c.c. of water which must be added to the remaining solution, N the total number of c.c. remaining after one titration, n the number of c.c. consumed in one titration, and d the difference between the number of c.c. theoretically required and that actually used in one titration. The solution having thus been properly diluted, the correctness of its strength is again tested and a further correction made, if necessary, until absolute accuracy has been attained.

1000 c.c. of the one-tenth normal solution containing 4 grammes of NaOH are equivalent to 3.65 grammes of HCl, as is seen from the equation:

$$\underset{40}{NaOH} + \underset{36.5}{HCl} = NaCl + H_2O$$

1000 c.c of the $\frac{1}{10}$ normal solution represent 3.65 grms. of HCl.
100 " " " " " " 0.365 grm. " "
10 " " " " " " 0.0365 " " "
1 " " " " " represents 0.00365 " " ".

Application to the gastric juice: 5 or 10 c.c. of the filtered gastric juice are titrated with the one-tenth normal solution of sodium hydrate, using two or three drops of a 1 per cent. alcoholic solution of phenolphthalein as an indicator, until the rose color which appears after the addition of every drop of the sodium hydrate solution no longer disappears on stirring or becomes deeper after the addition of a further drop. The number of c.c. of the one-tenth normal solution employed multiplied by 0.00365 will then indicate the acidity of the 5 or 10 c.c. of gastric juice in terms of HCl, from which the percentage-acidity is readily calculated.

Example: 10 c.c. of gastric juice required the addition of 6.5 c.c. of the one-tenth normal solution; 6.5×0.00365 (*i. e.*, 0.0237) would hence indicate the acidity of the 10 c.c. of gastric juice in terms of HCl, and $0.0237 \times 10 = 0.237$, the percentage-acidity.

As these figures express only the amount of HCl in pure gastric juice obtained from normal individuals, it has been found more convenient for clinical purposes to indicate merely the degree of acidity by the number of c.c. of the one-tenth normal solution employed. In the above example, in which 6.5 c.c. of the latter were used, the percentage-acidity would thus be indicated by the figure 65; *i. e.*, the number of c.c. of the one-tenth normal solution necessary to neutralize 100 c.c. of gastric juice.

Under normal conditions figures varying from 40 to 60 are usually found one hour after the ingestion of Ewald's test-breakfast, while in pathologic conditions considerable variations are observed. It may be stated, as a general rule, that in the acute and chronic inflammatory conditions of the stomach, as well as in some of the neuroses, the acidity of the gastric contents is below normal. Higher figures are met with in cases of ulcer, in some cases of dilatation, and especially frequently in some of the neuroses, in which a degree of acidity corresponding to 90 or even more is not infrequently observed. Increased acidity, usually associated with

hypersecretion of gastric juice, is met with in the so-called *hypersecretio acida et continua* of Reichmann.

It has been pointed out that the reaction of normal gastric juice is always acid, owing to the presence of free HCl, and the same may be said to hold good for the gastric contents in general obtained from a normal individual. Pathologically an acid reaction is also the rule, as in those cases in which HCl is absent fatty acids and lactic acid in considerable amount usually make their appearance. It is, therefore, not at all surprising that an alkaline, neutral, or amphoteric reaction is but rarely, or, at least, not commonly, observed in the gastric contents artificially obtained, and practically only seen in the so-called mucous form of chronic gastritis. In vomited material such observations are quite common, not so much so, however, in the specimens first brought up as in those that are subsequently ejected. The vomited material in cases of so-called *vomitus matutinus*, which is usually referable to a chronic catarrhal condition of the pharynx, generally presents an alkaline reaction, owing to the fact that the fluid brought up is largely unchanged saliva.

The Source of the Hydrochloric Acid.

That the HCl is not directly derived from the chlorides ingested is shown by the fact that it is still secreted by a starving animal. The same point is also proved by the observations of Schreiber, which go to show that the secretion of HCl, as indicated above, is continuous, not to mention the well-known fact that material free from chlorine, when ingested, will cause the secretion of an acid gastric juice. It is apparent, then, that the chlorides of the blood must furnish the necessary chlorine, and as the pyloric glands, which contain no parietal cells, furnish an alkaline, and the fundus glands, which do contain parietal cells, an acid secretion, it is thought that these parietal cells are in some manner concerned in the production of the HCl. The exact manner in which this takes place has not been definitely ascertained, but it is not at all improbable that the HCl results from a "Masseneinwirkung" on the part of carbonic acid, which is present in large quantities in the blood as such, upon the sodium chloride, and that, owing to a specific action on the part of the parietal cells, the hydrochloric acid is secreted into the ducts of the glands of the stomach, while the sodium carbonate formed at the same time is returned to the blood.

Two factors are thus necessary in order that a normal amount of HCl should be secreted—*i. e.*, a normal condition of the blood and a normal condition of the cells. Whenever the integrity of either of these two factors becomes impaired it is clear that an abnormal secretion of HCl or none at all will result. The nervous system, furthermore, must be taken into consideration as a third factor, as, according to our present knowledge, normal innervation is the *sine qua non* for the normal activity of any organ. The secretion of HCl is impaired whenever the nutrition of the cells of the stomach suffers, whether this be the result of inflammatory lesions, new growths, or hyperæmic conditions of the stomach, the effect of renal, hepatic, or pulmonary diseases, etc., or in consequence of central or peripheral nervous influences.

In the *secondary dyspepsias*, then, the result of renal, hepatic, cardiac, or hæmic diseases, etc., an examination of the gastric juice for free HCl is of comparatively little value from a diagnostic point of view, although it may suggest valuable points for the dietetic treatment of such patients.

Significance of the Free Hydrochloric Acid.

It was formerly thought that the principal function of the stomach was a digestive one, and that in the stomach, owing to the action of hydrochloric acid and pepsin, albumins were, to a large extent, transformed into peptones and albumoses. As pepsin is active only in the presence of a free acid, it was thought, moreover, that the power of the hydrochloric acid to render pepsin physiologically active constituted its entire field of usefulness.

It had already been noted one hundred years ago, however, by the Abbé Spalanzani that pieces of meat immersed in gastric juice resisted the process of putrefaction for days, and when it was shown later on that the free mineral acids ranked among the most powerful of antiseptics, and that the stomach secreted an amount of free hydrochloric acid sufficient to prevent the development of most of the putrefactive organisms, the time had come to doubt the correctness of the view previously held.

Numerous experiments have been made in order to test the *antiseptic* and *germicidal power* of the gastric juice. Among the more important results achieved the following may be mentioned: The comma-bacillus of cholera Asiatica is destroyed by the normal acid

gastric juice, while infection results when this has been previously neutralized—a most important observation. The same holds good for numerous other pathogenic organisms which are of special interest to the clinician. Among these may be mentioned the various species of streptococcus, staphylococcus pyogenes aureus, the bacillus of anthrax, etc. Unfortunately, however, not all species of pathogenic organisms are destroyed by the acid of the gastric juice, and the spores of some of those, moreover, that are destroyed are possessed of a considerable degree of resistance. This is especially true of the tubercle-bacillus and in many cases of the spores of the anthrax-bacillus.

Those bacteria also which cause lactic acid and butyric acid fermentation resist the anti-fermentative power of the gastric juice to a certain extent, as may be concluded from the fact that they are always present in the intestines. At the beginning of the process of gastric digestion, when the hydrochloric acid secreted is immediately taken up by the albuminous bodies present, traces of lactic acid can usually be demonstrated in the gastric contents if carbohydrochlorates have been ingested. Later on, when free hydrochloric acid appears, lactic acid fermentation ceases. This observation is in perfect accord with the fact that the action of the lactic acid producers is prevented by the presence of 0.7 p. m. of free HCl.

From what has been said it may be argued that as the principal function of the stomach consists in the furnishing of an antiseptic and germicidal fluid, under suitable conditions life could go on in the absence of the stomach. That this is possible has actually been demonstrated by Czerny, who succeeded in removing almost the entire organ from a dog. Five to six years later the same animal was killed in Ludwig's laboratory, and it was found at the autopsy that "near the cardia a small portion of the stomach had remained, surrounding a globular cavity filled with food." This dog then had lived for almost six years practically without a stomach, had gained in weight, and was to all intents and purposes as healthy an animal as one provided with an entire organ. In human beings the subjects of carcinoma of the stomach, not the entire organ, it is true, but a considerable portion has been removed by operation, with the result that the patients enjoyed perfect health as far as could be ascertained, notwithstanding the fact that the remainder of the organ was incapable of secreting gastric juice. It is very probable, then, that the stomach, so far as the process of diges-

tion is concerned, is not absolutely necessary for the maintenance of life.

It has, furthermore, been demonstrated that a deficient secretion of HCl is noted in all cases in which an increased degree of intestinal putrefaction occurs, and while indol, phenol, and skatol, as well as their compounds with sulphuric acid, in the amounts observed in physiologic and pathologic conditions, are not thought to exert any toxic influence upon the body, it must be admitted that the observations were made upon animals, and that the results obtained may not be directly applicable to the human being. While a single large dose may not produce symptoms, moreover, it is not to be inferred that a *continuous* intoxication with the products of intestinal putrefaction may not lead to decided pathologic results.

The Amount of Free Hydrochloric Acid.

Pure gastric juice, according to Ewald, Szabo, and Boas, contains from 2 to 3 p. m. of free HCl.

In the digesting organ such amounts are met with at the height of digestion only after all albuminous and basic affinities have been saturated. The time at which free HCl can be demonstrated in the gastric contents after the ingestion of a meal will, hence, vary with the character of the food and its amount. When but little work is to be accomplished, free HCl is found much sooner than otherwise. After Ewald's test-breakfast, for example, free HCl appears after thirty-five minutes, the point of maximum acidity being reached after from fifty to sixty minutes, corresponding to the presence of 1.7 p. m. Following Riegel's meal, on the other hand, free HCl appears after 135 minutes and reaches its highest point, corresponding to 2.7 p. m., in from 180 to 210 minutes. (Figs. 31 and 32.)

Clinically it is necessary to distinguish between euchlorhydria, or the secretion of a normal amount of free HCl (0.1 to 0.2 per cent.), hypochlorhydria, or the secretion of a deficient amount of free HCl (less than 0.1 per cent.), hyperchlorhydria, in which more than 0.2 per cent. is found, and, finally, anachlorhydria, in which no HCl at all is secreted.

Euchlorhydria. Euchlorhydria, when associated with clinical symptoms pointing to gastric derangement, is most commonly observed in nervous dyspepsia. A chronic gastritis can always be excluded in the presence of a normal amount of free HCl, thus

constituting a most important point in the differential diagnosis between these two conditions, which can but rarely be definitely made from the clinical symptoms alone. A normal secretion of free HCl is, furthermore, observed in some cases of atony or hypatony of the muscular walls of the stomach.

Hypochlorhydria. Hypochlorhydria is associated with all those diseases in which the secretory elements have been more or less damaged, as in subacute and chronic gastritis, in some cases of ulcer of the stomach or the duodenum, in incipient carcinoma, dilatation, and atony.

Anachlorhydria. Not many years ago it was thought that the absence of free HCl from the gastric contents was pathognomonic of carcinoma of the stomach. This view, however, was soon abandoned, as it was shown that cases of carcinoma occur in which HCl is not only present, but present in excessive amounts. This is true especially of those cases in which the malignant growth has started upon the base of an old ulcer. It was, furthermore, shown that anachlorhydria exists in almost all cases of advanced chronic gastritis, and is a very common occurrence in neurasthenic and hysterical individuals, constituting the so-called hysterical anacidity.

Hyperchlorhydria. The existence of hyperchlorhydria is generally indicative of a gastric neurosis, and is thus frequently met with in its simplest form in certain neurasthenic individuals. Associated with a continuous hypersecretion of gastric juice it constitutes the neurosis that has been described under the term *hypersecretio acida et continua.* Hyperchlorhydria is also of frequent occurrence in cases of gastric ulcer, and may even occur in carcinoma, notably in those cases in which, as has been stated above, the new growth has started from an old ulcer.

Test for Free Acids.

Following a physical examination of the gastric contents, and, if acid, a determination of the general acidity, the next step will be to determine whether or not the acid reaction is referable to the presence of a free acid, of combined acids, or of acid salts.

The Congo-red Test. Congo-red is a carmine-colored powder, while its solutions are of a peach- or brownish-red color, which changes to azure-blue upon the addition of a free acid, but remains unaffected in the presence of an acid salt. Congo-red may be em-

ployed in solution or in the form of a test-paper, which latter, however, is less delicate than the solution, indicating the presence of 0.01 per cent. of HCl, while a positive reaction can still be obtained with the aqueous solution in the presence of 0.0009 per cent. of free HCl. The solution to be employed should be moderately dilute. The test-paper is prepared by soaking filter-paper, free from ash, in this solution, drying and cutting it into suitable strips. In order to test for the presence of a free acid it is only necessary to immerse a strip of the test-paper in the filtered gastric juice, or to add a drop or two of the solution to a small amount of the juice, when in the presence of free acid a blue color will develop, which varies from a sky-blue to a deep azure, according to the amount present.

A negative result will at once exclude the possibility of peptic activity, as pepsin acts only in acid solutions.

If, however, the result of the test be positive, the nature of the free acid must still be ascertained, and it is, therefore, necessary to test for free HCl, for lactic acid, and for certain fatty acids.

Tests for Free Hydrochloric Acid.

The various reagents which may be employed are given below arranged according to their degree of delicacy, viz.:

1.	Dimethyl-amido-azo-benzol	0.02 p.m.
2.	Phloroglucin-vanillin	0.05 "
3.	Resorcin	0.05 "
4.	Methyl-violet	0.2 "
5.	Tropæolin 00	0.3 "
6.	Emerald-green	0.4 "
7.	Mohr's reagent	1.0 "

The Dimethyl-amido-azo-benzol Test. This test has recently been introduced by Töpfer, and to judge from his observations, as well as from the author's experience, is destined soon to replace the phloroglucin-vanillin and resorcin tests in the clinical laboratory. The reagent may also be employed in the direct estimation of the amount of free HCl present. The delicacy of the reagent is such that the neutral yellow color of the indicator is changed to a reddish tinge upon the addition of but one drop of a one-tenth normal solution of HCl in 5 c.c. of distilled water. Organic acids yield a red color only when present in amounts exceeding 0.5 per cent.; but even then a negative reaction is obtained, if as in the stomach small quantities of albumin, peptones, and mucin are at the same time

present. A positive reaction can then only be obtained when organic acids are present in amounts far exceeding 0.5 per cent. Loosely combined HCl and acid salts do not produce this change in color. Its superior delicacy, as compared with the phloroglucin-vanillin and resorcin tests, is apparent from the fact that 5 c.c. of a 0.5 per cent. solution of egg-albumin, to which six drops of a one-tenth normal solution of HCl have been added, still give a positive reaction with dimethyl-amido-azo-benzol, while the phloroglucin-vanillin and resorcin reactions are negative.

For practical purposes a 0 5 per cent. alcoholic solution is employed. One or two drops of this are added to a trace of the gastric contents, which need not be filtered: in the presence of free HCl a beautiful cherry-red color develops, which varies in intensity according to the amount of free HCl present. A test-paper, prepared by soaking strips of filter-paper, free from ash, in the 0.5 per cent. solution and allowing them to dry, may also be employed. With gastric juice containing no free HCl, as with distilled water, a yellow color results, the fluid at the same time becoming cloudy and beautifully fluorescent.

The Phloroglucin-vanillin Test. The solution employed contains 2 grammes of phloroglucin and 1 gramme of vanillin, dissolved in 30 c.c. of absolute alcohol: a yellow color results, which gradually turns a dark golden-red, changing to brown when exposed to light. The solution should, therefore, be kept in a dark-colored bottle. Lenhartz suggests using separate solutions of phloroglucin and vanillin, one or two drops of each being employed in the test. Boas recommends a solution of the phloroglucin and vanillin in the proportions indicated in 100 grammes of 80 per cent. alcohol as still more sensitive and more stable. If a few drops of gastric juice, or even of the unfiltered gastric contents, containing 0.05 or more per cent. of free HCl, be treated with the same number of drops of the reagent, no change in color results, while upon the application of gentle heat—*boiling and rapid evaporation are to be avoided*—a rose-tint or exceedingly fine rose-colored lines develop, which are characteristic of the presence of free HCl.

For practical purposes it is best to carry on this slow evaporation upon a thin porcelain butter-dish, the porcelain cover of a crucible, or in a small evaporating-dish of the same material. The color obtained in the presence of free HCl is a rose color in every case, varying in intensity with the amount of acid present. A brown,

brownish-yellow, or brownish-red color always indicates that excessive heat has been applied or that free HCl is absent.

Organic acids never produce this reaction; it is not interfered with by their presence, or by albumins, peptones, or acid salts, which may occur in the gastric contents.

A phloroglucin-vanillin test-paper, prepared by soaking strips of filter-paper, free from ash, in the solution and drying them, may also be employed. If a strip of this be moistened with a drop of gastric juice and gently heated in a porcelain dish, as already described, the rose-red color will be seen to develop in the presence of free HCl, and does not disappear upon the addition of ether.

The Resorcin Test. The solution consists of 5 grammes of resublimed resorcin and 3 grammes of cane-sugar dissolved in 100 grammes of 94 per cent. alcohol. It is of equal delicacy as the phloroglucin-vanillin solution and has, besides, the advantage of greater stability.

Five or six drops of gastric juice are treated with three to five drops of the reagent and slowly evaporated to complete dryness over a small flame, when a beautiful rose- or vermilion-red mirror will be obtained, which gradually fades on cooling. If the reagent be employed in the form of a test-paper, a violet color at first develops, which upon the application of heat turns brick-red and does not disappear upon the addition of ether.

The presence of acid salts, organic acids, albumins, or peptones does not interfere with the reaction.

The methyl-violet and emerald-green tests cannot be recommended, as they are uncertain and may lead to error.

The Tropæolin Test. Tropæolin 00, when employed according to the method suggested by Boas, is a very reliable reagent, indicating the presence of 0.2 to 0.3 per cent. of free HCl. Three or four drops of a saturated alcoholic solution of tropæolin 00, which has a brownish-yellow color, are placed in a small porcelain dish or cover and allowed to spread over the surface. A like amount of gastric juice is then added and likewise allowed to flow over the surface of the dish; upon the application of gentle heat beautiful lilac or blue stripes appear, which are said to be absolutely characteristic of free HCl.

A tropæolin test-paper may also be prepared by soaking filter-paper, free from ash, in the alcoholic solution for some time, and then drying and cutting it into strips. A few drops of gastric juice

containing free HCl produce a more or less pronounced brown color upon this paper, which turns lilac or blue upon the application of gentle heat. Organic acids, when present in large amounts, likewise produce a brown color, which disappears, however, upon the application of heat, and a lilac or blue color never results.

For ordinary purposes this test is sufficient, and recourse need only be had to the more delicate reagents when a negative or a doubtful result is obtained.

Mohr's Test, as Modified by Ewald. Two c.c. of a 10 per cent. solution of potassium sulphocyanide are treated with 0.5 c.c. of a neutral solution of ferric acetate and diluted to 10 c.c. with distilled water, a ruby-red solution resulting. Of this a few drops are placed in a porcelain dish, and a drop or two of the filtered gastric contents allowed to come slowly into contact with the reagent. In the presence of free HCl a light violet color develops at the point of contact between the two fluids, which turns a deep mahogany-brown upon mixing.

The test is not interfered with by the presence of acid salts or peptones, but is not sensitive enough for practical purposes.

The Benzopurpurin Test. Benzopurpurin 6B has been highly recommended by v. Jaksch as a very sensitive test for HCl. It is best used in the form of a test-paper, prepared by soaking strips of filter-paper, free from mineral ash, in a concentrated watery solution of the reagent and allowing them to dry.

In the presence of more than 0.4 gramme of HCl in 100 c.c. of gastric juice the dark-red color of the test-paper immediately turns a deep blackish-blue. Should a brownish-black color develop, it is likely due to the presence of organic acids, or a mixture of these and HCl. If the color be caused by organic acids only, it will disappear upon washing the strip with a little neutral ether, and the original color of the test-paper be restored; but if due to a mixture of the two, the reaction is less marked, and does not disappear. According to Hellström, 0.39 milligramme of HCl dissolved in 6 c.c. of water can be recognized by the addition of only 5 milligrammes of benzopurpurin.

Acid salts, peptones, and serum-albumin do not seriously interfere with the reaction.

Benzopurpurin test-paper v. Jaksch claims to be more sensitive than the Congo-red paper.

The Combined Hydrochloric Acid.

It has been stated (see p. 122) that the determination of the total acidity of the gastric juice can only be referred to HCl when organic acids and acid salts are absent. At the same time the free acid is titrated together with the loosely combined. The presence of free hydrochloric acid in normal amounts implies, of course, the existence of peptic activity, and indicates that all albuminous affinities have been saturated. From a practical standpoint, however, in the absence of free HCl it is most important to know whether or not hydrochloric acid is secreted—*i. e.*, whether peptic digestion is at a standstill or whether an amount is secreted that is only sufficient to saturate certain albuminous affinities without appearing in the free state. In the treatment of the various forms of gastric disease, more especially those associated with an absence of free HCl, accurate knowledge in this respect is important. If no hydrochloric acid at all is secreted, the stomach can be regarded only as a storehouse, as it were, and proteids must be ordered in such form that they may be subjected to the process of pancreatic digestion with as little delay as possible, the nutrition of the body being aided, if necessary, by a suitable administration of predigested food. If, on the other hand, an amount of hydrochloric acid is secreted sufficient to saturate the albuminous affinities of an ordinary meal, or at least of moderate amounts of proteids, the dietetic directions need not be so stringent. While in the former case the absence of loosely combined hydrochloric acid usually indicates complete destruction of the glandular elements of the stomach—in other words, an irreparable condition—a fair prognosis may be given when the amount of acid secreted is sufficient for the saturation of the albuminous affinities of an ordinary meal. The following table[1] shows the amount of HCl necessary to saturate the affinities of known amounts of various articles of diet, the figures given referring to 100 c.c. or 100 grammes :

[1] Taken from Ehrlich : Dissert. Erlangen, 1893.

Milk	0.32–0.42 gramme of pure HCl.
Beef (boiled)	2.0 grammes " "
Mutton boiled)	1.9 " " "
Veal (boiled)	2.2 " " "
Pork (boiled)	1.6 " " "
Sweetbread (boiled)	0.9 gramme " "
Calves' brain (boiled)	0.65 " " "
Ham (raw)	1.9 grammes " "
Ham (boiled)	1.8 " " "
Liver sausage	0.8 gramme " "
Cervelat sausage	1.1 grammes " "
Mettwurst	1.0 gramme " "
Blood sausage	0.3 " " "
Graham bread	0.3 " " "
Pumpernickel	0.7 " " "
Wheat bread	0.3 " " "
Rye bread	0.5 " " "
Swiss cheese	2.6 grammes " "
Fromage de Brie	1.3 " " "
Edam cheese	1.4 " " "
Roquefort cheese	2.1 " " "
Beer (German)	0.07–0.15 gramme " "

The Quantitative Estimation of the Hydrochloric Acid of the Gastric Juice.

Töpfer's Method. The free and combined HCl is most conveniently estimated according to Töpfer's method, which is both simple and sufficiently accurate for clinical purposes.

In this method the total acidity (*a*) of a given amount of gastric juice—*i. e.*, the acidity referable to the presence of free HCl, combined HCl, acid salts, and any organic acids that may be present—is first determined (lactic acid and the fatty acids, if present, need not be removed), using phenolphthalein as an indicator. This is followed by a determination of the acidity referable to free acids and acid salts in the same amount of gastric juice (*b*), using alizarin (alizarin monosulphonate of sodium) as an indicator. As this does not react with loosely combined HCl, the difference between "*a*" and "*b*" will indicate the amount of the latter. The free HCl (*c*) is finally estimated with dimethyl-amido-azo-benzol as an indicator, the difference between *a* and *b* + *c* giving the acidity referable to organic acids and acid salts.

The solutions required are the following:

1. A decinormal solution of NaOH.

2. A 1 per cent. alcoholic solution of phenolphthalein.

3. A 1 per cent. aqueous solution of alizarin.

4. An 0.5 per cent. alcoholic solution of dimethyl-amido-azo-benzol.

Three separate portions of 5 or 10 c.c. of filtered gastric juice are measured off into three small beakers or porcelain dishes. To the first portion one or two drops of phenolphthalein are added, when it is titrated with the one-tenth normal solution of NaOH. It is necessary, however, to titrate to the point of a deep red, and not to the rose hue which first appears. It will be seen that upon the addition of the first few drops of the one-tenth normal solution of NaOH the red color, which first appears, disappears on shaking. Upon further addition a point is finally reached when this no longer occurs, and the color of the entire solution suddenly turns to a rose. This rose color, however, is not the end-reaction that is to be obtained. If the titration is continued, it will be observed that a dark-red cloud forms in the light rose-colored solution, which disappears on shaking; finally a point is reached when an additional drop no longer intensifies the color of the solution. This point is the end-reaction which must be reached.

To the second portion three or four drops of the alizarin solution are added, when it also is titrated with a one-tenth normal solution until a pure violet color is obtained. As some little practice is required in order to determine this point with accuracy, Töpfer advises to make previously the following simple tests:

1. To 5 c.c. of distilled water add 2 or 3 drops of alizarin solution, when a yellow color will result.

2. To 5 c.c. of a 1 per cent. solution of disodium phosphate add the same number of drops, when a red or slightly violet color will be obtained.

3. Five c.c. of a 1 per cent. solution of sodium carbonate treated with 2 or 3 drops of the alizarin solution will strike a pure violet, this being the color to be reached in the titration.

In the third portion of the gastric juice the free HCl is titrated, after the addition of 3 or 4 drops of the dimethyl-amido-azo-benzol, until the last trace of red—in the presence of free HCl—has disappeared. A yellow color resulting upon the addition of the indicator demonstrates the absence of free HCl, as has been shown on page 131. The results are then calculated as shown in the following example:

Ten c.c. of gastric juice, using phenolphthalein as an indicator, required 10 c.c. of the one-tenth normal solution in order to bring about the end-reaction, while a like amount titrated in the same manner with alizarin required 7 c.c. in order to bring about the same result. The difference between 10 and 7—*i. e.*, 3—would thus indicate the number of c.c. necessary to neutralize completely the amount of hydrochloric acid in combination with albuminous material. As 1 c.c. of the one-tenth normal solution represents 0.00365 gramme of HCl, the amount of the acid thus held will be equivalent to $0.00365 \times 3 = 0.01095$ gramme of HCl; *i. e.*, 0.1095 per cent.

In the estimation of the free HCl 3.2 c.c. of the one-tenth normal solution were required, using dimethyl-amido-azo-benzol as an indicator, corresponding to 0.00365×3.2; *i. e.*, 0.1168 per cent., of HCl. The value of the total acidity in terms of HCl is $10 \times 0.00365 = 0.0365$ gramme for every 10 c.c. of gastric juice, or 0.365 per cent.

By deducting the amount of the free and combined HCl, viz., $0.1095 + 0.1168 = 0.2263$, from this, it is found that the acidity of the gastric juice referable to organic acids and acid salts amounts to 0.1387 per cent., so that the results can be tabulated as follows:

Free HCl	0.1168 per cent.
Combined HCl	0.1095 "
Organic acids and acid salts	0.1387 "
Total acidity	0.3650 per cent.

The Method of Martius and Lüttke (modified). This method is equally exact, but requires a greater expenditure of time.

It is based upon the fact that upon incineration of the gastric juice the free HCl and that loosely combined with albuminous material escape, while the chlorine in combination with inorganic bases remains in the mineral ash, unless a very intense heat is applied for some time. By subtracting the amount of chlorine present in the latter form from the total amount, the quantity in combination with albuminous material and that occurring as free acid will be found. The total acidity of the gastric juice is then determined, and that referable to the presence of the free and combined HCl subtracted therefrom, the difference giving the amount of organic acids present. By determining the acidity due to the presence of free HCl according to Töpfer's method, and deducting the amount found from that

referable to the presence of free and combined HCl, the amount of the latter is obtained.

Reagents required:

1. A solution of nitrate of silver in nitric acid of such a strength that 1 c.c. shall represent 0.00365 gramme of HCl.
2. Liquor ferri sulphur. oxydati.
3. A decinormal solution of ammonium sulphocyanide.
4. A one-tenth normal solution of NaOH.
5. A 1 per cent. alcoholic solution of phenolphthalein.
6. A 0.5 per cent. alcoholic solution of dimethyl-amido-azo-benzol.

Preparation of the solutions:

1. The silver nitrate solution: As a solution is required of such a strength that 1 c.c. shall be equivalent to 0.00365 gramme of HCl, the amount of silver nitrate that must be dissolved in 1000 c.c. of water is ascertained in the following manner: Since 169.66 (molecular weight of $AgNO_3$) parts by weight of $AgNO_3$ combine with 36.5 parts of HCl (molecular weight of HCl), the amount of $AgNO_3$ required for each c.c. is found from the equation:

$$169.66 : 36.5 : : x : 0.00365;\ 36.5\ x = 0.6192590;\ x = 0.0169.$$

In one c.c. of the silver nitrate solution 0.0169 gramme of $AgNO_3$ must thus be present, or 16.9 grammes in the litre. This quantity, or roughly 17 grammes, is weighed off and dissolved in 900 c.c. of a 25 per cent. solution of nitric acid, as the acid must be present in excess, the solution being purposely made too strong. To this solution 50 c.c. of the liquor ferri sulphurati oxydati are added. The solution is then brought to the proper strength by titrating a known number of c.c. of a one-tenth normal solution of HCl with the same, and correcting as usual.

2. The ammonium sulphocyanide solution: A normal solution of ammonium sulphocyanide contains 75.98 grammes (molecular weight) per litre, and a decinormal solution 7.598 grammes. This quantity, or roughly 8 grammes, is dissolved in about 900 c.c. of water and the solution brought to the proper strength by titrating a known number of c.c. of the $AgNO_3$ solution with it, when every c.c. should correspond to 1 c.c. of the $AgNO_3$ solution; *i. e.*, to 0.00365 gramme of HCl. It is corrected as described elsewhere.

Method:

1. To determine the total amount of Cl present: 10 c.c. of filtered gastric juice—Martius and Lüttke make use of the unfiltered gastric contents—are measured off into a small flask bearing a 100 c.c. mark, and treated with an excess of the one-tenth normal solution of $AgNO_3$. Experience has shown that 20 c.c. are sufficient. The mixture is agitated and allowed to stand for ten minutes. Distilled water is then added to the 100 c.c. mark, the mixture agitated once more and filtered through a dry filter into a dry beaker. Fifty c.c. of the filtrate are titrated with the one-tenth normal solution of ammonium sulphocyanide until the blood-red color which appears upon the addition of every drop—due to the formation of ferric sulphocyanide—no longer disappears on stirring. By multiplying the number of c.c. of the ammonium sulphocyanide solution used by 2 (the number of c.c. that would have been necessary for the precipitation of the excess of silver in 100 c.c.) and deducting the result from the number of c.c. of the one-tenth normal solution of $AgNO_3$ employed, viz., 20, the number of c.c. of the latter solution is found which was necessary to precipitate the chlorine contained in 10 c.c. of the gastric juice. As 1 c.c. of the solution represents 0.00365 gramme of HCl, it is only necessary to multiply this figure by the number of c.c. used in the precipitation of the chlorine. The resulting value, "T," expresses the total amount of chlorine present.

As a general rule, it is not necessary to decolorize the gastric juice. If required, however, 5 to 15 drops of a 5 per cent. solution of potassium permanganate may be added to the 10 c.c. employed, after the mixture has stood for ten minutes.

2. Determination of the amount of Cl in combination with inorganic bases, "F." Ten c.c. of the filtered gastric juice are carefully evaporated to dryness in a platinum crucible over a water-bath or upon a plate of asbestos, in order to avoid sputtering (as the heat applied in the process of incineration is not very intense, a porcelain crucible may also be employed). The residue is then carefully incinerated over the open flame, the process being only carried to the point when the organic ash no longer burns with a luminous flame. Intense heat should be avoided, as the chlorides are volatilized upon the application of red heat. On cooling the ash is moistened with a few drops of distilled water and mixed with a stirring-rod, when the residue is extracted in separate portions with

100 c.c. of hot, distilled water and filtered. This amount is usually sufficient to dissolve out the chlorides present. If any doubt should exist, however, it is only necessary to add a drop of $AgNO_3$ solution to a few drops of the last portion of the filtrate: the formation of a cloud, referable to silver chloride, will necessitate still further washing. The whole filtrate is then treated with 10 c.c. of the one-tenth normal solution of $AgNO_3$, and the amount of $AgNO_3$ consumed in the precipitation of the chlorides determined by titration with the one-tenth normal solution of ammonium sulphocyanide, as described above. The HCl present in combination with inorganic bases is thus determined. The difference between the amount of HCl present in combination with inorganic bases and the total amount of chlorine in terms of HCl will then indicate the amounts of the free and of the combined HCl present, termed "L" and "C," respectively; hence $T - F = L + C$.

3. The total acidity in terms of HCl is further determined according to the method given elsewhere (see p. 122) and indicated by the letter "A." The difference between the total acidity and the amount of free and combined HCl will represent the amount of organic acids and acid salts, "O"; hence $O = A - (L + C)$.

The free HCl finally is determined according to the method of Töpfer. The difference between the value thus found and that expressing the amount of free and combined HCl will indicate the amount of the latter; hence $(L + C) - L = C$.

Leo's Method. This method is based upon the observation that calcium carbonate combines with free and combined HCl at ordinary temperatures to form neutral calcium chloride, while the acid phosphates are not affected. It is thus clear that by determining the total acidity of the gastric juice, and deducting from this the acidity referable to acid salts, the amount of the physiologically active HCl —*i. e.*, of free and combined HCl—is obtained.

As it has been shown that in the presence of $CaCl_2$ (formed, as indicated above, upon the addition of $CaCO_3$), owing to the formation of calcium monophosphate—$CaHPO_4$, twice the quantity of NaOH is taken up by the same quantity of the diacid salt, it is necessary to titrate after the addition of an excess of $CaCl_2$.

Reagents required:

1. A one-tenth normal solution of NaOH.
2. A 1 per cent. alcoholic solution of phenolphthalein.
3. A concentrated solution of $CaCl_2$.

4. Chemically pure $CaCO_3$. The purity of the salt may be tested by stirring a small piece with water; the solution should not color red litmus-paper blue. A solution of the salt in dilute HCl should not yield a precipitate when treated with sulphuric acid.

Method: Organic acids that may be present are first removed by shaking with ether, 50 to 100 c.c. of this being required for every 10 c.c. of gastric juice. The total acidity of the gastric juice is then determined in 10 c.c. of the filtered liquid after the addition of 5 c.c. of the concentrated solution of calcium chloride, the result being termed "A."

The acidity referable to the presence of acid phosphates is determined as follows: 15 c.c. of filtered gastric juice are treated with a pinch of dry and chemically pure calcium carbonate; the mixture is thoroughly stirred, and passed at once through a dry filter. Ten c.c. of the filtrate, from which the CO_2 formed is expelled by means of a current of air, are then treated with 5 c.c. of the calcium chloride solution and titrated as above, the resulting value being termed "P." A — P is, hence, equivalent to L + C. The value of "C" can then be ascertained by determining the acidity referable to free HCl according to Töpfer's method, and deducting the value found from L + C.

This method is sufficiently accurate for practical purposes, and has the additional advantage of not requiring the expenditure of much time.

The Ferments of the Gastric Juice and their Zymogens.

Pepsin and Pepsinogen. According to our present views, the zymogen of pepsin, viz., pepsinogen or propepsin, and not pepsin itself, is secreted by the chief cells of the fundus glands. This view is based upon the observation that an aqueous extract of the mucous membrane of the stomach of a fasting animal recently killed does not lose its digestive power when treated with a 1 per cent. solution of sodium carbonate at a temperature of from 38° to 40° C. for a considerable length of time, whereas pepsin itself is rapidly destroyed by very dilute solutions of the alkaline carbonates. It is thus natural to conclude that the glands of the stomach do not contain pepsin, but some other substance during the process of fasting which is capable of resisting the action of sodium carbonate, and which can be transformed into pepsin by the addition of HCl. This

substance has been termed *pepsinogen* or *propepsin*. As a rule, *pepsin* is only obtained from the mucous membrane of the digesting organ, while at other times the physiologically inactive zymogen is found. As the zymogen, moreover, is probably always present together with pepsin in the gastric juice obtained from healthy individuals during the process of digestion, it is not clear whether the transformation of the zymogen into its ferment takes place in the body of the cell or after secretion. The greater part of the evidence so far is in favor of the latter view.

This is not the place to enter into a detailed consideration of the various properties of pepsin, and it will suffice to say that the activity of the ferment is destroyed by even very dilute solutions of the alkaline carbonates. The same result is reached by exposing a watery solution of pepsin to a temperature of 70° C., while in its dry state a temperature of 100° C. will not destroy its activity, as is shown by the fact that a specimen of pepsin thus treated is, on cooling, still capable of digesting albumins in the presence of HCl.

While pepsin is capable of digesting albumins in the presence of other acids, viz., phosphoric, sulphuric, oxalic, acetic, lactic, and salicylic acid, the solutions must be stronger than in the case of HCl. With lactic acid, for example, a satisfactory result is only reached with a concentration of from 12 to 18 p. m., while of HCl 2 to 4 p. m. are sufficient. Larger or smaller amounts do not act so promptly.

Very important from a practical standpoint is the fact that but small quantities of pepsin are required to digest large amounts of albumin, and Petit, for example, claims that a pepsin preparation from his own laboratory was capable of dissolving 500,000 times its weight of fibrin in seven hours. This property on the part of pepsin of doing an amount of work that is entirely out of proportion to the amount of ferment present is common to all ferments, and is dependent upon the fact that the ferment itself undergoes no change during the process.

Exact figures expressing the quantity of pepsin or of its zymogen produced in the twenty-four hours are lacking, and inferences can hence only be drawn as to the physiologic activity of the ferment from the rapidity with which given amounts of albuminous material are digested. This, however, depends to a large extent upon the nature and the concentration of the free acid present. In physiologic conditions 25 c.c. of gastric juice will dissolve 0.05 to 0.06

gramme of serum-albumin in one hour, the same amount of coagulated egg-albumin in three hours, and a like amount of fibrin in one hour and a half.

As abnormalities in the circulation and innervation of the stomach do not apparently influence the production of pepsin, or rather of its zymogen, a diminution in the degree of peptic activity, or its total absence, may be referred directly to disease of the stomach itself, viz., its glandular apparatus. The determination of the presence or absence and relative amount of pepsin in the gastric juice, hence, actually furnishes us with more directly useful information than the recognition of the presence or absence of free HCl, as the secretion of the latter is influenced by many factors which, as has been shown, only indirectly affect the process of digestion.

As pepsin is formed from pepsinogen through the agency of a free acid, notably of HCl, its presence, in the absence of organic acids, in notable quantities at once indicates the presence of hydrochloric acid. It may be said, *vice versa*, that if free HCl be present in the gastric juice, and the latter digest albumins, pepsin also will be found. Should the zymogen alone be present digestion will take place only upon the addition of an acid, while an entire absence of digestion upon the addition of HCl will indicate the absence of both pepsin and its zymogen. At times, though rarely, a "gastric juice" is met with which is capable of digesting albumin in the absence of HCl, owing to the presence of pancreatic juice—a point which may be of great value, both from a diagnostic and a prognostic point of view.

In the differential diagnosis of a chronic gastritis and a neurosis, or a dyspeptic condition referable to hyperæmia of the gastric mucous membrane, the demonstration of the presence of the zymogen in the absence of HCl may, at times, be very important, bearing in mind the fact that circulatory and nervous disturbances do not apparently influence the production of pepsinogen. An entire absence of the latter would, of course, warrant the diagnosis of complete anadeny of the stomach.

Tests for Pepsin and Pepsinogen. *Test for the enzyme:* If the presence of free HCl has been previously ascertained, 25 c.c. of filtered gastric juice are set aside and kept at a temperature of from 37° to 40° C., a bit of coagulated egg-albumin, fibrin, or serum-albumin being added. In order to permit of a comparison of results the same amounts should always be taken; 0.05 to 0.06

gramme of egg-albumin, as has been shown, ought, under physiologic conditions, to be digested after three hours.

Test for the zymogen : Should HCl be absent the test is made in the same manner after the addition of from 3 to 5 drops of the officinal solution of HCl to 25 c.c. of the filtrate. Under such conditions—*i. e.*, in the absence of free HCl—pepsinogen alone is found as a rule.

Quantitative estimation of pepsin. Accurate methods for the quantitative estimation of pepsin, as such, do not exist, and relative values only can be obtained. Most convenient is the method suggested by Hammerschlag: Three Esbach's tubes (albuminimeters) are employed. Tube A is filled to the mark U with a mixture of 10 c.c. of a 1 per cent. solution of serum-albumin in 0.4 per cent. of hydrochloric acid, and 5 c.c. of filtered gastric juice. The second tube, B, which is the standard, is likewise filled to the mark U, but 0.5 gramme of pepsin is added to the serum solution, instead of the gastric juice. The third tube, C, merely contains a mixture of the serum solution and 5 c.c. of water. After having been kept in the thermostat for one hour at a temperature of 37° C., Esbach's reagent is then added to each tube to the mark R. After standing for twenty-four hours the amount of precipitated albumin is read off, and the difference between that in A and C compared with that in B.

Estimation of pepsinogen. In order to estimate the amount of pepsinogen the method of Boas may be conveniently employed. To this end the gastric juice is diluted with distilled water in varying proportions, such as 1 : 5, 1 : 10, 1 : 20, etc. A known quantity of coagulated albumin is added to each specimen, as also one or two drops of an officinal solution of HCl for every 10 c.c. employed. These tubes are kept at a temperature of from 37° to 40° C., and the degree of dilution noted at which the bit of egg-albumin continues to be dissolved. The greater the degree of dilution at which digestion still takes place, the greater the amount of pepsin or of its zymogen present.

If it is desired to definitely exclude the presence of pepsin and pepsinogen in the stomach, the method of Jaworski should be employed. To this end about 200 c.c. of a decinormal solution of hydrochloric acid are poured into the stomach through a tube and aspirated after one-half hour. If the fluid removed contains no pepsin, the absence of both enzyme and zymogen may be inferred.

The Milk-curdling Ferment and its Zymogen, viz., Chymosin and Chymosinogen. A great deal of what has been said above regarding pepsin and its zymogen also holds good for chymosin and its proenzyme. The proenzyme thus also appears to be formed by the cell, as a neutral aqueous extract of the mucous membrane of the stomach does not, as a rule, contain the ferment, but the zymogen, the former only resulting when the latter is treated with a free acid. It differs from pepsin in that it can exert its physiologic activity in feebly acid, neutral, and even feebly alkaline solutions. Exposure of an active solution of chymosin containing 3 p. m. of free HCl, moreover, to a temperature of from 37° to 40° C., leads to its destruction, while pepsin is not affected under the same conditions.

Its specific action is exerted upon milk or lime-containing solutions of casein, leading to a coagulation of the latter in neutral or feebly alkaline solutions.

In this connection it is important to note that the addition of a few c.c. of a solution of calcium chloride, or any other soluble lime salt, results in a transformation of the zymogen into the physiologically active ferment, and that HCl, while it normally causes such transformation, is not absolutely necessary in the presence of calcium chloride.

Under physiologic conditions chymosin and its zymogen are always present in the gastric juice. In disease the inferences that can be drawn from a quantitative estimation of the ferment and its zymogen have been well formulated by Boas, to whom we are especially indebted for a great deal of valuable information in this connection:

1. Notwithstanding the absence of free HCl, chymosin may still be present, although in minimal traces; *i. e.*, demonstrable with a dilution of from 1 : 10 to 1 : 20 (see method given on p. 146).

2. In the absence of free HCl the zymogen may still be present in normal amounts—*i. e.*, with a dilution of from 1 : 100 to 1 : 150. The presence of the zymogen, especially when repeatedly observed, permits of the conclusion with a high degree of probability, and even with absolute certainty, that we are not dealing with an organic disease of the stomach, but with a neurosis, or a hyperæmic condition of the mucous membrane referable to disease of other organs.

3. The zymogen may occur in moderately diminished amount, 50 per cent. only being present. This is usually owing to the exist-

ence of a gastritis which has not as yet reached its highest degree of severity. The nearer the amount of zymogen approaches to normal, the greater will be the probability of an ultimate recovery under suitable treatment.

4. The amount of the zymogen is greatly diminished (dilutions of 1 : 10 to 1 : 25 yielding a negative result), or may be absent altogether. In cases of this kind a severe and usually incurable gastritis exists, either primary or occurring secondarily to carcinoma, amyloid degeneration, etc.

5. In 1, 2, and 3 the re-establishment of the secretion of HCl may be attempted with some prospect of success by means of stimulating remedies.

These conclusions are based upon the employment of Ewald's test-breakfast, and cannot be applied to observations made after other test-meals, without previous studies in this direction.

Testing for the presence of chymosin and its zymogen, moreover, is of decided value in cases in which alkaline material is vomited, and where we may be called upon to decide whether this contains constituents of the gastric juice or not.

Tests for Chymosin and Chymosinogen. *Test for the enzyme:* Five to ten c.c. of milk are treated with from three to five drops of the filtered gastric juice and kept at a temperature of from 37° to 40° C. for ten to fifteen minutes. If coagulation occurs during this time, it may be definitely concluded that the enzyme is present.

Test for the zyomgen : 10 c.c. of filtered and feebly alkaline gastric juice are treated with 2 or 3 c.c. of a 1 per cent. solution of calcium chloride, and kept at a temperature of from 37° to 40° C., when the formation of a thick cake of casein will be observed within a few minutes in the presence of the zymogen.

Quantitative Estimation. *Of the enzyme:* This is based upon the fact that upon gradually diluting a specimen of gastric juice a point is finally reached at which a chymosin reaction can no longer be obtained, the value being, of course, a relative one. Under physiologic conditions a positive reaction can still be obtained with a degree of dilution varying between 1 : 30 and 1 : 40.

The gastric juice is neutralized with a very dilute solution of sodium hydrate and tubes prepared containing from 5 to 10 c.c. of the gastric juice, variously diluted in the proportion of 1 : 10, 1 : 20, 1 : 30, etc., to which an equal amount of neutral or amphoteric milk is added. The tubes, properly labelled, are kept at a temperature

of from 37° to 40° C., and the degree of dilution noted at which coagulation still occurs.

Of the zymogen: The gastric juice is rendered feebly alkaline and tubes are prepared containing equal amounts of milk and gastric juice, the latter variously diluted as above directed; the examination is then carried on in the same manner. Normally a positive reaction is obtained with a dilution varying between 1 : 100 and 1 : 150. Allowance must, of course, be made for the error incurred in diluting the gastric juice during the process of neutralization.

The Products of Gastric Digestion.

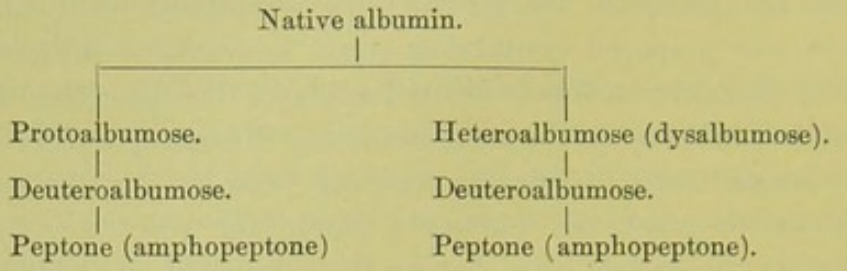
The Digestion of Native Albumins. The first step in the process of albuminous digestion in the stomach is one of swelling, which may be readily observed when a flake of fibrin, for example, is placed in gastric juice, and the temperature of the latter maintained between 37° and 40° C. Very soon simple dissolution takes place, which is followed by the process of "denaturization," as Neumeister terms it, in which the native albumins are transformed into acid albumins or syntonins, owing to the continued activity of the HCl and pepsin. The pepsin, however, only acts as an adjuvant to the acid, and HCl alone is capable of effecting the same result. While in the absence of pepsin more concentrated solutions of the acid and a higher temperature are required, the temperature of the body and the amount of HCl secreted by the stomach are sufficient when pepsin is present. The latter, in the absence of free HCl, is perfectly inert.

The "denaturization" of the native albumins is followed by a splitting up of the albuminous molecule and a process of hydration, the so-called primary albumoses, of which there are two, viz., protoalbumose and heteroalbumose, being the first products thus formed.

Dysalbumose, it may be stated in passing, is merely a modified form of heteroalbumose, which results from the latter when this is dried or kept under water for some time.

During the further process of digestion a deuteroalbumose results from each of the primary albumoses, and from these finally peptones, to which, in contradistinction to the peptones formed during the process of *pancreatic* digestion, the term "amphopeptone" has been applied by Kühne.

The relation existing between the various products of gastric digestion may be seen from the table below (taken from Neumeister):



The transformation of native albumins into peptones, as described, was first worked out for fibrin, but was subsequently shown to hold good for all native albumins of both vegetable and animal origin. Chittenden proposes the generic term "proteoses" for these various products of digestion, in contradistinction to those resulting from albuminoids. Vitellin thus first yields two primary vitelloses, viz., a proto- and a heterovitellose, which are transformed into deutero-vitelloses and finally into peptones. The albumoses of fibrin are similarly termed fibrinoses; those of the globulins, globulinoses; and those of myosin, myosinoses.

The digestion of casein, which belongs to the class of nucleoalbumins, differs from the process described. The casein of the milk is present in solution as a neutral calcium salt, and as casein has the character of a polybasic acid, $CaCl_2$, and the corresponding acid casein salt will result in the presence of the HCl of the stomach; still later, when more HCl has been secreted, insoluble casein as such will be found. While HCl is thus capable of causing the precipitation of casein, it has also been shown that the same result may be reached in the absence of HCl, and, according to Hammarsten, is brought about in consequence of a hydrolytic action on the part of the chymosin present, the Ca salt of paracasein (cheese) and a small amount of albumose-like posset-albumin being formed. This latter process is now supposed to take place in the stomach after the HCl has previously transformed the neutral into the acid casein salt. When this stage is reached the paracasein is split up into an albumin and an insoluble nuclein, owing to the action of HCl and pepsin. The albumin is then further digested as described, two primary caseoses first resulting, which are then transformed into deutero-caseoses, and these finally into peptones.

The remaining proteids, such as hæmoglobin, glucosides, etc., are similarly acted upon by the gastric juice, being first split up into

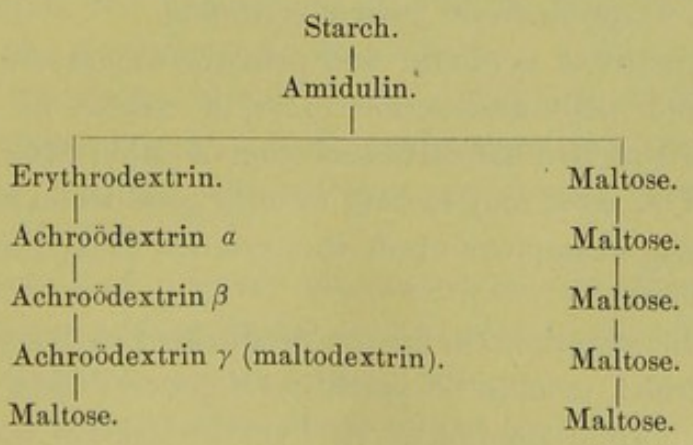
the corresponding albumins and their pairlings. Hæmoglobin is thus broken down into hæmatin and an albumin, which latter undergoes the same process of digestion as seen in the case of the native albumins.

The Digestion of the Albuminoids. Of the albuminoid bodies only collagen and elastin undergo digestion in the stomach, gelatoses and elastoses being formed during the process, while keratin passes off undigested. Heteroproteoses, however, are formed from neither collagen nor elastin, but merely protoproteoses, which in turn are transformed into deuteroproteoses, of which there is only one kind, viz., that corresponding to the protoproteose, peptone finally resulting.

The Digestion of Carbohydrates. The secretion of the stomach itself is not capable of digesting carbohydrates. There appears to be no doubt, however, that a transformation of starches into sugar takes place during the earlier stages of digestion. This is owing to the continued action of the pytalin of the saliva (see p. 102) in the stomach, which goes on until the amount of HCl secreted reaches 0.01 or more per cent., it being remembered that the transformation of starches into sugar goes on best in a neutral or feebly alkaline medium.

The question whether or not a diastatic ferment occurs in the mucus secreted by the stomach itself is unimportant, as cases have but rarely been observed in which there was an absence of ptyalin from the saliva.

As indicated in the chapter on Saliva, a large number of intermediary products are formed in the transformation of starch into sugar, of which an idea may be had from the accompanying table:



In the mouth this transformation is very rapidly effected in the case of certain starches, such as corn-starch and rye-starch, and it is

possible to demonstrate the presence of sugar after from two to six minutes. Potato-starch, on the other hand, requires a much longer time, viz., from two to four hours. This difference is entirely dependent upon the varying degrees of resistance offered to the action of the saliva by the enclosing envelope of cellulose, as is apparent from the fact that a paste made from potatoes is just as rapidly digested as one made from rye.

For practical purposes, the digestion of carbohydrates in the stomach may be disregarded as insignificant.

Fats are not Digested at all in the Stomach.

From the above considerations it is apparent that under physiologic conditions a mixture of these various products is met with in the stomach at the height of digestion, and it might be expected that from a preponderance of one over the other definite and valuable conclusions as to the digestive power of the organ could be reached. While this is true in a certain sense, the quantitative methods of analysis that would have to be employed in order to obtain definite data are as yet too complicated for the purposes of the clinician, and from the simple qualitative tests not much information can be derived. The recognition of the presence of peptones would thus merely indicate the presence of HCl and pepsin in a general way, as peptones may be formed in the absence of HCl and in the presence of organic acids, which may be found in pathologic conditions. Moreover, a portion of the albumin of milk, eggs, meat, etc., is already peptonized, so to speak, during the process of boiling. It is not surprising that peptones may probably be demonstrated in every specimen of gastric contents.

A large amount of syntonin and primary albumoses in the presence of a feeble peptone-reaction must, of course, be regarded as abnormal, pointing to a defective secretion of either HCl or enzymes, or of both. The same may be said to hold good when a pronounced peptone-reaction disappears upon the removal of syntonin and the primary albumoses.

As far as the examination for the products of carbohydrate digestion is concerned, it may be stated, as a general rule, that in the presence of a normal amount of HCl erythrodextrin can usually be demonstrated near the end of gastric digestion, while achroödextrin is almost always obtained at the same time in the absence of free

HCl, so that the tests for the presence of these two bodies may be regarded as roughly indicating the presence or absence of free HCl, and as therefore yielding the same information as the tests for this. Boas draws attention to the fact, however, that ptyalin may, at times, though rarely, be absent, when conclusions drawn from these tests as to the presence of HCl would be erroneous.

The tests for sugar in the gastric juice do not furnish any information that is of practical value.

Analysis of the Products of Albuminous Digestion.

In order to separate the various bodies referred to from each other the following procedure is employed:

The filtered gastric contents are carefully neutralized with a dilute solution of NaOH, using litmus-paper to determine the reaction, a small drop of the mixture being placed upon the paper from time to time during the addition of the NaOH, until no change in color is produced either on the red or the blue paper. If syntonin be present, it will be precipitated, and can be collected on a small filter. Upon the addition of an excess of dilute acid or an alkali this precipitate will again be dissolved. The filtrate is feebly acidified by the addition of a few drops of a very dilute solution of acetic acid, treated with an equal volume of a saturated solution of common salt, and brought to the boiling-point. Any native albumin that may be present in solution is thus coagulated and can be filtered off on cooling. In the filtrate the albumoses and peptones remain. The presence of the former may be demonstrated by adding a few drops of HNO_3 to a specimen, when a precipitate will form which dissolves upon the application of heat, to reappear on cooling; if necessary, the specimen may be diluted.

Should the deuteroalbumoses of vitellin or myosin be present, this test yields a negative result, and a precipitate only occurs when the solution, acidified with nitric or acetic acid, is completely saturated with NaCl.

The presence of primary albumoses, on the other hand, may be established by adding pieces of rock-salt to the neutral solution, when a precipitate occurs in their presence. The albumoses may be roughly separated from the peptones by saturating the acidified filtrate just obtained with pulverized ammonium sulphate, whereby the albumoses are almost entirely precipitated. A small portion of

the deuteroalbumoses, however, resulting from the protoalbumoses remains in solution and passes into the filtrate, which also contains all of the amphopeptone. In the filtrate these products may be demonstrated by adding a concentrated solution of NaOH, care being taken to keep the temperature from rising too high by immersion in cold water until all ammonium sulphate has been transformed into sodium sulphate and a slight excess of the NaOH is present. The sodium sulphate, which separates out during this process, is allowed to settle, and a 2 per cent. solution of sulphate of copper carefully added drop by drop to a specimen taken from the supernatant fluid. In the presence of peptones a rose to a purplish-red color will develop.

The peptones may be obtained after careful neutralization of the filtrate, having first diluted this with an equal volume of distilled water, by the addition of a solution of tannic acid, care being taken to avoid an excess, as the peptone-precipitate is soluble under such conditions.

From the following table an idea may be formed of the reactions of these various bodies:

REACTION OF THE INDIVIDUAL PROTEIDS.

	Globulin.	Syntonin.	Hemialbumose.	Peptone.
Soluble in	Dilute solutions of sodium chloride and of magnesium sulphate.	Dilute acids and alkalies.	Water acids, alkalies, and salts.	Water, acids, acids + salts, alkalies.
Insoluble in	Water.	Water and neutral salt solutions.		
Precipitated by	Much water, heating to 75° C., saturation with magnesium sulphate from its solutions in neutral salts.	Neutralization of its solutions in dilute acids, by means of sodium chloride or heating to 75° C. from acid solutions.	Acetic acid + sodium chloride, concentrated nitric acid, acetic acid, and potassium ferrocyanide in the cold.	Bichloride of mercury, tannic acid, iodo-mercuric iodide of potassium, phospho-tungstic, and phospho-molybdic acids.
Biuret reaction	Violet.	Violet.	Rose to purple.	Rose to purple.

Tests for the Products of Carbohydrate Digestion.

Starch may be recognized by the fact that it strikes a blue color with a solution of iodo-potassic iodide, while the same solution gives a violet or mahogany-brown with erythrodextrin. To this end it is only necessary to add a drop or two of Lugol's solution to a few

c.c. of the filtered gastric juice. The presence of achroödextrin may be inferred if no change in color is produced upon the addition of the reagent.

Maltose and dextrose, which both react with Fehling's solution and undergo fermentation, differ from each other by the fact that the former does not reduce Barfoed's reagent, which is prepared by adding a 1 per cent. solution of acetic acid to a 0.5 to 4 per cent. solution of acetate of copper. Upon boiling a few c.c. of this solution, and adding a small amount of gastric juice, red cuprous oxide will be precipitated in the presence of maltose.

Lactic Acid.

Mode of Formation and Clinical Significance. It was formerly thought that the acidity of the gastric juice was referable to the presence of lactic acid, as this can always be demonstrated in the beginning, at least, of the process of digestion, and the HCl was even thought to result from an action of the lactic acid upon the chlorides ingested. That this view was erroneous C. Schmidt succeeded in demonstrating beyond a doubt, as has been shown on p. 120. An explanation of the presence of lactic acid suggested itself when Miller found that normally various bacteria occur in the mouth capable of forming lactic acid from sugar, and that a number of bacteria can be isolated from the gastric contents which are capable of causing an acid fermentation in sugar-containing media.

There would, hence, be nothing surprising in the constant occurrence of lactic acid, as the two principal factors necessary for its formation are probably always present after the ingestion of an ordinary meal, viz., carbohydrates and bacteria capable of causing lactic-acid fermentation. The absence of the lactic acid during the later stages of digestion was, furthermore, explained by the fact that lactic-acid fermentation ceases in the presence of from 0.7 to 1.6 pro mille of HCl; *i. e.*, in the presence of the amount of HCl which is found in normal gastric juice. The occurrence of lactic-acid fermentation in the stomach was, hence, until quite recently regarded as an established fact. At this stage Martius and Lüttke, employing the method already described, found "that the accurately determined curve of acidity referable to HCl coincided in all respects, even at the beginning of the process of digestion, with the curve referable to the total acidity," so that lactic acid as a physio-

logic constituent could not have been present in the gastric contents examined.

Recent researches of Boas, moreover, appear to prove beyond a doubt that in physiologic conditions no appreciable amounts of lactic acid are formed during the process of digestion, and that the lactic acid found after an ordinary meal has been introduced into the stomach as such. That lactic acid is actually present in the various kinds of bread has been definitely proved, and it is, hence, not permissible to make use of any test-meal containing lactic acid when the question as to its formation in the stomach is to be considered. For these reasons Boas suggests the use of simple oatmeal-soup to which salt only has been added. For practical purposes this is probably not always necessary, as the amount of lactic acid found after Ewald's test-breakfast may be disregarded in health, and an increased amount be directly referred to pathologic conditions.

The fact that the lactic acid disappears, or at least is no longer demonstrable, at the height of digestion, Boas refers to resorption or a carrying off of the acid introduced on the one hand, or to an interference of the HCl with the delicacy of the reagent usually employed—*i. e.*, Uffelmann's reagent—on the other. Pathologically the same rule may be said to hold good, since Boas was unable to demonstrate its presence after the exhibition of his test-meal in various diseases of the stomach, viz., chronic gastritis, atony and dilatation referable to myasthenia, or pyloric stenosis following ulcer. Mere traces, which were occasionally observed, are of no significance, and possibly referable to lactic-acid fermentation having taken place in the mouth. In all of the cases examined, moreover, no organic acids could be demonstrated by the method of Hehner-Seemann (see p. 163).

It is apparent then that notwithstanding stagnation of the gastric contents and the absence of free HCl in normal amounts, lactic acid is not necessarily formed in the stomach, even in the presence of carbohydrates. In only one disease of the stomach was lactic acid found by Boas in notable quantities, viz., carcinoma. This observation is in accord with the fact that Uffelmann's test here yields a marked reaction—*i. e.*, a deep lemon or canary-yellow color—even upon the addition of but a few drops of the gastric juice, while in the benign affections only a pale-yellow, brownish, or grayish color is obtained.

Boas' test-meal should be given the evening before the examination, the stomach having been previously washed free from all remnants of food, and the remaining contents examined the next morning.

In an analysis of fourteen cases of carcinoma Boas was able to demonstrate the presence of lactic acid in amounts varying between 1.22 and 3.82 p. m. in all cases but one. In this connection it may be mentioned that under physiologic conditions the amount of lactic acid obtainable after Ewald's test-breakfast varies between 0.1 and 0.3 p. m.

That stagnation of the gastric contents and the absence of free HCl alone are not capable of causing the formation of lactic acid has been seen, and it is, hence, difficult to explain why in carcinoma only lactic-acid fermentation should occur. Whether the malignant growth itself must be regarded as one of the principal factors in this connection, as Boas suggests, must still remain an open question.

If the difficulties that may be encountered in the diagnosis of carcinoma, and notably in the beginning of the disease, be remembered, Boas' observation must be regarded as of the greatest importance, for, if confirmed, we should actually be in possession of a "specific" symptom of carcinoma of the stomach. The fact that lactic acid is present in the beginning of the disease makes Boas' observations still more important, as satisfactory results from operative interference can only be expected during the earliest stages of the malady.

Owing to the interest which attaches to this subject, it may not be out of place to refer briefly to the following observation of Koch: In a case in which ulcer of the stomach existed, associated with the presence of free HCl, suddenly a positive HCl reaction could no longer be obtained, while lactic acid appeared and increased steadily in amount from week to week. A tumor could not be demonstrated on physical examination. Soon after the patient died, and at the autopsy a carcinoma of the stomach was found upon the base of the pyloric ulcer.

Unfortunately recent investigations have shown that notable amounts of lactic acid may also be found in gastric anadeny, and in cases of dilatation referable to benign causes.

Such cases, however, are rare, and it may be safely stated that the presence of large amounts of lactic acid will almost invariably justify the diagnosis of carcinoma of the stomach, and, according to the writer's experience, Boas' test is at least as important as Widal's

serum-test for typhoid fever. Negative results, however, do not exclude the existence of the disease.

Chemically the formation of lactic acid from starch may be represented by the following equations:

$$\text{I.}\quad 2C_6H_{10}O_5 + H_2O = C_{12}H_{22}O_{11}\ \text{(milk sugar).}$$
$$\text{II.}\quad C_{12}H_{22}O_{11} + H_2O = 2C_6H_{12}O_6\ \text{(glucose).}$$
$$\text{III.}\quad 2C_6H_{12}O_6 = 4C_3H_6O_3\ \text{(lactic acid).}$$

It should, finally, be mentioned that only that form of lactic acid which results from fermentative processes is of interest in this connection, and not the sarcolactic acid contained in meat—a point which interferes with the general usefulness of Riegel's test-meal.

Tests for Lactic Acid. For the reasons indicated Boas' test-meal (see p. 114) should be employed whenever it is desired to test for lactic acid in the gastric contents. If the case under examination shows well-marked symptoms of stagnation of the gastric contents, the stomach should be washed out completely in the evening, the soup given then, and the gastric contents procured the next morning, before any food or liquid is taken. Otherwise the test-meal may be given in the morning on an empty stomach, without previous lavage, and the contents examined one hour later.

Uffelmann's Test. Heretofore Uffelmann's reagent was quite constantly employed in testing for lactic acid, but everyone who has had occasion to make frequent use of this reagent in clinical work must have been struck with the unreliability of the results so often obtained. In a large majority of the cases thus examined, particularly if Ewald's test-breakfast is employed, a characteristic reaction —*i. e.*, the occurrence of a lemon or canary-yellow color—is not seen, notwithstanding the presence of lactic acid, but a pale-yellow, brownish, grayish-white, or even gray color obtained instead, often leaving it doubtful whether lactic acid be present or not. Aside from doubtful results, the value of the test is greatly diminished by the facts that glucose, acid phosphates, butyric acid, and alcohol give the same reaction, and that in the presence of such amounts of HCl as are found at the height of normal digestion lactic acid is not indicated by the reagent. All these difficulties have long been appreciated, and in order to obviate at least some of them it was proposed to apply the test to an aqueous solution of the ethereal extract of the gastric contents:

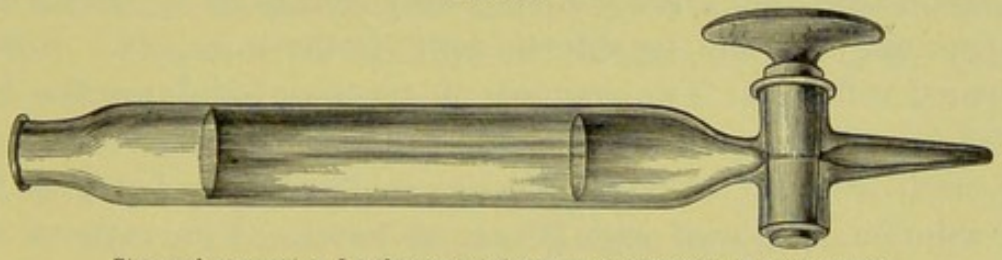
To this end 5 to 10 c.c. of the filtered gastric juice are extracted by shaking with from 50 to 100 c.c. of neutral sulphuric ether in

a stoppered separating-funnel for about twenty to thirty minutes, and the ethereal extract evaporated over a water-bath, or the ether distilled off (*no flame*). The residue is then taken up with from 5 to 10 c.c. of distilled water, and tested as follows: Three drops of a saturated aqueous solution of the sesquichloride of iron are mixed with three drops of a concentrated solution of pure carbolic acid and diluted with water until an amethyst-blue color is obtained. To this solution a portion of the ethereal extract is added, when in the presence of only 0.1 per cent. of lactic acid a lemon or canary-yellow color is obtained.

KELLING'S METHOD. Five to ten c.c. of gastric juice are diluted from ten to twenty times with water and treated with one or two drops of a 5 per cent. aqueous solution of the sesquichloride of iron. In the presence of lactic acid a distinct green color is obtained if the tube be held to the light. This test is more reliable than that of Uffelmann, as a positive reaction is only obtained in the presence of lactic acid.

STRAUSS' METHOD. Instead of evaporating the ether as in the above method, the ethereal extract may be directly examined by

FIG. 33.



Strauss' apparatus for the approximative estimation of lactic acid.

shaking with a freshly prepared solution of the sesquichloride of iron, as suggested by Fleischer. Making use of this principle Strauss has recently constructed an apparatus (Fig. 33) which may be found very convenient and which permits of roughly determining the amount of lactic acid present. The instrument is essentially a separating-funnel of 30 c.c. capacity, bearing two marks, of which the one corresponds to 5 c.c., the other to 25 c.c. The apparatus is filled with gastric juice to the mark 5, when ether is added to the 25 c.c. line. After shaking thoroughly the *separated* liquids are allowed to escape by opening the stopcock until the 5 c.c. mark is reached. Distilled water is then added to the 25 mark, and the mixture treated with two drops of the officinal tincture of the sesquichloride of iron, diluted in the proportion of 1 : 10. Upon

shaking the water will assume an intensely green color if more than 1 p. m. of lactic acid be present, while a pale green is obtained in the presence of from 0.5 to 1 p. m. The tincture of iron should be kept in a dark-colored dropping-bottle of about 50 c.c. capacity.

It will be observed that only large amounts of lactic acid, which are alone of importance from a diagnostic point of view, are indicated by the apparatus. Small amounts, as those introduced with Ewald's test-breakfast, or referable to lactic-acid fermentation in the mouth, are not indicated, so that confusion as to the presence or absence of the acid can never arise.

Boas' Method. In doubtful cases the following method should be employed, as with it, following the exhibition of Boas' test-meal, all possible errors already referred to can be avoided.

Principle of the method: When a solution of lactic acid is treated with a strong oxidizing agent and heated the lactic acid is decomposed into acetic aldehyde and formic acid, according to the equation:

$$\underset{\text{Lactic acid.}}{CH_3 - CH(OH) - CO.OH} = \underset{\text{Acetic aldehyde.}}{CH_3.CHO} + \underset{\text{Formic acid.}}{H.CO.OH}.$$

Practically, then, the test for lactic acid resolves itself into a test for acetic aldehyde, which can be readily recognized by testing with various reagents, and notably so with Nessler's reagent. This is prepared as follows: Two grammes of potassium iodide are dissolved in 50 c.c. of water and treated with iodide of mercury, while heating, until some of the latter remains undissolved. Upon cooling the solution is diluted with 20 c.c. of water. Two parts of this solution are then treated with 3 parts of a concentrated solution of potassium hydrate; any precipitate that may have formed is filtered off and the reagent kept in a well-stoppered bottle. When aldehyde is added to such a solution a yellowish-red or red precipitate results, the exact color depending upon the amount of aldehyde present. One part of the aldehyde may still be recognized when diluted with 40,000 parts of water.

An alkaline solution of iodo-potassic iodide may also be advantageously used. With this solution aldehyde in a dilution of 1 : 20,000 will still produce a cloudiness, referable to the formation of iodoform, which is readily recognized by its characteristic odor (Lieben's test for acetone).

Method: The filtered gastric juice is tested for the presence of free acids with Congo-red (see p. 129). If present, from 10 to 20

c.c. are evaporated to a syrup on a water-bath, after the addition of an excess of barium carbonate, while the latter is unnecessary in the absence of free acids. The syrup is treated with a few drops of phosphoric acid, the CO_2 removed by bringing it to the boiling-point once only, when it is allowed to cool and extracted with 100 c.c. of neutral sulphuric ether (free from alcohol), by shaking for half an hour. The layer of ether is poured off after half an hour, the ether evaporated (*no flame*), the residue taken up with 45 c.c. of water, shaken and filtered, and finally treated with 5 c.c. of sulphuric acid and a pinch of the dioxide of manganese in an Erlenmeyer flask. This is closed with a perforated stopper carrying a glass tube bent to an obtuse angle, the longer limb of which passes into a narrow glass cylinder containing from 5 to 10 c.c. of Nessler's reagent or a like quantity of an alkaline solution of iodo-potassic iodide. If heat be now carefully applied, the aldehyde, formed by the oxidation of the lactic acid with MnO_2 and H_2SO_4, passes over when the boiling-point is reached, causing the precipitation of yellowish-red aldehyde of mercury in the tube containing the Nessler's reagent, or of iodoform if the alkaline solution of iodine be employed. The test is an accurate one.

Quantitative Estimation of Lactic Acid According to Boas' Method. The principle already set forth also applies to the quantitative estimation of lactic acid.

Solutions required:

1. A one-tenth normal solution of iodine.
2. A one-tenth normal solution of sodium arsenite.
3. Hydrochloric acid (sp. gr. 1.018).
4. A potassium hydrate solution (56 : 1000).

Preparation of these solutions:

1. A normal solution of iodine should contain 126.53 (mol. weight of iodine) grammes of iodine in the litre, and a one-tenth normal solution, hence, 12.6 grammes. In order to dissolve the iodine 25 grammes of potassium iodide are dissolved in about 200 c.c. of distilled water and the 12.6 grammes of resublimed iodine added. Distilled water is then added to the 1000 c.c. mark. This solution requires no further correction.

2. The one-tenth normal solution of sodium arsenite is prepared by dissolving 19.2 grammes of the salt (mol. weight 191.87) in about 900 c.c. of distilled water, when the solution is brought to the proper strength by titrating with it a known number of c.c. of

the one-tenth normal solution of iodine, as described below, and determining the necessary amount of water to be added.

Method: 10 to 20 c.c. of the filtered gastric juice are first treated, as indicated above, viz., evaporated to a syrup after the previous addition of barium carbonate, if free acids be present. A few drops of phosphoric acid are added, the CO_2 removed by boiling, and the residue extracted on cooling with 100 c.c. of ether free from alcohol; the ether is evaporated after separation, the residue taken up with 45 c.c. of distilled water, and treated with H_2SO_4 and MnO_2. The flask is closed by a doubly perforated stopper; through one aperture a bent tube passes to the distilling-apparatus, and a straight tube provided with a piece of rubber tubing, clamped off, through the other. The mixture is then distilled until about four-fifths of the contents have passed over, excessive heat being carefully avoided, as otherwise the aldehyde will be decomposed, according to the equations:

$$\underset{\text{Lactic acid.}}{CH_3-CH(OH)-CO.OH} = \underset{\text{Aldehyde.}}{CH_3.CHO} + \underset{\text{Formic acid.}}{HCOOH}. \quad \text{I.}$$

$$\underset{\text{Aldehyde.}}{CH_3.CHO} + \underset{\text{Formic acid.}}{HCOOH} + 2O = \underset{\text{Acetic acid.}}{CH_3.COOH} + CO_2 + H_2O. \quad \text{II.}$$

To the distillate, which is best received in a high Erlenmeyer flask, well stoppered, 20 c.c. of the one-tenth normal solution of iodine are added, mixed with 20 c.c. of the 5.6 per cent. solution of potassium hydrate. The mixture is shaken thoroughly and allowed to stand for a few minutes. In order to liberate the hypiodite and the iodine in combination with potassium, not used in the reaction, 20 c.c. of HCl and an excess of sodium bicarbonate in substance—some of the latter should remain undissolved at the bottom—are added, and the excess of iodine determined by titration with the one-tenth normal solution of sodium arsenite. The titration is carried to the point of decolorization, when freshly prepared starch solution is added, and the mixture again titrated with the one-tenth normal solution of iodine until the blue color is permanent. The number of c.c. of the one-tenth normal solution employed, viz., 20, minus the number of c.c. of the one-tenth normal solution of Na_3AsO_3, will then indicate the number of c.c. of the former required in the formation of iodoform, viz., the amount of lactic acid present in 10 or 20 c.c. of gastric juice, as the case may be. As 1 c.c. of the one-tenth normal solution of iodine has been found to indicate the presence of 0.003388 gramme

of lactic acid, it is only necessary to multiply the number of c.c. used by this figure, and the result by 10, in order to obtain the percentage.

The method described is reliable and sufficiently accurate for clinical purposes. At the same time it may be said that no more time is required than in an ordinary quantitative estimation of sugar by means of Fehling's method, or of HCl according to the method of Martius and Lüttke.

Boas' rapid method : This method is less accurate than the preceding, but may be advantageously employed in the absence of the various reagents necessary with the former. Ten c.c. of filtered gastric juice are treated with a few drops of dilute H_2SO_4 and the albumin present removed by heat. The filtrate is evaporated to a syrup on a water-bath, water added to the original amount, and this again evaporated to a small volume, fatty acids being thereby removed. The lactic acid remaining is now extracted with ether (200 c.c. for every 10 c.c. of the gastric juice), the ether evaporated, the residue taken up with water, and titrated with a one-tenth normal solution of NaOH, using phenolphthalein as an indicator. As 40 parts by weight of NaOH (mol. weight) combine with 90 parts by weight of lactic acid (mol. weight), and as 1 c.c. of the one tenth normal solution of NaOH contains 0.004 gramme of NaOH, the amount of lactic acid corresponding to the latter is found from the equation: $40 : 90 : : 0.004 : x$; $40\,x = 0.360$; $x = 0.009$. The value of 1 c.c. of the one-tenth normal solution in terms of $C_3H_6O_3$ is thus 0.009. By multiplying the number of c.c. used by this figure the amount of lactic acid present in 10 c.c. of gastric juice is readily determined. The result multiplied by 10 will indicate the percentage.

The Fatty Acids.

Mode of Formation and Clinical Significance. Unless much milk or carbohydrates have been ingested, fatty acids do not occur in the gastric contents under physiologic conditions, and it would appear from the researches of Boas that their formation is intimately associated with that of lactic acid. After the exhibition of his test-meal (see p. 154) he was unable to demonstrate their presence either in normal conditions or in various diseases of the stomach, such as chronic gastritis, atony, or dilatation referable to benign causes, etc.

In carcinoma fatty acids, just as lactic acid, were quite constantly found.

That butyric acid can be derived from lactic acid has been demonstrated for milk by Flügge, the reaction taking place according to the equation:

$$2(C_3H_6O_3) = C_4H_8O_2 + 2CO_2 + 4H.$$

This observation is probably explained by the fact that most of the organisms causing butyric-acid fermentation are anaërobic, while the bacillus acidi lactici and the oïdium lactis at the same time eagerly absorb oxygen.

Acetic-acid fermentation, on the other hand, presupposes the presence of alcohol, whether this be introduced into the stomach as such or the result of the action of yeast (saccharomyces cerevisiæ) upon sugar, the transformation of alcohol into acetic acid being represented by the equation:

$$C_2H_5OH + 2O = C_2H_4O_2 + H_2O,$$

while the formation of alcohol during the process of fermentation from glucose is shown below:

$$\text{I. } C_6H_{12}O_6 + 2H_2O = 2C_2H_6O + 2H_2CO_3.$$
$$\text{II. } 2H_2CO_3 = 2H_2O + 2CO_2.$$

It is, hence, necessary, whenever acetic acid is met with in the gastric contents, to exclude the existence of alcoholism, as it is only then permissible to refer its presence to stagnation and advanced decomposition of carbohydrates.

If the examination be confined to an analysis of the gastric contents, obtained otherwise than after the exhibition of Boas' or even Ewald's test-meal, the diagnosis of pyloric stenosis with dilatation is probably always justifiable in the presence of notable quantities of butyric acid and acetic acid, while the same observations after a previous washing out of the stomach and the exhibition of Boas' test-meal would more strongly suggest carcinoma as the cause of the stenosis.

That butyric acid may occur in the gastric contents when butter or fats in general have been ingested is, of course, not surprising, and its presence then should be looked upon as a physiologic occurrence. At the same time it should not be forgotten that butyric acid, just as lactic acid, may possibly have been formed in the mouth, and conclusions should, hence, only be drawn when such

sources of error can be definitely excluded and the amount found exceeds mere traces.

In conclusion, it may be said that in pathologic conditions butyric acid is far more frequently encountered in the gastric contents than acetic acid, while the significance of the two in the absence of alcoholism is the same.

Tests for Butyric Acid. 1. Butyric acid can usually be recognized by its odor alone, which is that of rancid butter. Often, however, it will be necessary to resort to more definite tests, such as the following:

2. Ten c.c. of filtered gastric juice are extracted with 50 c.c. of ether. The ether is evaporated and the residue taken up with a few c.c. of water. If a trace of calcium chloride in substance be now added, the butyric acid will separate out in the form of small oil-droplets, the nature of which is readily recognized by their pungent odor. If, instead of adding calcium chloride, a slight excess of baryta-water is used, strongly refractive rhombic plates or granular, wart-like masses of barium butyrate are obtained upon evaporation.

Tests for Acetic Acid. 1. Like butyric acid, acetic acid can usually be recognized by its odor.

2. Ten c.c. of filtered gastric juice are extracted with ether. The ether is evaporated, the residue dissolved in a few drops of water, and accurately neutralized with a dilute solution of NaOH, sodium acetate being formed. If to this a drop or two of a very dilute solution of the perchloride of iron be added, a dark-red color results in the presence of acetic acid. With nitrate of silver a precipitate is obtained which is soluble in hot water.

Quantitative Estimation of the Fatty Acids. Method of Cahn-Mehring, modified by McNaught: The total acidity is determined in 10 c.c. of filtered gastric juice, and the acidity obtained, upon titration of another 10 c.c., after evaporation to a syrup, subtracted from the former, the difference giving the acidity referable to fatty acids.

Quantitative Estimation of the Organic Acids. Method of Hehner-Seemann: This method is based upon the observation that if a certain amount of a one-tenth normal solution of NaOH be added to organic acids and the mixture be evaporated and incinerated, the organic acids escape as CO_2, leaving their alkali behind in the form of a carbonate, the amount of which can be

determined by titrating with a one-tenth normal solution of HCl. The amount of physiologically active HCl can be determined at the same time by deducting from the total acidity the acidity referable to organic acids.

Method: 10 or 20 c.c. of filtered gastric juice are neutralized with a one-tenth normal solution of NaOH, evaporated to dryness, and incinerated, the application of heat being discontinued as soon as the ash has ceased to burn with a luminous flame. The residue is taken up with water and neutralized with a one-tenth normal solution of HCl. This is prepared by diluting 146 grammes of HCl (sp. gr. 1.14) with distilled water to about 900 c.c., when the solution is brought to its proper strength by comparing it with a one-tenth normal solution of NaOH, according to directions given elsewhere. The number of c.c. of the one-tenth normal solution of HCl employed multiplied by 0.00365 will give the amount of fatty acids, in terms of HCl, contained in the 10 c.c. of gastric juice, from which the percentage is readily calculated by multiplying by 10 or 5, as the case may be. By deducting the number of c.c. employed from that of the one-tenth normal solution of NaOH first used the number of c.c. of the latter required for the neutralization of the physiologically active HCl is ascertained, and the amount of the HCl determined by multiplying by 0.00365.

Gases.

The stomach always contains a certain quantity of gases which have partly been swallowed and partly passed into the stomach from the duodenum. As fermentative processes in physiologic conditions occur only when carbohydrates or fats have been ingested, and then only to a slight degree, nitrogen, oxygen, and carbon dioxide are the only gases found during the process of albuminous digestion. As the oxygen swallowed is, moreover, largely absorbed by the blood, and two volumes of carbon dioxide are returned for one volume of oxygen, the presence of large amounts of the former and small amounts of the latter is readily explained. In an analysis of the gases contained in the stomach of a dog which had been fed on meat Planer found the following proportions:

CO_2	25.2 vol. per cent.
O	6.1 " "
N	68.7 " "

With a strictly vegetable diet, on the other hand, hydrogen may also be found (Planer):

	Man.		Dog.	
CO_2 . . .	20.79	33.83	32.9	vol. per cent.
O . . .	.....	0.37	0.8	" "
N . . .	72.50	38.22	66.3	" "
H . . .	6.71	27.58		

The presence of H is readily understood if it be remembered that during the process of butyric-acid fermentation H and CO_2 are formed. Lactic-acid or acetic-acid fermentation does not give rise to the formation of gases.

Marsh gas, CH_4, a product of the fermentation of cellulose, may also be found in pathologic conditions, formed according to the equation:

$$(C_6H_{10}O_5)n + (H_2O)n = 3(CO_2)n + 3(CH_4)n.$$

It is yet an open question whether CH_4 is formed in the stomach or passes into the stomach from the small intestine.

Such observations must, however, be regarded as rarities. In one case of this kind, examined by Ewald and Ruppstein, in which alcohol, acetic acid, lactic acid, and butyric acid were found in the vomited material, an analysis of the gases gave the following result:

CO_2	20.6	vol. per cent.
O	6.5	" "
N	41.4	" "
H	20.6	" "
CH_4	10.8	" "

Traces of olefiant gas and of sulphuretted hydrogen were also found. It is curious to note that in this case the patient, who, according to his own statement, had "acetic acid works in his stomach on one day and gas works on another day," was occasionally able to light the eructated gas at the end of a cigar-holder, where it burnt with a faintly luminous flame. McNaught has reported a similar case, in which the analysis furnished the following results: $CO_2 = 56$ per cent.; $H = 28$ per cent.; $CH_4 = 6.8$ per cent.; atmospheric air = 9.2 per cent.

Ammonia and sulphuretted hydrogen are also at times met with, and are always due to albuminous putrefaction.

Boas found that sulphuretted hydrogen is quite commonly present in cases of dilatation referable to benign causes, while it is almost always absent in carcinoma. He adds that it is never found when

lactic acid is present. In acute gastritis it may be temporarily observed. In a number of cases of carcinoma the writer never found sulphuretted hydrogen. In one case reported by Strauss the bacillus coli communis was apparently concerned in its production.

To obtain a knowledge of the gases formed in the stomach during the process of digestion it is only necessary to fill an ordinary Doremus' ureometer, or an Einhorn's saccharimeter, with the unfiltered gastric contents, and to keep it at a temperature of from 37° to 47° C., when the evolution of gas can be closely followed and the necessary tests made. The presence of CO_2 is readily recognized by passing a small amount of NaOH, in concentrated solution or in substance, into the tube, after the evolution has entirely ceased, when the fluid will rise. If other gases be present at the same time, they will remain after the CO_2 has been absorbed. H_2S is readily recognized by its odor and by the fact that it will color a piece of filter-paper moistened with a few drops of NaOH and acetate of lead a more or less pronounced brown. The test is conveniently made by filling a test-tube about half-full with the gastric contents and closing it with a cork-stopper to which a strip of lead-paper, prepared as indicated, is fastened.

The eructation of gas formed in the stomach should not be confounded with the so-called *eructatio nervosa*, in which either no gas is eructated, or air simply enters the œsophagus and is expelled again with a loud, explosive noise. This may be frequently observed in neurasthenic and hysterical individuals, and is to a greater or less degree under the control of the will. It is hardly likely, however, that the physician will be called upon in the laboratory to differentiate between this form and that of true ructus caused by fermentative processes taking place in the stomach. The gases brought up in the former conditions are without odor or taste, and thus differ from those found in true dyspepsia.

Acetone.

The presence of acetone in the gastric contents in pathologic conditions has been repeatedly observed, especially by v. Jaksch and Lorenz, and it is curious to note that the latter was at times able to demonstrate larger quantities of the substance in the gastric contents than in the urine.

In the chapter on Acetonuria the relation existing between diges-

tive diseases and the elimination of acetone will be dealt with more fully, but it may here be mentioned that in the "primary" diseases of the gastro-intestinal tract acetone is quite constantly met with in the gastric contents, while it is but rarely observed in the secondary forms, and never seen in the gastric neuroses.

This statement, however, is denied by Sovelieff, who claims to have found traces of acetone only in one case of nervous dyspepsia, while negative results were obtained in all other diseases of the stomach. The writer has repeatedly been able to demonstrate the presence of acetone in cases of carcinoma of the stomach, and has never found it in neurotic conditions.

In order to test for acetone the gastric contents are distilled after the previous addition of a small amount of phosphoric acid (1 : 1000), so as to prevent an excessive evolution of gases, and the tests of Reynolds and Gunning (see Urine) applied to the distillate. If both reactions furnish a positive result, the presence of acetone may be regarded as demonstrated.

Ptomaïnes and Toxalbumins.

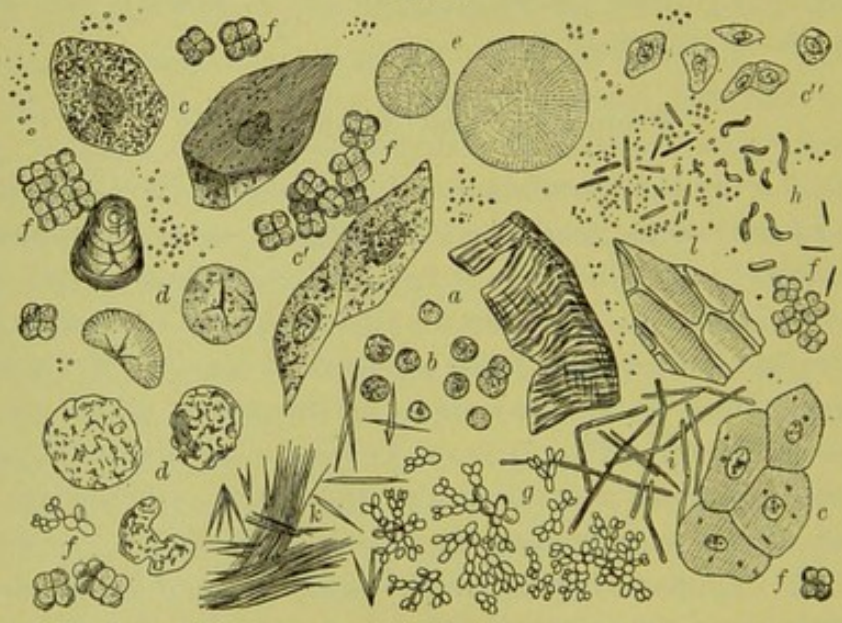
Remembering that ptomaïnes and toxalbumins have been directly obtained from tainted meat, sausage, fish, clams, crabs, cheese, etc., it is probable and, indeed, to be expected that these bodies should be present in the gastric contents also. At the same time it may be mentioned that the stomach appears to possess the power of eliminating from the system poisons of this nature which are circulating in the blood. This is shown by the observations of Alt, who found that the water with which the stomach of an animal had been irrigated after the subcutaneous injection of the poison of Pelias berus and Echidna arictans, or the direct bite of the snake, produced the same symptoms of poisoning when injected into another animal. It is interesting to note that with lavage of the stomach the poisoned animal recovered. Similar observations have been made in cholera Asiatica. Certain vegetable alkaloids, such as morphine, are also known to be eliminated to a large extent by the stomach.

Vomited Material.

Food-material. The vomiting of large amounts of totally undigested meat two to three hours after its ingestion is a rare occurrence, and is only met with in conditions associated with an entire

absence of digestive power in the stomach—*i. e.*, in cases of atrophic cirrhosis of the stomach (anadeny of Ewald). This condition is not to be confounded with the regurgitation of undigested food, mixed with mucus and saliva, seen in cases of stricture of the œsophagus or of the cardiac orifice of the stomach. While at the outset of the latter disease the regurgitation of food occurs immediately or at least very soon after a meal, it may take place between meals in the later stages of the disease. The recognition of the origin of the material brought up may then be exceedingly difficult. In such cases an examination should be made for biliary coloring-matter, which, if present, will, of course, immediately exclude the œsophagus as the source of the material ejected. Unfortunately, however, the reverse does not hold good. Small amounts of undigested meat are of no significance.

FIG. 34.



Collective view of vomited matter. (Eye-piece III., objective 8 A, Reichert) *a*, muscle-fibres; *b*, white blood-corpuscles; *c*, *c'*, squamous epithelium; *c''*, columnar epithelium; *d*, starch-grains, mostly changed by the action of the digestive juices; *e*, fat-globules; *f*, sarcinæ ventriculi; *g*, yeast-fungi; *h*, forms resembling the comma-bacillus found by the author once in the vomit of intestinal obstruction; *i*, various micro-organisms, such as bacilli and micrococci; *k*, fat-needles, between them connective-tissue derived from the food; *l*, vegetable cells. (v. JAKSCH.)

The vomiting of well-digested food is observed in some of the neuroses of the stomach, and also in certain cases of acute and subacute gastritis, ulcer of the stomach, and chronic gastritis in its early stages. The vomiting referable to cerebral and spinal diseases also belongs to this category.

In this connection it is very important to inquire into the existence of nausea previous to the vomiting, for, as is well known, considerable amounts of saliva and mucus may be swallowed if much nausea has existed, the result being that the process of digestion is arrested before the occurrence of vomiting, when it would be entirely erroneous to conclude that, because the material ejected has not reached that stage of digestion which should be expected at the time of the vomiting, the stomach is incapable of properly performing its functions.

Mucus. The constant presence of large amounts of mucus in the gastric contents, obtained with the stomach-tube, is almost pathognomonic of the mucous form of gastritis, while its presence in vomited matter may be referable to its having been swallowed, owing to pre-existent nausea. In cases of pharyngitis moderate amounts of mucus are frequently found. The vomiting of pure mucus, according to Boas, is always pathognomonic of the absence of dilatation of the stomach, a statement founded on reason, as it is altogether unlikely that no particles of food should be brought up at the same time.

Under the term *gastrosuccorrhœa mucosa* Dauber has recently described a condition in which large amounts of mucus are secreted by the non-digesting organ in the absence of any symptoms pointing to a gastritis. The writer has observed a similar case occurring in a neurasthenic patient, in which enormous quantities of mucus could at times be obtained from the fasting organ, but never during the process of digestion. A mild degree of hyperchlorhydria existed at the same time, as well as enteritis mucosa and rhinitis mucosa. The motor power was practically normal.

Mucus is readily recognized on simple inspection by its glossy appearance. Chemically it is distinguished by its behavior toward acetic acid. (See Urine.)

Saliva. The vomiting of pure saliva in the morning upon rising is a fairly common symptom of chronic pharyngitis, which in turn frequently carries in its trail a chronic gastritis, constituting the so-called *vomitus matutinus*. Saliva, like mucus, is, of course, always present in the gastric contents in small amounts. Larger amounts are usually referable to an increased secretion and a swallowing of the same, owing to the existence of nausea. Chemically, saliva is best recognized by testing for the presence of the sulphocyanides (see Saliva, p. 102).

Bile. Bile is rarely observed in the gastric contents brought up by the stomach-tube, but is frequently seen in vomited matter, of which it may be said to be a constant constituent whenever the vomiting has been very intense or frequently repeated. Its presence in the former case should always excite suspicion of the existence of a stenosis of the descending or horizontal portion of the duodenum, or the beginning of the jejunum. This diagnosis becomes the more probable the more constant its presence.

Pancreatic Juice. Mixed with bile, there is probably always present some pancreatic juice, and it has even been suggested that the constant absence of the constituents of this, associated with the presence of bile, is strongly suggestive of pancreatic disease or of obstruction of the pancreatic duct (the ductus Wirsungianus).

Blood. The presence of unaltered blood in the gastric contents is usually recognized without difficulty. As marked alterations in color, varying from a deep red to a coffee or chocolate brown may occur, however, when free acids are present, it is at times necessary to resort to a more detailed examination. In order to recognize mere traces, when the macroscopic and even the microscopic examination do not point to the presence of blood, the method of Müller and Weber should be employed. Kuttner claims that he was thus able to demonstrate the presence of blood in numerous cases of chlorosis, in which other tests only furnished negative results. The writer has been less successful in the disease in question, but admits that in cases of carcinoma and ulcer of the stomach it is with this method often possible to find traces of blood which would otherwise have remained unnoticed.

Method of Müller and Weber: The gastric contents are treated with a few c.c. of concentrated acetic acid and extracted with ether. Should the ether not separate out in a clear layer after a few minutes, a few drops of alcohol are added. If the ether then remains colorless, no blood-pigment is present, while a brownish-red color indicates the presence of acetate of hæmatin. As a similar but yellowish-brown and much less intense discoloration of the ether may be produced by other pigments, such as biliary coloring-matter, it is well in doubtful cases to test the ethereal extract with tincture of guaiacum. A positive result indicates the presence of blood coloring-matter. The same may be said if, upon spectroscopic examination of the ethereal extract, an absorption-band is discovered at the junction of the red and yellow.

Hemorrhage from the stomach, *hæmatemesis*, may be observed in the most diverse conditions, being either dependent upon a primary disease of the organ, such as ulcer and carcinoma, or occurring secondarily to diseases of other organs, leading to a hyperæmic condition of the gastric mucosa, such as the various forms of cardiac, renal, and hepatic disease, in connection with menstrual abnormalities, etc. In melæna, purpura hemorrhagica, pernicious anæmia, etc., the cause of the hemorrhage cannot always be determined. It appears to be certain, however, that nervous influences may also take part in the causation of gastric hemorrhage.

Pus. The occurrence of pus in the vomited matter, referable to disease of the stomach itself, is quite rare, and practically only seen in cases of phlegmonous and diphtheritic gastritis. More frequently it indicates the perforation into the stomach of an accumulation of pus from a neighboring organ. An abscess of the liver, a suppurative pancreatitis, an abscess of the colon, may thus prove to be the primary source of the pus. When present in considerable amount pus is, of course, readily detected by the naked eye; if any doubt should arise, a microscopic examination will determine the question.

Stercoraceous Material. Very important from a clinical standpoint is the vomiting of stercoraceous matter, which is notably observed in cases of ileus. This is usually recognized without difficulty by its odor, which is referable to the presence of skatol. If, however, any doubt should arise, it is only necessary to distil the vomited matter after the addition of a little phosphoric acid, and to test for the presence of phenol, indol, and skatol in the distillate, as described in the chapter on Feces (see p. 192). When chiefly derived from the small intestine the vomited matter, according to v. Jaksch, will contain bile-acids and bile-pigment together with an abundance of fat, which may be detected by chemical or microscopic examination. The reaction is usually alkaline or feebly acid.

Recently the author had occasion to examine the vomited matter of a patient in whom an almost complete obstruction existed immediately above the ileo-cæcal valve; the color of the material was a golden-yellow, the reaction neutral; no bile-pigments or biliary acids were found, while hydrobilirubin was demonstrated. Formed masses of feces, if found at all in the vomited matter under such conditions, are certainly of extreme rarity.

Parasites. Of parasites, ascarides, segments of tæniæ, trichinæ,

anchylostoma duodenale, and oxyuris vermicularis are, at times, encountered, for a description of which see the chapter on Feces.

The Odor. But little information, as a rule, is derived from the odor of the gastric contents. The odor of normal gastric juice is quite characteristic, suggesting the presence of some acid, which can be sharply distinguished, however, from the well-known odor referable to acetic acid or butyric acid. If blood be present in large amounts, the vomited matter emits an odor which is so characteristic as never to be mistaken. A feculent odor is met with in cases of enterostenosis, or in the presence of an abnormal communication between the stomach and the small or large intestine. A putrid odor may be observed in cases of ulcerative carcinoma, pyloric stenosis referable to ulcer, simple carcinoma of the stomach, muscular hypertrophy of the pylorus, stenosis due to inflammatory adhesions, etc.

It may finally be mentioned that in cases of phosphorus-poisoning the vomited matter emits an odor of garlic; the odor observed in uræmic conditions is referable to ammonia; a carbolic-acid odor is met with in cases of poisoning with this substance.

MICROSCOPIC EXAMINATION OF THE GASTRIC CONTENTS.

In the gastric juice obtained from the non-digesting stomach the various morphologic constituents of mucus and saliva, which have been described elsewhere, are found. Microscopic particles of food, such as elastic tissue-fibres, starch-granules, fat-droplets, fatty acid crystals, vegetable and muscle fibres, are, furthermore, quite constantly seen. Leucocytes and isolated nuclei are also observed; the latter are set free by the action of the gastric juice upon mucous corpuscles and epithelial cells.

If gastric juice be allowed to stand, small tapioca-like bodies will collect at the bottom of the vessel, which upon microscopic examination will be seen to contain numerous snail-shell-like formations, occurring either singly or collected in groups. These probably consist of altered mucin, as they can be artificially produced by adding a sufficient amount of dilute HCl to saliva. According to Boas, they are of no diagnostic significance.

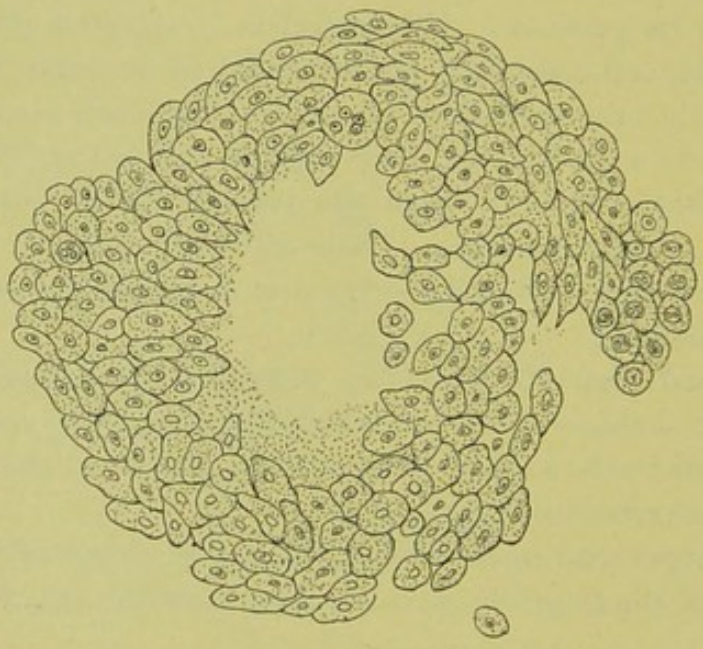
Epithelial cells, fragments of the epithelial lining of the ducts of glands, as well as goblet-cells, are not infrequently met with in the

large numbers and in pure culture. In cases of carcinoma of the curvatures and the walls, as also in advanced pyloric carcinoma, sarcinæ were never found, while they may be present in incipient cases of pyloric carcinoma as long as hydrochloric acid is still secreted.

The occurrence of blood and pus in the gastric contents has been considered (see p. 170).

It not infrequently happens that small shreds of mucous membrane are brought away by the stomach-tube, and in cases of chronic gastritis, hyperchlorhydria not dependent upon ulcer, and

FIG. 35.

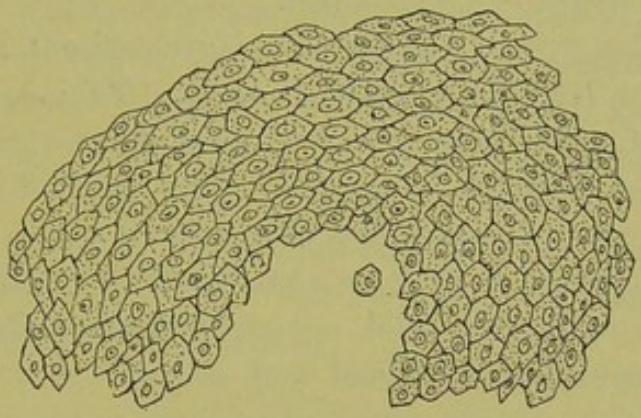


Cancer-cells from the gastric contents. (EWALD.)

in some of the neuroses this is indeed not at all uncommon. Boas even suggests that in the latter case, where fragments of mucous membrane are so readily detached, this may possibly be etiologically connected with the formation of ulcers, and there can be no doubt that the mere action of the abdominal muscles exerted during the process of defecation may be sufficient to detach such fragments. From the microscopic appearance of the particles the diagnosis between a gastric neurosis and one of the various forms of chronic gastritis may be frequently made, and the same may be said to hold good for the differential diagnosis between a true gastritis and a glandular insufficiency referable to passive congestion of the gastric mucosa.

Not infrequently *tumor particles* are found in the gastric contents. In the accompanying illustration (Fig. 35) a specimen obtained from

FIG. 36.



A fragment of mucous membrane derived from the stomach. (EWALD.)

a carcinomatous patient is represented, which is quite readily distinguished from similar fragments of mucous membrane (Fig. 36).

EXAMINATION OF THE MOTOR POWER OF THE STOMACH.

Under physiologic conditions the stomach should contain but few particles of food, or none at all, six hours after the ingestion of Riegel's meal, or one and one-half to one and three-quarters hours after that of Ewald. A delay in the removal of the gastric contents may be referable to the existence of a simple atony or to dilatation of the stomach. According to Boas, an atony may usually be diagnosed, if, following the exhibition of a supper consisting of bread and butter, cold meat, and a large cupful of tea, the stomach is found empty in the morning, providing, of course, that symptoms exist which point to atony or dilatation. It should be remembered, however, that in cases of acute and subacute gastritis, in the absence of a more serious lesion, food may be found in the stomach twenty-four hours after its ingestion. A dilatation may, on the other hand, be diagnosed if the stomach under the same conditions contains a considerable amount of food. In such cases it happens that not only remnants of the test-supper, but remains of meals taken one, two, three, or even more days previously are found. The quantities, moreover, which may be obtained at the time of the examination are often surprisingly great, and may amount to sixteen pounds or more. Portel cites the case of the Duc de

Chausnes, one of Paris' greatest gourmands, whose stomach could hold 4.5 liters—*i. e.*, 8 pints.

The following methods may be employed for the purpose of testing the motor power of the stomach:

Leube's Method. The stomach is washed out six hours after the ingestion of Riegel's meal with about 1000 c.c. of water. In the presence of only slight traces of food the motor power of the stomach may be regarded as normal. This method is undoubtedly the most convenient for practical purposes.

The Salol Test of Ewald and Sievers. This test is based upon the observation that salol, a compound ether of salicylic acid, is only decomposed into phenol and salicylic acid in an alkaline medium. As the salicylic acid is eliminated in the urine as salicyluric acid, it is possible to determine the time of the passage of the salol from the stomach into the small intestine.

A capsule containing one gramme of salol is given to the patient immediately after his breakfast or dinner, when separate portions of urine, passed one-half, one hour, two hours, and twenty-four hours later, are tested by the addition of a small amount of a solution of the sesquichloride of iron. In the presence of salicyluric acid a violet color results. Under normal conditions a positive reaction is obtained after from forty-five to seventy-five minutes. A further delay may usually be regarded as indicating the existence of motor insufficiency. If no result is obtained after twenty-four hours, a pyloric stenosis undoubtedly exists. Under normal conditions, furthermore, it will be observed that the salol elimination is completed after twenty-four hours, while in cases of dilatation of the stomach a positive reaction may still be obtained after thirty hours. It is thus possible to distinguish between dilatation and descent of the stomach.

The test, while it is convenient and usually yields fair results, is not altogether reliable, as the decomposition of the salol may, at times, occur in the stomach owing to the presence of alkaline mucus, or may be delayed in the intestines owing to the existence of acid fermentation, etc.

EXAMINATION OF THE RESORPTIVE POWER OF THE STOMACH.

To this end a capsule containing 0.2 gramme of potassium iodide is given to the patient shortly before a meal, and the saliva examined

for the presence of potassium iodide at intervals of from two to three minutes. (See Saliva, p. 106.)

Under normal conditions a violet color is obtained after from six and one-half to eleven minutes, and a bluish tinge after from seven and one-half to fifteen minutes. In pathologic conditions a delayed reaction is observed in almost all diseases of the stomach, and is especially marked in cases of dilatation and carcinoma, less so in chronic gastritis, and variable in cases of ulcer.

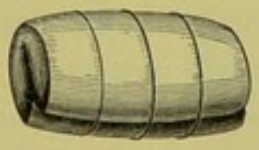
Absolute conclusions, however, cannot be drawn from results thus obtained, as a normal reaction-time has also been observed in cases of dilatation and chronic gastritis.

INDIRECT EXAMINATION OF THE GASTRIC JUICE.

Günzburg's Method. In those cases in which for any reason the introduction of the stomach-tube is contraindicated or impracticable the following method, suggested by Günzburg, may be employed:

A tablet of 0.2 to 0.3 gramme of potassium iodide is inserted into a piece of the thinnest possible, strongly vulcanized rubber-tubing, measuring about 2.5 cm. in length. The ends are folded as shown in Fig. 37, and the little package tied with three threads of fibrin

Fig. 37.



A fibrin potassium-iodide package of Günzburg.

hardened in alcohol. Every package should be examined before use, by immersion in warm water for several hours, to determine its tightness, testing for the presence of potassium iodide by means of starch-paper and fuming nitric acid. One of these packages is swallowed by the patient three-quarters to one hour after an Ewald's test-breakfast, and the saliva tested for potassium iodide at intervals of fifteen minutes, until a positive result is reached, or until six hours have elapsed. It is unnecessary to wait longer than six hours. In the presence of free HCl the threads of fibrin are dissolved and the potassium iodide absorbed. Under normal conditions a positive reaction is obtained after from one to one and

three-quarters hours, while anachlorhydria undoubtedly exists if no result is obtained within five to six hours. In cases of hyperchlorhydria and hypochlorhydria the reaction is delayed for more than two to three hours. Günzburg further advises that the resorption-test with potassium iodide be also made, and that the reaction-time be deducted from that taken up in the elimination of the iodide contained in the package. Several tests, moreover, should be made in the same case.

The author has had occasion to experiment with packages obtained from Germany and manufactured according to the directions of Günzburg.[1] In most of the packages the threads of fibrin had become brittle and were broken in transit. The results obtained with about twenty intact specimens, however, were entirely satisfactory, and it is to be regretted that the packages cannot as yet be obtained in the American market.

The Author's Test. Recent researches have led the author to believe that a close relation exists between the elimination of indican in the urine and the amount of free HCl present in the gastric contents. The results reached may be summarized as follows :

1. Euchlorhydria is never associated with an increased elimination of indican.

2. In cases of simple neurotic hyperchlorhydria a subnormal or normal amount of indican is found.

3. In cases of hyperchlorhydria associated with ulcer an increased indicanuria is quite constantly observed.

4. Anachlorhydria, referable to organic lesions of the stomach, is almost invariably associated with a highly increased indicanuria.

5. Hysterical anachlorhydria may be associated with the elimination of a normal or increased amount of indican.

6. In cases of hypochlorhydria increased indicanuria is the rule.

Given as premises :

1. That a resorption of decomposing pus is not taking place anywhere within the body, as such a process in itself is capable of causing an increased elimination of indican.

2. That a stenosis of the small intestine does not exist.

3. A normal mixed diet, containing no excessive amounts of red meat.

[1] Göthe, Apotheke, Frankfurt a. M.

Differential Table of the More Important Diseases of the Stomach.

Disease.	General appearance.	Reaction.	Free HCl.	Lactic acid.	Fatty acids.	Ferments.	Microscopic examination.
Acute gastritis.	Partly digested food; mucus; frequently a green color referable to bile-pigment.	Feebly acid.	Absent.	Absent, or present in traces only.	Often large amounts after a meal, otherwise absent.	Ferments diminished; proenzymes present.	Partly digested food; mucus; salivary corpuscles; bacteria; a few red corpuscles.
Simple chronic gastritis.	Imperfectly digested food; biliary coloring-matter frequently present; not much mucus.	Acidity never increased.	Diminished or absent.	Traces after Ewald's test-breakfast; absent after that of Boas.	Present at times after Ewald's test-breakfast; absent after that of Boas.	Ferments diminished; proenzymes present.	Partly digested food; at times shreds of mucous membrane.
Mucous gastritis.	Imperfectly digested food; much mucus.	Slightly acid or neutral.	Usually absent.	Absent after Boas' test-breakfast.	Absent after Boas' test-breakfast.	Ferments almost absent; proenzymes diminished.	Undigested food; shreds of mucous membrane.
Chronic atrophic gastritis.	Unaltered food; no mucus.	Neutral or alkaline.	Absent.	Absent after Boas' test-breakfast.	Absent after Boas' test-breakfast.	Ferments absent; proenzymes absent.	Undigested food; no morphologic secretory elements.
Gastric ulcer.	Blood frequently present.	Usually increased acidity.	Frequently increased.	Absent after Boas' test-breakfast.	Absent.	Ferments and proenzymes in normal amount.	If blood be present, this usually occurs in the form of amorphous masses of pigment; well-preserved red corpuscles are only exceptionally seen.
Dilatation of the stomach, not referable to carcinoma.	Particles of undigested food in various stages of decomposition.	Acidity normal or somewhat increased.	Diminished or increased; more frequently increased.	Absent after Boas' test-breakfast.	Large amounts at times after Ewald's test-breakfast; absent after that of Boas.	Ferments and proenzymes usually present.	Numerous micro-organisms; bacteria and yeast-fungi.
Carcinoma.	The vomited matter has at times the appearance of coffee-grounds.	Acidity below normal.	Absent or diminished, unless the carcinoma has developed from the base of an old ulcer, when it may be increased.	Usually present in large amounts.	Usually present in large amount.	Ferments and proenzymes frequently absent.	Blood present at times; sarcinæ present in large numbers. Boas-Oppler bacillus almost always present.

Method: The urine of twenty-four hours is carefully collected and a specimen taken for examination. A few c.c. of urine are mixed with an equal amount of concentrated hydrochloric acid and two or three drops of a concentrated solution of sodium hypochlorite and 1 or 2 c.c. of chloroform added. The mixture is thoroughly agitated and set aside. The indigo which has been liberated in this manner is taken up by the chloroform, coloring this blue to a greater or less extent, the degree of increase as compared with the normal being determined by the intensity of the color obtained. For the sake of comparison it is well to employ the same quantities of urine and of reagents in every case, marked tubes being very convenient for this purpose.

CHAPTER IV.

THE FECES.

DEFINITION.

THE feces may be defined as being a mixture of undigested particles of food and unabsorbed secretions of the gastro-intestinal tract, together with intestinal mucus, epithelial cells, and bacteria.

THE EXAMINATION OF NORMAL FECES.

General Characteristics.

Number of Stools. The number of stools which may be passed in the twenty-four hours is even under physiologic conditions subject to wide variations, but usually constant for one and the same individual. One or two stools *pro die* may be regarded as normal. Exceptions, however, are frequent. Persons are thus met with who have but one stool every two to four days, and cases are on record in which one passage only occurred every seven to fourteen days, the individuals evidently enjoying perfect health. On the other hand, the number of stools may be increased to three and even four under strictly normal conditions. *Hence the importance of accurately ascertaining the habitual number of stools in every individual.* It would thus be manifestly wrong to regard the passage of three stools daily as diarrhœa, or the passage of only one stool in forty-eight hours as constipation, if this number has been habitual throughout life.

Whether or not it is permissible to regard as normal those rare instances in which one stool only occurs every two to six weeks, or even less frequently, appears rather doubtful.

Amount. In those cases in which more than one or two stools occur in twenty-four hours it is well to ascertain the amount actually passed. The figures given by different observers as expressing the total amount vary somewhat, from 100 to 200 grammes being about the normal. This quantity is increased by a diet rich in

vegetable and starchy foods, and diminished by one rich in animal proteids, so that 60 and 250 grammes may be regarded as the extreme limits in health. Such amounts as 500 and 1000 grammes are certainly abnormal.

Consistence and Form. The consistence of a stool depends essentially upon the amount of water present, and hence upon the character of the food ingested, being softer with a purely vegetable diet (80–85 per cent. of water) than with a diet rich in animal proteids (60–65 per cent.). With a mixed diet the amount of water corresponds to about 75 per cent. As a general rule, normal stools exhibit the characteristic cylindrical form and are fairly firm. Mushy stools, however, are also seen quite frequently, and round, scybalous masses, although by far more common in cases of constipation, may likewise be observed in health.

Odor. The repugnant odor of the feces is, to a large extent, due to the presence of indol and skatol, products of albuminous decomposition; sulphuretted hydrogen, methane, and traces of phosphin may add still further to their disagreeable odor.

Color. The color of the feces varies, according to the nature of the food ingested, from light to almost a blackish-brown, a firm stool being in general darker in color than a thin stool. A stool that has remained exposed to the air is also somewhat darker upon its outer surface than in its interior, owing to processes of oxidation. In nursing-infants, in consequence of the exclusive ingestion of milk, the color is light yellow.

Under normal conditions the color is never due to native biliary coloring-matter, the presence of this substance being always indicative of some pathologic process, but is largely dependent upon the presence of hydrobilirubin—*i. e.*, reduced bilirubin. It is, furthermore, influenced by the nature of the food, chlorophyll tending to produce a greenish color, starches a yellowish tinge. If much blood be present in the food, the feces may be almost black, owing to the formation of hæmatin. Huckleberries and red wine likewise produce a blackish color, chocolate and cocoa a gray; preparations of iron, manganese, and bismuth color the feces dark brown or black, owing to the formation of the sulphides of these metals; the green color of calomel stools was formerly supposed to be due to the formation of a sulphide, but is more likely caused by the presence of biliverdin. Santonin, rheum, and senna produce a yellow color.

Macroscopic Constituents.

Alimentary Detritus. Upon further examination of the feces it is possible to find visible to the naked eye undigested particles of food, which are partly indigestible and partly digestible, such as stones of cherries, grape-seeds, woody vegetable fibre, the skins of berries, large pieces of connective tissue, undigested pieces of apple, pear, potato, grains of corn, etc. The latter are found in abundance when the food is insufficiently masticated or taken in excessive amounts.

Flakes of casein, recognizable with the naked eye, are also frequently seen. Care should be taken, however, not to confound these with particles of stool composed of fatty acid crystals. This mistake is often made, and can readily be avoided by a microscopic examination.

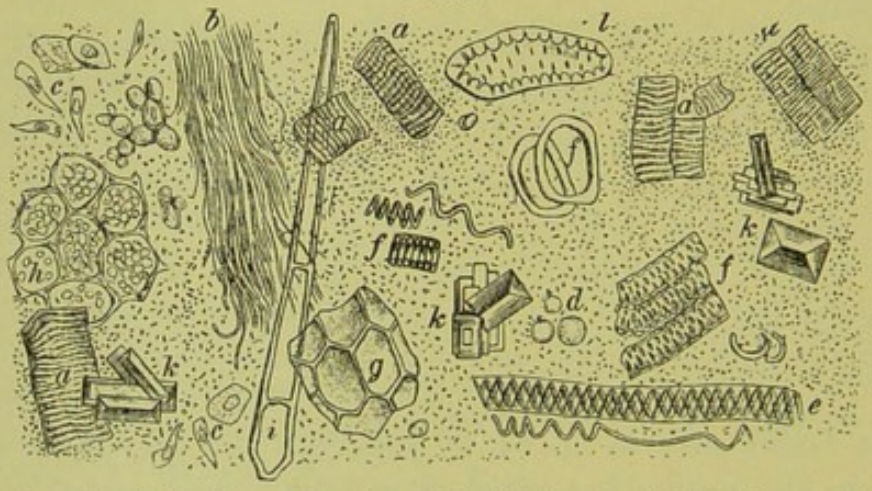
Foreign Bodies. In children, the insane, cases of hysteria, and even in people who are otherwise possessed of their normal senses, the physician must be prepared to find at times all kinds of foreign bodies, such as pins, coins, buttons, false teeth, tooth-plates with ragged edges, and even dirk-knives, all of which have been known to pass through the alimentary canal with perfect safety; certainly a wonderful fact, when it is remembered that so small and innocent-looking an object as a grape-seed may, at times, prove the cause of death. It must not be forgotten, however, that in certain cases of hysteria bodies may be shown by patients which they claim have passed by the rectum, but which have been wilfully added to the stools, such as snakes, frogs, etc.

Microscopic Constituents.

Constituents derived from Food. Microscopically indigestible and undigested constituents of food may be seen (Fig. 38), such as the framework of vegetable material, sometimes still containing starch-granules or remnants of chlorophyll; muscle-fibres, usually colored yellow and more or less altered in structure; elastic-tissue fibres are readily recognized by their double contour and bold outlines. Connective-tissue fibres of the white fibrous variety can also generally be distinguished; when present in large quantities, however, they are usually indicative of some digestive derangement, unless they be observed following the ingestion of a meal particularly rich in meat. Flakes of casein are also frequently seen.

Muscle-fibres are found in every stool whenever meat has been eaten. Under normal conditions, however, they are not numerous, unless particularly large quantities have been ingested. Their appearance under the microscope may vary considerably. On the one hand, fibres are met with which still retain their characteristic features; others are split up either partially or entirely into the well-known disks; but more common than both are more or less roundish, yellow, apparently homogeneous fragments, which at first sight do not resemble muscle-fibres in the least. Upon closer investigation, however, their true nature will become apparent. It will then be seen that two of the sides in some portions at least are more or less parallel, and if the specimen be examined with an oil-immersion lens some traces of cross-striation can probably always be discovered.

FIG. 38.



Collective view of the feces. (Eye-piece III., objective 8 a, Reichert.) *a*, muscle-fibres; *b*, connective tissue; *c*, epithelium; *d*, white blood-corpuscles; *e*, spiral cells; *f*, *i*, various vegetable cells; *k*, triple phosphate crystals in a mass of various micro-organisms; *l*, diatoms. (v. JAKSCH.)

Isolated starch-granules are scarcely ever found under normal conditions, excepting in young children who have been fed with much starchy material. Starch-granules enclosed in vegetable cells are likewise not found as a general rule, but are more common than the isolated granules. The presence of either in large numbers is usually indicative of the existence of some pathologic condition affecting the gastro-intestinal tract. Their presence is easily recognized by treating microscopic preparations with a solution of iodo-potassic iodide (Lugol's solution), when the granules or fragments will assume a blue color.

The presence of fat in the feces is quite constant, even in health.

It may occur in the form of needle-like crystals, as fat-droplets, or as polygonal masses which are highly refractive and often colored yellow or a yellowish-red. Their true nature is easily recognized by adding a drop of concentrated sulphuric acid and heating, when they will be transformed into the characteristic fat-droplets.

Morphologic Elements derived from the Alimentary Canal.

1. Epithelial cells. Well-preserved cylindrical or goblet cells are only exceptionally found in the feces, while transition forms from the normal cell to mere spindles, in which a nucleus can no longer be recognized, are quite constantly observed. These degenerative changes, according to Nothnagel, are the result of an abstraction of water from the cells, which may alter their appearance to an extent that only the experienced eye is capable of recognizing their true character. Pavement epithelial cells, when present, are derived from the anal orifice.

2. Leucocytes are almost always absent in normal stools or present only in very small numbers.

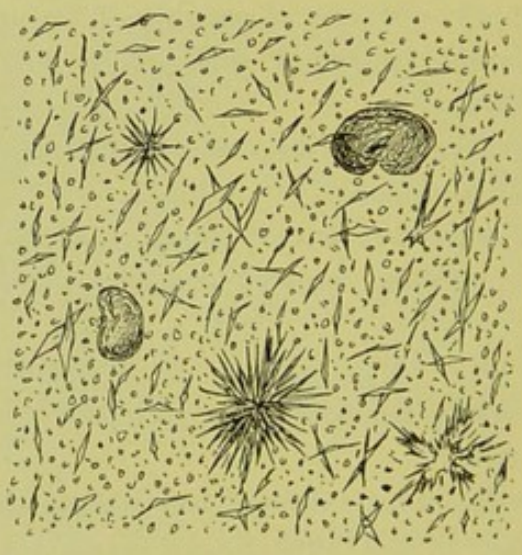
3. Red blood-corpuscles in very small numbers are occasionally observed under apparently normal conditions, but are then of no significance.

4. In every stool a large number of structureless granules may be seen, lying either by themselves or collected into heaps; they are designated as detritus.

Crystals. Needle-like crystals of free fatty acids, and the calcium and magnesium salts of the higher members of this group, occurring either single or arranged in sheaves, may be found in every stool. (Fig. 39.) They are of no significance, unless present in very large numbers. Nothnagel speaks of the frequent occurrence of certain calcium salts (of fatty acids, as he believes) in normal as well as pathologic stools. He states that they are almost always bile-stained and occur in irregular, sometimes eliptical, oval, or circular masses, in which a crystalline structure cannot be distinguished. They are apparently of no importance. Quite common, also, are crystals of neutral calcium phosphate and ammonio-magnesium phosphate, the former occurring in the form of more or less well-defined wedge-shaped crystals, collected into rosettes, the latter presenting the well-known coffin-shape when the stool is mushy, while in firm stools irregular fragments are mostly found. At one

time the ammonio-magnesium phosphate crystals were supposed to be characteristic of typhoid stools, but it is now known that they occur in normal feces, as well as under the most varied pathologic conditions. Their presence is of no diagnostic significance. It is important to note that the neutral phosphates are never stained by bile-pigment, and the triple phosphates only in rare instances. Both are easily soluble in acetic acid. Crystals of oxalate of calcium may be found in abundance following the ingestion of certain vegetables, such as sorrel and spinach. They are usually found imbedded in the vegetable débris. They are readily recognized by their characteristic envelope-form, their insolubility in acetic acid, and their solubility in hydrochloric acid. Not infrequently they are bile-stained.

FIG. 39.



Fatty crystals obtained from the feces.

Lactate of calcium is frequently seen in stools of children receiving a milk-diet, occurring in the form of sheaves composed of radiating needles. Calcium carbonate is rarely observed, but occasionally occurs in the form of amorphous granules or dumb-bell shaped crystals. Calcium sulphate crystals are likewise rare, but may be produced artificially by the addition of sulphuric acid, when beautiful needles and platelets may be observed. Cholesterin, while always present in solution, is rarely observed in crystalline form. (Fig. 40.) The writer found it only twice in several hundred examinations. Hæmatoidin crystals are never found in normal stools. Charcot-Leyden crystals occur principally under pathologic condi-

tions, and, according to the writer's experience, are never found in normal stools.

Parasites. The parasites which occur in normal feces may be divided into vegetable and animal parasites.

Vegetable Parasites. These are always present in enormous numbers. What relation they bear to the process of digestion is as yet an open question. The idea held by Pasteur and many others, that animal life cannot go on in the absence of bacteria from the digestive tract has recently been disproved by Nuttall and Tierfelder. A guinea-pig removed by Cæsarean section from the uterus of the mother-animal under antiseptic precautions was placed in a sterilized glass cage and nourished for a week with sterilized food. The air which the animal breathed was likewise sterilized. During this week the animal consumed about 330 c.c. of milk and appeared to be normal in every respect. At the expiration of the week it was killed, when a microscopic examination of the intestinal contents revealed the entire absence of bacteria. Culture-experiments were likewise negative.

Macfayden, Nencki, and Sieber likewise found that their now so often quoted fistula patient continued in good health, and even gained flesh, although the entire large intestine, in which bacterial activity is always greatest, was thrown out entirely for a period of many weeks.

Fungi. Fungi, with the exception, perhaps, of the oïdium albicans, which has at times been observed, are but rarely found in the feces.

Schizomycetes. Saccharomyces cerevisiæ belongs to the normal constituents, as it were, of the feces, and is found in its characteristic forms, three or four buds, however, being but ordinarily observed. Owing to the glycogen present in their substance, they assume a mahogany color when treated with a solution of iodo-potassic iodide. They should not be confounded with a class of bacteria which closely resemble the saccharomyces in appearance, but are colored blue when treated in the same manner (see below).

Bacteria. The bacteria are the micro-organisms *κατ' ἐξοχήν* which are found in the feces. Their number is truly enormous. Sucksdorff thus found in his own person that on an average 53,124,000,000 were eliminated in the twenty-four hours under normal conditions. About 97 per cent. of these are directly derived from the ingested food, and the remaining 3 per cent. from swallowed saliva. If we

recall the strongly bactericidal power of the gastric juice, such an observation must at first sight appear most surprising. It should be remembered, however, that the spores of the bacteria are far less susceptible to the action of the hydrochloric acid, and that large amounts of the ingesta are carried into the small intestine at a time already when hydrochloric acid has not as yet appeared in the free state.

On the whole, the bacteriologic flora of the intestinal contents is fairly constant, but, as in the other cavities and channels of the body where bacteria are invariably met with, transient guests are also not uncommon. The majority of the bacteria which are here encountered are, as a general rule, harmless, but it is important to note that under suitable conditions a number of these may develop pathogenic properties. Roughly speaking, the bacteria which may be normally found in the feces can be divided into two classes. Those belonging to the first order are stained a yellow or a yellowish-brown with iodo-potassic iodide, while those belonging to the second class are colored blue or violet by the same reagent. To the former belong the bacterium termo, the bacillus subtilis, and a large number of micrococci, into a description of which, however, it is not necessary to enter at this place. Under the second heading v. Jaksch describes the following forms:

1. Micrococci occurring in the zoöglœa stage, which are colored a violet-red.

2. Short, thin rods, tapering slightly at both ends, and in their microscopic appearance much resembling the bacillus of the septicæmia of mice; sometimes they contain one or two little bodies, which are not stained by the reagent.

3. Short or long rods, which resemble the leptothrix buccalis in their behavior toward iodo-potassic iodide.

4. Bacilli resembling the bacillus subtilis.

5. Bacillus butyricus. This micro-organism, according to Brieger, is the cause of butyric-acid fermentation. It occurs in the form of broad rods with rounded-off extremities, but may also be elliptical or spindle-shaped. With Lugol's solution it is colored blue or violet either entirely or only in its central portion.

6. Large round forms, characterized, when unstained, by a pale lustre, and which very much resemble yeast-cells (see above).

7. Micrococci, which assume a reddish, but not very pronounced tint.

It should be mentioned that this second class of micro-organisms is not so largely represented in the feces as the first.

To speak more specifically, the following bacteria have thus far been isolated from the feces: bacillus coli communis, bacterium lactis aërogenes, bacillus subtilis, proteus vulgaris, bacillus putrificus coli, bacillus liquefaciens ilei, bacterium ilei, bacterium ovale ilei, bacillus gracili ilei, the veil bacillus of Escherich, bacillus butyricus, bacillus Utpadel; streptococcus coli gracilis, streptococcus coli brevis, streptococcus liquefaciens ilei, streptococcus pyogenes duodenalis, staphylococcus liquefaciens albus, staphylococcus liquefaciens flavus, micrococcus ovalis, the porcelain-coccus of Escherich, tetradencoccus. In addition various other bacteria have been found, but have not as yet been obtained in pure culture. This is especially true of certain forms of spirillum.

The specific pathogenic bacteria which may be found in the feces as well as those above mentioned, which may at times develop pathogenic properties, will be described in detail later on.

Animal parasites are probably never present under strictly normal conditions.

Chemistry of Normal Feces.

Reaction. The reaction of the feces is usually alkaline, sometimes neutral, rarely acid, the alkalinity being due to ammoniacal fermentation, the acidity to lactic- and butyric-acid fermentation taking place in the intestines. In infants the stools are normally acid.

General Composition. The following table, taken from Gautier, will give an idea of the composition of fresh feces, calculated for 1000 parts by weight:

	Adult man.	Suckling.
Water	733 00	851.3
Solids	267.00	148.7
Total organic material	208.75	137.1[1]
Total mineral material	10.95[2]	13.6
Alimentary residue	83 00	

The organic material yielded:

Aqueous extract	53.40	53.5
Alcoholic extract	41.65	8.20
Ethereal extract	30.70	17.6[3]

[1] Including 54 parts of mucin, epithelium, and calcareous salts.

[2] Not comprising earthy phosphates.

[3] Of this, 3.2 cholesterin.

In addition, there are gases, which vary considerably in amount according to the nature of the food ingested, such articles as beans, heavy bread, potatoes, etc., increasing their amount very considerably.

	Milk diet. Per cent.	Meat diet. Per cent.	Vegetable diet. Per cent.
Carbon dioxide	9–16	8–13	21–34
Hydrogen	43–54	0.7–3	1.5–4
Marsh gas	0.09	26–37	44–55
Nitrogen	36–38	45–64	10–19

Of these gases, CO_2 is referable to alcoholic and butyric-acid fermentation, as well as to albuminous putrefaction, taking place in the intestines. Marsh gas, CH_4, is similarly formed during the fermentation of cellulose, while the nitrogen has been partly swallowed and is partly referable to albuminous putrefaction. A portion also is probably derived from the blood, and it may be mentioned in this connection that the enormous quantities of CO_2 so often discharged in cases of hysteria are undoubtedly attributable to this source, the gas passing from the blood through the gastro-intestinal mucous membrane into the stomach and intestines.

In order to give a general idea of the chemical constituents of the feces these may be divided into:

1. Food-material, which could be assimilated, but which was taken in excess, such as starches, fats, and a small amount of non-assimilated albuminous material.

2. Indigestible substances, such as chlorophyll, gums, pectic products, resins, various coloring-matters, nuclein, chitin, and insoluble salts, viz., silicates, sulphates, earthy phosphates, ammonio-magnesium phosphate, etc.

3. Products derived from the digestive canal, as mucus, partly transformed biliary acids, dyslysin, cholesterin, lecithin.

4. Substances in process of absorption, as emulsified fats, fatty acids, leucin, and biliary acids.

5. Products of decomposition, referable to microbic activity; fatty acids, comprising the entire series from acetic to palmitic acid, the latter being especially abundant; butyric and iso-butyric acid, lactic acid, phenol, cresol, indol, skatol, excretin, amido-acids, and acid-amides, leucin and tyrosin, phenyl-proprionic, phenyl-acetic, hydro-paracumaric, and parahydroxylphenyl-acetic acid, ammonium carbonate and ammonium sulphide.

6. Products of metabolism eliminated through the intestines: urea, uric acid, and xanthin bases.

7. Pigments: stercobilin, hæmatin, hydrobilirubin, coloring-matters derived from the blood, and, in abnormal conditions, bile-pigments.

8. Water.

9. Gases, as CO_2, CH_4, H, and N.

The study of these substances as a whole, as well as in detail, is of considerable importance, not only from the standpoint of the physiologist, but also from that of the clinician, giving, together with a careful urinary analysis, the clearest idea of the metabolic processes taking place in the body.

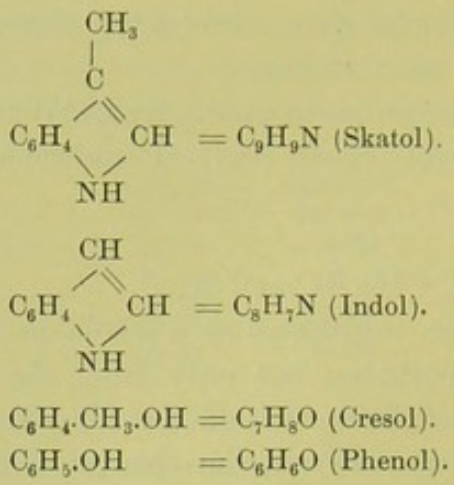
The chemical study of the feces has so far not received the attention which it deserves, and data of but little practical importance have been obtained from the work accomplished. This field will, without doubt, furnish highly important results in the course of time, those gained in the microscopy of the feces being certainly of a nature to encourage a detailed chemical study also. Up to the beginning of the eighties the morphologic and bacteriologic study of the feces had been similarly neglected, but brilliant results have been achieved within the last few years. It is only necessary to recall the discovery of the cholera bacillus by Koch in 1884; of the amœba coli by Lösch and Kartulis, and its relation to tropical dysentery; the relation of bothriocephalus latus and anchylostoma duodenale to certain forms of severe anæmia; not to speak of the generally recognized importance which the examination of the feces for the eggs of parasites in general has assumed within late years.

It is impossible to give here a detailed description of the various chemical constituents which have been mentioned. Only the most important ones and those especially interesting from a physiologic and pathologic standpoint will be considered.

Phenol, Indol, and Skatol. Tyrosin, produced during the process of albuminous putrefaction, and also during tryptic digestion, must be regarded as the mother-substance of phenol, cresol, indol, and skatol. It may be represented by the formula:

$$C_6H_4\begin{cases}CH_2—(NH_2)—COOH\\OH\end{cases} = C_9H_{11}NO_3.$$

The relation which phenol, cresol, indol, and skatol bear to tyrosin may be seen from the following formulæ:



As the tyrosin, however, is very readily decomposed, it is usually not found in the feces, but the products of its decomposition instead, viz., the phenols, indol, and skatol.

As will be seen more especially in the chapter on Urine, these bodies, after having undergone oxidation, unite with sulphuric acid, or, if this be not present in sufficient amount, with glycuronic acid, and are excreted as phenol, indoxyl, and skatoxyl sulphates or glycuronates in the urine. In the feces, on the other hand, phenol, cresol, indol, and skatol are found as such. From these they may be obtained in the following manner:

The feces are diluted with water, acidified with phosphoric acid, and distilled. The volatile fatty acids present, together with phenol, indol, and skatol, pass over. The distillate is then neutralized with sodium carbonate and again distilled. During this process phenol, indol, and skatol pass over, the fatty acids remaining behind as sodium salts. In order to separate the phenol from indol and skatol the distillate is alkalinized with potassium hydrate and again distilled. The phenol now remains behind, and may be obtained in pure form by distilling with sulphuric acid; in this final distillate its presence may be demonstrated by the following reactions:

1. With perchloride of iron phenol yields an amethyst-blue color.
2. With bromine-water a crystalline precipitate of tribromophenol results.
3. Treated with Millon's reagent—*i. e.*, the acid nitrate of mercury—a red color develops.

Indol and skatol, on the other hand, pass over after treating the above mixture of the three with potassium hydrate and distilling.

These two bodies may then be separated from each other by taking advantage of their different degrees of solubility in water.

Indol forms small plates, melting at 52° C., which are easily soluble in hot water, alcohol, and ether; its odor is feculent.

Reactions of indol: 1. When treated with nitric acid and a little sodium nitrite a crystalline red precipitate of the nitrate of nitroso-indol is obtained. 2. A small piece of pine-wood, moistened with an alcoholic solution of indol, acidified with hydrochloric acid, is colored a cherry-red.

Skatol also crystallizes in plates, which melt at 95° C. They are soluble with more difficulty in water than indol, and emit a feculent odor.

Reactions of skatol: 1. With nitric acid and sodium nitrite only a milky cloudiness results. 2. Pure skatol does not yield any color with pine-wood moistened with hydrochloric acid; but if a bit of the wood be saturated with a dilute alcoholic solution of skatol and then immersed in strong hydrochloric acid, it assumes a cherry-red and later a bluish-violet color. 3. With nitric acid of a specific gravity of 1.2 it gives upon boiling a marked xanthoproteic reaction—*i. e.*, a yellow color which turns to orange upon adding an excess of ammonia.

Finally, the determination of cresol in the presence of phenol, together with which it is obtained, is, when only small quantities of these substances are present, a difficult matter. They may be separated from each other by transforming both into their sulpho-acids, the barium salt of parasulphophenol being practically insoluble in barium hydrate.

Fatty Acids. The fatty acids present in the feces, as well as the relation existing between these, are given in the table below. The formula $C_nH_{2n+1}COOH$ or $C_nH_{2n}O_2$ expresses their general structure:

Formic acid	H.COOH	CH_2O_2
Acetic "	CH_3COOH	$C_2H_4O_2$
Proprionic acid	$CH_3.CH_2.COOH$	$C_3H_6O_2$
Butyric "	$CH_3.(CH_2)_2.COOH$	$C_4H_8O_2$
Isobutyric "	$(CH_3)_2.CH.COOH$	$C_4H_8O_2$
Valerianic "	$CH_3.(CH_2)_3.COOH$	$C_5H_{10}O_2$
Caproic "	$CH_3.(CH_2)_4.COOH$	$C_6H_{12}O_2$
Capric "	$CH_3.(CH_2)_8.COOH$	$C_{10}H_{20}O_2$
Palmitic "	$CH_3.(CH_2)_{14}COOH$	$C_{16}H_{32}O_2$
Stearic "	$CH_3.(CH_2)_{16}.COOH$	$C_{18}H_{36}O_2$

These acids are derived partly from fats, partly from carbohydrates, and to some extent also from proteids.

Separation of the fatty acids from the feces: If the distillate, neutralized with sodium carbonate, referred to in the above method (p. 192), be again distilled, the sodium salts of the fatty acids remain behind, the process taking place being one of saponification; *e. g.:*

$$2C_{15}H_{31}COOH + Na_2CO_3 = 2C_{15}H_{31}COO.Na + H_2O + CO_2.$$

The solution is then evaporated to dryness on a water-bath, the residue extracted with alcohol, the alcohol evaporated, and the final residue dissolved in water. This solution may now be further examined. In order to separate the different fatty acids from each other it is best, if the quantity be sufficiently large, to transform them into their silver or barium salts, and to separate these by their varying degrees of solubility in water or by fractional distillation.

General properties of the fatty acids: They are all monobasic, soluble in water, alcohol, and ether. Their alkaline salts are readily soluble in water and alcohol, but insoluble in ether. The silver salts are dissolved with difficulty.

1. Formic acid is a colorless liquid, of a penetrating odor, boiling at 100° C. A concentrated solution of its alkaline salts is precipitated by $AgNO_3$; the silver salt becomes black on standing, and reduction takes place at once upon the application of heat. Treated with perchloride of iron in a neutral solution it yields a blood-red color, which disappears upon boiling, while a rust-colored precipitate is formed at the same time.

2. Acetic acid is a liquid of a pungent odor, which boils at 119° C. Upon neutralization a blood-red color is obtained on the addition of perchloride of iron. Neutral solutions of its salts with alkalies yield a precipitate with nitrate of silver, soluble in hot water, without reduction taking place.

3. Proprionic acid is an oily fluid, boiling at 117° C. With perchloride of iron no red color results; with silver nitrate it behaves like formic acid.

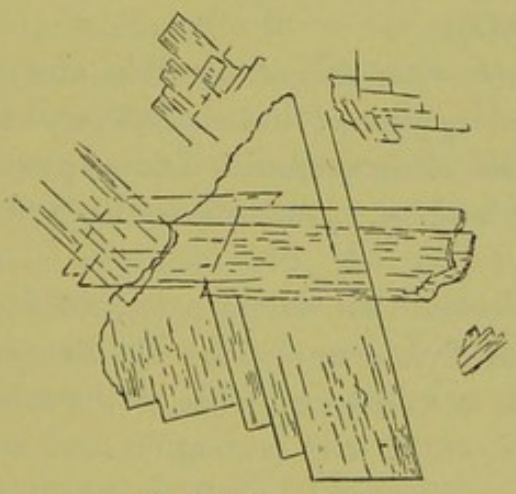
4. Butyric acid is an oily liquid, boiling at 137° C., which has an odor similar to rancid butter. Its salts, when treated with an acid, give off the characteristic odor; with perchloride of iron it yields no red color; with $AgNO_3$ its alkaline salts form a crystalline precipitate insoluble in cold water.

5. Valerianic acid boils at 176.3° C., and has a penetrating, disagreeable odor. Its silver salt crystallizes in plates, which are soluble with difficulty.

Cholesterin. Cholesterin ($C_{26}H_{44}O$) occurs in small amounts in almost all animal fluids. It is also found in various tissues of the body, especially in the brain. Its origin and mode of formation in the various organs of the body, as well as the cause of its presence in the alimentary canal, are as yet unknown. It crystallizes in colorless, transparent plates, the margins and angles of which usually present a ragged appearance (Fig. 40). It is soluble in water, dilute acids, and alkalies. In boiling alcohol it is readily soluble, crystallizing out from this solution on cooling; it is likewise very soluble in ether, chloroform, and benzol.

In order to obtain cholesterin from the feces, in which it is always present, though rarely in crystalline form, the fatty acids, phenols, indol, and skatol must first be distilled off, as described, when the residue is strongly acidified with sulphuric acid, extracted with alcohol, and then with ether. The ethereal extract is filtered, the ether distilled off, and the residue digested with carbonate of sodium, in order to transform any fatty acids which may still be

FIG. 40.



Cholesterin crystals.

present into their salts. This mixture is then evaporated to dryness, and again extracted with ether. The alcoholic extract above mentioned is also filtered, supersaturated with sodium carbonate, the alcohol distilled off, the residue dissolved in water, and likewise extracted with ether. In the watery alkaline residue there remain bile acids, oleic, palmitic, and stearic acids, which can be separated

by transforming them into their barium salts. The cholesterin and fats pass over into the ether. This is distilled off and the residue treated with an alcoholic solution of potassium hydrate. The alcohol is evaporated on a water-bath, the remaining liquid diluted with water, and again extracted with ether. The fats remain in the aqueous solution as soaps, while the cholesterin has passed over into the ether.

Tests for cholesterin: 1. Under the microscope add a drop of concentrated sulphuric acid to some of the crystals; they gradually disappear, the edges assuming a yellowish-red color.

2. Dissolve a few crystals in chloroform, add concentrated sulphuric acid, and shake the mixture: the chloroform assumes a blood-red to a purplish-red color, while the sulphuric acid at the same time shows marked fluorescence.

The solution of soaps obtained above is acidified with dilute sulphuric acid, when the fatty acids, which have separated out, may be filtered off and identified individually by their boiling-points and the analysis of their barium salts.

The filtrate finally obtained, when neutralized with ammonium hydrate, contains glycerine.

The Biliary Acids. The biliary acids found in the feces are: Glycocholic acid ($C_{26}H_{43}NO_6$), taurocholic acid ($C_{26}H_{45}NSO_7$), and cholalic acid ($C_{24}H_4O_5$).

The two former occur normally in the bile, and can be decomposed into cholalic acid and glycocoll and cholalic acid and taurin respectively; as this process of decomposition takes place ordinarily in the intestines, the third acid—*i. e.*, cholalic acid—is always found in the feces.

In order to demonstrate the biliary acids, the fatty acids, phenols, indol, and skatol are first removed by distillation with phosphoric acid. The residue is taken up with water and boiled, and the filtered liquid precipitated with acetate of lead and a little ammonium hydrate. The biliary salts of lead are contained in the precipitate, from which they can be removed by washing with water and finally boiling the precipitate with alcohol. The washings are then filtered and the lead salts transformed into sodium salts by treating the filtrate with sodium carbonate. After further filtration the filtrate is evaporated to dryness and the residue extracted with hot alcohol. Upon evaporating this the salts of the acids sometimes crystallize out as such, while more often a dirty amorphous precipi-

tate is obtained, which may be rendered crystalline by treating with ether. The amorphous residue, however, can be employed for making the necessary tests:

Pettenkofer's test: A small amount of the substance is dissolved in water, and two-thirds of its volume of concentrated sulphuric acid added, care being taken that the temperature does not exceed 60° or 70° C. A 10 per cent. solution of cane-sugar is added, drop by drop, stirring constantly. If biliary acids be present, the solution assumes a beautiful red color, which upon standing turns a bluish-violet. This test depends upon the action of furfurol, derived from the sulphuric acid and cane-sugar, upon the biliary acids.

Pigments. Among the pigments present in normal feces stercobilin and hydrobilirubin must be considered.

Stercobilin is spoken of by Gautier as the principal coloring-matter of the feces, derived from bilirubin by a process of reduction. Owing to its great similarity to hydrobilirubin it has even been said to be identical with this. It has been obtained by extracting the feces with acidulated alcohol; this extract is diluted with water and shaken with chloroform, which latter dissolves the pigment.

The difference between stercobilin and *hydrobilirubin* appears to be a spectroscopic one, the spectrum of the former, when treated with chloride of zinc and ammonium hydrate, giving rise to four bands of absorption, while only three are obtained with the latter. The pronounced green fluorescence, however, is common to both.

By means of the spectroscope it is also possible to distinguish between normal urobilin and stercobilin; the latter is possibly identical with the pathologic urobilin observed in febrile urines.

Hydrobilirubin is identical with the urobilin of Jaffe and the febrile urobilin of MacMunn, and shows, as has just been mentioned, three bands of absorption. Its chemical formula is $C_{32}H_{40}N_4O_7$. According to v. Jaksch, it is obtained in the same manner as stercobilin.

PATHOLOGY OF THE FECES.

General Characteristics.

Number of Stools. As has been pointed out (p. 181), one or two stools a day may be considered as normal; but here, as elsewhere, the proverb, "One man's food, another man's poison," holds good. Having definitely determined in a given case the

number of stools in the twenty-four hours in health, it is possible to state whether the particular case may be considered as normal in this respect—*i. e.*, whether diarrhœa or constipation exists.

As the consistence of the stools is altered in *diarrhœa*, this condition may be defined as one in which too frequent and liquid passages exist, while the reverse may be said to hold good for *constipation*, the consistence of the stools in this condition being usually also altered.

The term *obstruction*, on the other hand, denotes a state of affairs in which no stools are voided. In a general way it may be said that whatever causes give rise to increased peristalsis likewise produce diarrhœa, and that whatever causes diminish peristalsis give rise to constipation. In the former condition the number of stools may vary from one to thirty, forty, or even fifty in the twenty-four hours, as in Asiatic cholera. The consistence of the stool when only one is passed in the twenty-four hours will, of course, decide the question whether the case should be regarded as one of diarrhœa or not. One stool passed in the twenty-four hours may under certain conditions be regarded as a symptom of constipation, but more commonly this term is applied to a condition in which a stool occurs only every two, three, four or more days, or even weeks or months.

Consistence and Form. The consistence of the stools may undergo variations, which run a course parallel to their number. They may be thin, mushy, and even watery, which latter condition is met with most commonly in cholera Asiatica and dysentery, but may also occur in any severe enteritis.

In constipation, on the other hand, owing to an increased absorption of water, the feces may be passed as very hard and perfectly dry, roundish, scybalous masses, the rotundity of which is undoubtedly referable to their long sojourn in the haustra of the colon. The individual scybala usually vary in size from that of a hazelnut to that of a walnut, and are frequently provided with one or two indentations which represent impressions of the tæniæ of the colon. Still smaller masses, closely resembling the dejecta of sheep, may also be seen. Their presence was formerly regarded as characteristic of stricture of the colon, but they are likewise found in ordinary cases of chronic constipation. Fecal ribbons and columns of the diameter of a pencil are found in cases of enterospasm as well as in stricture of the colon.

Amount. The absolute amount of feces voided in the twenty-four hours bears an inverse relation to the number of stools and their consistence, providing, of course, that no abnormally large ingestion of food has occurred, in which case an abnormally large stool of moderate firmness may be passed. Two exceptions must, however, be noted to this rule—*i. e.*, the passage of large quantities of firm feces following an attack of constipation of long duration or an attack of severe obstruction.

Odor. As the normal offensive odor of the feces is largely due to products of intestinal putrefaction, an increase in offensiveness will naturally be referable to conditions in which the putrefactive processes are increased. A most disagreeable odor is thus met with in the so-called acholic stools. The odor of fatty acids is observed in the lighter grades of infantile diarrhœa, while a markedly putrid odor is associated with its severer forms. A very characteristic odor is further noted in the stools of cholera and dysentery, owing to the presence of considerable quantities of cadaverin. A truly rotten stench is present in the gangrenous form of dysentery, and in carcinomatous and syphilitic ulcerations of the rectum. An ammoniacal odor is due to an admixture of urine undergoing ammoniacal decomposition.

Reaction. The reaction of the stool is so variable under pathologic conditions that it is really of no diagnostic importance. In typhoid fever, it is true, an alkaline reaction is so constantly met with that this symptom could possibly be of some value in doubtful cases. Unfortunately, however, it may also be neutral, amphoteric, and even acid. In acute infantile diarrhœa an acid reaction is the rule, but exceptions are also not infrequent.

Color. The color of pathologic feces may vary a great deal. When unaltered bile is present, the stools may assume a golden-yellow, a greenish-yellow, or even a green color. In cases of biliary obstruction or suppression, on the other hand, they become pasty and have a grayish or even a white color. This, however, is not so much due to the absence of coloring-matter derived from the bile as to an insufficient absorption of fats, as was shown by Strümpell, who succeeded in obtaining stools of a light-brown color after feeding patients affected with catarrhal jaundice upon a diet containing a minimum amount of fat. *Such acholic or colorless stools,* as it would be better to say, are not only found associated with biliary obstruction, however, but may also occur when the ducts are patent.

They have thus been observed in various cases of leukæmia, carcinoma of the stomach or intestine, in simple infantile enteritis, chronic nephritis, chlorosis, scarlatina, tubercular enteritis, and especially frequently in debilitated consumptives and in cases of chronic tubercular peritonitis of children. In some of these conditions, as in tuberculosis of the intestines and of the peritoneum, the lack of color is probably due to a diminished absorption of fats, as above. In others, however, this explanation does not hold good, as abnormally large amounts of fat are not necessarily present. In such cases the lack of color is probably referable to the formation of colorless decomposition-products of bilirubin, such as the leukourobilin of Nencki, but as yet nothing definite is known of the conditions which favor the formation of these products. In this connection it may be interesting to note that in those cases in which the biliary ducts are patent the color of the stools may vary not only from day to day, but even within the twenty-four hours. A neurasthenic patient occurring in the practice of the writer thus passed an acholic stool almost every morning and usually colored feces in the afternoon for a period of several weeks.

Generally speaking, the color of the stools becomes lighter the larger the number of movements, and *vice versa*. In Asiatic cholera and dysentery they may thus be colorless, while in severe constipation the scybalous masses may almost be black.

If *blood* be present, the stools may present a scarlet-red, a dirty brownish-red, a coffee, or even a perfectly black color. *Adherent blood*, usually bright red in color and found on scybalous masses, is probably always derived from the rectum or anus, while a change in color, indicating an earlier date of the bleeding, usually points to the colon.

An *intimate admixture of blood* with the stool, the color of the former being at the same time altered, so as to vary from a brownish-red to black (owing to the presence of sulphide of iron), is indicative of hemorrhage into the stomach or the small intestine. The darker the color of the blood the more remote from the anus will be, as a rule, the seat of the hemorrhage. Black or coffee-colored stools are thus observed in cases of ulcer of the stomach or of the duodenum, in melæna neonatorum, and similar conditions.

When profuse intestinal hemorrhages take place, however, as in some cases of typhoid fever and melæna, and particularly when

diarrhœa exists at the same time, the blood which appears in the stools may be changed but very little or not at all.

While, as a rule, simple inspection or a microscopic examination of the feces will determine whether or not blood be present, it may at times be necessary to resort to more delicate tests, as the hemorrhage may have been so slight as to escape detection with the naked eye or, at the same time, so far removed from the anus that blood shadows even cannot be found with the microscope. Hemorrhages of such trivial extent have been reported by Hässlin as occurring quite frequently in cases of chlorosis. This statement, however, the writer has not been able to confirm. If an investigation in this direction is to be made, the method of Müller and Weber (see p. 170), or that of Korczynski and Jaworski should be employed.

Korczynski and Jaworski's Test. A small amount of the fecal material is treated with a pinch of potassium chlorate and a drop of concentrated hydrochloric acid. The mixture is carefully heated until it has become decolorized, more hydrochloric acid being added if necessary. The chlorine is then driven off, when one or two drops of a dilute solution of potassium ferrocyanide are added. In the presence of blood coloring-matter a distinctly blue color is obtained, owing to the formation of Prussian blue.

An admixture of *pus* with the feces in notable amounts also gives rise to a characteristic color, as is seen in cases of dysentery, syphilitic and carcinomatous ulceration of the colon and rectum, following the perforation of a parametritic or periproctitic abscess into the rectum, etc.

Green stools are observed especially in infants, and may be referable to two different causes, being dependent on the one hand upon the presence of a bacillus, described by Le Sage, which produces a green coloring-matter, while on the other it may be referable to biliverdin. When green stools occur frequently this condition is associated with the clinical symptoms of a severe cholera infantum.

Quite characteristic also are the ipecacuanha stools, which closely resemble the so-called acholic stools. The green color produced by calomel, the yellow by santonin, rheum, and senna, the black by iron, manganese, and bismuth, have already been mentioned (see p. 182).

Macroscopic Constituents.

Alimentary Constituents. After having thus considered the number of stools, their consistence, reaction, odor, and color, it is

now necessary to look for gross admixtures, and especially for the presence of undigested food-material, such as pieces of meat, flakes of casein—this especially in the stools of children—and fragments of amylaceous food. The occurrence of such a condition, constituting what was formerly known as *lientery*, is always indicative of disturbed intestinal or gastric digestion, or both. It is, hence, observed in cases of chronic intestinal catarrh, febrile dyspepsia, following the use of cathartics, etc.

Occasionally also a condition of affairs is seen in which almost unaltered food in large amounts is found in the feces, owing to a direct communication between the stomach and the colon, as in cases of perforating ulcer or carcinoma of the stomach.

When fat is present in abnormally large amounts it can usually be recognized with the naked eye. To this condition the term *steatorrhœa* has been applied. In typical cases the fat is seen in the form of whitish or grayish masses, varying in size from that of a pea to that of a walnut, which are more or less intimately mixed with the fecal material, and may at first sight be mistaken for flakes of casein. From these it may be distinguished, however, by its chemical reactions and its peculiarly glistening appearance. In other cases stools may be seen in which the fecal column is covered, to a greater or less extent, with a grayish, dense, asbestos-like substance, while the core itself presents the usual color. Nothnagel states that this appearance is referable to the congealment of the fat when it is exposed to a lower temperature than that of the body. The writer, however, has repeatedly observed this appearance in stools which had just been voided. The passage of liquid oil in the absence of fecal material has also been recorded, but it seems doubtful to the writer that the oil in such cases entered the body by the mouth. Following the use of oil enemata such stools may, of course, be seen.

The elimination of abnormally large quantities of fat may be due to the ingestion of correspondingly large amounts. More frequently, however, it is referable to distinct pathologic conditions. A steatorrhœa will thus naturally occur when an insufficient supply of bile is poured into the small intestine, and is hence constantly observed in cases of biliary obstruction. In these cases, however, the microscope is usually necessary to demonstrate the presence of the abnormally large quantities of fat. True steatorrhœa, on the other hand, viz., the presence of fat recognizable with the naked

eye, is more commonly met with in diseases affecting the resorptive power of the small intestine, such as extensive atrophy or amyloid degeneration of the intestinal mucosa, tubercular ulceration, etc., or in diseases involving the integrity of the lymphatic glands and vessels of the mesentery, as in chronic tubercular peritonitis, caseous degeneration of the mesenteric glands, etc. In simple catarrhal conditions, however, steatorrhœa may also occur, and not only in infants, but, according to the writer's experience, also in adults. The question whether or not steatorrhœa is constantly observed in cases of pancreatic disease, as some observers have claimed, may now be answered in the negative, although it must be admitted that the two conditions are very frequently associated. Le Nobel, who has recently investigated this subject, arrived at the conclusion that the steatorrhœa in itself is of little practical importance, but that its association with the absence of products of putrefaction from the stools, the absence of the salts of the fatty acids, and the presence of maltose in the urine, may possibly be regarded as indicating the existence of pancreatic disease.

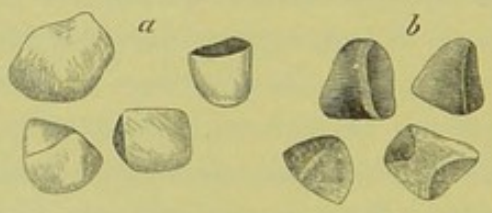
Mucus and Mucous Cylinders. As long as mucus occurs in small particles only adherent to otherwise normal feces it is of no pathologic significance. Larger amounts are almost always indicative of a catarrhal condition of the colon or rectum, no matter whether the stool be otherwise normal or whether diarrhœa exist at the time. Peculiar formations are occasionally seen, viz., so-called *mucous cylinders*, which are passed in large or small fragments in a condition which has been described by Nothnagel as *enteritis membranosa*, or *colica mucosa*. Such masses, which at times measure a foot or more in length, are ribbon- or net-shaped, and are frequently passed in the absence of fecal matter, with severe tenesmus. They closely resemble Curschmann's spirals, but lack the central thread and Charcot-Leyden crystals. They are probably indicative of chronic constipation associated with catarrh of the colon. Not to be confounded with this condition is the passage of masses of mucus which do not present the cylindrical form, but which also may be passed with a great deal of tenesmus and in the absence of fecal matter, in cases of nephroptosis, associated with gastroptosis and enteroptosis. These are, in all probability, also referable to a catarrhal condition of the colon. In cholera Asiatica particles of mucus are seen which resemble grains of rice, the presence of

which was formerly regarded as characteristic of the disease; they occur, however, also in ordinary catarrhal conditions.

Biliary and Intestinal Concretions. Most important from a diagnostic standpoint is the examination of the feces for the presence of biliary concretions, which should never be neglected in cases of colicky abdominal pain of doubtful origin, whether associated with jaundice or not.

When searching for gallstones the feces should be digested with water and passed through a fine sieve. Biliary concretions may then be found as small, crumbling masses or as hard stones presenting an irregular contour or the smooth, characteristic facets. In size they may vary from that of a millet-seed to that of a pigeon's egg; large stones are but rarely passed by the bowel unless perforation has occurred into the intestines and usually into the colon.

FIG. 41.



Gallstones.
a, cholesterin ; *b*, pigment-stones.

Some calculi consist almost entirely of cholesterin, while others are composed essentially of inspissated bile, and still others of calcareous salts. The former are the most common, and are readily recognized by their softness and color, which may be white, grayish, bluish, or greenish. Their specific gravity is lower than that of water. Very frequently they contain a nucleus, composed of earthy sulphates or phosphates. An analysis by the author of a large stone of this kind, weighing 10.548 grammes, gave the following results:

Cholesterin	72.59 per cent.
Mineral salts	0.247 "
Fats	5.09 "
Biliary pigments	13.93 "
Organic matter	7.27 "

Calculi, which consist largely of biliary pigments, are brown in color. They are hard, and heavier than water. Frequently they contain traces of copper and zinc. (Fig. 41.)

Calculi composed of calcareous salts generally present an irregular, roughened contour.

Within recent years Welch observed the presence of pure colonies of the bacillus coli communis in gallstones, apparently forming their nuclei.

Analysis of Gallstones. The stone is finely powdered and dried at a temperature of 100° C. It is then extracted with boiling water and the washings concentrated upon a water-bath to about 100 c.c. One portion of this amount is evaporated to dryness, and the soluble residue, as well as the mineral ash, determined after desiccation at a temperature of 105° C. The other portion is likewise evaporated to dryness and extracted with alcohol containing a small amount of ether, sodium glycocholate being thus obtained. After treatment with hot water, as described, the substance is successively extracted with alcohol and ether. In the alcoholic extract fats and a small amount of cholesterin will be found. The greater portion of the latter is contained in the ethereal extract. The residue, which is insoluble in hot water, alcohol, and ether, is treated with a moderately strong solution of hydrochloric acid, the earthy phosphates and oxides being thus obtained united to pigments. The bilirubin is removed from the latter by extracting with boiling chloroform. The pigments which are not dissolved in this manner are biliprasin, bilihumin, etc.

Intestinal concretions (enteroliths) are rare and usually come from the appendix. At times they contain some foreign body, such as a grape-seed, as a nucleus, upon which calcium and magnesium salts have become deposited.

Fecal calculi or *coproliths* are likewise only rarely found in the feces. They represent inspissated fecal material which has become impregnated with lime and magnesium salts. More commonly they are found at the post-mortem table in the cæcum, in the haustra of the colon, and in the rectum.

Microscopic Examination.

Attention should be directed to the presence of eggs of parasites, protozoa, certain pathogenic bacteria, remnants of food, blood-corpuscles, epithelial cells, pus-corpuscles, and mucus.

Technique. In hospital work the stool should be passed into a well-warmed bed-pan and examined at once. This is particularly

important in the search for amœbæ. In private practice patients should be instructed to send their stools to the physician at once, when suspicious-looking particles should be placed upon the warm-stage or examined upon a well-warmed slide. A very convenient form of warm-stage, which may be obtained from instrument-makers at low cost, is composed of brass and made to be held in position on the stage of the microscope by spring clips. It is about 8 cm. long and 3 cm. broad, and has cemented to a recessed bottom an ordinary glass slip; an opening of 1.35 cm. is in the centre of the stage. To one of the long sides of the brass stage is fitted a projecting stem, about 10 cm. long, to which the heat of a spirit-lamp is applied.

For ordinary purposes it is well to place the stool, if watery, in a conical glass and to cover it with a layer of ether, so as to diminish the disagreeable odor. If mushy or firm, it should be spread out upon a plate and covered with a layer of turpentine, or a 5 per cent. solution of carbolic acid or thymol.

Remnants of Food. It has already been pointed out that various microscopic remnants of food are observed in normal feces. In pathologic conditions it is necessary to determine whether or not such remnants be present in abnormal amount, presupposing, of course, that excessive quantities of food have not been ingested. It is often possible to draw definite conclusions as to the state of intestinal digestion from the excess of one form of non-digested material over another. The presence of large quantities of undigested starch may be regarded as indicating a serious catarrhal condition of the small intestine. It may, indeed, be said that the occurrence of more than mere traces of this material should always be regarded with suspicion. An increase in the number of muscle-fibres will likewise be observed under the same conditions.

The so-called acholic stools are usually very rich in fat, and particularly so in cases of biliary obstruction associated with jaundice. At other times, however, the lack of color, as has been mentioned above, is not referable to the secretion of an insufficient amount of bile, but to the presence of colorless decomposition-products of bilirubin, such as the leukourobilin of Nencki. In these cases abnormally large quantities of fat are not always present. The conclusion that a stool contains excessive amounts of fat because it is apparently acholic is hence not justifiable unless a microscopic examination has been made.

Epithelium. Epithelial cells, when present in large numbers, always indicate an inflammatory condition of some portion of the intestinal tract.

Cylindrical epithelial cells are found in abundance in all inflammatory conditions affecting the intestinal mucosa. They are almost exclusively seen imbedded in mucus, and it is interesting to note that the cloudy appearance of the latter is referable to the presence of these elements and not to leucocytes, as is the case in the sputum. When bile-stained specimens are met with the conclusion is justifiable that the small intestine is involved. Degenerative forms are mostly seen; well-preserved cylindrical or goblet cells may, however, also be found, and are, according to the writer's experience, very much more common than under normal conditions.

Epithelioid cells are sometimes found in cases of carcinoma of the rectum.

Red Blood-corpuscles. Unaltered red blood-corpuscles, according to Nothnagel, are but rarely observed in the feces, no matter how intensely red they may be colored, provided that an ulcerative process affecting the colon or the rectum can be excluded, in which case large numbers may be observed, as, for example, in the severer forms of dysentery. If the hemorrhage has occurred higher up in the intestine, large and small masses of brownish-red color are seen, which consist of hæmatoidin, instead of red blood-corpuscles. They are mostly amorphous, but in the same or other specimens the characteristic rhombic crystals of hæmatoidin may be observed. In general it may be said that the higher the seat of the hemorrhage the darker will be the color of the pigment and the less the chances of finding well-defined red corpuscles. In such cases recourse must be had to the hæmin- (p. 40) or the iron-test of Korczynski and Jaworski (p. 201).

Mucus. Small hyaline particles of mucus, visible only with the microscope, are not infrequently met with under pathologic conditions, and are of distinct diagnostic significance. When bile-stained their presence is always indicative of disease of the small intestine proper, while colorless particles point to a catarrhal condition of the upper portion of the large intestine or the lower portion of the small intestine. Beginners should be careful not to mistake apparently hyaline particles of vegetable residue for mucus. The latter never yields a blue color when treated with iodine or iodine and sulphuric acid, and examination with a high power will show the

entire absence of any definite structure. Both forms, viz., colorless and colored particles, are found intimately mixed with the feces, and may be very abundant. In addition to these forms Nothnagel has described the occasional occurrence of large numbers of roundish or irregular, very pale hyaline or opaque formations, which are entirely devoid of structure. Some specimens are homogeneous, while others present a distinctly rimous appearance. They have thus far only been found in liquid stools, and are apparently of no diagnostic importance. To judge from their optic behavior they probably consist of mucus.

Leucocytes. The presence of a large number of leucocytes usually indicates a severe catarrhal, if not an ulcerative, condition of the intestines, the number of leucocytes or pus-corpuscles standing in a direct relation to the intensity of the inflammatory process. Pure pus in large amounts is observed especially in dysentery and in cases in which accumulations of pus have perforated into the gut from adjacent organs or cavities. (See also p. 201.)

Crystals. The crystals which may occur in the feces have already been briefly considered (p. 185). Of these the so-called Charcot-Leyden crystals deserve more detailed consideration. While occurring at times in normal stools, as also in those of typhoid fever, dysentery, and phthisis, such observations are rare. They appear to be quite constantly present, on the other hand, in cases of anchylostomiasis and anguilluliasis. They are also frequently associated with ascaris lumbricoides, oxyuris, tænia solium and saginata. In cases of trichocephalus they are seen but rarely, while they are always absent in the case of tænia nana. These observations, made by Leichtenstern, are very important, and, according to the same observer, the occurrence of Charcot-Leyden crystals should always excite suspicion as to the existence of helminthiasis and lead to a careful examination of the feces for parasites or their ova. Their persistence in the feces after the evacuation of what would appear to be a complete tænia should be regarded as indicating the non-removal of the head. In a case of amœbic colitis, occurring in the practice of Dr. Lewis, of Baltimore, these crystals were also observed in fairly large numbers.

ANIMAL PARASITES.

I.—Protozoa:
- Rhizopoda,
  - Monera,
  - Amœbina, Amœba coli.
- Flagellata s. mastigophora,
  - Monadina,
    - Cenomonadina, Cercomonas.
  - Isomastigoda,
    - Tetramitina, Trichomonas,
    - Polymastigina, Megastoma entericum.
- Infusoria ciliata s. vera,
  - Holotricha, Balantidium coli.
- Gregarina s. sporozoa,
  - Coccidia.

II.—Vermes:
- Platodes,
  - Cestodes,
    - Tænia saginata.
    - Tænia solium.
    - Tænia nana.
    - Tænia diminuta.
    - Tænia cucumerina.
    - Bothriocephalus latus.
    - Krabbea grandis.
  - Trematodes,
    - Distoma hepaticum.
    - Distoma lanceolatum.
    - Distoma Buskii.
    - Distoma sibiricum.
    - Distoma spatulatum.
    - Distoma conjunctum.
    - Distoma heterophyes.
    - Amphistoma hominis.
    - Distoma hæmatobium.
    - Distoma pulmonale.
- Annelides,
  - Nematodes,
    - Ascarides,
      - Ascaris lumbricoides.
      - Ascaris mystax.
      - Ascaris maritima.
      - Oxyuris vermicularis.
    - Strongyloides,
      - Anchylostomum duodenale.
    - Trichotrachelides,
      - Trichocephalus hominis.
      - Trichina spiralis.
    - Rhabdonema strongyloides,
      - Anguillula intestinalis.

III.—Insecta:

Piophila casei.
Drosophila melanogastra.
Homialomyia.
Hyodrothœa meteorica.
Cystoneura stabulans.
Calliphora erythrocephala.
Palleuria rudis.
Lucilia cæsar.
Lucilia regina.
Sarcophaga hæmatoides.
Eristalis arbustorum.
Anthomyia.

Protozoa. The *rhizopoda* are essentially characterized by the fact that locomotion does not take place by the aid of independent organs, but by means of pseudopodia, viz., protoplasmic processes which the animal is capable of protruding from any portion of its body. Six orders have been described by zoölogists, but only one, possibly two, have thus far been found in the feces.

Whether or not representatives of the *monera* occur in the feces of man is still an open question. If so, they are apparently of no pathologic significance.

Of the *amœbina*, on the other hand, a most important member has been found, viz., the amœba coli, Lösch.

The history of the discovery of this parasite and its relation to those severe forms of tropical dysentery and liver-abscess which are met with even in our more temperate zones is of much interest, and at the same time illustrates the great importance which attaches to a systematic examination of the feces in all aggravated forms of diarrhœa.

In 1875 Lösch discovered, in the stools of dysenteric patients, actively moving, cell-like bodies of a roundish, pear-shape, oval or irregular form. He did not regard these as the cause of the disease, however, but looked upon them as being only accidentally present. Similar bodies have been observed in Hong-Kong by Normand in cases of colitis; and also by v. Jaksch. Sansino found them in a case in Cairo, and Koch in East Indian dysentery. It is interesting to note that Koch was the first to suspect the existence of a definite relation between dysentery and these organisms. Cunningham claims to have found amœbæ frequently in the stools of cholera patients at Calcutta, and Grassi in normal stools, but especially abundant in cases of chronic diarrhœa. Whether all

these observations are correct, and whether the organisms observed were identical in all cases, is, of course, difficult to say. So much is certain, that the subject was still a very unsettled one when Kartulis announced "that dysentery and tropical liver-abscess associated with dysentery are caused by the presence of the amœba coli," basing his conclusion upon an examination of 500 cases. The fact that this parasite was absent in all other intestinal diseases, such as typhoid fever, intestinal tuberculosis, the ordinary forms of diarrhœa, etc., speaks most strongly in favor of Kartulis' view.

In perfect accord with these observations were those made at the Johns Hopkins Hospital by Osler, Lafluer, and Councilman. Osler was the first in this country to demonstrate the presence of the amœba coli in a case of liver-abscess, both in the pus of the abscess and in the stools. Stengel, Musser, Dock, and others confirmed these observations, so that the pathogenic character of the amœba

FIG. 42.



The amœba coli.

coli may now be regarded as an established fact. This statement is based not only upon the few facts, more historical in character than otherwise, which have just been detailed, but rather upon the *ensemble* of collected data, among which the absence of micro-organisms other than the amœba in the pus of the liver-abscesses, and the constant presence of the latter in such cases, rank among the most important.

The size of the amœbæ varies from 10 μ to 20 μ. When at rest their outline is, as a rule, circular, occasionally ovoid; but when in

motion they present the extremely irregular contour of moving amœboid bodies (Fig. 42). The protoplasm can be differentiated into a translucent, homogeneous ectosarc or mobile portion, and a granular endosarc, containing the nucleus, vacuoles, and granules. Within the endosarc the vacuoles constitute the most striking feature. Sometimes the interior seems to be made up of a series of closely set clear vesicles of pretty uniform size. As a rule, one or two larger vacuoles are present, the edges of which are not infrequently surrounded by fine dark granules. True contractile vesicles displaying rhythmic pulsations have not been observed, although the vacuoles at times may be seen to undergo changes in size. In some the nucleus is quite distinct, while in others it may be altogether invisible.

Most distinctive are the movements of these bodies. From any part of the surface a rounded, hemispherical knob will project, and with a rapid movement the process extends and the granules in the interior flow toward it. In these movements the clear ectosarc seems to play the most important part.

In this connection the author wishes to refer to the occurrence of Laveran's *plasmodium malariæ* enclosed in red corpuscles, in the stools of cases of malarial colitis. In one case of chronic malarial intoxication with dysenteric symptoms the diagnosis was first made after an examination of the stools for amœbæ, which, however, were absent, while a number of plasmodia could be demonstrated, pointing out the probable nature of the colitis.

The *flagellata s. mastigophora* differ from the rhizopoda in being provided with from one to eight flagella which serve as organs of locomotion and possibly also for the apprehension of food-particles. Representatives of two orders only, viz., *monadina* and *isomastigoda*, have been found in the feces. Of the monadina in turn only one family, viz., cenomonadina, and of the isomastigoda only two families, viz., tetramitina and polymastigina, are represented.

The *cenomonadina* are small, oval, frequently elongated bodies, provided with one long flagellum at the anterior end, at the base of which food vacuoles are situated. At the posterior end amœboid movements may be observed, and there can be no doubt that the taking up of food, to some extent at least, also occurs by the aid of pseudopodia. To this family belongs the *cercomonas* of Davaine and Lambl. The tetramitina are small, elongated bodies, provided with four flagella and a lateral, undulating membrane, which was

formerly mistaken for a posteriorly directed flagellum. The tail end of the organism tapers to a point. The nucleus is located at the base of the flagella. To this family belongs the parasite which was first discovered by Donné in the vagina, and which was later also found in the feces and variously designated as trichomonas hominis, cercomonas coli hominis, etc.

The *polymastigina* are small, somewhat oval bodies, provided with two or three flagella, situated either anteriorly or laterally—two or three on each side—while at the same time two additional flagella issue from the posterior end, which may either be rounded off or taper to a point. To this family belongs the megastoma entericum of Grassi.

FIG. 43.



Cercomonas intestinalis.

a, cercomonas of Davaine, after Leuckart; *b*, cercomonas intestinalis, after Lambl; *c*, *d*, same, ordinary forms; *e*, *f*, same, well-developed forms; *g*, *h*, *i*, same, degeneration-forms; *k*, *l*, same, abortive forms.

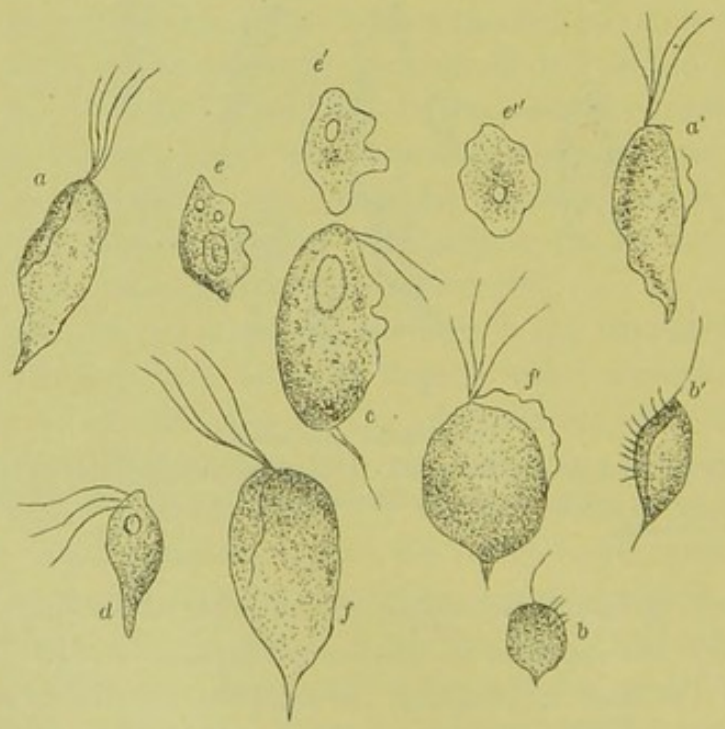
Only three parasites belonging to the order of the flagellata have thus far been encountered in the human feces, viz., the cercomonas hominis of Davaine and Lambl, the trichomonas of Donné, and the megastoma entericum of Grassi. To judge from the earlier literature upon the subject, many others have also been found, but more modern investigations have shown that these are in reality identical with the three just mentioned. The question whether or not these flagellate bodies are of pathologic importance still remains *sub judice*. They are apparently only met with in diseases associated with diar-

rhœa, and it appears that in some cases at least this is directly dependent upon their presence. In others the impression is gained as though they merely maintained an already existing diarrhœa, referable to other causes, while in a third class of cases no relation can be discovered between their presence and the disease in question.

Cercomonas of Davaine-Lambl, *syn.*, cercomonas hominis (Davaine); monas (Marchand); monas lens (Grassi); monas monomitina (Grassi). The adult organism (see Fig. 43) is oval or roundish in form, and provided anteriorly with a single long flagellum and posteriorly with a tail-like appendage. Its length varies from 0.005 to 0.014 mm. The younger forms are pear- or S-shaped, and sometimes entirely irregular in outline; the flagellum is either absent or only rudimentary.

Upon prolonged observation it will be seen that the adult parasite loses its flagellum and may protrude a protoplasmic process instead, while vacuolation occurs at the same time, indicating approaching death.

FIG. 44.



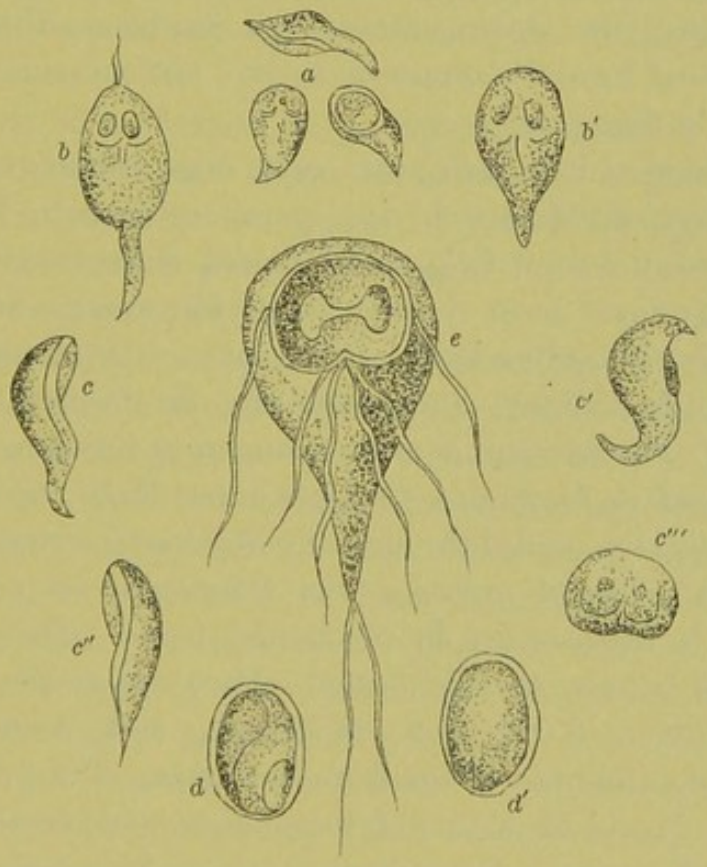
Trichomonas intestinalis.

a, *a'*, *c*, trichomonas of the urine, after Marchand; *b*, trichomonas vaginalis, after Donné; *b'*, same, after Scanzoni and Köllicker; *d*, trichomonas intestinalis, after Piccardi; *e*, *e'*, *e''*, same, amœbold forms; *f*, *f'* trichomonas of the urine, after Dock.

Trichomonas, Donné, *syn.*, trichomonas vaginalis (Donné); trichomonas hominis (Grassi); monocercomonas (Grassi); cimænomonas

(Grassi); protorycomyces coprinarius (Cunningham and Lewis); cercomonas coli hominis (May); trichomonas intestinalis (Leuckart and Roos); cercomonas s. bodo urinarius (Künstler). The parasite (Fig. 44) is oval or spindle-shaped and measures from 0.012 to 0.030 mm. in length by 0.010 to 0.015 mm. in breadth. From its anterior pole four flagella are given off, which are almost as long as the organism itself. From this point an undulating membrane extends laterally to the posterior pole, which may be rounded off or tapers to a tail-like appendage. This membrane is best seen when the movements of the flagella have ceased or in specimens fixed in bichloride of mercury solution (1 : 5000). The nucleus is situated at the base of the flagella, but is usually only visible in stained specimens (methylene-blue). At times the organism may be observed to assume an amœboid form; the movements of the flagella have then ceased, and pseudopodia-like processes are protruded. The parasite is identical with the trichomonas which has been found in the vagina and in the urine.

FIG. 45.



Megastoma entericum.

a, *b*, *b'*, *c*, *c'*, *c''*, *c'''*, various forms of cercomonas intestinalis, after Lambl; *d*, *d'*, encysted forms of megastoma entericum, after Grassi and Schewiakoff; *e*, megastoma entericum, adult form.

Megastoma entericum, Grassi, *syn.*, cercomonas intestinalis (Lambl); megastoma intestinale (Bütschli); lamblia intestinalis (Blanchard); dimorphus muris (Grassi). The parasite (Fig. 45) is pear-shaped, and measures from 0.01 to 0.021 mm. in length by 0.0075 to 0.05 mm. in breadth. In its anterior portion a more or less well-marked depression can be made out, which constitutes the peristome or mouth opening of the organism. It is provided with eight flagella, grouped in pairs. The first pair originates on the sides of the peristome and is directed backward. The second and third pair are situated somewhat posteriorly and are likewise directed backward, while the fourth pair issues from the tapering tail-end of the body. In fresh specimens the eighth flagella can usually not be made out, as the third and fourth pair are frequently agglutinated. The best results are obtained when the organism has been killed with bichloride solution. The individual flagella vary from 0.009 to 0.014 mm. in length. In the anterior portion of the peristome two round, hyaline bodies can be recognized which represent nuclei. Vacuoles are absent, and nutrition occurs through osmosis, the parasite adhering to epithelial cells by its peristome. When treated with fixing solutions the chitinous envelope can be readily recognized. In the encysted form the organism is oval and measures from 0.007 to 0.1 mm. in diameter.

Grassi observed it in mice, rats, cats, dogs, rabbits, and sheep.

Balantidium coli (Malmsten), *syn.*, paramœcium coli. The organism is egg-shaped, 0.1 mm. long, and covered entirely with fine cilia, which are grouped most densely about the mouth, while the anus is surrounded by only a few. In its interior are found a nucleus, two contractile vesicles, and frequently fat-droplets, particles of starch, etc. The parasite is most common in Sweden, but has also been observed in Germany, Cochin-China, Italy, and the United States. Infection occurs through the dejecta of swine.

The fourth class of protozoa, viz., the *Gregarina* or *sporozoa*, is also said to be represented in the human feces. The coccidia and psorosperms belong to this order. They are small, oval bodies, measuring about 0.022 mm. in length, and contain in their interior a large number of small nuclei, arranged in groups. They are entirely devoid of organs of locomotion, and obtain their nutriment by endosmosis. Reproduction occurs in a common capsule, which bursts at a certain time and sends forth a whole generation of fully developed organisms. In human pathology they have

become of interest in so far as certain observers have ascribed to them a *rôle* in the etiology of neoplasms. A disease of the liver analogous to the *psorospermiasis* of rabbits has also been described in man, and parasites belonging to the same order have recently been observed in the skin. The two cases reported by Gilchrist and Rixford ended fatally, and post-mortem examination revealed extensive infection of the spleen, adrenal glands, testes, lymphatic glands, and lungs.

Vermes. The class vermes has interested physicians since time immemorial, and is referred to in the writings of Hippocrates and others, special mention being made of the ascarides, called lumbrices, and the platodes, called lati. Speaking of the former, Lucas Tozzi, in 1686, says: "They find their way into the heart and its pericardium, into the brain, the lungs, the veins, and gall-bladder, where they are difficult to 'catch.'" The same author, speaking of their effects upon the body, enumerates the following conditions as caused by their presence: epilepsy, vertigo, sopors, delirium, convulsions, headache, syncope, palpitations, feelings of anxiety, cough, vomiting, nausea, diarrhœa, hiccough, prickling, borborygmus, erosions, tabes, acute and chronic fevers, and innumerable other maladies.

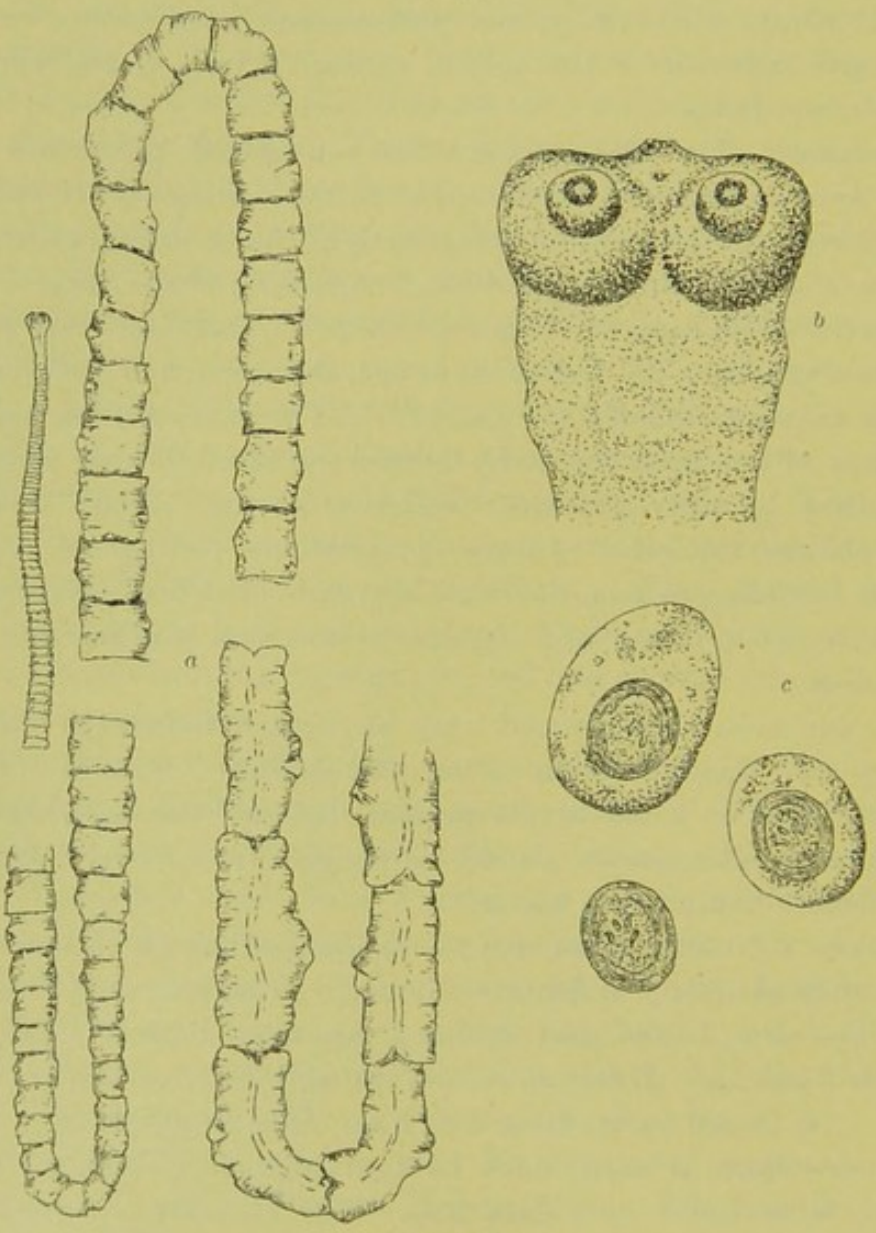
It was even then deemed very important to make a diagnosis before the administration of an anthelmintic—a point which is well to bear in mind at the present day, and the eggs, segments, or parasites themselves should be sought for in every suspected case before treatment is begun.

Tænia saginata, Goeze, *syn.*, t. mediocanellata (Küchenmeister); t. inermis (Huber); t. dentata (Nicola). This parasite (Fig. 46) is now known to be the most common tapeworm both in Europe and North America. Infection occurs through the ingestion of measly beef. Its length varies from 4 to 8 m. The head, which is devoid of a rostellum, is surrounded by four pigmented suckers, each of which is encircled by a dark line. The individual segments are quite thick and opaque, and diminish in length as the head is approached, the largest measuring from 2 to 3 cm. They are each provided with a very much branched uterus, which opens laterally, the primary branches numbering about twenty on each side. The ova are elliptical in form, of a brown color, and usually enclosed in a distinct vitelline membrane. Upon careful observation a double contour with delicate radiating striæ can be discerned.

In the interior the embryos are seen imbedded in a brown, granular material.

Thus far the cysticercus of tænia saginata has not been observed in the human being.

FIG. 46.



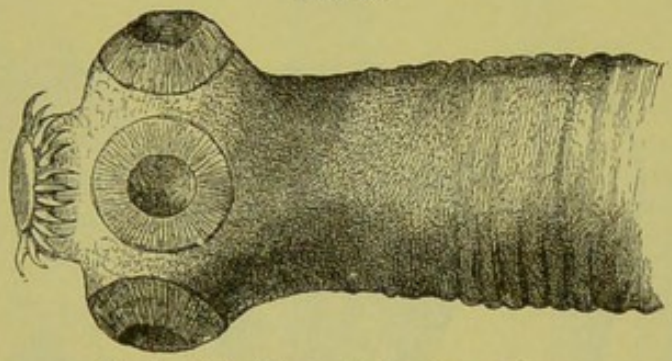
Tænia saginata.

a, natural size; *b*, head much enlarged; *c*, ova much enlarged.

Tænia solium, Rudolphi. This parasite (Fig. 47) is far less common in this country than tænia saginata, and may indeed be regarded as a curiosity. In Germany, also, it is only rarely met with now, while formerly it was the most common tapeworm in that country. This change is undoubtedly owing to the fact that raw pork

is now eaten less frequently. In Asia and Africa it is more common. Tænia solium is usually much shorter than tænia saginata, rarely exceeding 3.5 m. in length. Most characteristic is the head, which is provided with four pigmented suckers and a rostellum furnished with from twenty-four to twenty-six hooklets, arranged in a double row. The mature segments measure from 1.0 to 1.5 cm. in length by 6 to 7 mm. in breadth, and contain a uterus which has only five to seven branches, thus differing greatly from that of tænia saginata. The ova are round, of a brownish color, and surrounded with a thick, radially striated membrane; in their interior the hooklets of the embryos can usually be made out.

FIG. 47.

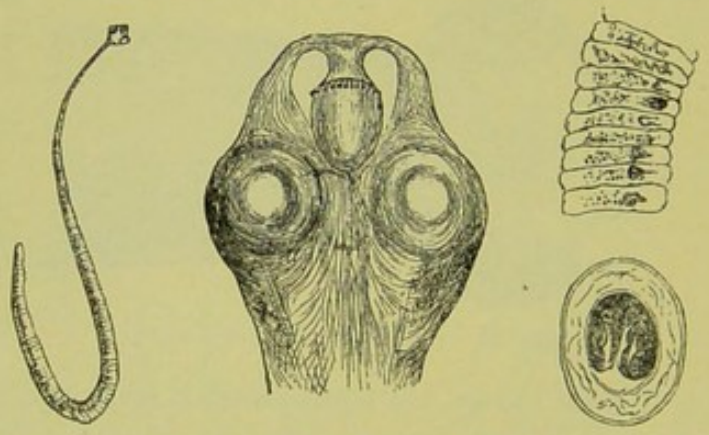


Head of T. solium. × 45. (LEUCKART.)

At times, though rarely, an autoinfection with the proglottides of tænia solium has been observed in the human being. Under such conditions the embryos of the worm are set free in the stomach, and may then migrate into various parts of the body, where they become encysted, constituting the so-called *cysticercus cellulosæ* stage in the development of the parasite. Most commonly the cysticerci are found in the skin; they have, however, also been observed in the heart, lymphatic glands, liver, bones, tongue, spinal canal, the brain, and the eyes. The author had occasion to observe a case of this kind at the Johns Hopkins Hospital (reported by Osler). The patient, a laboring-man, had never worked as a butcher or a cook, and never had a tapeworm. The cysticercus nodules, which were situated between the skin and fascia, were very numerous, seventy-five being counted on one day. One of these nodules was removed for examination and shown to be referable to the cysticercus of tænia solium. The only subjective complaints in this case were pains and stiffness in the arms and legs. The individual cysticercus is elliptical or roundish in form, measuring from 1 to 10 mm. in diameter. In its interior the characteristic hooklets were seen.

Tænia nana, v. Siebold, *syn.*, hymenolepsis (Weinland). This parasite (Fig. 48) has not been observed in America, but seems to be the most common tapeworm in Italy and Egypt, being found especially in young people, and often causing severe nervous symptoms, such as convulsions, loss of consciousness, and even melancholia. It is only 8 to 25 mm. long and 0.5 mm. broad. The head is ball-shaped and provided with four suckers and a rostellum, bearing twenty-four to twenty-eight hooklets arranged in a single row along its anterior edge. The individual segments are of a yellowish color and about four times as broad as long. The uterus is oblong and contains numerous ova, which are colorless,

FIG. 48.



Tænia nana. Head, with rostellum drawn in; proglottis; egg. (v. JAKSCH.)

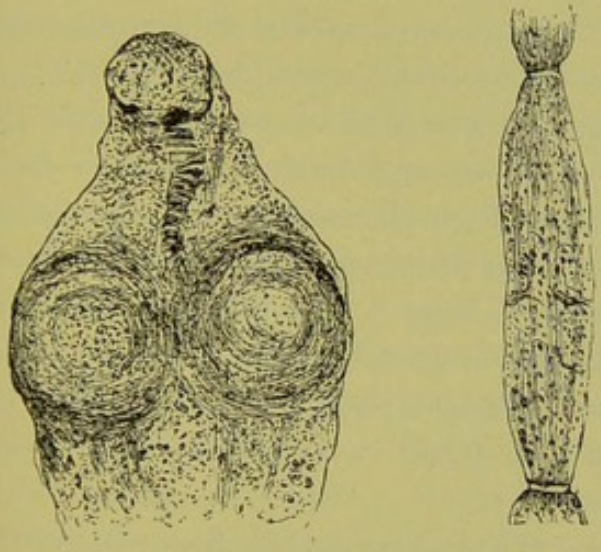
oval, and surrounded by a distinct non-striated membrane. They measure from 0.039 to 0.060 mm. in size. In their interior the embryonic worm, provided with five or six hooklets, may be distinguished. The number with which this parasite at times infests the digestive tract is most astonishing, 5000 and even more having been counted at various times. The cysticercus stage occurs in snails, which are frequently eaten raw in Egypt and Italy.

Tænia diminuta, Rudolphi, *syn.*, tænia flavapunctata (Weinland); tænia minima (Grassi); tænia varerina (Parona); tænia leptocephala (Creplin). Tænia diminuta was first described in man by Leidy, Grassi, and Parona. It measures 20 to 60 mm. in length, and is armed with two suckers, but without a rostellum. The ova resemble those of tænia solium. The cysticercus occurs in certain caterpillars and cocoons. In man it has only been found in six instances.

Tænia cucumerina, Bloch, *syn.*, tænia canina (Linné); tænia elliptica (Batsch). (Fig. 49.) The parasite is almost exclusively found

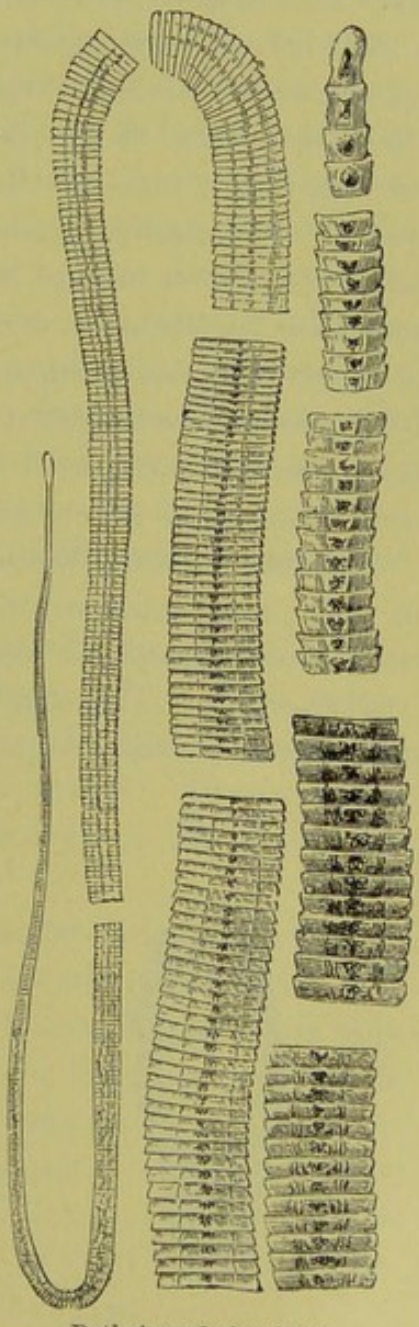
in children, the infection occurring through dogs and cats. Its length varies from 10 to 40 mm. The head is provided with about sixty hooklets, surrounding a rostellum in irregular rows. When the latter is protruded it appears as a club-shaped protuberance. The ripe segments have a reddish color, and are very much longer than broad. The ova contain embryos already armed with hooklets. The cysticercus occurs in fleas.

FIG. 49.



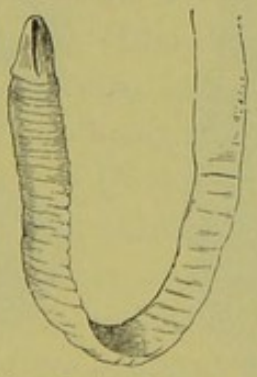
Tænia cucumerina. Head; proglottis; magnified. (v. JAKSCH.)

FIG. 50.



Bothriocephalus latus.

FIG. 51.



Bothriocephalus latus. Head.

Bothriocephalus latus, Bremser, *syn.*, tænia lata (Linné); dibothrium latum (Rudolphi). (Figs. 50 and 51.) This worm is 5 to

9 m. long. Its head is shaped like a bean, and upon its flat surfaces two distinct grooves can be discerned, which probably act as suckers. The ripe segments are almost square in form, with the genital apparatus opening in the median line. The uterus presents four to six convolutions on each side, which become especially distinct when the segments are placed in water or exposed to the air. A rosette-like appearance is then obtained, which is quite characteristic. The eggs are oval, 0.07 mm. long and 0.045 mm. broad; they are enclosed in a brown envelope, at the anterior end of which a little lid can be recognized. Their contents consist of protoplasmic spherules, all of about the same size, which are lighter in color in the centre than at the periphery. The larvæ have been found in various fishes, such as the perch, trout, and burbot, but most frequently in the pike. It is thus readily understood why the parasite is most common in lake regions, as in Switzerland, northern Russia, southern Scandinavia, and northern Italy. Outside of Europe it is most common in Japan. In the United States it has only been found in a few imported cases. From a pathologic standpoint it is of much interest, as it appears to stand in a genetic relation to certain forms of severe anæmia.

Krabbea grandis, Blanchard. This parasite has been observed in only one instance—in eastern Asia. It is said to resemble certain bothriocephali which are found in seals.

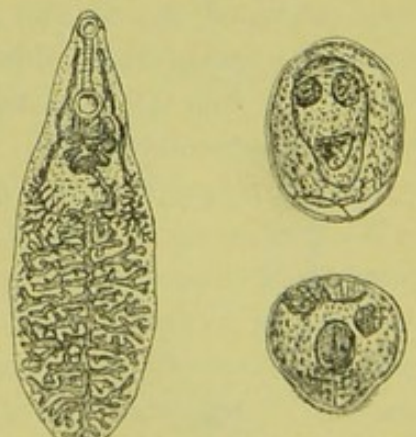
Trematodes. The various forms of distoma which belong to this order are essentially *hepatic parasites*, and rarely occur in the feces.

FIG. 52.



Distoma hepaticum. (LEUCKART.)

FIG. 53.



Distoma lanceolatum (× 8) and eggs. (v. JAKSCH.)

Distoma hepaticum, Abildgaard, *syn.*, fasciola hepatica (Linné). (Fig. 52.) This, the most common liver-fluke, is 28 mm. long

and 12 mm. broad, being formed like a leaf. The head is provided with a sucker, and a second sucker may be found at its ventral surface. Between the two the genital opening is located, leading into a skein-shaped uterus. The edges are oval, measuring 0.13 mm. in length and 0.08 mm. in breadth, the anterior end being provided with a lid; their color is brown. In the United States the organism is practically unknown, while in Germany it is most common in sheep. In the human being it is rare in both countries. Infection occurs through a small snail, the Linnæus minutus, which is found, in Germany especially, upon watercress.

Distoma lanceolatum, Mehlis, has only been found in five cases, all of which occurred in Germany. (Fig. 53.) It is much smaller than distoma hepaticum, measuring 8 to 9 mm. in length by 2 to 3.3 mm. in breadth. It is lancet-shaped, tapering toward the head end, but otherwise closely resembles the above parasite. The ova are 0.04 mm. long, 0.03 mm. broad, and contain fully developed embryos. In the ruminants the organism is quite common.

Distoma Buskii, Lancester, *syn.*, distoma rhatonisii (Poirier); distoma cranum (Busk). The parasite has been observed in only three cases—in China. It is much larger than the common liver-fluke. Infection probably occurs through certain fishes and oysters.

Distoma sibiricum, Winigradoff, *syn.*, distoma felineum (Rivolta). This parasite was found in Tomsk by Winigradoff in eight autopsies out of 124. Its length may reach 13 mm. The ova are 0.026 to 0.038 mm. long and 0.010 to 0.022 mm. broad. The intestines are simple and extend to the posterior extremity of the body. Its surface is smooth.

Distoma spatulatum, Leuckart, *syn.*, distoma endemicum (Bälz); distoma japonicum (Blanchard); distoma sinense (Cobbold). The habitat of the organism is in cats. In the human being it has only been observed in Japan, where it appears to be quite common in certain localities. It is about 11.75 mm. long and 2 to 2.75 mm. broad. The living parasite is of a reddish color and translucent, so that it is possible to distinguish all its interior organs. The ova measure 0.028 to 0.030 mm. in length by 0.016 to 0.017 mm. in breadth, and are enclosed in a colorless envelope.

Distoma conjunctum, Cobbold, *distoma heterophyes*, v. Siebold, and *amphistomum hominis*, Lewis and McConell, are other parasites which have been observed in a few isolated cases, but are as yet

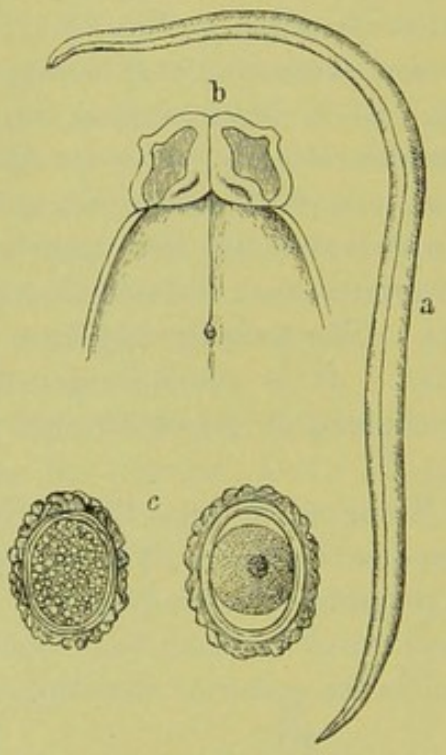
of no special interest. The last-named appears to be common in elephants.

Distoma hæmatobium and *distoma pulmonale* are described in the sections on Blood and Sputum, respectively.

The *annelides* are very common intestinal parasites, and of these especially the *nematodes*.

Ascaris lumbricoides (Linné) (Fig. 54) is the cylindrically shaped worm so commonly seen in children and in the insane. The head consists of three projections or lips, which are provided with

FIG. 54.



Ascaris lumbricoides. (V. JAKSCH.)

a, worm, half natural size; *b*, head, slightly magnified; *c*, eggs. (Eye-piece I, objective 8 A, Reichert.)

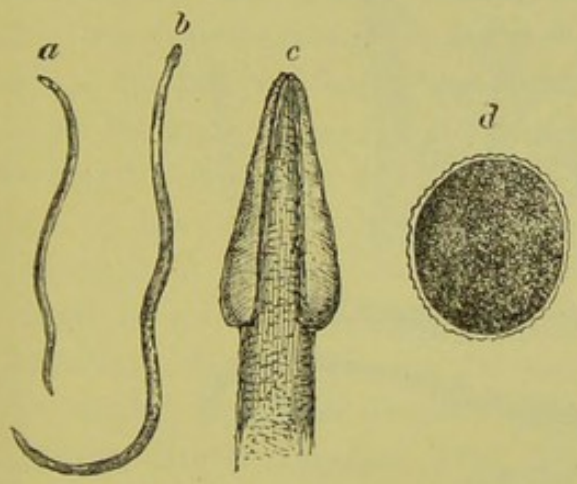
suckers and fine teeth. The male measures about 215 mm., the female about 400 mm. in length. The tail-end of the male is rolled up on its ventral surface like a hook and provided with papillæ. The genital aperture of the female is situated directly behind the anterior third of the body. The eggs are yellowish-brown in color, almost round, and measure 0.06 mm. by 0.07 mm. in size; they are surrounded by an irregular albuminous envelope, which is covered by a tough shell; the contents are coarsely granular.

Ascaris lumbricoides occurs all over the world, and also infests

the pig and the ox. Its presence may occasion very severe nervous symptoms, but fortunately this is but rarely the case.

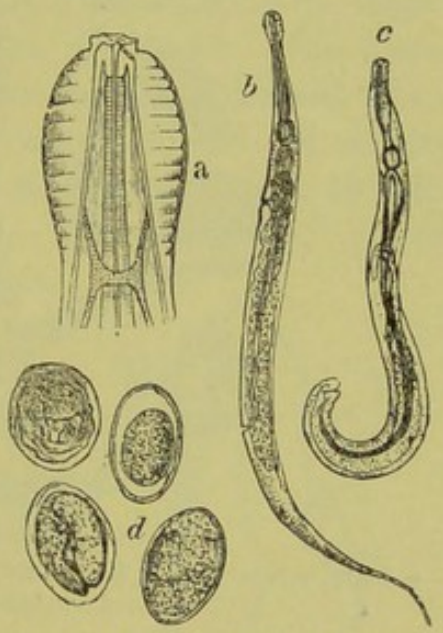
Ascaris mystax, Zeder, *syn.*, ascaris marginata (Rudolphi); ascaris alata (Bellingham); (Fig. 55) is smaller and thinner than ascaris lumbricoides, but otherwise very similar. The head is pointed and provided with wing-like projections, which constitute the main point of difference between the two. The male measures 45 to 60 mm. in length, the female 110 to 120 mm. Its ova are round, larger than those of ascaris lumbricoides, and enclosed in a membrane which is covered with numerous small depressions. The worm is very common in dogs and cats, but very rare in man.

FIG. 55.



Ascaris mystax. (v. JAKSCH.)
a, male; *b*, female; *c*, head; *d*, egg.

FIG. 56.



Oxyuris vermicularis. (v. JAKSCH.)
a, head; *b*, male; *c*, female; *d*, eggs.

Ascaris maritima, Leuckart, also belongs to this class. It has only been observed in one case—in Greenland.

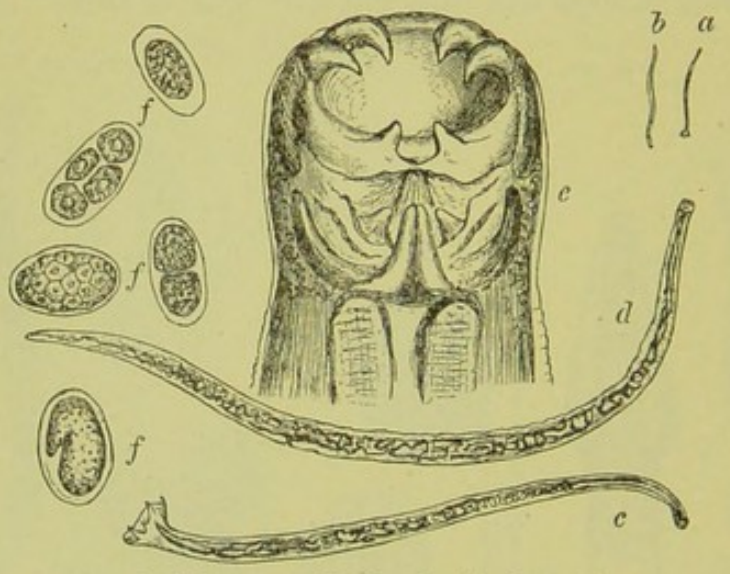
Oxyuris vermicularis, Bremser, *syn.*, ascaris vermicularis (Linné); ascaris græcorum (Pallas). (Fig. 56.) The male is 4 mm., the female 10 mm. long. At the head three lip-like projections with lateral cuticular thickenings may be seen. The tail of the male is provided with six pairs of papillæ, and the female with two uteri. The eggs are 0.05 by 0.02 to 0.03 mm. in size, and covered by a membrane, showing a double or triple contour; in the interior, which is coarsely granular, the embryos are contained.

The female worm lives in the cæcum, but after impregnation travels downward to the rectum. Here it causes most annoying

symptoms, which are especially distressing at nights, when the organism emerges from the anus. In doubtful cases of pruritus ani *aut* vulvæ an examination of the feces should be made for this parasite. The ova themselves do not occur in the feces.

Anchylostomum duodenale (Dubini); anchylostoma duodenale (Dubini); strongylus quadridentatus (v. Siebold); dochmius anchylostomum (Molin); sclerastoma duodenale (Cobbold); strongylus duodenalis (Schneider); dochmius duodenalis (Leuckart); uncinaria duodenalis (Roilliet). (Fig. 57.) The organism belongs

FIG. 57.



Anchylostomum duodenale. (v. JAKSCH.)

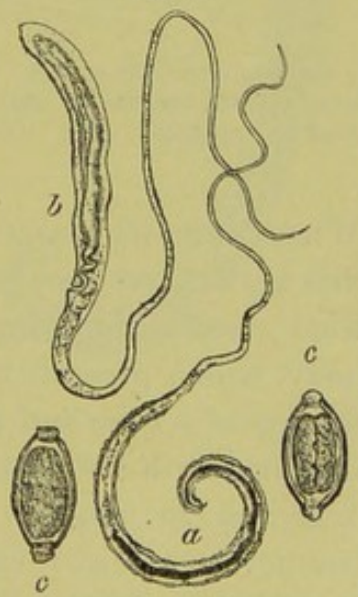
a, male, natural size; *b*, female, natural size; *c*, male, magnified; *d*, female, magnified; *e*, head (eye-piece II., objective C, Zeiss); *f*, eggs.

to the family *strongyloides*, and is one of the most dangerous parasites met with in the human being. It has been found in Italy, Germany, Switzerland, Belgium, Egypt, and in the West Indies (Jamaica). Within the last year a few cases have also been reported in the United States. From a pathologic standpoint the parasite is of special interest, as its presence gives rise to severe and often fatal anæmia. Griesinger was the first to point out that the so-called Egyptian chlorosis is produced by this organism. In every case of severe anæmia, particularly when occurring in patients who have been working in mines, tunnels, and brickyards, the feces should be carefully examined for the ova of this parasite. The worm itself is only rarely found. Its habitat is in the jejunum. Infection takes place through contaminated drinking-water.

The male is 6 to 11.5 mm. long, the female 10 to 18 mm. The head, which tapers somewhat, is turned toward the back; the mouth capsule is hollowed out and surrounded by four teeth; the tail of the male forms a three-lobed bursa, while that of the female tapers conically; the genital opening is behind the middle of the body. Its eggs have an oval form and a smooth surface, measuring 0.05 to 0.06 by 0.03 to 0.04 mm. In their interior two or three segmenting bodies are found, which rapidly develop outside of the human body, so that after twenty-four to forty-eight hours embryos may be found in the same feces in which the eggs were observed, or fully developed ova may be found after allowing the feces to stand for only a few hours.

Trichocephalus hominis, Schwank, *syn.*, trichocephalus dispar (Rudolphi); mastigodes (Zeder); trichuris (Büttner). This parasite, which belongs to the family *trichotrachelides*, is formed like a whip, the last-end being the head-end, while the tail-end is very much thicker. The male measures 46 mm. and the female 50 mm. in length. The eggs are brownish in color, measuring 0.05 by 0.06 mm. in size, and presenting a doubly contoured shell, with a depression at each end closed by a lid. The contents are coarsely granular. It is said to be the most widely distributed intestinal parasite, occurring in Europe, North America, Asia, Africa, and Australia. Its habitat is in the cæcum. The living worm is only rarely found in the feces.

FIG. 58.



Trichocephalus dispar. (V. JAKSCH.)

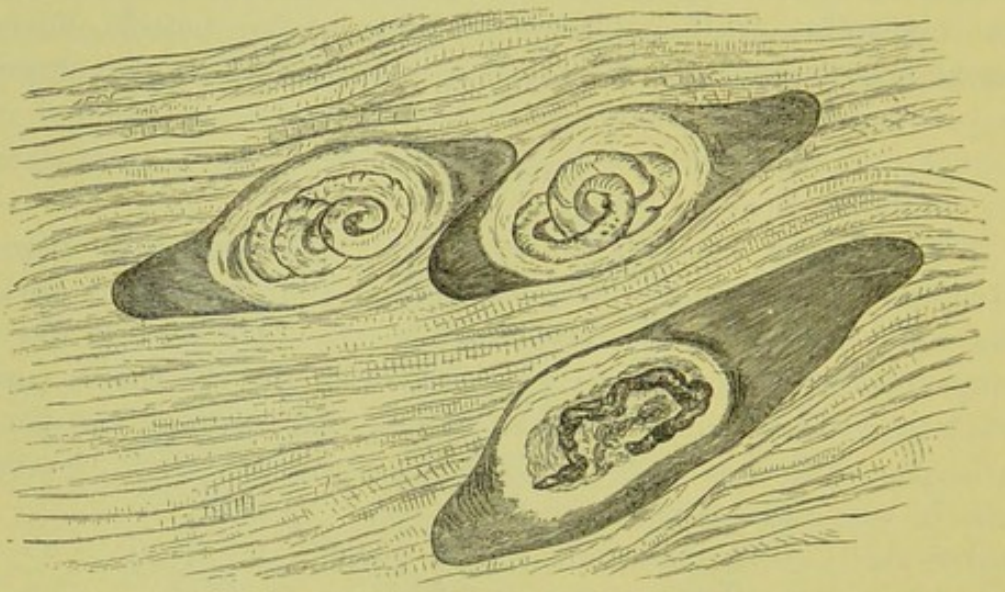
a, male, slightly magnified; *b*, female, slightly magnified; *c*, eggs (eye-piece II., objective 8 A, Reichert).

Trichina spiralis (Owen) (Fig. 59) is rarely found in the feces. The male measures 1.5 mm. in length, and is provided with four papillæ between the conical lips. The female is 3 mm. long. The uterus is situated nearer the head than the ovary, which opens into it. Fertilization occurs in the intestinal canal. The eggs develop into embryos in the uterus, emerge from this, and penetrate the intestinal walls, whence they are carried by the blood-current to the muscles. Trichinosis is far less common in the United States than in Europe.

Anguillula intestinalis is 2.25 mm. long and 0.04 mm. broad; its

mouth is three-cornered and bounded by three little lips. The genital aperture is located between the middle and posterior third of the body. Its eggs are similar to those of anchylostomum duodenale, but longer and more elliptical, with tapering poles; they are never found in the feces, only the embryos occurring here.

FIG. 59.



Trichina spiralis in muscle. The elongated shape of the cysts is due to the fact that these were near the insertion of the muscle into its tendon. In the lowest specimen the worm is dead and calcified. × 90. (COATS.)

When sexually mature the parasite is called anguillula stercoralis; this again gives rise to embryos, which may in turn enter the intestinal canal. The anguillula stercoralis (Fig. 60) nas a rounded body, which presents an indistinct cross-striation. Its head is like the top of a cane and provided with two lateral jaws, each of which is armed with two teeth. The male measures 0.08 mm., the female 1.22 mm. in length. The pathologic significance of this parasite has not as yet been definitely ascertained, but from its resemblance to anchylostomum duodenale it has become important from a diagnostic point of view.

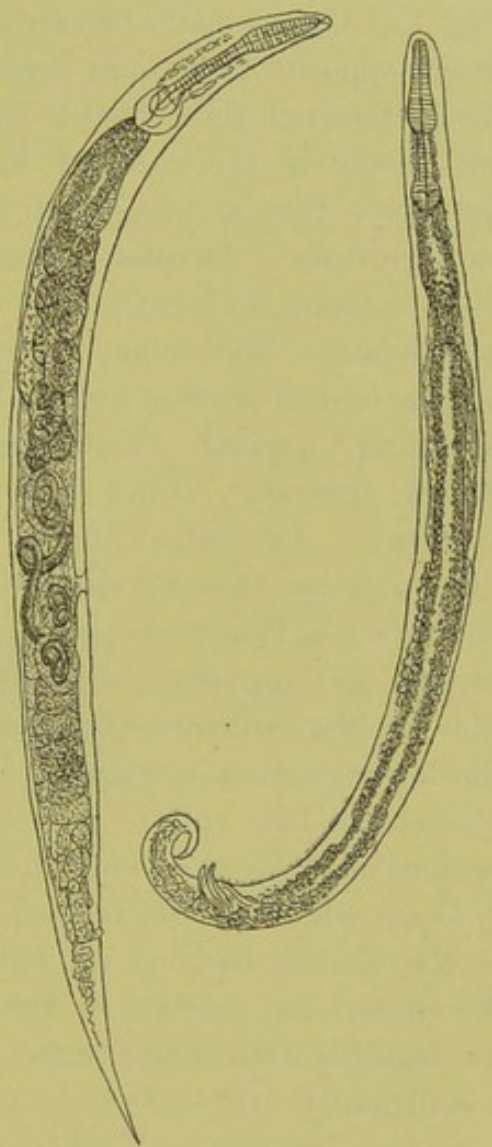
Insecta. As the larvæ of the various insects met with in the feces have so far been very little studied, they will not be considered at this place, particularly as they do not appear to possess any points of clinical importance.

VEGETABLE PARASITES. Among the pathogenic vegetable parasites the bacillus of cholera, of typhoid fever, and of tuberculosis, as

well as the bacilli of Booker, the bacillus coli communis, the bacillus lactis aërogenes, and the proteus vulgaris deserve especial consideration.

As early as 1848 certain "vibrios" were observed in abundance in the stools of *cholera* patients by Virchow, and in 1849 by Pouchet, Britton, and Swayne, no importance, however, being attached to their presence at the time.

FIG. 60.



Anguillula stercoralis. (BIZZOZERO.)

The first accurate and detailed studies of the organism found in cholera stools were made in 1883 by the members of the French and German commissions sent to Egypt to investigate the true nature of the dreaded disease. The results of their work were first published by Koch in his report to the Berlin Sanitary Office in 1883, and in 1884 by Strauss, Roux, Nocard, and Thuillier.

The clinical recognition of cholera Asiatica has become a fairly simple matter since Pfeiffer demonstrated that the blood-serum of cholera patients possesses the property of causing arrest of motility and the agglutination of the specific bacilli. Bouillon-cultures, however, can usually not be employed, as particles of the film, when broken up, may easily be mistaken for agglutinated bacilli. It is best in every case to make use of agar-cultures sixteen to twenty-four hours old, and to prepare emulsions in bouillon or normal salt-solution as occasion requires. The emulsion, moreover, should always be examined microscopically before use, so as to insure the absence of any conglomerations of bacilli. The blood is then diluted in the proportion of 1 : 10 or 1 : 15. If the test-tube method is employed, the tubes should only be kept in the incubator (37° C.) for one or two hours. Upon the slide the

reaction is obtained in from five to twenty minutes. If no distinct agglutination is observed at the end of one hour, the diagnosis of cholera is rendered improbable. Dried blood preserves its agglutinative properties for a considerable length of time, and may also be used for examination.

The *comma-bacillus* is a slightly arched or even half-moon-shaped little rod, somewhat shorter than the tubercle-bacillus (Plate VIII., Fig. 1). Occasionally two are placed end to end with their convexities in opposite directions, presenting the appearance of the letter S. Koch detected these bacilli in the intestinal contents and feces, but rarely in the vomited matter, in Asiatic cholera only. In the stools they at times occur in such numbers as to constitute pure cultures. In plate-cultures kept at a temperature of 22° C. white colonies with serrated borders may be observed after twenty-four hours. The color of such a colony is slightly yellow or rose-red, its central portion gradually assuming a deeper tint, and finally becoming liquefied. Upon agar-plates the bacilli form a grayish-yellow, irregular, slimy coating, but do not liquefy the culture-medium. In stab-cultures, after twenty-four hours a whitish color may be observed along the line of the stab; around this there is formed a funnel-shaped depression, which gradually increases in size and apparently contains a bubble of gas. The upper portion of the culture-medium at the same time becomes liquefied, the lower portion remaining solid for days. In a suspended drop spirochætæ-like spirals are observed at the margins, which often present as many as twenty distinct arches.

Upon what may be termed specific reactions in the recognition of the cholera-bacillus no reliance can as yet be placed, and even the cholera-red reaction of Brieger, obtained by treating cultures of the bacillus with concentrated hydrochloric acid, does not rest upon a sufficiently firm basis to be of much service.

Closely related to Koch's comma-bacillus and possibly bearing to *cholera nostras* the same relation that the former bears to cholera Asiatica is the *bacillus of Finkler and Prior*, discovered in 1884 and 1885 (Plate VIII., Fig. 2). This is, however, readily distinguished from the former by the following characteristics: It is larger and thicker than the comma-bacillus; the colonies on gelatin plate-cultures show equally round and sharp-edged forms, which present a granular appearance under a low or medium power, and are usually of a brown color. The organism liquefies gelatin very rapidly, a

PLATE VIII.

FIG. 1.



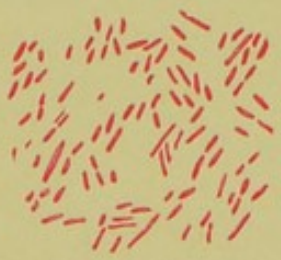
Spirillum of Asiatic Cholera. Impression Cover-slip from a Colony Thirty-four Hours Old. (Abbott.)

FIG. 2.



Bacillus of Finkler and Prior. (Cornil and Babes.)

FIG. 3.



Bacillus of Typhoid Fever from a Culture Twenty-four Hours Old, on Agar-agar. (Abbott.)

penetrating, excessively fetid odor being developed at the same time. In stab-cultures the bacillus of cholera Asiatica forms a funnel-shaped depression, while the bacillus of Finkler and Prior forms a stocking-like depression. Further work is still necessary in this direction, which may not be altogether unprofitable and may even yield most important results.

The *typhoid bacillus*, discovered by Eberth in 1880 in the abdominal organs of patients dead with typhoid fever, is, unfortunately, not so readily recognized in the feces as the organisms just considered. The main difficulty lies in its differentiation from the bacillus coli communis, with which it has many points in common.

A few years ago Elsner reported a method which, it was claimed, would enable the general practitioner to make the diagnosis of typhoid fever in twenty-four hours, and in the hands of some observers, such as Brieger, satisfactory results were obtained. Others, however, were less successful, and since the discovery of Widal that the blood-serum of typhoid patients possesses the property of arresting the motility of typhoid bacilli and of causing their agglutination, the method has practically been abandoned. His procedure was the following: An aqueous extract of potato (500 grammes to the liter) is treated with 10 per cent. of gelatin and boiled. The solution is then treated with 2.4 to 3.2 c.c. of a one-tenth normal solution of sodium hydrate in order to secure the necessary degree of acidity, and then filtered and sterilized.

When needed, a portion is placed in an Erlenmeyer flask and treated with 1 per cent. of potassium iodide. The mixture is inoculated with fecal material and the necessary plates prepared. Upon this medium only a few species of bacteria will grow, principally the bacillus coli and the typhoid bacillus. After twenty-four hours the bacillus coli colonies are already mature, while the typhoid bacillus colonies can scarcely be made out with a low power. After forty-eight hours, however, the latter appears as small, highly refractive, extremely fine granular colonies, closely resembling drops of water, which can be readily distinguished from the large, much more granular, brownish colonies of the bacterium coli. *This difference is brought out particularly well if diluted plates have been prepared.*

Brieger, who carefully repeated the experiments of Elsner, states that typhoid bacilli are found in abundance in the stools as long as fever exists, but with approaching convalescence they diminish in

number and ultimately disappear. If, notwithstanding the absence of fever, bacilli are found in notable numbers during convalescence, a relapse may be anticipated. Others, as has been stated, have not obtained such satisfactory results, and Widal's method (see p. 79), which is much simpler and perhaps also more reliable, has already replaced that of Elsner. The latter, however, undoubtedly deserves recognition and further investigation.

In pure cultures the typhoid bacilli present the following features: They occur in the form of rods of almost one-third the size of a red blood-corpuscle, or in threads composed of several rods, joined end to end. (Plate VIII., Fig. 3.) The ends are rounded off; their length is equivalent to about three times their breadth. On bouillon-peptone-gelatin they grow very readily, and after twenty-four hours colonies begin to appear. When slightly magnified these present a faintly yellowish color; macroscopically they are barely visible. When kept at a temperature of 37° C. the formation of spores may be observed, especially when grown on media colored by phloxin-red or benzopurpurine. The rods and threads present quite active movements; they do not liquefy gelatin.

Tubercle-bacilli, when present in the feces, in which they may be demonstrated as described in the chapter on Sputum, are indicative of intestinal tuberculosis, providing they be observed upon repeated examination and there be clinical symptoms pointing to the bowels as the seat of the disease, as otherwise they may be referable to swallowed sputa.

In this connection the *green bacillus of Le Sage*, discovered by him in a certain form of infantile diarrhœa, must be briefly referred to, the stools, as has been mentioned, being of a grass-green color. The production of this pigment in cultures is one of the characteristics of the organism; when injected into the intestines of animals it is said to produce diarrhœa and a catarrhal inflammation of the mucous membrane.

Booker has described nine different bacilli occurring in cases of infantile diarrhœa. Seven of these closely resemble the bacillus coli communis. Bacillus "A" is a bacillus with rounded ends, measuring from 3 μ to 4 μ in length by 0.7 μ in breadth. It is motile and liquefying. Colonies on agar and potato present a dirty-brown color.

The *bacillus coli communis*, while constantly present in normal feces, is described at this place, as modern researches have shown

that it may at times develop pathogenic properties. It has thus been found in the pus in cases of purulent perforating peritonitis, angiocholitis, pyelonephritis, etc., and, as indicated elsewhere, at times forming the nucleus of gallstones. It occurs in the form of delicate or coarse rods, measuring about 0.4 μ in length, which manifest a certain degree of motility, due to the presence of one or two polar flagella. The organism is stained by the usual aniline dyes, and is decolorized by Gram's method. The colonies upon gelatin closely resemble those of the bacillus of typhoid fever, forming small whitish specks *in* the gelatin, and delicate films with serrated borders *upon* the same medium, which, moreover, is not liquefied. They also grow upon potato. As in the case of the cholera bacillus the nitroso-indol reaction can be obtained when the organism is grown upon peptone-containing media. In solutions of glucose active fermentation takes place.

The *bacterium lactis aërogenes* (Escherich) closely resembles the organism just described, and may also at times develop pathogenic properties. It was recently found by Heyse in a case of pneumaturia. It is seen quite constantly in the stools of sucklings, but may also be met with in those of adults. It occurs in the form of rather stout rods, which frequently lie in pairs, resembling diplococci. The organism is non-motile. Like the bacillus coli communis it is decolorized by Gram's method. In plate-cultures it forms dense white films; in stab-cultures a chain of white colonies resembling beads is seen. In the latter, moreover, if the stab be closed, bubbles of gas will be seen to form, which rapidly increase in number and size. Milk is coagulated in large lumps in twenty-four hours; the formation of gas is, at the same time, much more intense than in the case of the bacillus coli communis.

Proteus vulgaris, Hauser. This organism, while usually regarded as non-pathogenic, should be numbered among the bacteria which may at times develop pathogenic properties. Baginsky and Booker have frequently found it in the stools in cases of infantile summer diarrhœa. Escherich observed it at times in the meconium. Others have encountered it in inflammatory conditions of exposed surfaces, in appendicitis, in perforative peritonitis, and even in closed abscesses, either alone or in association with other bacteria (Welch). A mixed infection of the proteus and Löffler's bacillus has also been observed. The organism forms little rods, measuring about 0.6 μ in diameter, while their length is variable; at times a more roundish form is

observed; at others little rods measuring from 1.25 μ to 3.75 μ in length, or even long threads. They are readily stained, but are easily decolorized by alcohol or Gram's method. Most characteristic is their growth upon nutrient gelatin. At the temperature of the room little depressions will be observed after six to eight hours, which are surrounded by a narrow zone of bacilli from which a thin, wide film, provided with irregular projections, extends over the culture-medium. From this film small islets become separated, which slowly wander over the gelatin and cause its liquefaction. The organism is motile. It decomposes urea and causes albuminous putrefaction. The nitroso-indol reaction is readily obtained in bouillon-cultures.

Chemistry of the Feces.

According to Hoppe-Seyler, mucin is a constant constituent of the feces, both under physiologic and pathologic conditions. Under normal conditions, however, it is never possible to recognize its presence either with the naked eye or with the microscope. In order to demonstrate the presence of mucin in the feces they are digested with water and treated with an equal volume of milk of lime, the mixture being allowed to stand for several hours, when it is filtered and the filtrate tested with acetic acid. In the presence of mucin a cloud develops upon the addition of the acid.

Albumin is demonstrated in the feces by treating them repeatedly with water slightly acidified with acetic acid. The filtrate is then examined for albumin according to methods given elsewhere (see Urine). Under normal conditions these reactions prove negative. Pathologically, serum-albumin has been observed in cases of typhoid fever and chlorosis.

Peptones are normally absent from the feces. They have been observed in typhoid fever, dysentery, tuberculous ulceration, purulent peritonitis with perforation into the gut, atrophic cirrhosis, and carcinoma of the liver. Acholic stools are also usually rich in peptones.

The peptones are demonstrated in the following manner: The feces are digested with water, so as to form a thin mush; they are then boiled, filtered while hot, and the filtrate examined for albumin, so as to be sure that all of this has been removed. The mucin is removed by treating with acetate of lead, when the filtrate is examined for peptones as described in the chapter on Urine (which see).

Among the *carbohydrates* starch, glucose, and certain gums may be found. In order to demonstrate these the feces are boiled with water, filtered, and evaporated to a small volume. This solution may now be tested with phenylhydrazin or Trommer's reagent for the presence of glucose (see Urine), and with a solution of iodo-potassic iodide for starch (see Saliva, p. 152). The residue is extracted with alcohol and ether, as described under the heading of fatty acids, and then with water. The filtrate of the aqueous extract is concentrated, boiled with dilute sulphuric acid, and then over-saturated with sodium hydrate. This mixture is treated with sulphate of copper and boiled in order to test for dextrin and gums.

Bile-pigment, normally absent from the feces, occurs in large amounts in catarrhal conditions of the small intestine, and may be demonstrated by Gmelin's method, viz., a drop of the filtered liquid, or a particle of highly colored fecal matter, is brought into contact with a drop of fuming nitric acid, when the yellow color will be seen to pass through the various shades of the spectroscope, the green shade being the most characteristic.

At times, however, it is not possible to obtain a positive reaction in this manner, although bile-pigment be present. In such cases the examination should be conducted under the microscope, and attention directed to bile-stained epithelial cells, leucocytes, particles of mucus, and crystals.

Whenever there is increased intestinal putrefaction the fatty acids, phenol, indol, and skatol will, of course, be found in increased amounts.

THE PHYSIOLOGY OF DIARRHŒA AND CONSTIPATION.

Before passing on to a consideration of the condition of the stools in the more important diseases of the intestinal tract it may be well briefly to consider the most common causes of diarrhœa and constipation.

Diarrhœa.

Supposing normal peristalsis to result from the stimulation of the nervous mechanism situated in the intestinal walls—*i. e.*, the plexuses of Meissner and Auerbach—by normal chyme, it is apparent that an increased peristalsis indicates either that the intestinal con-

tents possess more irritating properties, or that the irritability of the intestinal nervous mechanism is increased.

Among such abnormal stimuli the following may be mentioned:

1. *Thermic stimuli.* The effect of these may be said to increase or decrease peristalsis in the same proportion as the thermic stimulus differs from the normal temperature of the body. A cold injection thus acts more promptly than a warm one, and in many people a glass of cold water, taken early in the morning, before breakfast, is often followed by vigorous peristalsis.

2. *Mechanical stimulation.* As an example of this the loose stools may be mentioned which follow a very large meal. A large injection similarly acts more energetically than a small one. In such cases it is supposed that the increased peristalsis is referable to the stimulation of a larger number of nerve-endings at the same time.

3. *Chemical stimuli.* These are certainly the most important and those which are probably responsible for most cases of diarrhœa. Among these must be mentioned:

a. Certain medicinal substances belonging to the class of laxatives, drastics, cathartics, etc., some of which manifest a selective action for the intestinal tract, as their injection into a vein or hypodermically will also cause an increase in the peristalsis.

b. Poisons: All the drugs of the Pharmacopœia, with few exceptions, belong to this class, as when given in poisonous doses diarrhœa is produced.

c. Poisons contained in tainted food.

d. Poisons produced in the intestinal tract itself, referable to abnormally active fermentative and putrefactive processes.

e. Certain poisons produced by specific microbes, such as those of typhoid fever, cholera, etc.

4. *Psychic stimuli.* As an example of these the diarrhœa of the student before examinations may be mentioned.

As indicated above, peristalsis will also be increased when the nerve-endings in the intestinal mucosa are in a condition of increased irritability. This will naturally always be the case in any inflammatory condition of the intestine, the abnormally filled blood-vessels, and at the same time an altered condition of the transudate, causing stimulation of the fine nerve-endings. In acute ulcerative conditions this state is, of course, met with in its most marked form, while in chronic ulcerations, where there is a gradual death of nerve- and muscle-substance, increased peristalsis is not so often observed,

the stools, as regards consistence and number, scarcely differing from the normal.

It may thus be said that whenever intestinal peristalsis through one of these causes has become abnormally active diarrhœa must result, manifested by the passage of an increased number of stools, which are at the same time abnormally rich in water. The increase in the amount of water may be due to one or two causes: first, to increased ingestion, and, second, to diminished absorption. The first of these, however, can hardly ever be said to cause diarrhœa, and the latter will not result as long as resorption is undisturbed.

The liquid stools following the administration of salts can probably be explained by assuming a retention of water in the alimentary canal, referable to their presence. By far the most frequent cause of watery stools, however, following the administration of a drug is an abnormally active peristalsis.

Whether in pathologic conditions associated with the destruction of epithelium the abnormal quantity of water observed in the stools can be ascribed to diminished absorption is a question which is difficult to answer, since inflammatory and ulcerative processes which, as has been seen, are in themselves sufficient to produce increased peristalsis, and hence watery stools, are taking place at the same time.

On the other hand, it appears highly probable that the frequent and persistent diarrhœa which occurs so constantly in cases of amyloid degeneration is due to passive hyperæmia in consequence of the degenerative changes taking place in the bloodvessel-walls, resorption being thereby impeded.

Remembering at the same time that the resorptive processes in the large intestine determine the form in which the intestinal contents leave the body, it is readily understood that increased peristalsis of this portion of the gut is the deciding factor in the production of diarrhœa, and without it an increased peristalsis alone, confined to the small intestine, would hardly ever be capable of causing this result. It follows also that the more the peristalsis of the entire alimentary tract is increased, the more will the feces assume the character of the contents of the small intestine.

Constipation.

Hitherto the effects of increased peristalsis upon the number and consistence of the stools have been considered. If now peristalsis

becomes diminished, the opposite condition—*i. e.*, constipation—will result, and inversely, as in diarrhœa, this may be due to a diminished irritability on the part of the nervous mechanism of the intestinal wall. This is especially the case in the condition generally designated as "habitual constipation," the degree of which will depend upon the part that the small and large intestines separately or together play in the process. In such cases, however, resorption is not increased in proportion, as might at first thought be imagined, and it appears to be a fairly well-established fact that for the carrying on of an efficient degree of resorption a certain degree of peristalsis is necessary. This is most beautifully exemplified in cases of *cholera sicca*, in which constipation exists, although the intestines are filled with liquid. Whether central influences play a part in some of the cases must as yet remain an open question.

Different from this condition are those cases of constipation which are not referable to a diminished peristaltic energy, but in which, instead of successive contractions and relaxations, a tonic contraction of the intestinal walls occurs. In some cases this is probably of central origin, as in basilar meningitis, while in others, as in lead colic, it may be secondary to a primary vaso-constriction along the intestines. It differs from ordinary constipation in the fact that everything that can be absorbed is here taken up.

In atony of the intestinal muscles, finally, constipation will also result. This occurs, for example, after the use of cathartics, in peritonitis (in consequence of prolonged circulatory disturbances), and in alcoholics the subjects of fatty degeneration of the muscular walls of the intestines.

THE FECES IN VARIOUS DISEASES OF THE INTESTINAL TRACT.

Acute Intestinal Catarrh. This condition follows the ingestion of excessive quantities of normal food, of tainted food (meat, fish, cheese, etc.), beer, and of certain poisons, such as acids, alkalies, arsenic, corrosive sublimate, etc., when taken in toxic quantities. It is also observed, furthermore, as the result of a general infection, as in summer diarrhœa, cholera nostras, typhoid fever, and severe malaria, and is associated with disturbed circulatory conditions producing a passive hyperæmia of the gastro-intestinal mucosa, as in diseases of the liver and portal system, in chronic heart

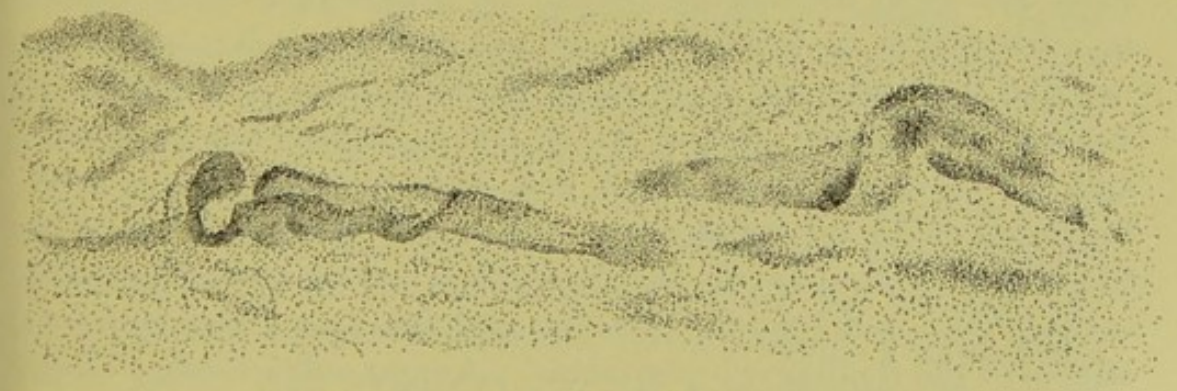
and lung diseases, etc. How far these circulatory disturbances may be considered as primary causes remains to be seen. Possibly they merely act as predisposing causes of certain chemical processes taking place in the intestinal contents.

The stools are usually increased in number in proportion to the degree in which the large intestine is affected. Two or three, or ten or more, stools may be passed within the twenty-four hours. In consistence they are mushy or even watery, containing in some cases 90 or 95 per cent. Their color is usually light yellow, but may, at times, be green. Microscopically, remnants of food may be found in large quantities, as also numerous bacteria, triple phosphates, isolated pus-corpuscles, and desquamated cylindrical epithelial cells.

A *duodenal catarrh* can only be diagnosed when icterus exists at the same time.

In *catarrh of the jejunum and ileum*, when the large intestine is not affected the stools are firm, formed, and speckled with small hyaline particles of mucus, visible only with the microscope. Usually, however, the large intestine is also affected when the stools are loose and contain undigested particles of food, the latter indicating abnormal conditions in the small intestine. Bile-pigment is also met with, as only the contents of the small intestine give Gmelin's reaction.

FIG. 61.



Rectal discharge from a case of enteritis membranosa.

Catarrh of the large intestine is probably always present whenever diarrhœa exists.

When the *colon* is extensively affected mucus appears in larger masses than otherwise, and if the catarrh is very low down the feces may be formed, but are covered with mucus.

Chronic Intestinal Catarrh. This may follow an acute attack, and may also occur after dysentery, severe malaria, typhoid fever, etc. Diarrhœa usually alternates with constipation. It is rare in adults, while in children it is quite frequently observed. Macroscopically and microscopically it presents the same picture as in the acute form.

Enteritis membranosa is a form of chronic intestinal catarrh characterized essentially by the evacuation of cylindrical masses of mucus, as described on p. 203. (Fig. 61.)

Cholera Nostras. This is an infectious disease affecting both stomach and intestines, being probably dependent upon the presence of the bacillus of Finkler and Prior.

The stools are first feculent, but soon become colorless and more and more watery, until they ultimately resemble the so-called rice-water stools of cholera Asiatica, and contain much serum-albumin and mucin.

Summer Diarrhœa of Infants. In this disease six or seven stools are passed daily, which are more liquid than normally, of a fetid odor, and contain flakes of casein. They are often green when passed, or may assume that color on standing. Mucus is present, and when the colon is especially affected may occur in sago-like particles. In severe forms pus-corpuscles, epithelial cells, and small amounts of blood may be present.

Booker, in his classical work upon the summer diarrhœa of infants, arrives at the conclusion that the disease in question cannot be attributed to the presence of any one particular micro-organism, but that the "affection is the result of the activity of a number of varieties of bacteria, some of which belong to well-known species and are of ordinary occurrence and wide distribution, the most important being the streptococcus and proteus vulgaris." He also found that in the colon the bacillus lactis aërogenes occurs in greater number than in the normal intestine, and that it may even predominate over the bacillus coli communis. Among other forms of bacteria which occur frequently and in great abundance are small, short, faintly staining bacilli; long, very slender bacilli; large bacilli with pointed ends, and small, faintly staining spirilla.

Dysentery. This is an infectious disease, probably caused by a bacillus discovered by Chantemesse and Widal. The stools during the first few days are irregular. A moderate diarrhœa then sets in, the stools being thin, but still feculent, numbering five or six

per diem. After several days the diarrhœa increases and the stools now assume a definite character, numbering from ten to twenty or even fifty or sixty in the twenty-four hours. At the same time they become scanty in amount, usually not exceeding 10 to 15 grammes at a time. They are now sero-sanguineous in character, and in them may be found smaller or larger pieces of necrotic tissue. Microscopically blood-corpuscles, particles of mucus, pus-corpuscles, and numerous bacteria are seen. According to the preponderance of blood, pus, mucus, etc., the stools are termed sanguineous, sero-sanguineous, puriform, or mucoid, etc. Shreds of mucus, resembling frogs' eggs or kernels of tapioca, which are, in all probability, casts of follicles, are also found. Typical dysenteric stools do not, as a rule, emit a marked odor, but in the gangrenous form they are very offensive.

Amœbic Dysentery. This form of dysentery is especially interesting, not so much on account of its prevalence, however, as of the importance attaching to an early diagnosis, a successful treatment being altogether dependent thereupon, and differing entirely from that employed in the more usual forms.

The number of stools may vary within very wide limits—from six to twenty or even thirty in the twenty-four hours. They may be wholly mucoid, streaked here and there with pus, and presenting a few grayish threads. Others seem to be made up of a greenish, pultaceous mass, in which at times large greenish, irregular sloughs are observed. Such stools are usually slight in amount. Occasionally large brownish, liquid evacuations are seen, in which small grayish-white masses occur, imbedded in blood-stained mucus. Such stools contain the diagnostic amœbæ most abundantly.

For a satisfactory examination of the stools the bed-pan ought to be well warmed and brought to the laboratory *immediately* for examination. If this be impracticable, some of the material may be deposited in a suitable receptacle, and the small, grayish-white masses placed upon a warmed slide, if a warm stage be not at hand. One preparation after another must now be carefully looked over for actively moving amœbæ, or for amœba-like bodies which exhibit definite movements. (For a description of these parasites see p. 229.)

In addition to the amœbæ other animal parasites may here be met with, such as the trichomonas intestinalis, which is at times present in very large numbers.

Red blood-corpuscles in greater or less abundance, numerous pus-corpuscles, more or less degenerated cylindrical epithelial cells, bacteria of all kinds, and even large pieces of necrotic tissue may also be found.

Cholera Asiatica. In this disease the stools are very numerous, being at first feculent, but soon becoming rice-water-like. As large a quantity as 200 grammes may be passed at each evacuation. The stools are colorless, almost odorless, watery, and on standing a finely granular, grayish-white sediment may be seen to form at the bottom. The reaction is neutral or alkaline. They contain only 0.5 per cent. of solids, a little serum-albumin, and a large amount of sodium chloride. In severe cases blood is present in variable amount. Microscopically, epithelial cells, triple phosphate crystals, and numerous micro-organisms are found. Of the latter the comma-bacillus is, of course, the most important (see p. 230.)

Typhoid Fever. Typhoid stools are usually described as resembling pea-soup both in consistence and color. Their odor is usually highly offensive and characteristic. They contain a large amount of biliary coloring-matter and have always an alkaline reaction. Microscopically many bile-stained epithelial cells, some leucocytes, many triple phosphate crystals, and an enormous number of micro-organisms, especially the clostridium butyricum of Nothnagel and Eberth's bacillus, are found. Later on they may assume the appearance of ulcerative stools and become almost black, owing to the presence of blood.

MECONIUM.

By meconium are meant those masses which are first excreted from the bowel after birth. It is a thick, tenacious, greenish-brown material which has accumulated during the intra-uterine life of the infant. Microscopically a few cylindrical epithelial cells, a few fat-droplets, numerous cholesterin-crystals, bilirubin-crystals, and lanugo-hairs are found.

Micro-organisms are absent, but soon after suckling has commenced bacteria appear in abundance. The most important ones of those which are then constantly present are the bacillus lactis aërogenes, which predominates in the small intestine, and the bacillus coli communis, which is found more particularly in the large intestine. Both have already been described (see pages 232 and 233).

In addition to these proteus vulgaris, streptococcus coli brevis, micrococcus ovalis, tetradencoccus, torula cerevisiæ, torula rubra, and a few less important micro-organisms have at times been found.

Chemically meconium contains bilirubin in considerable amount (recognizable by Gmelin's reaction), biliary acids, fatty acids, chlorides, sulphates, phosphates of the alkalies and their earths. It does not contain urobilin, glycogen, peptones, lactic acid, tyrosin, or leucin.

An idea may be formed of its composition from the following table of Zweifel:

Water	79.8–80.5	per cent.
Solids	20.2–19.5	"
Mineral matter	0.978	"
Cholesterin	0.797	"
Fats	0.772	"

CHAPTER V.

THE NASAL SECRETION.

In the nasal secretion, which is small in amount, transparent, colorless, odorless, tenacious, and of a slightly saline taste, pavement-epithelium cells in large numbers, ciliated epithelial cells, as well as some leucocytes and an enormous number of micro-organisms, are found. (Fig. 62.) Its reaction is alkaline.

Fig. 62.



Epithelial cells and mucous corpuscles found in the nasal secretion.

In acute coryza the amount is at first diminished, but soon a very copious secretion occurs, which is rich in epithelial cells and micro-organisms. When complicated with an ulcerative condition pus is observed in considerable amount.

Occasionally, in cases of traumatism, cerebral tumors, etc., cerebro-spinal fluid is discharged through the nose, which may be recognized by the fact that it is free from albumin and contains a substance which reduces Fehling's solution.

Of pathogenic organisms the tubercle-bacillus and the bacillus of glanders may occur in ulcerative diseases of the nose, their presence indicating the existence of the corresponding affection. In ozæna a large diplococcus has been described by Löwenberg, which is said to be characteristic of the disease. Oidium albicans has been observed in rare cases. The same may be said of the occurrence of ascarides and other entozoa, which at times find their way into the nasal passages. Charcot-Leyden crystals (which see) have been observed in the nasal discharge in cases of true bronchial asthma.

CHAPTER VI.

THE SPUTUM.

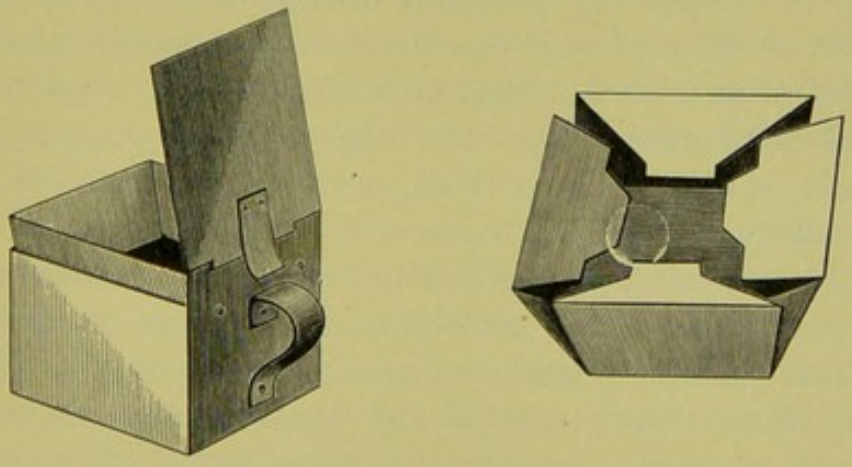
Definition.

WITHOUT entering into the physiology of the act of coughing, it may be stated in a general way that cough is the first and most essential factor in the elimination of irritating matter derived from the respiratory passages—*i. e.*, the alveoli of the lungs, the bronchi, trachea, larynx, pharynx, and posterior nares. The material which is thus removed is spoken of as expectoration or sputum, the study of which forms one of the most important chapters in clinical diagnosis.

General Technique.

The sputum should be collected in suitable receptacles, constructed in such a manner as to permit of their complete and easy disinfection. The paper spit-cups (Fig. 63) which have been introduced within late years are admirably adapted to this purpose, as they may be destroyed immediately after use.

FIG. 63.



Sanitary spit-cup.

When working with sputa which are known or suspected to be of tubercular origin, the greatest care should be exercised to keep the expectoration from drying and becoming disseminated in the air.

Negligence in this respect may result in the most serious consequences.

The macroscopic examination of sputa is most conveniently carried out by placing small portions of the material upon a plate of ordinary window-glass, of suitable size, which has been painted black upon its lower surface, and covering the same with a second and smaller plate. If it is desired to examine individual constituents which have been discovered in this manner, the upper plate is slid off until the particle in question is uncovered, when it may be removed to a microscopic slide and examined under a higher power.

It is also very convenient to have a portion of the laboratory table painted black, when unstained plates of glass may be utilized. If these measure about 15 by 15 cm. and 10 by 10 cm., respectively, fairly large quantities of sputum may be examined *in situ* with a low power.

General Characteristics of the Sputa.

The Amount. The amount of sputum expectorated in the twenty-four hours varies within very wide limits, depending largely upon the nature of the disease. Thus, only a few c.c. may be eliminated, or an amount reaching 600 to 1000 c.c., or even more. Very large amounts are expectorated in cases of pulmonary hemorrhage and œdema of the lungs, also following the perforation of accumulations of pus from the thoracic or abdominal cavities into the respiratory passages; furthermore, in cases in which large vomicæ of tubercular or gangrenous origin exist, and finally in cases of abscess of the lung, bronchiectasis, and even in simple bronchial blennorrhœa. On the other hand, the amount may be very small, as in incipient phthisis, acute bronchitis, and in the first and second stages of pneumonia.

In private practice, as well as in hospital work, an idea should always be formed of the amount of sputum expectorated in the twenty-four hours, especially in cases in which this is abundant. It is apparent that a copious and long-continued expectoration cannot go on without exerting very detrimental effects upon the patient's general nutrition; in cases of pulmonary phthisis, for example, Renk has shown that 3.8 per cent. of all nitrogen eliminated in such cases is removed in this manner. Lanz in his recent experiments even found 5 per cent.

Consistence. The consistence of the sputum corresponds, in a general way at least, to its amount, and may vary from a liquid to a highly tenacious state. The cause of the tenacity of the sputum is but imperfectly understood. The mucin present does not appear to be the most important factor, as this has been observed to occur in diminished amount in pneumonic sputa, which are noted for their high degree of tenacity. Kossel has suggested that this phenomenon may be due to the presence of nuclein or nuclein derivatives, while others again refer it to the presence of abnormal albuminous bodies of unknown character. However this may be, sputa are at times and not at all infrequently seen where it is possible to invert the cup without losing a drop of its contents. This is observed especially in cases of acute croupous pneumonia up to the time of the crisis, providing that a catarrh of the bronchi does not exist at the same time. It is noted, furthermore, in cases of acute bronchial asthma, immediately after an attack, and also in the initial stage of acute bronchitis.

In cases of œdema of the lungs, on the other hand, the sputa are liquid and present the general characteristics of blood-serum, being covered, like all albuminous liquids when brought into contact with the air, by a frothy surface-layer. The sputa observed in cases of acute pulmonary gangrene, pulmonary abscess, putrid bronchitis, and following perforation into the lungs of an empyema or an accumulation of pus situated beneath the diaphragm, are fluid and consist of pure pus.

Color. The color of the sputa may vary greatly. They may be perfectly clear and transparent, gray, yellow, green, red, brown, or even black. Purely mucoid expectoration is almost transparent and colorless, as is also the sputum of pulmonary œdema when not mixed with blood or pus.

The larger the number of leucocytes the more opaque does the sputum become, assuming at first a white, then a yellow, and finally a greenish color, the two latter colors being usually indicative of the presence of pus. Green sputa, however, may also be observed when bile-pigment has become admixed with the sputa, as in cases of perforation of a liver-abscess into the lung, for example. Green-colored sputa may also be observed in cases of jaundice, and especially in pneumonia when accompanied by icterus. In cases of amœbic liver-abscess with perforation into the lung the sputa present a color resembling anchovy sauce, which is very

characteristic. In one case the author recognized the nature of the disease by simple inspection of the sputa.[1]

The inhalation of particles of carbon gives the sputum a grayish or even a black color; the same or an ochre-yellow or red color is observed in cases of siderosis.

A red color is usually indicative of the presence of *blood*, the intensity of the shade depending upon the character of the disease. It is seen especially after the formation of cavities in caseous pneumonia, in incipient phthisis, heart-disease, etc. In general it may be said that a clear, bright-red color indicates an arterial, a dark-red or bluish-red a venous origin of the hemorrhage. The exact shade will depend upon the length of time that the blood, no matter what its origin may be, has remained in the lungs. In pulmonary gangrene a dirty brownish-red color is observed, owing to the presence of methæmoglobin, and, to some extent also, of hæmatin. Quite characteristic is a chocolate-color, which is observed when a croupous pneumonia terminates in necrosis and gangrene. Equally characteristic is the rusty and prune-colored expectoration seen in cases of pneumonia. Occasionally a breadcrust-brown color of the sputa is observed in cases of gangrene and abscess of the lung, which is said to be quite characteristic, the color being due to the presence of hæmatoidin or bilirubin.

Rust-colored, punctate, or striped sputa, moreover, are said to be diagnostic of brown induration of the lung.

Odor. Most sputa are odorless. Under certain conditions, however, the odor may be very marked. In cases of pulmonary gangrene or putrid bronchitis the odor is of a kind never to be forgotten, the stench, indeed, being frightful. A somewhat similar, slightly sweetish odor is observed in certain cases in which putrefactive organisms have entered the lungs and there exerted their action upon the accumulated sputa, in the absence of gangrene, as in cases of bronchiectasis, perforating empyema, and where ulcerative processes are taking place in the lungs, whether these be of tubercular origin or not. An odor like that of old cheese is occasionally observed in cases of perforating empyema; under such conditions tyrosin is usually found. This body, however, has nothing to do with the odor of the sputa, both factors being merely indicative of certain putrefactive changes going on in the lungs. According to Leyden, the occurrence of tyrosin in sputa

[1] See Johns Hopkins Hospital Bulletin, November, 1890.

is usually indicative of the perforation of an old accumulation of pus into the lungs.

Specific Gravity. The specific gravity of sputa varies within wide limits, mucous sputa having a specific gravity of 1.004 to 1.008, purulent sputa one of 1.015 to 1.026, and serous sputa one of 1.037 or more. The determination of the specific gravity, however, will scarcely ever be of value in diagnosis.

Configuration of Sputa. As a general rule, the following forms of sputa, which may be termed pure sputa, present a homogeneous appearance:

Mucoid sputa,
Purulent sputa,
Serous sputa,
Sanguinous sputa,
} Homogeneous sputa,

with one exception, perhaps—the typically rusty sputa of croupous pneumonia; while mixtures of any two or three of these may be classed as heterogeneous sputa:

Muco-purulent sputa,
Muco-serous sputa,
Sero-sanguinous sputa,
Sanguino-muco-purulent sputa,
} Heterogeneous sputa.

The so-called *sputum crudum* of the first stage of acute bronchitis may be regarded as an example of a purely mucoid sputum. A purely purulent sputum is usually indicative of one of the following conditions, viz., the perforation of an empyema or any other accumulation of pus into the lungs or bronchi, pulmonary abscess, or bronchial blennorrhœa. A purely serous sputum is found in cases of pulmonary œdema, and a purely hemorrhagic sputum in cases of severe pulmonary hemorrhage.

Of the heterogeneous sputa, the most important are the so-called *nummular sputa* of phthisis in the second and third stages. These are characterized by the fact that when thrown or expectorated into water they sink to the bottom and there form more or less roundish coin-like disks, from which property they have received their name. Such sputa are muco-purulent in character, and contain imbedded in a more or less homogeneous mass of mucus a focus of almost pure pus. Quite different from these are the so-called *sputa globosa* of the ancients, which consist of fairly dense, roundish, grayish-white masses, secreted in old cavities which have become lined with a granulation-membrane.

Very important is the presence of small, *cheesy particles*, which are occasionally found at the bottom of the spit-cup. They vary in size from that of a millet-seed to that of a pea, and are observed especially in the second and third stages of phthisis. Usually they contain tubercle bacilli in large numbers, and frequently also elastic tissue.

Not to be confounded with these, however, are certain small, caseous masses which are at times expectorated by perfectly normal individuals, and also by patients suffering from acute tonsillitis, ozæna, etc., and which probably come from the tonsils or mucous cysts. These were formerly regarded as tubercles, and in hypochondriac individuals their expectoration may cause unnecessary anxiety. They are quite readily distinguished from the true caseous masses expectorated by phthisical individuals by the following characteristics: As a rule, they are expectorated unaccompanied by any admixture of pus or even of mucus; rubbed between the fingers they emit an extremely offensive odor, which is referable to the presence of fatty acids; an examination for tubercle bacilli, moreover, will prove entirely negative. Quite characteristic, furthermore, is the peculiar, finely flocculent, granular appearance of the sputa seen after the perforation of an empyema into the lungs through a small aperture, which is not followed by pneumothorax.

Occasionally, as in putrid bronchitis and gangrene of the lungs, and also in chronic bronchitis, ultimately leading to the formation of bronchiectatic cavities, an exquisite *sedimentation* is observed. Such sputa, when collected in a conical glass, usually present three distinct zones, the one at the bottom containing the cellular elements of the sputum, the second the pus-serum, and the third or superficial layer consisting of mucus and containing many air-bubbles.

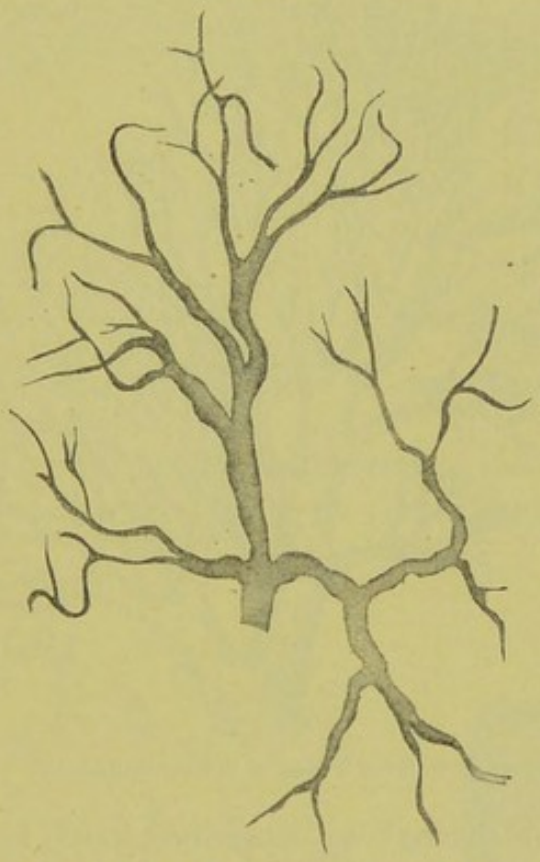
Macroscopic Constituents of Sputum.

Elastic Tissue. Of macroscopic constituents which may be observed in sputa there may be mentioned, first of all, the occurrence of threads of elastic tissue and pulmonary parenchyma, which are seen in cases of phthisis, pulmonary abscess, and gangrene. As their ultimate recognition, however, largely depends upon a microscopic examination, this subject will be considered later on.

Fibrinous Casts. Fibrinous casts are observed especially in cases of croupous pneumonia (Fig. 64) immediately before or after resolution has taken place. They are also seen in cases of so-called

fibrinous bronchitis (Fig. 65), and in cases of diphtheria, as in the latter disease the fibrinous exudation may not only attack the walls of the larynx and trachea, but may even extend into the finest ramifications of the bronchi. These casts may vary in size from 12 cm. in length by several mm. in thickness to small fragments which measure only from 0.5 to 3 cm. in length. The fibrinous casts observed in cases of pneumonia, usually from

FIG. 64.



Fibrinous coagulum from a case of croupous pneumonia. (BIZZOZERO.)

the third to the seventh day, are of the latter size or even smaller, being derived from the ultimate twigs of the finest bronchioles. Those found in the rather rare disease, fibrinous bronchitis, stand between these two in size, being casts of the smaller and medium-sized bronchi. Attention is usually attracted to the presence of such casts by their white color; often, however, they are yellowish-brown or reddish-yellow, owing to the presence of blood-coloring matter which has become deposited upon the casts, while at other times they are enveloped in mucus, when their recognition may become quite difficult. Such casts, when examined more carefully, will be seen to branch dichotomously, and to

contain a cavity in their larger portion, while the finer branches appear to be soild. Microscopically they may be shown to consist of a large number of longitudinal and often net-like arranged fibres, containing blood-corpuscles and epithelial cells in their meshes. When treated with Weigert's fibrin-stain they are beautifully resolved. Charcot-Leyden crystals have been observed by some in these formations.

FIG. 65.



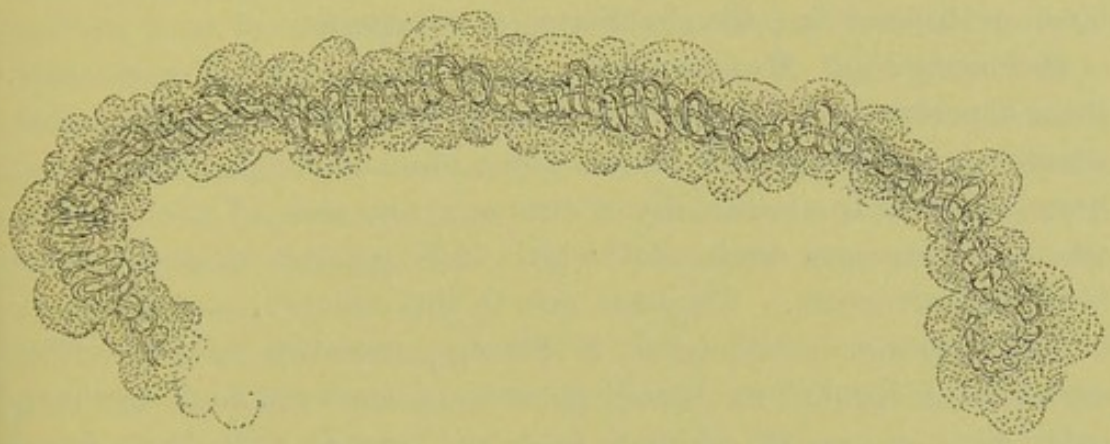
Fibrinous coagulum from a case of plastic bronchitis. (V. JAKSCH.)

Whenever it is desired to examine sputa for casts it is best to pick out particles that look promising upon a dark or light surface, and then to shake these out in water in order to unravel them. For such purposes Krönig's sputum-plate can be strongly recommended.

Curschmann's Spirals. Quite distinct from the formations just described are the so-called spirals of Curschmann, observed especially in cases of true bronchial asthma, but also occurring in chronic bronchitis, and even in croupous pneumonia. Upon careful examination they will be seen to occur in the form of thick, yellowish-white masses, which exhibit a spirally twisted appearance, and which are characterized, moreover, by their more solid consistence and light color. Microscopically Curschmann's spirals are seen to consist of a spirally twisted network of extremely delicate

fibrils, containing epithelial cells and especially leucocytes, which have lately been shown to belong almost exclusively to the type of eosinophiles. Usually, but not invariably, Charcot-Leyden crystals are also seen. The spirally twisted mass is found to be wound around a central, very light and clear thread, which usually has a zig-zag course (Fig. 66).

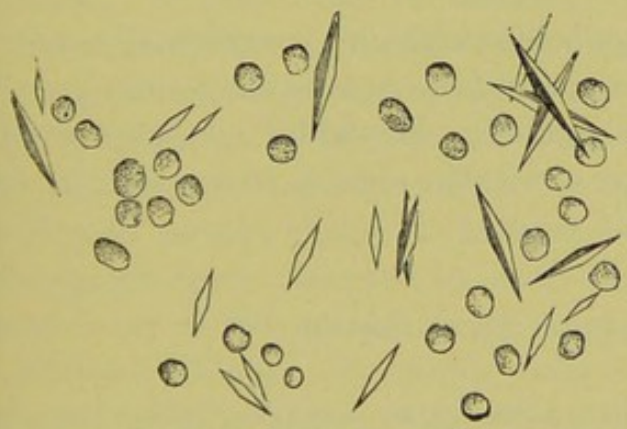
FIG. 66.



A Curschmann's spiral from a case of true bronchial asthma.

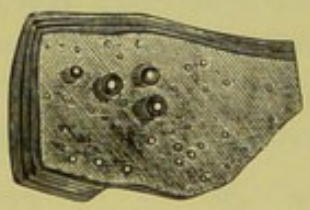
Other formations, probably mere varieties of those just described, have also been observed, in which the central thread is absent or

FIG. 67.



Charcot-Leyden crystals. (SCHEUBE.)

FIG. 68.



Wall of a hydatid cyst, showing the laminated structure, not magnified. (DAVAINE.)

in which the spiral arrangement is deficient. The spiral form, however, with the central thread, must be considered as the most characteristic. Their length and breadth may vary a great deal, but rarely exceed 1 to 1.5 cm. Their occurrence seems always to indicate a desquamative catarrh of the bronchi and alveoli, but practically nothing is known concerning their formation. If, in a given case, the diagnosis rests between true bronchial and what may be termed reflex asthma, the presence of these formations points to

the existence of the former disease. Chemically the spirally wound mass seems to consist of a mucinous substance, while the central thread is possibly of fibrinous origin.

Charcot-Leyden crystals (Fig. 67), which are usually absent at the beginning of an attack of asthma, at which time only the spirals are observed, may be seen to develop from the spirals when these are kept for several days. They will be considered later on, in studying the chemistry of the sputum.

Echinococcus Membranes. Echinococcus membranes come from a perforating cyst of the liver, kidney, or lung. They constitute rather thick, and at the same time tough, pieces of membrane (Fig. 68); occasionally entire sacs are seen, of the color of white porcelain, in sections of which it is possible to make out a fibrillated structure. They are rare in this country.

Concretions. Still rarer is the expectoration of concretions which have formed in dilated portions of the bronchi or in tubercular cavities, or of calcified bronchial glands that have found their way into the lungs. Curious examples of the occurrence of such concretions have been reported. Andral thus cites a case of phthisis in which within eight months as many as 200 stones were expectorated, and Portal mentions a case in which 500 were thus expelled.

Foreign Bodies. Foreign bodies which have accidentally entered the air-passages and have remained there for a long time are also occasionally found in the sputum. Heyfelder mentions a case in which a man coughed up a wooden cigar-holder with pus and blood after eleven and a half years.

Microscopic Examination.

Under this heading it is necessary to consider leucocytes, red blood-corpuscles, epithelial cells, elastic fibres, corpora amylacea, parasites, and crystals.

Leucocytes. Leucocytes, usually polynuclear in character, are found in every sputum in considerable numbers, imbedded in a homogeneous, more or less tenacious material. At times they appear very granular, containing fat-droplets in their interior, or granules of pigment, such as carbon, or hæmatoidin. Most interesting is the occurrence of large numbers of eosinophilic and even of basophilic leucocytes in asthmatic sputa. The number of leuco-

cytes varies a great deal, being naturally greatest in cases of perforating abscess, empyema, putrid bronchitis, etc.

Red Blood-corpuscles. The presence of red blood-corpuscles in small numbers does not by any means indicate serious pulmonary or cardiac disease, as they are found, according to v. Jaksch, in almost every sputum, and especially in that of individuals who smoke much or live in a smoky atmosphere, being, without doubt, derived from the catarrhally inflamed bronchial or tracheal mucosa. Whenever they occur in large numbers, however, their presence becomes important. They may thus be observed in acute bronchitis, pneumonia, œdema of the lungs, bronchiectasis, abscess, gangrene—in fact, in all pulmonary diseases. Their occurrence is most important in phthisis, being, in fact, one of the most constant symptoms of the disease.

The form of the red corpuscles will depend upon the length of time that they have remained in the lungs, and all gradations from the typical red corpuscle to its shadow, or even fragments, may thus be observed. In pneumonia the microscopic examination may at times be disappointing, the appearance of the sputum suggesting that red corpuscles in large numbers are present, while, as a matter of fact, they are almost all destroyed, the color being due to altered pigment. It may even be necessary at times to depend upon chemical methods to clear up any doubt as to the source of the color of the sputum. It should always be remembered that the presence of blood-pigment is not always indicated by a red color, but that it may also assume a golden-yellow or even a greenish tinge, having undergone certain chemical changes. The golden-yellow and the grass-green sputa observed in cases of pneumonia during convalescence are of this class.

Epithelial Cells. Epithelial cells may also be observed in the sputum. While a great deal of information would be expected from their presence from a diagnostic point of view, as accurately indicating the parts of the respiratory tract attacked by disease, the data obtained are of little value.

Cylindrical epithelial cells, providing they do not come from the nose, indicate in a general way an inflammatory condition of the lower larynx, trachea, or bronchi. They are not of much importance, however, their form being usually so much altered that it is often difficult to recognize them, having become polyhedral, cuboidal, or even round, so as to be hardly distinguishable from

a leucocyte. Actively moving cilia can be found only in perfectly fresh sputa, immediately after being expectorated. If ciliated epithelial cells can be definitely recognized in a sputum, it may be inferred that we are dealing with a pathologic condition of an acute nature, providing, of course, they did not come from the nose.

FIG. 69.



Epithelium, leucocytes, and crystals of the sputum (eye-piece III., objective 8 A. Reichert): *a*, *a'*, *a''*, alveolar epithelium; *b*, myeline forms; *c*, ciliated epithelium; *d*, crystals of calcium carbonate; *e*, hæmatoidin crystals and masses; *f*, *f*, *f*, white blood-corpuscles; *g*, red blood-corpuscles; *h*, squamous epithelium. (V. JAKSCH.)

Much importance was formerly attached to the so-called *alveolar epithelial cells* (Fig. 69) as an aid in diagnosis. Buhl thus imagined these, particularly when undergoing fatty or myeline degeneration, to be absolutely pathognomonic of pulmonary disease, and especially of that form of pneumonia which has been termed essential idiopathic desquamative pneumonia. Bizzozero, however, as well as others, has shown that these cells do not only occur in almost every known pulmonary disease, but also in the so-called "normal" expectoration which at times is obtained upon making a very forcible expiration.

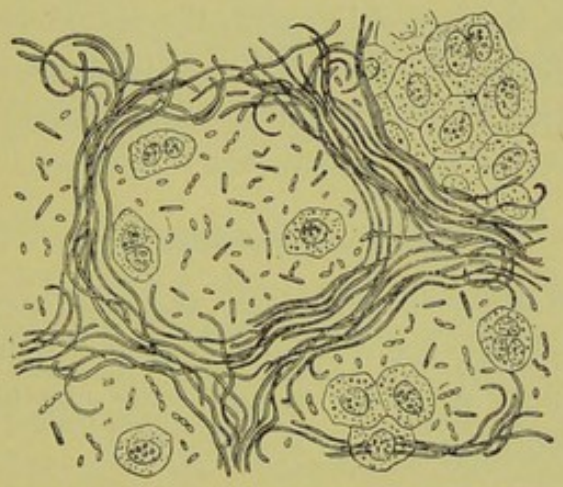
Bizzozero describes these cells as round, oval, or polygonal bodies, varying in size from 20 μ to 50 μ. They may contain one, two, or three oval nuclei, which are rather small and provided with nucleoli. The latter are usually hidden beneath numerous granules. Some of these granules are albuminous, but most of them belong to one of the following categories: pigmented granules, fatty granules, and myeline granules. The *myeline granules* were first discovered by Virchow in 1854, and termed myeline granules on account of their resemblance to mashed nerve-matter. They are distinguished from the other forms by their clear, pale, colorless appearance and the

fact that at times fine concentric striations can be detected. These forms may be round, but more often they are irregular in form. At times fatty, myeline, and pigment granules may be seen in one and the same cell. Possibly they are derived from the pulmonary alveoli, but this is still an open question.

Liver-cells may at times be observed in the sputa in cases of liver-abscess, and are easily recognized by their characteristic form.

Elastic Tissue. Much more important from a clinical standpoint are the elastic fibres and shreds of elastic tissue which may be found in sputa. They vary very much in length and breadth and are provided with a double, undulating contour; they are usually curled up at their ends. Very often they exhibit an alveolar arrangement (Fig. 70), which at once determines their origin.

FIG. 70.



Elastic fibres in the sputum (eye-piece III., objective 8 A, Reichert). (v. JAKSCH).

Whenever present, elastic tissue is an absolute indication that a destructive process is going on in the lungs. It is found in cases of abscess of the lung, bronchiectasis, occasionally in pneumonia, and, most important of all, in phthisis. In gangrene of the lung, elastic tissue is usually not found, probably owing, as suggested by Traube, to its destruction by a ferment.

In every case it is necessary to determine whether the elastic tissue may not be owing to the presence of animal food in the sputum, and it may, hence, be stated as a safe rule that it can only be regarded as absolutely characteristic when showing the alveolar arrangement.

In order to demonstrate the presence of elastic tissue in the sputum it is necessary to examine large quantities with a moder-

ately low power, best after the addition of a strong solution of sodium hydrate. The sputum may also be boiled with a 10 per cent. solution of the reagent, an equal volume being added; after dilution with four times its own volume of water it is allowed to settle for twenty-four hours. The centrifugal machine will here be found of great assistance.

The following method, in use at the Johns Hopkins Hospital, is most convenient: "A small amount of the thick, purulent portion of the sputum is pressed out into a thin layer between two pieces of plain window-glass, 15 by 15 cm. and 10 by 10 cm. The particles of elastic tissue appear on a black background as grayish-yellow spots, and can be examined *in situ* under a low power. Or the upper piece of glass is slid off till the piece of tissue is uncovered, when it is picked out and examined on a microscopic slide, first with a low and then with a higher power. At first there will be some difficulty in distinguishing with the naked eye between elastic fibres and particles of bread, or milk-globules, or collections of epithelium and débris, but with practice such mistakes are rarely made, and the microscope always reveals the difference." (Musser.)

Animal Parasites.

Portions of echinococcus cysts, viz., pieces of membrane (Fig. 69) and hooklets (Fig. 71), are occasionally seen, when the parasite has lodged in the lungs or in the neighboring organs. The disease, however, is exceedingly rare in this country.

FIG. 71.

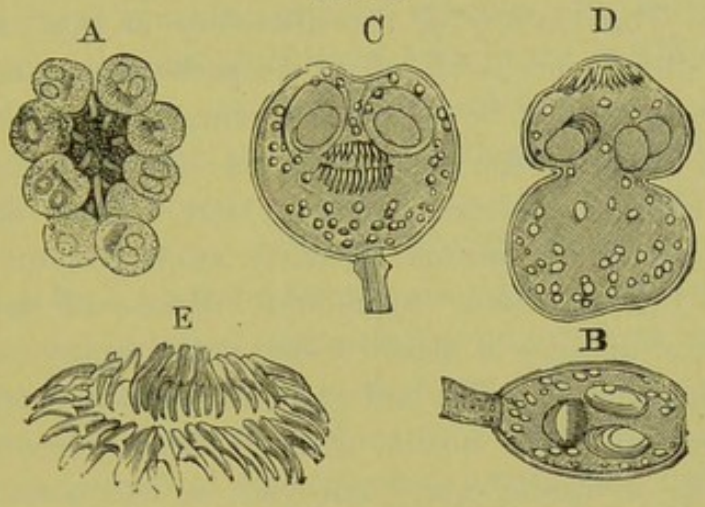


Hooks from tænia echinococcus. × 350.

The adult parasite (Fig. 72), *tænia echinococcus* (v. Siebold), is found in the intestinal canal of dogs. It measures from 3 to 5 mm. in length. If the eggs of the parasite are introduced into the diges-

tive tract of man, the embryos may make their way into the lungs, liver, or other organs, and there give rise to the formation of cysts, which are often of enormous size.

FIG. 72.



Human echinococcus. (From Finlayson, after Davaine.) *A*, a group of echinococci, still adhering to the germinal membrane by their pedicles. × 40. *B*, an echinococcus with head invaginated in the body. × 107. *C*, the same compressed, showing suckers and hooks of the retracted head. *D*, echinococcus with head protruded. *E*, crown of hooks, showing the two circles. × 350.

Trichomonades have at times been observed in cases of gangrene of the lung and in the pus removed post-mortem from lung-cavities. They are identical with the trichomonas vaginalis of Donné. Most important is the presence of the *amœba coli*, as the diagnosis of hepatic abscess with perforation into the lung may be made in every instance in which this organism is encountered in the sputa (see Feces).

A certain form of pulmonary disease, closely simulating phthisis, is very common in Japan, and has been shown to be referable to the presence of a distinct parasite in the lungs, the *distoma pulmonale*, Bälz: *syn.*, distoma Westermanni (Kerbert), distomi Ringeri (Cobbold). The worm and its ova are found in the sputum. "The parasite is 8 to 10 mm. long, 5 to 6 mm. wide, of a club shape, rounded off very markedly in front, less rounded posteriorly. The color during life is almost like that of earth-worms. The two sucking disks are almost equal in size. The ova are brown, with a thin shell, lidded, 0.1 mm. long and 0.05 mm. wide." (Huber.)

In this country the parasite has been found in the cat and in the dog; in the human being one case at least, occurring in a Japanese student, has already been reported.

It is interesting to note that many Charcot-Leyden crystals are at the same time found in the sputum.

Vegetable Parasites.

Pathogenic Organisms. *The tubercle bacillus.* The most important vegetable parasite met with in the sputa is the *bacillus of tuberculosis.* The history of the discovery of this organism, and the theories which were held before its pathognomonic importance was established, cannot be considered here. Suffice it to state that the study of bacteriology has given no other discovery of equal importance from a clinical point of view. How primitive and wholly inadequate the means formerly employed in making the diagnosis of this, the most formidable disease of modern times! The presence or absence of elastic tissue in the sputa was practically all that physicians formerly had to guide them beyond the history of the patient and the results of a physical examination. The demonstration of elastic tissue, however, as has been pointed out, indicates merely the existence of a destructive process in the lungs. Under such conditions it was of necessity impossible to diagnose tubercular disease in its incipiency. It is true that cases are occasionally observed in which tubercle bacilli are never present in the sputa, and are only discovered post mortem. Such cases, however, are rare, and do not in the least detract from the importance which attaches to careful and repeated examinations of the sputa in all doubtful cases.

From a macroscopic examination it is impossible to decide whether or not a particular sputum is of tubercular origin. At times a certain sputum may have a suspicious appearance, but it is never possible to speak with certainty from simple inspection, as a mucoid sputum may contain tubercle bacilli in large numbers, while a muco-purulent sputum may be entirely free from them. Reliance should, hence, only be placed upon a careful microscopic examination. When found their presence is, of course, pathognomonic. A negative result, however, does *not* exclude the existence of tubercular disease. The possibility that they may be altogether absent from the *sputum* has been mentioned. In some instances they may be present at times and absent at others. In all cases in which the existence of phthisis is suspected it is imperative to make use of every device which may aid in their detection. In this connection the author wishes to insist strongly upon the method of "growing the bacilli," as it were, in the warm chamber for from twenty-four to forty-eight hours, and then re-examining the sputa

in doubtful cases, as Nuttal demonstrated beyond a doubt that the tubercle bacillus will multiply in the sputum itself at a certain temperature. The value of this observation is obvious, and the author has been able repeatedly to demonstrate their presence in this manner when it was impossible to detect them in the fresh sputum.

The centrifugal machine in such cases is also useful and yields valuable results, the probabilities of finding the bacilli when present in small number being very much increased.

If but few bacilli be present, the following procedure may also be employed: About 100 c.c. of sputum are boiled with double the amount of water to which from six to eight drops of a 10 per cent. solution of sodium hydrate have been added, until a homogeneous solution has been obtained, water being added from time to time to allow for evaporation. This is then set aside for twenty-four to forty-eight hours and examined for tubercle bacilli and elastic tissue.

In the examination of tubercular sputa the fine, caseous particles described on page 250 should be carefully sought for, as they contain the largest number of bacilli. In their absence reliance should be placed upon the examination of a large number of preparations.

If, notwithstanding the fact that all due precautions have been taken, no bacilli can be demonstrated in the sputum, and the clinical history and the physical signs are indefinite or negative, the probabilities are that we are dealing with a benign process. From an examination of the sputa alone in such cases it is utterly impossible to reach a definite conclusion. When the amount of sputum, moreover, is small and contains but little pus, the absence of tubercle bacilli in doubtful cases is less suggestive of the absence of tubercular disease than in cases in which the sputum is more abundant and muco-purulent.

It has been pointed out that the discovery of the etiologic relation existing between the bacillus of tuberculosis and tubercular disease—notably phthisis—must be regarded as one of the most important for the clinician, if not the most important in itself, made by bacteriologists. This is certainly true, but the discovery of certain characteristics of the tubercle bacillus which are of direct practical utility in its recognition and differentiation from other organisms is equally important. Reference is had to the behavior of the micro-organism toward certain staining reagents and the difference which exists between it and other bacteria, and which renders its recognition an easy matter. The bacillus of leprosy might possibly

be confounded with the tubercle bacillus, but it is so rarely met with that it need not be considered.

The tubercle bacillus is essentially characterized by the difficulty with which it takes up basic coloring-matters and the great tenacity with which it retains these when once stained upon treatment with mineral acids.

Methods of staining the tubercle bacillus. Various methods have been suggested for the purpose of staining the bacillus, all of which, however, are modifications of that suggested by Weigert and Ehrlich.

1. *The Weigert-Ehrlich method:* A drop of sputum, or, better, one of the cheesy particles described, is carefully spread between two cover-glasses; these are then drawn apart, dried in the air, and passed through the flame of a Bunsen burner or of an alcohol lamp three times, in order to fix the preparations. At the Charité of Berlin larger quantities of sputum are spread upon slides, dried, fixed, stained, and examined directly in oil. In order to stain the specimens they are floated for twenty-four hours, face downward, upon a solution of aniline-water and fuchsin prepared in the following manner:

A small test-tube full of water is shaken for some time with about twenty drops of pure aniline oil (1 : 20), and then filtered through a moistened filter after standing for a few minutes. To this solution a few drops of concentrated alcoholic solution of fuchsin or of methyl-violet are added until the mixture becomes slightly cloudy—*i. e.*, until a slightly metallic lustre is noted on the surface. After twenty-four hours the preparation is washed with distilled water in order to remove an excess of the staining-fluid. The preparation is then immersed for several seconds in a dilute solution of nitric or hydrochloric acid (1:6, 1:3, or 1:2), and washed again with water or with absolute alcohol. At this time the preparation should have a faintly red or violet color. It is then dried between layers of filter-paper or in the air, and mounted in a drop of water.

If it be desired to make a double stain, which may at times aid in the recognition of the organism, Bismarck-brown, vesuvin, or methylene-blue in watery solutions may be used for this purpose. Into this solution the specimen is placed after treatment with nitric acid and washing in water.

2. *Gabett's method:* The dried preparation is placed for two minutes in a solution composed of 1 part of fuchsin (S), 100 parts of a 5 per cent. solution of carbolic acid, and 10 parts of absolute alco-

PLATE IX.

FIG. 1.



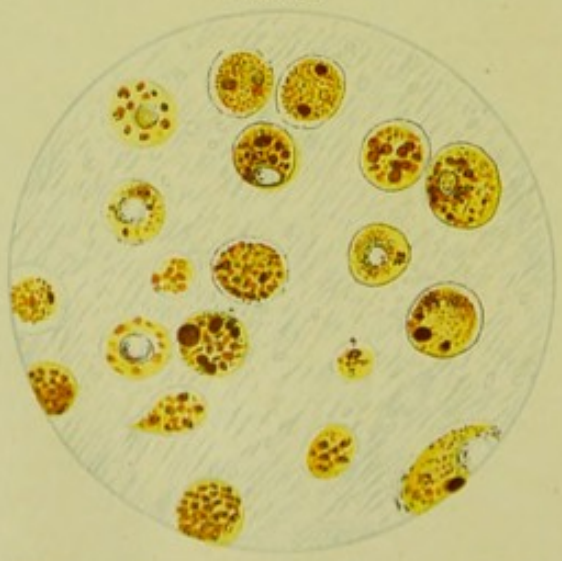
Tuberculous Sputum Stained by Gabbett's Method. The Tubercle Bacilli are seen as Red Rods, all else is Stained Blue. (Abbott.)

FIG. 2.



The Diplococcus Pneumoniæ, Stained with Methylene Blue and Fuchsin as a Counterstain. Taken from the Sputum of a Case of Acute Croupous Pneumonia.

FIG. 3.



Heart-Disease Cells, showing Alveolar Epithelial Cells, Loaded Down with Granules of Hæmatin.

hol, and then immediately transferred for one minute to a solution of 2 parts of methylene-blue in 100 parts of a 25 per cent. solution of sulphuric acid. It is then washed with water and mounted. This method of staining the writer regards as the most convenient.

3. *Ziehl-Neelsen's method:* A mixture of 90 parts of a 5 per cent. solution of carbolic acid and 10 parts of a concentrated alcoholic solution of fuchsin is used. The procedure to be followed is the same as that described under the Weigert-Ehrlich method.

When method 1 or 3 is used, however, it is unnecessary to stain the preparation for twenty-four hours, it being sufficient to place a few drops of the staining-fluid upon the cover-glass and to boil this for a few seconds over the free flame, when the specimen is further treated as described. In this manner excellent results may be obtained in a few minutes.

Stained according to one of these methods, the bacilli appear as rods measuring about 3 μ to 4 μ in length by 0.3 μ to 0.5 μ in breadth (Plate IX., Fig. 1). Usually they are not swollen at their extremities, but simply rounded off. They form homogeneous rods or may present within their stained bodies small round or ovoid granules placed end to end, which do not stain. They may also have a straight or a curved form, or the bacillus may appear to be doubled upon itself in the form of the letter S. The small, hyaline bodies in the bacilli have been regarded as spores.

The number of bacilli which may be found in a sputum varies greatly, and while in general it may be said that it is in direct ratio to the intensity of the disease, and may thus be considered as of some prognostic value, too much reliance should not be placed upon this statement, as in acute miliary tuberculosis, and in cases that have gone on to the formation of cavities the walls of which have become dry and cicatrized, the number found may be very small or they may be altogether absent. In an incipient case, on the other hand, in a little mucoid sputum the number may be very large.

Of the variations in number and form of the tubercle bacilli during the treatment with Koch's tuberculin it is unnecessary to speak here, as the prognostic significance attaching to such variations is as yet but imperfectly understood.

The diplococcus pneumoniæ. In doubtful cases the sputum may be examined for the diplococcus pneumoniæ, and it may be accepted at the present time that its presence in a given case, providing that

the clinical history and the physical signs point to a pneumonia, renders the diagnosis of acute *croupous* pneumonia very probable.

Method: Cover-glass specimens, prepared as indicated above, are placed for one or two minutes in a 1 per cent. solution of acetic acid; they are then removed, the excess of acetic acid drawn off by means of a pipette, when they are allowed to dry in the air and subsequently placed for several seconds in saturated aniline-water and gentian-violet solution, washed in water and examined. Rod-shaped diplococci (Plate IX., Fig. 2) surrounded by a capsule, which latter is considered as the characteristic feature of this microbe, will be seen in cases of acute croupous pneumonia.

The *bacillus of influenza* has already been considered in Chapter I. (p. 86).

In *whooping-cough* protozoa have been observed by Deichler; his observations, however, have not as yet been confirmed, and other observers attribute the disease to the presence of a bacillus described by Affanasiew.

FIG. 73.



Actinomyces. (MUSSER.)

Actinomycosis of the lungs may possibly be diagnosed from the presence of the characteristic granules and thread-like formations in the sputum. In America the disease is very rare.

The organism in question (Fig. 73) probably belongs to the species cladothrix, occupying a unique position among the pathogenic bacteria. Infection in man and animals (cattle and pigs) possibly occurs through ears of barley or rye, a supposition with which the observation that the disease frequently begins in the autumnal months accords.

In the pus derived from ulcerating actinomycotic tumors, in the sputum in cases of pulmonary actinomycosis, as also in the feces when the disease has attacked the intestines, small yellow granules will be observed, measuring from 0.5 to 2 mm. in diameter. If such a granule be examined microscopically, slight pressure being applied to the cover-glass, it will be seen to consist of numerous threads, which radiate out from a centre in a fan-like manner, and present club-shaped extremities.

The organism may be demonstrated in the following manner: Dried cover-glass preparations are stained for five to ten minutes with a saturated aniline-water and gentian-violet mixture (see p. 262), when they are rinsed in normal salt-solution, dried between filter-paper, and transferred for two or three minutes to a solution of iodo-potassic iodide (1 or 2 : 100). They are then again dried between layers of filter-paper, decolorized in xylol-aniline oil (1 : 2), washed in xylol, and mounted in balsam. The mycelium assumes a dark-blue color.

Non-pathogenic Organisms. Of the non-pathogenic microorganisms which may be observed in sputa but little is known.

Oïdium albicans may be observed in children, and is usually derived from the mouth.

Of other fungi which are occasionally observed in the sputum, there may be mentioned the aspergillus fumigatus and mucor corymbifer. Saccharomyces has been seen in the pus derived from pulmonary abscesses. *Sarcina pulmonalis* has been found at times, and especially in the so-called mycotic bronchial props occurring in putrid bronchitis. They are usually smaller than the sarcinæ ventriculi, but larger than the sarcinæ observed in the urine; they present the characteristic form of the latter. Various other bacilli and micrococci, in addition to those mentioned, are also found in sputa in large numbers, but have not as yet been closely studied, excepting the pus-organisms, which may be almost always demonstrated.

Crystals. Of crystals which may occur in sputa it will be necessary briefly to consider the crystals of Charcot-Leyden, hæmatoidin, cholesterin, margarin, tyrosin, oxalate of calcium, and triple phosphates.

Charcot-Leyden crystals (Fig. 67) were discovered in the sputa of patients suffering from asthma, and were supposed to stand in a causative relation to the disease. While the crystals are usually

present in this disease, they are also exceptionally met with in acute and chronic bronchitis, phthisis pulmonalis, etc.

Chemically, they appear to be phosphate of spermin, which has the composition C_2H_5N, and has been shown to be identical with ethylenimine. The phosphate crystallizes in the form of colorless, elongated octahedra, which vary very much in size, specimens being at times met with measuring from 40 μ to 60 μ in length. It is soluble with difficulty in cold water; insoluble in alcohol, ether, chloroform, and dilute saline solution; slowly soluble in acids and alkalies and even in ammonia. Its chemical composition and the fact that the same crystals are found in decomposing viscera, at times forming a complete covering of old anatomical preparations, render the supposition very probable that the substance in question is closely related to the ptomaïnes; the occurrence of the crystals may, indeed, be regarded as indicating a retrogressive metamorphosis of the cellular elements of a part. They are found not only in the sputa in the diseases mentioned, but also in leukæmic blood, in the mucus which has accumulated in a dilated biliary duct, and in normal and leukæmic bone-marrow. As has been stated, the crystals are also quite constantly met with in the feces in anchylostomiasis, anguilluliasis, and other helminthiases (see p. 208). Bizzozero found them in his own sputum at times when suffering from a simple acute bronchitis.

Hæmatoidin-crystals may be observed in the sputa following extravasation of blood into the lung. They frequently occur in the form of ruby-red columns or needles (Plate I., Fig. 2); amorphous granules, however, are also at times seen enclosed in the bodies of leucocytes, in which case they are probably always indicative of a previous hemorrhage, while the needles are generally observed when an abscess or empyema has perforated into the lungs. Chemically, hæmatoidin is derived from blood-pigment, and appears to be closely related to bilirubin.

Cholesterin-crystals are at times seen in the sputa in cases of phthisis, pulmonary abscess, and in general whenever old accumulations of pus have entered the lung from a neighboring organ. They are readily recognized by their characteristic form and chemical properties (see Feces, p. 195).

Fatty-acid crystals are frequently observed in cases of putrid bronchitis and gangrene of the lung, and also in cases of bronchiectasis and phthisis. They occur in the form of single needles or groups

of needles which are long and pointed. They are easily soluble in ether and hot alcohol; insoluble in water and acids. Chemically, they are probably composed of the higher fatty acids, such as palmitic and stearic acids.

Tyrosin-crystals have been observed in cases of putrid bronchitis, perforating empyema, etc. *Leucin* is likewise probably always present, occurring in the form of highly refractive globules. For the recognition of these bodies, particularly of tyrosin, a chemical examination should always be made, as crystals of the soaps of fatty acids have frequently been mistaken for those of tyrosin (see Urine).

Oxalate of calcium crystals are rarely seen. Fürbringer observed them in large numbers in a case of diabetes, and Unger found them in a case of asthma. They are readily recognized by their envelope-form, but they occur also in amorphous masses. They are soluble in mineral acids; insoluble in water, alkalies, organic acids, alcohol, and ether.

Triple phosphate crystals are also, though very rarely, seen, as in cases of perforating abscesses, etc. They are recognized by their coffin-lid shape and the readiness with which they dissolve in acetic acid.

Chemistry of the Sputum.

In addition to the substances described, sputum contains certain albumins, volatile fatty acids, glycogen, ferments, and various inorganic salts.

Among the albumins which have been observed in sputa may be mentioned serum-albumin, and especially mucin, which is often present in large amounts. In pneumonic and purulent sputa peptone also has been found.

In order to demonstrate the presence of serum-albumin the sputa are treated with dilute acetic acid, when the filtrate may be tested with potassium ferrocyanide, as described in the chapter on Urine. Serum-albumin is, of course, found in notable quantities in cases of œdema of the lungs.

The volatile fatty acids contained in sputa may be obtained by diluting these with water, acidifying with phosphoric acid, and distilling, when the distillate is further examined as described in the chapter on Feces. Acetic, butyric, propionic, and capronic acids have been found.

The fats or fixed fatty acids are extracted from the residue with

ether, and shaken with a solution of sodium carbonate in order to transform them into their sodium salts, when the ether is decanted and evaporated, leaving the fats behind.

Glycogen has been repeatedly demonstrated in sputa and may be detected by Brücke's method. (See p. 46.)

The sputa of gangrene of the lung and putrid bronchitis have been shown to contain a ferment resembling trypsin. In order to test for this ferment the sputa are extracted with glycerine, and the examination is continued as described in the chapter on the Examination of Cystic Contents.

The following are the inorganic salts which may be demonstrated in the sputum: The chlorides of sodium and magnesium, phosphates of the alkalies and the alkaline earths, viz., calcium and magnesium, the sulphates of calcium and sodium, carbonates, phosphate of iron, and silicates.

The Sputa in Various Diseases.

Acute Bronchitis. In the beginning of the disease the expectoration is small in amount, transparent, and contains very few cellular elements, constituting the so-called *sputum crudum* of the ancients. Microscopically there is evidence of the existence of a desquamative process extending toward the pulmonary alveoli to a greater or less extent, implicating especially the bronchi and trachea. Epithelial cells of various forms are found, and are probably derived from cells which were originally ciliated. Ciliated cells may occasionally be observed in perfectly fresh specimens, but are usually absent. Leucocytes in small numbers and alveolar cells are also seen. The presence of a few red blood-corpuscles is a common occurrence, and probably due to rupture of a capillary bloodvessel. Later on the sputa become more abundant, opaque, and assume a yellow color tending to green, owing to an increase in the number of leucocytes, while the other cellular elements diminish in number.

Chronic Bronchitis. The amount and consistence of the sputum in this condition vary greatly; it is most abundant in cases of so-called bronchorrhœa, in which whole mouthfuls may be expectorated at a time. The color is usually a yellowish-green, owing to the presence of numerous pus-corpuscles in various stages of degeneration. Microscopically enormous numbers of micro-organisms are found, especially in cases in which the sputa have remained for some

length of time in the bronchi. In addition some red corpuscles and epithelial cells are found; the latter, however, are not so abundant as in the first stage of an acute bronchitis. A few alveolar epithelial cells in a state of fatty and myeline degeneration will also usually be discovered, as in the case of acute bronchitis.

Putrid Bronchitis and Pulmonary Gangrene. The sputa of putrid bronchitis and pulmonary gangrene resemble each other so closely that it is only possible to distinguish between the two by the presence of débris of pulmonary parenchyma in the latter disease. In pulmonary gangrene an exquisite *sedimentation* is also quite commonly observed when the sputum is placed in a conical glass, the bottom layer being of a greenish-yellow or brownish color, containing a large amount of pus and small greenish or brownish masses, varying in size from that of a millet-seed to that of a bean. Fragments of lung-tissue are also quite frequently seen. Microscopically more or less degenerated leucocytes, crystals of ammonio-magnesium phosphate, and perhaps also of tyrosin and leucin, as well as hæmatoidin, are found. The greenish or brownish masses referred to contain amorphous masses of pigment, probably derived from hæmoglobin, at times elastic tissue, fatty-acid crystals, fat droplets, and innumerable micro-organisms, among which the *leptothrix pulmonalis* is quite conspicuous, and may be recognized by the violet or bluish color which it assumes when treated with Lugol's solution. Most important in the differential diagnosis between this affection and putrid bronchitis is the occurrence of elastic fibres arranged in an alveolar manner. The middle layer is whitish, transparent, and contains flakes of mucus in suspension. The superficial layer is frothy and of a dirty greenish-yellow color, the entire mass emitting an odor never to be forgotten.

Fibrinous Bronchitis presents all the characteristics of an ordinary chronic bronchitis; the sputa, however, contain in addition well-defined fibrinous casts, which have been described (see p. 250).

Bronchial Asthma. In this affection, and especially at the commencement of an attack, the expectoration is scanty, frothy, and grayish, or at times rose-colored, owing to an admixture of blood. Most characteristic are plug-like masses of a greenish-yellow or grayish color, containing spirals of Curschmann, Charcot-Leyden crystals, and a large number of eosinophilic and some basophilic leucocytes.

Pulmonary Abscess. The sputum as long as it is fresh does not emit a fetid odor, thus differing from that observed in cases

of gangrene of the lung. It consists almost entirely of pus; elastic fibres are present in abundance, as also brownish or yellow pigment-hæmatoidin. Fragments of lung-tissue enclosed in a mass of pus have at times been observed, together with fatty-acid and cholesterin crystals.

Abscess of the Liver with Perforation into the Lung. The sputa are of a reddish-yellow or reddish-brown color, viscid and muco-purulent, being frequently discharged in large amounts. Microscopically, pus-corpuscles, red blood-corpuscles, pigmented alveolar cells, often undergoing fatty degeneration, as well as elastic tissue and granular detritus, are found. The presence of actively moving amœbæ is, of course, most important from a diagnostic point of view, and is at the same time absolutely pathognomonic. Liver-cells, pieces of echinococcus-membranes, and hooklets may be observed in other cases.

Pneumonia. During the first and third stages a simple catarrhal sputum is observed which does not offer any special characteristics. During the second stage, however—*i. e.*, that of hepatization—the sputum is usually quite characteristic. Its color is then reddish-brown—the classical *rust-colored expectoration.* The sputum at the same time is generally so tenacious that the spit-cup can actually be inverted without losing a drop of its contents. Microscopically the following elements may be found: red corpuscles (to the presence of these the reddish color is principally due); at times, however, only a small number is observed, when the color is referable to hæmoglobin which has been dissolved out from the corpuscles, and in such cases but few, if any, corpuscles are found. Leucocytes are always present in considerable numbers. Fibrinous casts of the finer bronchioles may also be seen, and may, in fact, be visible to the naked eye. Alveolar epithelial cells, often loaded with granules of pigment, fat, and myeline, as well as others derived from the larger bronchi and the trachea, are also seen. Should abscess of the lung or gangrene complicate the case, the elements described above under these headings will be found in addition, the presence of elastic tissue being, of course, the most important.

Note may be taken at the same time of the occurrence of pneumococci, bearing in mind, however, that their presence is not absolutely pathognomonic. In doubtful cases, as indicated, their presence may be regarded as pointing to croupous pneumonia, providing that the clinical history and the physical signs are in accord.

Phthisis Pulmonalis. The appearance of the sputum in phthisis offers nothing that is characteristic, depending wholly upon the stage of the disease, its extent, the existence of complications, etc. In a general way it may be said that the sputa in incipient cases are usually small in amount, of a grayish-yellow color, and tenacious, the amount increasing gradually as the disease progresses, the largest quantities at this stage being expectorated in the morning upon rising. When well advanced the nummular sputa are seen. The macroscopic examination of the sputa of tubercular patients offers no characteristic features, the elements found being practically the same as those observed in cases of simple chronic bronchitis, with one exception—*i. e.*, the occasional admixture of blood, which is usually visible to the naked eye, but may vary greatly in amount. On the one hand, small specks or streaks of blood may be thus observed, while, on the other, the sputa may consist almost entirely of blood. The color of the sputum is, of course, largely influenced by the amount of blood present and the length of time that this has remained in the lungs, varying from a bright red to a dirty brown. In cases in which a considerable hemorrhage has taken place it is, of course, necessary to exclude every other source before attributing the hemorrhage to a pulmonary origin, and in cases of rupture of an aneurism, or long-continued hyperæmic conditions of the lungs so frequently observed in cases of heart-disease, in hemorrhage of gastric origin, and in hemorrhage from the mouth or pharnyx, it may at times be difficult to determine the source of the blood.

The diagnosis of phthisis is thus altogether dependent upon a microscopic examination, and, above all, upon the demonstration of the presence of tubercle bacilli and elastic tissue, which have both been considered in detail. In addition leucocytes, alveolar epithelial cells, hæmatoidin-crystals, and granules are met with, which latter may be present in large numbers if a hemorrhage have occurred some time before. If the process has gone on to the formation of cavities, various constituents are also observed pointing to putrefactive processes taking place in the lung.

Œdema of the Lungs. The sputa here are abundant, thin, liquid, and frothy, the color of the foam varying from white to a dirty reddish-brown. Chemically, such sputa consist almost entirely of transuded serum, and are hence particularly rich in serum-albumin. Microscopically, only a small number of leucocytes and a

variable number of red blood-corpuscles are found, the number of the latter, however, being scarcely large enough to account for the red color, which v. Jaksch ascribes to the presence of methæmoglobin.

Heart-disease. The sputa observed in chronic bronchitis the result of chronic heart-disease are characterized by the presence of so-called "heart-disease cells"—*i. e.*, alveolar epithelial cells containing numerous hæmatoidin-granules (Plate IX., Fig. 3). If, in consequence of the existence of chronic heart-disease, hemorrhagic infarcts have occurred in the lungs, the patient may at times expectorate numerous masses presenting a markedly red color, while later on—*i. e.*, after several days—these masses assume a brownish-red appearance, the sputum then presenting the characteristics noted some time after a hemorrhage.

The Pneumoconioses. Among the pneumoconioses, anthracosis, siderosis, chalicosis, and stycosis may be briefly considered. These conditions are interesting not only from a physiologic but also from a pathologic stand-point.

Anthracosis. To some extent particles of carbon may be found in the sputum of almost every individual, and especially in tobacco-smokers. The sputum in such cases is of a pearl-gray color, and is expectorated in larger or smaller masses, especially in the morning upon rising. Larger amounts are, of course, noted in miners and those who are brought into close contact with coal-dust. Microscopically particles of carbon and epithelial cells, especially of the alveolar type, as well as leucocytes, loaded with the pigment, are seen.

Siderosis. In siderosis the sputum presents a brownish-black color and contains cells enclosing particles of the oxide of iron. These may be readily recognized by treating the preparation with a drop of ammonium sulphide or potassium ferrocyanide solution in the presence of hydrochloric acid, when a black color on the one hand or a blue color on the other is obtained in the presence of iron.

Chalicosis. In chalicosis silicates are found in the sputa.

Stycosis. This condition was described for the first time by A. Robin in a man, aged seventy, who from his seventeenth year suffered from cough and frequent attacks of diarrhœa, and whose condition had been diagnosed as phthisis pulmonalis et intestinarum at various times, no examination having been made for tubercle bacilli. The patient died from acute pericarditis complicating an attack of acute

mono-articular rheumatism. Post mortem the lungs were found to be perfectly normal; the bronchial and anterior mediastinal glands, as well as the mesenteric glands, however, were completely solidified and composed almost wholly of calcium sulphate. The man, it was then found, had been working in plaster-of-Paris all his life, and the symptoms observed—viz., cough, expectoration, and diarrhœa—Robin is inclined to attribute to pressure of the solidified glands upon the bronchi and intestines.

CHAPTER VII.

THE URINE.

GENERAL CONSIDERATIONS.

This is not the place to enter into a discussion of the various hypotheses which have been advanced from time to time to explain the manner in which waste-material is removed from the body through the kidneys. It will be sufficient to state that, while the water and mineral constituents of the urine undoubtedly pass into the uriniferous tubules by a process of transudation, a selective glandular activity of the cells lining the convoluted tubules and the loop of Henle, at least, appears to be necessary for the elimination of the most important organic constituents.

As the physical characteristics of the urine, as well as its chemical composition, are influenced not only by the age and sex of the individual, but also by the character of the food ingested, the process of digestion, exercise, climate, temperature, race, etc., it is apparent that a quantitative analysis of any one urine, or even average figures, can give only an approximate idea of its composition. The reader is referred for information to the special paragraphs concerning the variations in the individual constituents observed in health. It is important, however, to note that, notwithstanding the fairly wide variations here observed, the composition of the blood, as already pointed out in a previous chapter, remains quite constant, showing the perfect manner in which the nervous system through the kidneys guards against an undue accumulation of what may be termed normal waste-products in the blood, and in virtue of which abnormal substances are also immediately eliminated. Moreover, as will be pointed out later on, a perfect mechanism appears to exist which prevents an undue accumulation of material in the blood that can hardly be regarded as waste. The presence of an amount of sugar in the blood exceeding 6 p. m., for example, appears to be invariably followed by glycosuria, and the introduction of excessive quantities of sodium chloride similarly and almost immediately leads to an elimination of the excess.

GENERAL CHARACTERISTICS OF THE URINE.

General Appearance.

Normal urine, just voided at an ordinary temperature, is either perfectly clear or but faintly cloudy, owing to the fact that the acid and normal salts present are all soluble in water. It may be stated, as a general rule, that whenever a urine *freshly passed* manifests a distinct cloudiness some abnormality must exist.

When allowed to stand for a time a light cloud is seen to develop, which gradually settles to the bottom, constituting the so-called *nubecula* of the ancients. Examined under the microscope this is found to contain a few round, granular cells, somewhat larger than normal leucocytes, the so-called *mucous corpuscles*, and a few pavement-epithelial cells, derived from the bladder or genital organs. Chemically the nubecula probably consists of traces of mucus.

When kept for twenty-four hours at an ordinary temperature some crystals of uric acid are frequently observed in addition to the above elements, usually presenting the so-called whetstone-form. If, however, the temperature at which the urine is kept approaches the freezing-point, the entire volume of urine becomes cloudy, owing to a precipitation of acid urates. As these are very much less soluble in cold than in warm water, they gradually settle to the bottom of the vessel, forming what is known as a *sediment*, while the supernatant fluid again becomes clear.

If kept for a still longer time exposed to the air at the temperature of the room, the entire volume of urine again becomes cloudy, owing to a diminution of its normal acidity, the result being a precipitation of ammonio-magnesium phosphate, calcium phosphate, and still later, when the urine has become alkaline, of ammonium urate.

Gradually a heavy sediment, containing these salts in addition to the constituents of the primitive nubecula, forms at the bottom of the vessel, the supernatant fluid, however, remaining cloudy. On microscopic examination it will be seen that this cloudiness is due to the presence of enormous numbers of bacteria.

The changes which take place in a normal urine, when allowed to stand at an ordinary temperature, may thus be tabulated as follows:

I. Urine clear, no sediment—reaction acid.

II. Urine slightly cloudy, owing to the development of the nubecula—reaction acid.

Nubecula { Mucous corpuscles, Pavement-epithelial cells.

III. Urine clear, the nubecula has settled—reaction acid.

Sediment { Mucous corpuscles, Epithelial cells, Uric-acid crystals, A few bacteria.

IV. Urine cloudy, owing to the precipitation of phosphates—reaction faintly acid.

V. Urine cloudy, owing to the presence of bacteria—reaction alkaline.

Sediment { Bacteria, Mucous corpuscles, Epithelial cells, Triple phosphates, Tri-calcium phosphate, Ammonium urate.

Color.

The color of normal urine may vary from a very light yellow to a brownish-red, the particular shade depending essentially upon the specific gravity, becoming lighter with a diminishing, and darker with an increasing density. Pathologically the same rule holds good, excepting the urines of diabetic patients, in which a very high specific gravity is generally associated with a very light color. The reaction of the urine also exerts a marked influence upon its color, an acid urine being more highly colored than an alkaline urine, which can be readily demonstrated by allowing a specimen of acid urine to become alkaline, and by treating an alkaline urine with dilute hydrochloric or acetic acid. At the same time it may be said that every urine darkens slightly on standing, the reaction remaining acid.

The various shades observed in normal urines may be grouped under the following headings:

1. Pale urines vary from a faint yellow to a straw-color.

2. Normally colored urines are of a golden or of an amber-yellow.

3. Highly colored urines present a reddish-yellow to a red color.

4. Dark urines vary between brownish-red and reddish-brown.

As these shades may occur in both normal and pathologic urines, definite conclusions cannot, as a rule, be drawn from mere inspection. A very pale urine simply indicates an excess of water, which may be physiologic, but may also be associated with such diseases as chronic interstitial nephritis, diabetes mellitus, diabetes insipidus, hysteria, and the various anæmias, and may also occur during convalescence from acute febrile diseases, while a highly colored urine, also occurring in health, may indicate the existence of some febrile disease. It may be stated, as a general rule, that a pale urine always excludes the existence of a febrile disease of any severity, and that the continued secretion of a very pale urine is usually associated with a certain degree of anæmia.

The normal color of the urine is probably owing to the presence of several pigments, which are most likely closely related to each other and to hæmatin.

In addition to these colors others may be observed at times, which are either pathologic or accidental—*i. e.*, due to the presence of certain drugs. The former are, on the whole, of greater importance to the physician than those mentioned above, as more definite conclusions can be drawn from their presence.

Most important among such pathologic pigments are those due:

1. To the presence of blood coloring matter. The color in such cases may vary from a bright carmine to a jet-black, the exact shade depending upon the quantity of blood coloring-matter present, upon any change that the blood may have undergone, either before or after being passed, and also upon the presence of the pigment in solution or contained in red corpuscles.

2. Those due to the presence of biliary coloring-matter. The color of the urine varies from a greenish-yellow to a greenish-brown.

3. A milky-colored urine is observed in cases of chyluria.

Among the accidental abnormalities in color, on the other hand, are those due to the presence of substances like carbolic acid and its congeners, santonin, etc.

As the recognition of the causes of such alterations, normal, pathologic, and accidental, largely depends upon a more detailed study of the individual pigments, this subject will be dealt with more fully further on (see Pigments).

Odor.

The odor of the urine is usually of little significance. Normally it resembles that of bouillon, and in some cases that of oysters; it is probably due to the presence of several volatile acids. The odor of urines undergoing decomposition is characteristic and has been termed "the urinous odor of urine," an ill-chosen term, this odor being always indicative of an *abnormal* condition.

The ingestion of asparagus, onions, oil of turpentine, etc., produces a characteristic odor which is of no significance.

Consistence.

Urine, while normally fluid and but slightly viscid, may in pathologic conditions acquire a marked degree of viscidity, which becomes especially apparent upon attempting its filtration; the liquid passes through the paper with more and more difficulty, finally clogging its pores altogether.

Quantity.

The normal quantity of the urine is subject to great variations, the amount eliminated in the twenty-four hours being influenced by the amount of fluid ingested, the nature and quantity of the food, the process of digestion, the blood-pressure, the surrounding temperature, sleep, exercise, body-weight, sex, age, etc.

It is easy to understand, then, why the figures given by different observers in different countries should vary considerably. Salkowsky, in Germany, thus gives 1500 to 1700 c.c. as the normal amount; v. Jaksch, in Austria, 1500 to 2000 c.c.; Landois and Sterling, in England, 1000 to 1500 c.c.; Gautier, in France, 1250 to 1300 c.c. In the United States the author has found an average secretion of from 1000 to 1200 c.c. in the adult male, and 900 to 1000 c.c. in the adult female. It is thus seen that the secretion of urine is greatest in Germany and Austria, where the body-weight and ingestion of liquids are greater than in England, France, and the United States.

Children pass less, but relatively more urine, considering their body-weight, than adults.

The female passes somewhat less than the male.

During the summer months, when a larger proportion of water is removed from the body through the skin and lungs than in cold weather, less urine is voided. The same occurs during repose,

more urine being passed during active exercise, and hence less during the night than during the day.

The amount of urine secreted in the different hours of the day varies greatly, reaching its maximum a few hours after meals. It decreases toward night, and reaches its lowest point in the first hours of the night, after which it begins to rise rapidly until 2 or 3 o'clock in the morning.

The ingestion of large amounts of liquid, of course, increases the daily amount considerably, and 3000 c.c. may be passed by a man in good health, while it may decrease to 800 or 900 c.c. when but little liquid is taken.

After the ingestion of much solid food the secretion of urine is temporarily diminished.

Water containing no salts appears to possess diuretic properties, as do also beer, wine, coffee, tea, etc.

The most important medical diuretics are digitalis, squill, broom, spirits of nitrous ether, juniper, urea, etc.

Pathologically the amount of urine varies within very wide limits. It may be exceedingly difficult, however, to determine in a given case whether or not the secretion be within physiologic limits. As a general rule, whenever less than 500 c.c. or more than 3000 c.c. are passed some abnormal condition exists, providing all other causes which might lead to the secreton of such an amount can be eliminated.

Clinically we speak of *polyuria* and *oliguria.*

Polyuria. Polyuria has been observed in many different diseases, and under such varied conditions that a classification is at present only warrantable upon a hypothetic basis, especially as the causes concerned in its production are mostly unknown.

As this condition is almost invariably associated with diabetes mellitus, its existence in any case should always excite suspicion and lead to a more detailed examination. The quantity of fluid eliminated in diabetes is usually dependent upon the amount ingested. The excretion of a proportionately large amount of fluid, however, does not necessarily follow the ingestion directly, and a retention of a large amount may occur, it having been shown that the diabetic patient excretes liquids with greater difficulty than the healthy subject. At the same time it should be borne in mind that the polyuria in diabetes is not necessarily continuous, and that periods during which a normal or even a subnormal amount of urine

is observed may alternate with true polyuria. From 2 to 26 or even 50 liters may be passed within twenty-four hours. Intercurrent diseases of a febrile character may modify the amount very materially and cause the elimination of a normal or subnormal amount of urine.

The cause of the polyuria occurring in diabetes mellitus is at present unknown. The ingestion of large amounts of liquids, of course, leads to a correspondingly large elimination, and the existing polydipsia could, hence, be made responsible for the polyuria, and the latter be the result of an increased stimulation of the thirst-centre, possibly owing to the presence of some abnormal constituent of the blood. The polydipsia, however, may also be the result of a primary polyuria.

The polyuria associated with the resorption of large pericardial, pleural, ascitic, and subcutaneous effusions is more readily understood, although the primum mobile may be unknown, depending in such cases entirely upon the presence of excessive quantities of fluid in the bloodvessels.

A form of polyuria, which has been termed "epicritic polyuria," is quite frequently observed during convalescence from acute febrile diseases, and is of some prognostic importance. Its occurrence in a given case is regarded by many as a good omen, especially in typhoid fever; still it must not be forgotten that a polyuria may occur after the subsidence of the fever, and be followed by a considerable degree of oliguria, and in some cases may precede death. A polyuria of this kind probably always indicates the elimination of waste-products which had accumulated in the blood during the course of the disease, and may, at the same time, to some extent, be due to the presence of retained water.

Second in constancy is the polyuria associated with granular atrophy of the kidneys, constituting one of the most important symptoms of the disease. Cases have been reported in which as much as 10,000 c.c. of urine were secreted in the twenty-four hours, although 2000 to 4000 c.c. probably represent the usual amount in such cases. Polydipsia exists at the same time, and the explanation of the polyuria again becomes a very difficult matter. The explanation usually given is based upon the following considerations:

In granular atrophy of the kidneys large tracts of renal parenchyma are destroyed, the result being a diminution in the area

of glandular material, which in itself could lead to a diminished secretion of urine. The coexisting cardiac hypertrophy, however, by raising the blood-pressure in the kidneys, is supposed to counterbalance the renal deficiency and even lead to an increase in the amount of urine. There seems to be some doubt as to the correctness of such an explanation, as the existence of hypertrophy of the left ventricle in the absence of glandular disease of the kidneys by no means leads to a degree of polyuria at all comparable to that observed in this disease. It is possible that while cardiac hypertrophy in itself may be *one* of the causative factors, still another may be vicarious action of the sound glandular elements. If such be the correct explanation, the coexisting polydipsia is merely secondary. This, however, can be regarded only as an hypothesis, and the diminished renal secretion associated with a gradually developing cardiac dilatation cannot be upheld as an absolute proof of its correctness.

Polyuria, furthermore, has been observed in the most diverse diseases of the nervous system, both functional and organic, illustrating the influence of the nerve-centres upon renal activity, leaving the ultimate cause an open question. It is thus frequently observed both as a transitory and a permnent symptom in cases of hysteria. Large quantities of a very pale urine are secreted after the occurrence of severe hysterical seizures, but the same may be observed throughout the course of the disease. A similar condition is frequently seen in neurasthenia, migraine, chorea, and epilepsy.

On the whole, it may be said that a *paroxysmal* polyuria in nervous diseases is associated with functional derangements, while a *continuous* polyuria appears to be connected rather with true organic changes. It has been observed in certain cases of tabes, cerebro-spinal and spinal meningitis, the first stage of general paresis, tumors affecting the medulla, the cerebellum, and spinal cord, in injuries affecting the central nervous system, in Basedow's disease, etc.

Cases of idiopathic diabetes insipidus most probably must be classified under this heading; enormous quantities of urine may be secreted in this disease, being equalled only by cases of diabetes mellitus, and at times reaching 43 liters per diem.

Oliguria. Oliguria is, on the whole, more frequent than polyuria, being met with in almost all conditions associated with a lowered blood-pressure. First in order stand those cases of cardiac

disease in which compensation has failed, whether the cardiac weakness be primary or occurring secondarily to other diseases—*i. e.*, pulmonary, hepatic, and renal.

The oliguria observed in the so-called continued fevers, notably typhoid fever, is probably also referable to the existence of cardiac weakness. It should be remembered, however, that a larger proportion of water is eliminated through the skin and lungs than normally, and that a retention of fluids also undoubtedly occurs in fevers, not referable to cardiac weakness, while still other factors may be concerned in its production.

The oliguria occurring in acute nephritis and in chronic parenchymatous nephritis in all probability depends largely upon mechanical causes, the increased intra-canalicular resistance in the form of desquamated epithelium and tube-casts, as well as the pressure of the exudate upon the bloodvessels obstructing the passage of urine, while the functional activity of the diseased glandular elements is at the same time lowered.

Upon mechanical causes, also, depend all those cases of oliguria associated with the presence of a stone or tumor, which pressing upon any part of the urinary tract impedes the flow of urine. Oliguria may occur as a nervous manifestation in connection with puerperal eclampsia, lead-colic, hysteria, psychic depressions, preceding and during epileptic seizures, etc. Whenever there is a diminution in the amount of bodily-fluids oliguria is also observed, this being particularly marked in cholera and following severe hemorrhages.

Obstruction to the flow of blood in the vena cava or liver, leading to an increase of venous pressure and a decrease of arterial pressure in the kidneys, likewise results in oliguria, as is seen in atrophic hepatic cirrhosis, acute yellow atrophy, thrombosis of the vena cava and the renal vein, or in cases in which pressure is exerted upon these by tumors, ascitic fluid, etc.

In any case the oliguria may go on to complete anuria, which condition not infrequently precedes death. Anuria may, however, also occur independently of a pre-existing oliguria, notably so in cases of hysteria.

Specific Gravity.

The specific gravity of normal urine varies between 1.015 and 1.025, corresponding to 1200 to 1500 c.c., the normal amount of

urine voided in twenty-four hours. Pathologically a specific gravity of 1.002 on the one hand and 1.060 on the other may occur, depending upon the amount of solids and fluids present, increasing as the solids increase, the amount of urine remaining the same, and decreasing as the amount of fluid increases, the solids remaining the same. The specific gravity is thus an index, in a general way, of the metabolic processes taking place in the body.

The necessity of determining the specific gravity of the total amount of urine voided in a given case, and not that of an individual specimen passed during the twenty-four hours, becomes apparent upon considering the variations which can occur in the solids and liquids during the day. The ingestion of large amounts of water or beer would, of course, result in the passage of a correspondingly large quantity of urine within the next few hours, containing but a small amount of solids, and hence presenting a low specific gravity. It would be erroneous to infer a diminished excretion of solids for the day from such an observation, as succeeding specimens would in all probability be passed presenting a higher specific gravity. An observation, moreover, made upon a specimen taken from the collected quantity of urine of the twenty-four hours can only then convey a correct idea if the quantity falls within the normal limits. If this should not be the case, the volume of urine observed must first be reduced to the normal and the specific gravity then taken.

Supposing a known quantity of common salt to be dissolved in 1000 c.c. of water, so that the resulting specific gravity be 1.24, by doubling the amount of salt and water the specific gravity would still remain the same, while the amount of salt would actually be twice as large as at first. In order to obtain the specific gravity indicating the true amount of solids present it would be necessary to concentrate the fluid to 1000 c.c. The specific gravity being inversely proportionate to the amount of fluid secreted, the necessary correction is made according to the following formula:

$$\text{Sp. gr.} = \frac{qd}{N}$$

in which Sp. gr. indicates the specific gravity to be determined, q the amount of urine actually passed, d the specific gravity observed, and N the normal amount of urine—*i. e.*, 1200 c.c.

Example: A patient has passed 3000 c.c. of urine in the twenty-

four hours with a specific gravity of 1.017; this is corrected according to the above formula:

$$\text{Sp. gr.} = \frac{3000 \times 17}{1200} = 1.042.$$

From the specific gravity the amount of solids can be calculated with sufficient accuracy for clinical purposes by multiplying the last two decimal points by 2, the number obtained indicating the amount of solids in 1000 c.c. of urine.

To illustrate the necessity of either indicating the total amount of urine passed within the twenty-four hours, and of taking the specific gravity from this collected urine, or of correcting the specific gravity as shown above (which latter method is far preferable, and should be generally adopted in urinary reports), the following case may be supposed:

A "specimen" of urine is taken from a man, presenting a specific gravity of 1.002; by multiplying the 2 by 2, the person would be supposed to pass 4 grammes of solids in every 1000 c.c. of urine. Had the specific gravity been observed in the total amount of urine passed in the same twenty-four hours, it would have been found to be 1.012, the man having passed 3000 c.c. of urine; by multiplying 12 by 2, 24 grammes of solids would have represented the amount in every 1000 c.c.—*i. e.*, $24 \times 3 = 72$ grammes *in toto*. The same result would have been reached by correcting the specific gravity of 1.012 for the normal amount of urine.

The first calculation then would have indicated a considerable deficit as compared with the second.

The following rules for practice may thus be stated:

1. Whenever the specific gravity only is to be indicated in a urinary report it should always be the corrected one; if this is not done, the amount of urine should be stated in every case.

2. The specific gravity should always be taken from a specimen of the collected urine of the twenty-four hours, and never from a specimen *ad libitum*.

From the rule that the specific gravity of a urine is inversely proportionate to the amount of fluid eliminated it must follow that whatever causes produce oliguria will also produce a high specific gravity, while all those causes which will produce a polyuria will similarly produce a low specific gravity, with the following exceptions:

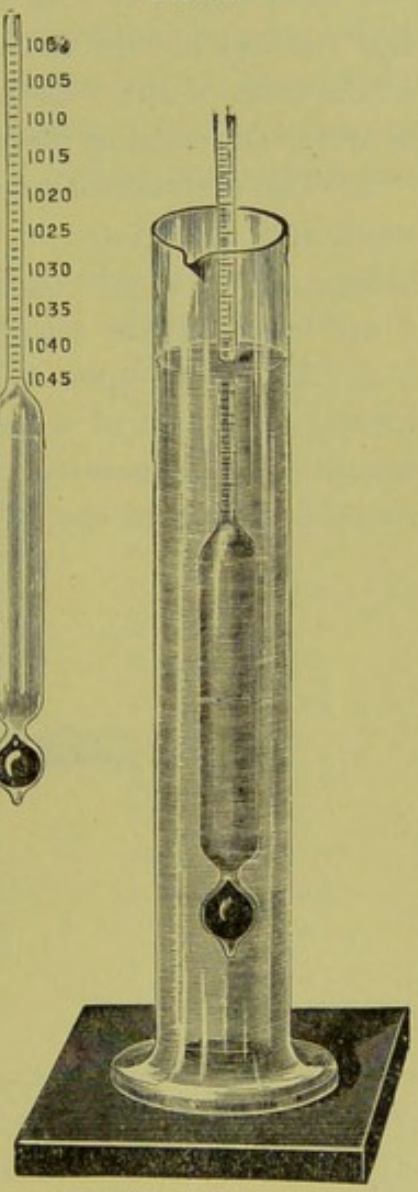
1. A diminished amount of urine with a lowered specific gravity occurs in many chronic diseases and toward the fatal termination of acute diseases, indicating a defective elimination of solids.

2. The same may be observed in certain cases of œdema.

3. Following copious diarrhœa, vomiting, and sweating.

4. A high specific gravity is associated with polyuria in diabetes mellitus.

Fig. 74.



Urinometer. (W. Simon.)

Unfortunately the determination of the specific gravity and the solids contained in urines does not furnish as valuable information in many cases as would be *à priori* expected, organic constituents in general being possessed of a lower specific gravity than the inorganic, among which the chlorides are especially important, as they occur in considerable amount in normal urine. It thus not infrequently happens that the nitrogenous constituents are considerably increased, while the specific gravity is relatively low, owing to the absence or a diminution in the amount of chlorides. In other words, while the specific gravity may be regarded as a fair index of the total amount of solids excreted, its increase or decrease furnishes no information as to the nature of the constituents causing such a change.

Determination of the Specific Gravity. The specific gravity of urine is most conveniently determined by means of a hydrometer indicating degrees varying from 1.002 to 1.040. Such instruments constructed especially for the examination of urine are termed *urinometers* (Fig. 74). A good instrument should have a stem upon which the individual divisions are at least 1.5 mm. apart, and in which each division should correspond to a half degree.

Urinometers may also be purchased which are provided with a thermometer, a matter of great convenience. Every instrument

should be carefully tested by comparison with a *standard* hydrometer.

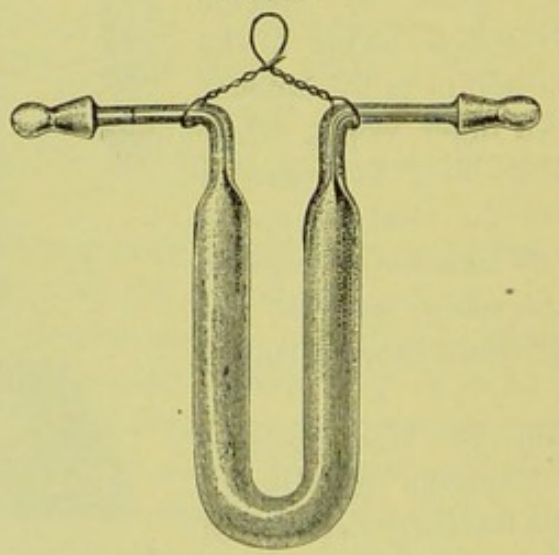
In order to determine the specific gravity in a given case a cylindrical vessel is nearly filled with urine and the urinometer *slowly* inserted, the reading being taken at the lower meniscus by bringing the eye on a level with it as soon as the instrument has come to a rest.

Precautions. 1. The urinometer must be given ample room, and the reading should never be taken when the instrument adheres to the sides of the vessel, as owing to capillary attraction it is otherwise raised, causing the reading to become too high.

2. The instrument must be perfectly dry and clean before being used, and should never be allowed to "drop" into the urine, as otherwise the weight of the instrument being increased by adhering drops of water, the reading becomes too low.

3. Any foam upon the surface of the urine should first be removed by means of a piece of filter-paper, as it interferes with the accuracy of the reading; bubbles of air adhering to the instrument, thereby raising it, should be carefully removed with a feather.

FIG. 75.



The pyknometer.

4. The specific gravity should always be determined in specimens taken from the twenty-four-hour urine, and corrected according to the formula given above.

5. If the quantity of urine is too small to determine its specific gravity with a urinometer, the following method may be advantageously employed:

About 50 c.c. of urine are measured off, preferably by means of a burette, into a small bottle provided with a ground-glass stopper or into a pyknometer like the one pictured in Fig. 75, and accurately weighed. The weight of the urine divided by its volume gives the specific gravity, which must, however, be corrected for the temperature of the urine. If accuracy be required, such a correction should be made in every case, as the specific gravity increases or decreases by 1° for every 3° C. above or below the point for which the instrument is registered, viz., 15° C. According to Bouchardat and Mercier, this method is not strictly accurate, and the following table has been constructed by which the proper corrections can readily be made:

Temperature.	Urine normal.	Glycosuric urine.	Temperature.	Urine normal.	Glycosuric urine.
0°	0.9	1.3	18°	0.3	0.6
1	0.9	1.3	19	0.5	0.8
2	0.9	1.3	20	0.9	1.0
3	0.9	1.3	21	0.9	1.2
4	0.9	1.3	22	1.1	1.4
5	0.9	1.3	23	1.3	1.6
6	0.8	1.2	24	1.5	1.9
7	0.8	1.1	25	1.7	2.2
8	0.7	1.0	26	2.0	2.5
9	0.6	0.9	27	2.3	2.8
10	0.5	0.8	28	2.5	3.1
11	0.4	0.7	29	2.7	3.4
12	0.3	0.6	30	3.0	3.7
13	0.2	0.4	31	3.3	4.0
14	0.1	0.2	32	3.6	4.3
15	0.0	0.0	33	3.9	4.7
16	0.1	0.2	34	4.2	5.1
17	0.2	0.4	35	4.6	5.5

Example: Supposing the specific gravity to have been 1.030 at a temperature of 20° C., it would be necessary to add 0.9 to the 1.030, making this 1.0309; at a temperature of 10° C., it would similarly be necessary to subtract 0.5.

Determination of the Solid Constituents. As indicated above, the amount of solids can be calculated with a degree of accuracy sufficient for clinical purposes by multiplying the last two figures of the specific gravity by 2, the number obtained indicating the amount of solids in every 1000 c.c. of urine. If greater accuracy be required, the following method may be employed:

Five c.c. of urine, accurately measured, are placed in a watch-

crystal containing a little dry sand (sand and crystal having been previously weighed); this is placed over a dish containing concentrated sulphuric acid, and under the receiver of an air-pump, which has been made perfectly air-tight by thoroughly lubricating the ground-glass edge of the bell with mutton tallow and applying the bell with a slightly grinding movement to the ground-glass plate. The receiver is now exhausted and the urine allowed to remain in the vacuum for twenty-four hours, when the bell is again exhausted and left for twenty-four hours longer; at the end of this time the crystal is weighed, the difference between the two weights obtained indicating the amount of solids in 5 c.c. of urine, from which the percentage and total amount are readily calculated.

The slight loss of ammonia which results when this method is employed scarcely affects the accuracy of the result.

REACTION.

The reaction of the twenty-four-hour urine is, as a rule, acid; individual specimens, passed in the course of twenty-four hours, may be either alkaline, acid, or amphoteric.

When a mixture of several different acids is brought into contact with a mixture of alkalies, the acids combine with the alkalies according to the degree of affinity which exists between the two and the amount present of each. Upon the excess of acids over alkalies, and *vice versa*, depends the resulting reaction. If the alkalies are not sufficient in amount to saturate the acids, an acid reaction will result, while an insufficient amount of acid will give rise to an alkaline reaction. The same principle holds good for the acids and alkalies giving rise to the salts present in the urine. As here the alkaline substances are not present in sufficient amount to saturate the acids, which can readily be seen from the following table, the acid reaction of normal urine is explained:

HCl	SO_3	P_2O_5	K	Na	NH_3	Ca	Mg
10.1265	2.3157	3.0334	2.5830	5.4780	0.5977	0.0405	0.0880
6.3811	1.3315	0.9827	1.5194	5.4780	0.8087	0.0233	0.0843

The figures in the first column indicate the average daily amount of the inorganic acids and alkalies present in the urine of twenty-four hours, and the figures in the second column their equivalents

in terms of Na, that of P_2O_5 having been estimated as NaH_2PO_4. From this it is seen that the acid equivalents, 8.6953, exceed the alkaline equivalents, 7.9137, by 0.7816 gramme of Na. There are present then in the urine, in addition to the normal salts of the monobasic acids, acid salts and especially diacid sodium phosphate, NaH_2PO_4. To the latter the acidity of the urine is due. If, on the other hand, the alkalies exceed the acids in amount, an alkaline urine will result, which may occur physiologically under various conditions.

The so-called amphoteric reaction may be observed at times when the diacid and neutral sodium phosphates, NaH_2PO_4 and Na_2HPO_4, are present in a certain definite proportion, the urine changing the color of red litmus-paper to blue, and *vice versa*.

A neutral urine is never observed under normal conditions. Moreover, the presence of a free acid is not possible, as it would immediately cause the formation of ammonia from the tissues of the body, and, finally, the urea in the urine would combine with any free acid which might be present.

The question now arises, Whence does the acidity of the urine result, and what are the ultimate causes which will produce an alkaline and an amphoteric reaction?

These are problems which as yet await a final decision. Our present ideas, however, may be formulated as follows: In the metabolism of the body-tissues acids are constantly produced, chief among these being sulphuric acid, resulting from albuminous decomposition, and hydrochloric acid, which at a certain period of digestion is reabsorbed into the blood together with peptones. As the alkalinity of the blood is due to neutral sodium phosphate and sodium carbonate, these salts are attacked by the free acids as soon as they enter the blood, the result being the formation of acid salts, and, as the latter diffuse more readily through an animal membrane than alkaline salts, the secretion of an acid urine from the alkaline blood is in part explained.

Nevertheless, it is impossible to exclude a certain specific action on the part of the glandular elements of the kidneys, as otherwise the secretion of all glands, supposing this to depend upon a process of filtration or diffusion only, would necessarily be acid.

As the alkalinity of the blood increases the acidity of the urine decreases, until finally an alkaline urine results. The degree of the alkalinity of the blood, however, depends essentially upon the

nature of the food and the secretion of the gastric juice, viz., hydrochloric acid. The ingestion of vegetable food rich in salts of organic acids, which become oxidized in the body to the carbonates of the alkalies, will result in the passage of an alkaline urine, as the alkalies thus formed when absorbed into the blood are more than sufficient to neutralize completely all the acids present, the elimination of neutral sodium phosphate alone taking place. In the case of animal food the reverse holds good. The alkaline carbonates here formed not being sufficient to neutralize the excess of acids, diacid phosphate of sodium is eliminated in large quantity.

An amphoteric urine results whenever the elimination of neutral and acid sodium phosphate is equal; such an occurrence must, therefore, be regarded as being more or less an accident.

As the alkalinity of the blood is increased during the secretion of the acid gastric juice, it may frequently happen, especially following the ingestion of a large amount of food, that an alkaline urine is voided. If this does not take place, the acidity of the urine is at least diminished, to increase again during the process of resorption of hydrochloric acid and peptones. The statement so generally made in text-books, that the urine secreted after a meal is alkaline, is not strictly correct; in a series of observations made by the author upon human subjects an alkaline urine was observed in only 20 per cent. of the cases examined.

It may then be stated that an alkaline urine will result under physiologic conditions whenever the alkaline salts present in the food are sufficient to neutralize all the acids formed, as occurs in the case of a vegetable diet, and, furthermore, whenever the period of gastric secretion is lengthened.

If an acid urine be allowed to stand exposed to the air for a certain length of time, its degree of acidity gradually diminishes, the reaction finally becoming alkaline. At the same time the urine becomes cloudy and deposits a sediment, consisting of ammoniomagnesium phosphate, $MgNH_4PO_4 + 6H_2O$, neutral calcium phosphate, $Ca_3(PO_4)_2$, and still later of ammonium urate, $C_5H_2(NH_4)_2N_4O_3$, in addition to the constituents of the primitive nubecula—*i. e.*, a few mucous corpuscles and pavement epithelial cells. The entire volume of urine, moreover, remains cloudy, owing to the presence of innumerable bacteria. The odor becomes extremely disagreeable, and distinctly "urinous." In short, "ammoniacal decomposition" has occurred. This has been shown to depend upon the action

of certain bacteria, notably the micrococcus ureæ and the bacterium ureæ, present in the air, these organisms causing the decomposition of the urea found in every urine, with the formation of ammonium carbonate, according to the following equation:

$$CO(NH_2)_2 + 2H_2O = (NH_4)_2CO_3$$
$$(NH_4)_2CO_3 = 2NH_3 + H_2O + CO_2.$$

Here as elsewhere, however, it is not the bacterium which directly produces the result, but a bacterial product, and in this case an enzyme.

An alkaline urine, the akalinity, however, not being due to ammoniacal fermentation, but to causes already mentioned, may, of course, undergo the same change as an acid urine; but it is necessary to distinguish sharply between these two varieties of alkaline urines, the recognition of the cause of the alkalinity being very often most important in diagnosis. The distinction is readily made by fastening a piece of sensitive red litmus-paper in the cork of the bottle containing the urine. If the alkalinity of the urine be due to the presence of ammonia, the litmus-paper will turn blue, but soon changes to red again when exposed to the air; while a urine, the alkalinity of which is due to the presence of fixed alkalies, will turn red litmus-paper blue only when immersed directly in the urine, the change in color at the same time persisting.

As ammoniacal decomposition can also occur within the urinary passages, it is important whenever an alkaline reaction due to the presence of ammonia is observed to test the urine at once upon being voided, or, still better, to procure a portion with the catheter. Such urines are frequently seen in cases of cystitis the result of paralysis, urethral stricture, gonorrhœa, etc.

An intensely acid reaction is observed in almost all concentrated urines, especially in fevers, in certain diseases of the stomach associated with a diminished or suspended secretion of hydrochloric acid, in gout, lithiasis, acute articular rheumatism, chronic Bright's disease, diabetes, leukæmia, scurvy, etc. Whenever a very acid urine is secreted for a considerable length of time the possibility of renal irritation and the formation of concretions should be borne in mind.

An alkaline urine, the alkalinity of which is not owing to the presence of ammonia, but to a fixed alkali, is observed in certain cases of debility, especially in the various forms of anæmia, following the resorption of alkaline transudates, the transfusion of blood,

frequent vomiting, a prolonged cold bath, etc. It may also be due to the ingestion of certain medicines, viz., salts of the organic acids and alkaline carbonates, the former being transformed into the latter, as has been mentioned. An increase in the degree of acidity may similarly take place after the ingestion of mineral acids.

It is apparent then that an increase or a decrease in the acidity of the urine cannot be immediately attributed to a certain disease. Conclusions can only be drawn if all other causes, both physiologic and pathologic, can be eliminated.

Determination of the Acidity of the Urine. The old method of titrating a certain amount of urine with a decinormal solution of sodium hydrate has now been abandoned and replaced by that of Freund. This is essentially based upon the observation that the acid reaction of the urine is referable exclusively to diacid phosphates.

Freund's method. In 50 c.c. of urine the total amount of phosphoric acid is estimated as described on p. 312. The result is termed T. In a second portion of 50 c.c. the monacid phosphates M are then precipitated with a normal solution of barium chloride—*i. e.*, one containing 122 grammes of the crystallized salt in 1000 c.c. of water—10 c.c. being added for every 100 mgrms. of the total amount of phosphoric acid found. After the addition of the barium the mixture is diluted to 100 c.c., filtered, and the phosphoric acid estimated in 50 c.c. of the filtrate. The result obtained is termed D. Owing to the fact that the monophosphates are not only precipitated upon the addition of the barium chloride, but also a small amount of normal phosphates, and that a small amount of diacid phosphate is formed at the same time and passes into solution, an error is thus incurred. This, however, remains constant, and amounts to 3 per cent. in favor of the diacid phosphates. As the total amount of phosphoric acid is subject to fairly wide variations, even in health, being increased especially after meals, it is best to calculate the relative proportion of T to D for 100 c.c. of urine, and then to determine the absolute degree of acidity for the twenty-four hours. Figures are thus obtained which are directly comparable with one another.

Example: Supposing that T amounted to 0.386 gramme for 100 c.c. of urine, and D to 0.338 gramme. Three per cent. of D would then have to be deducted for reasons just given, and added to M,

making the true value of D 0.3368. The relative proportion of T to D would then be 87.5, as determined according to the equation :

$$0.386 : 0.3368 : : 100 : x, \text{ and } x = 87.5.$$

Supposing, further, that the total amount of urine was 2000 c.c., the total acidity for the twenty-four hours would correspond to 1740, according to the equation $100 : 87.5 : : 2000 : x$, and $x = 1740$, and the total acidity per hour to $\frac{1740}{24}$, *i. e.*, 72.5.

The results obtained can also be expressed in terms of hydrochloric acid, 100 mgrms. of the diacid phosphates corresponding to 102.8 mgrms. of hydrochloric acid. This mode of indicating the total acidity of the urine would actually be the better. If the urine should be alkaline and cloudy, the sediment is first dissolved by carefully adding a one-tenth or one-fourth normal solution of hydrochloric acid, the amount added being then deducted from the total acidity. Should negative values be found, these could be expressed in terms of sodium hydrate.[1]

With this method a complete revision of all the work previously accomplished will be necessary, and the results given above have reference only to the old method of titration with a one-tenth normal solution of sodium hydrate.

An increase in the acidity of the urine upon standing has been repeatedly observed, and is probably due to the formation of new acids from pre-existing acid-yielding substances, such as certain carbohydrates, alcohol, etc., which have undergone fermentation. This phenomenon is frequently observed in the urine of diabetic patients.

A decrease in the acidity of normal urine upon standing is, on the other hand, the rule, owing to decomposition of urate of sodium by the acid phosphate of sodium, acid urate of sodium and, later on, uric acid resulting, which are thrown down as a sediment in consequence of the diminished acidity of the urine, and which, hence, no longer influences its reaction. This is shown in the equations:

I. $NaH_2PO_4 + C_5H_2Na_2N_4O_3 = Na_2HPO_4 + C_5H_3NaN_4O_3$
II. $NaH_2PO_4 + C_5H_3Na\ N_4O_3 = Na_2HPO_4 + C_5H_4N_4O_3$.

[1] The urine is carefully guarded against ammoniacal decomposition by the addition to the first portion voided of from 20 to 25 c.c. of a solution of 10 grammes of oil of peppermint in 100 c.c. of alcohol.

THE CHEMISTRY OF THE URINE.

General Chemical Composition of the Urine. It has been pointed out that, owing to the influence exerted upon the chemical composition of the urine by many factors, such as age, sex, temperature, digestion, exercise, etc., the figures given by different observers to express the absolute quantities of the various ingredients eliminated in the twenty-four hours vary within fairly wide limits. A general idea may, however, be formed of these constituents, and their average amounts under physiologic conditions, from the following table:

COMPOSITION OF NORMAL HUMAN URINE OF AVERAGE SPECIFIC GRAVITY, *i.e.*, 1.020.[1]

	Per liter.	Per 24 hours.
Water	956 grms.	1243 grms.
Organic matter	28–30 "	36–38 "
Urea	25.37 "	33.00 "
Uric acid	0.40 grm.	0.52 grm.
Hippuric acid	0.50 "	0.65 "
Creatin and creatinin	0.80 "	1.0 "
Xanthin bases	0.04 "	0.052"
Coloring-matter and extractives	4.5 grms.	5.850 grms.
Volatile fatty acids, Oxalic acid, Phenol sulphate, Indoxyl and skatoxyl sulphate, Paraoxyphenylacetic acid, Sugar, Mucus, pepsin, Fatty acids, Glycerine-phosphoric acid	Very little.	
Mineral matter	16–17 grms.	20–21 grms.
Sodium chloride	10.5 "	13.65 "
Alkaline sulphates	3.1 "	4.03 "
Earthy phosphates	0.76 grm.	0.98 grm.
Alkaline phosphates	1.43 "	1.86 "
Silicic acid, Nitric acid, Gases (O, CO_2, N)	Traces.	

In pathologic conditions the following substances may also be found in solution: Albumin, globulin, hemialbumose, peptone, mucin (nucleo-albumin), glucose, lactose, inosit, dextrin, biliary constituents, viz., bile-acids and bile-pigments, blood-pigment,

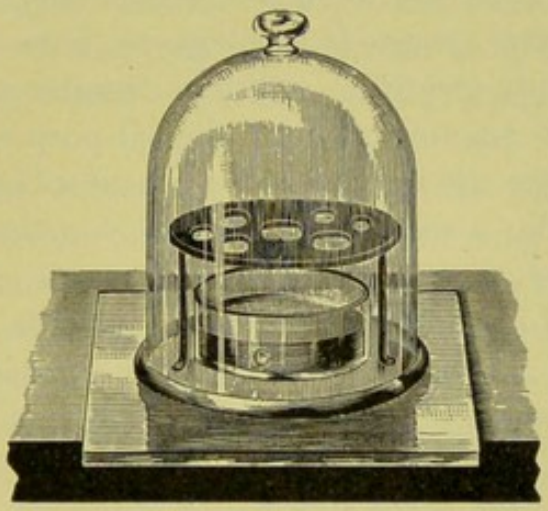
[1] Taken from Gautier.

urorubrohæmatin, urorubrofuscin, melanin, leucin, tyrosin, oxybutyric acid, allantoin, fat, lecithin, cholesterin, acetone, alcohol, Baumstark's substance, urocaninic acid, cystin, and sulphuretted hydrogen.

Quantitative Estimation of the Mineral Ash of the Urine. In order to estimate the amount of mineral ash in the urine the following method may be employed:

Fifty c.c. of urine are evaporated to dryness in a weighed porcelain dish at a temperature of 100° C., and then heated, while covered, over the free flame until gases cease to be evolved, care being taken not to heat too strongly in order to prevent sputtering. The residue

FIG. 76.



Desiccator. (W. SIMON.)

is taken up with distilled boiling water, and, after standing, filtered through a Schleich and Schüll's filter, the weight of the ash contained in this being known. The dish and the contents of the filter are well washed with hot water. Filtrate and washings are set aside and the dish and filter dried in the oven at 115° C. The filter is now placed in the dish and slowly incinerated. As soon as the ash has turned white the filtrate and washings are placed in the same dish, evaporated at 100° C., and then carefully heated over the free flame. Upon cooling in the desiccator (Fig. 76) the dish with its contents is weighed, the difference between its present and previous weight indicating the quantity of ash contained in 50 c.c. of urine.

Precautions: 1. Care should be taken to allow the dish to become faintly red only for a moment, since some of the chlorine is otherwise volatilized. Some phosphoric acid also may be volatilized, and too strong a heat, moreover, may cause the transformation of

sulphates into sulphides, the organic material present acting as a reducing agent.

2. If the organic ash is not completely incinerated, it is best to allow the dish to cool and then to moisten the ash with a few drops of distilled water, it being thereby brought into closer contact with the surface of the dish.

The Chlorides.

The chlorides excreted in the urine are derived from the food. As they are thus present in a much larger amount than all other inorganic salts combined, and in quantity more than sufficient to supply the needs of the body-economy, the relatively large amount of chlorides found in the urine under physiologic conditions, as compared with the other inorganic constituents, is readily explained.

Of the alkalies in the urine, sodium in combination with chlorine exists in greatest amount, and for clinical purposes it is most convenient to calculate the total quantity of chlorides found in terms of sodium chloride; a small proportion of chlorine also occurs combined with potassium, ammonium, calcium, and magnesium.

From 11 to 15 grammes of sodium chloride, representing the total quantity of chlorine, are normally eliminated in the twenty-four hours, the amount depending, of course, directly upon that contained in the food ingested. If the amount of nourishment is diminished, a decrease in the elimination of the chlorides is observed. If this be carried to the point of starvation, the chlorides disappear almost entirely from the urine, the traces remaining being derived from the body-fluids. The latter retain tenaciously a certain amount, which differs but slightly from that normally present. If at this stage food containing sodium chloride is again taken, a portion will be 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 causes an increased elimination of chlorides.

This tenacity on the part of the body in retaining sodium chloride is strikingly seen when the potassium salt is substituted for the sodium salt; in this case the amount of the sodium in the serum of the blood will be found to vary but very slightly.

It has also been shown that the excretion of sodium chloride can be very materially increased by the ingestion of potassium salts, notably the neutral potassium phosphate (K_2HPO_4). This is

supposed to decompose the sodium chloride present in the serum, resulting in the formation of potassium chloride and neutral sodium phosphate, which are both eliminated from the body as foreign matters; a point is finally reached, however, when the sodium chloride ceases to be excreted.

This provision of the economy, in virtue of which an increase in the elimination of the salt is followed by its retention, and a previous retention by an increased elimination, is supposed to be referable to the albuminous metabolism taking place in the body. It may be stated, as a general rule, that any increase in the amount of circulating albumin will be followed by an elimination of chlorides, these having been previously retained by the albuminous bodies in consequence of the great affinity which exists between them. At the same time the elimination of chlorides is influenced by the quantity of urine excreted, increasing and decreasing with its volume.

Pathologically the excretion of the chlorides may vary within wide limits, diminishing on the one hand to zero, and increasing on the other to as much as 50 grammes or more in the twenty-four hours. A marked diminution, going on in some cases to a total absence of the chlorides, was formerly thought to be pathognomonic of acute croupous pneumonia. Recent investigations, however, have shown that such a condition is present to a greater or less degree in most acute febrile diseases, such as scarlatina, roseola, variola, typhus and typhoid fevers, recurrens, and acute yellow atrophy.

The explanation of this phenomenon must be sought for, first, in a diminished ingestion of chlorides; secondly, in a retention of these in the blood, probably associated with an increase in the amount of circulating albumin; thirdly, in a diminished renal secretion of water; fourthly, in a possible elimination of a portion of the chlorides from the blood by other channels, as in cases of severe diarrhœa, the formation of serous exudates, etc. Intermittent fever appears to be an exception to this rule; the chlorides, it is true, are usually diminished, but not to the extent seen in the other diseases mentioned; they have, moreover, been found to increase during and sometimes immediately after a paroxysm, this increase being, of course, followed by a corresponding decrease.

The chlorides are diminished in all acute and chronic renal diseases associated with albuminuria, owing, to some extent, at least, to a diminished secretion of water. In all cases of carcinoma of

the stomach, chronic hypersecretion of gastric juice, associated with dilatation, a decrease is also observed, which in certain cases of hypersecretion and hyperacidity the result of gastric ulcer may go on to a total absence. In anæmic conditions the chlorides are likewise diminished, as also in rickets. In melancholia and idiocy a striking decrease is observed; in dementia, chorea, and pseudo-hypertrophic paralysis this is less marked. A total absence has been noted in pemphigus foliaceus, and a considerable diminution in the beginning of impetigo, as also in chronic lead-poisoning.

The chlorides are found in increased amount, on the other hand, in all conditions in which retention has previously occurred, chief among these being the acute febrile diseases and cases in which a resorption of exudates and transudates, associated with an increased diuresis, is taking place. A marked increase has also been noted in some cases of diabetes insipidus, in which 29 grammes of sodium chloride have been eliminated in the twenty-four hours. A similar increase may occur in prurigo, in which, in one instance, 29.6 grammes were passed in twenty-four hours. In cases of general paresis during the first stage an increased elimination goes hand in hand with an increased ingestion of food. In epilepsy the polyuria following the attacks is associated with an increase in the chlorides.

Of drugs, certain diuretics, and some of the potassium salts, as has been mentioned, produce an increase: the chlorine contained in chloroform, whether administered internally or as an anæsthetic, is in part excreted in the form of a chloride. Salicylic acid, on the other hand, is said to cause a temporary diminution.

It is of practical importance to note that in acute febrile affections the diminution in the chlorides appears to vary with the intensity of the disease, a decrease to 0.05 gramme *pro die* justifying the conclusion that the case under observation is of extreme gravity. It may at times also indicate the previous occurrence of severe diarrhœa or the formation of exudates of considerable extent. A continued increase, on the other hand, should lead to the conclusion that the patient's condition is improving.

The elimination of the chlorides also furnishes a fair index to the digestive powers of the patient. This rule also holds good for most chronic diseases. All other causes which might lead to an increase or decrease being eliminated, an excretion of from 10 to 15 grammes indicates a fair condition of the appetite and a normal digestive power, a decrease being associated with the reverse.

An increased elimination of chlorides occurring in cases of œdema, and associated with the existence of serous exudates, is always of good prognostic significance, pointing to a resorption of the fluid.

A continued elimination of more than 15 to 20 grammes, all other causes being excluded, may be considered as pathognomonic of diabetes insipidus.

Test for Chlorides in the Urine. The recognition of chlorides in the urine is based upon the fact that the addition of a solution of nitrate of silver causes their precipitation, the reaction taking place according to the following equation:

$$AgNO_3 + NaCl = AgCl + NaNO_3.$$

Silver chloride thus formed is insoluble in nitric acid.

The test is made in the following manner: After having removed any albumin that may be present, according to methods given elsewhere (see Blood), a few c.c. of urine are acidified in a test-tube with about 10 drops of pure nitric acid, and a few c.c. of silver nitrate solution (1 : 20) added. The occurrence of a white precipitate indicates the presence of chlorides. An idea may be formed at the same time as to the quantity present, the occurrence of a heavy, caseous precipitate pointing to a large amount.

Quantitative Estimation of the Chlorides by the Method of Salkowski-Volhard. When a solution of silver nitrate, acidified with nitric acid, is treated with a solution of potassium sulpho-cyanide or ammonium sulpho-cyanide in the presence of a ferric salt, the potassium sulpho-cyanide first causes the precipitation of white silver sulpho-cyanide, which, like silver chloride, is insoluble in nitric acid:

$$AgNO_3 + KSCN = AgSCN + KNO_3.$$

As soon as every trace of silver is precipitated it combines with the ferric salt to form iron sulpho-cyanide, which is of a blood-red color, according to the equation:

$$6KSCN + Fe_2(SO_4)_3 = Fe_2(SCN)_6 + 3K_2SO_4.$$

If the potassium sulpho-cyanide solution be of known strength, it is possible to estimate accurately the amount of silver present in the solution, the ferric salt serving as an indicator of the end of the reaction between the silver and the potassium sulpho-cyanide.

Application to the urine: To urine which has been acidified with nitric acid an excess of a silver solution of known strength is added, and the silver not used in the preciptation of the chlorides then esti-

mated according to the method given above. The difference between the quantity thus found and the total amount used will be that consumed in the precipitation of the chlorides, from which, knowing the strength of the silver solution, its equivalent in terms of sodium chloride is readily determined.

Reagents necessary:

1. A solution of silver nitrate of such strength that every c.c. corresponds to 0.01 gramme of sodium chloride.

2. A solution of potassium sulpho-cyanide of such strength that 25 c.c. correspond to 10 c.c. of the silver nitrate solution.

3. A solution of a ferric salt, such as ammonio-ferric alum, saturated at an ordinary temperature.

4. Nitric acid (specific gravity 1.2).

Preparation of these solutions:

1. As pointed out, the silver nitrate solution is made of such strength that every c.c. corresponds to 0.01 gramme of NaCl; in other words, a standard solution is employed.

The silver nitrate to be used for this purpose must be pure, the crystallized salt being used and not the sticks wrapped in paper, which latter always contain reduced silver. In order to test the purity of the salt, about 1 gramme is dissolved in distilled water, heated to the boiling-point, the silver precipitated by dilute hydrochloric acid and filtered off. The filtrate when evaporated in a platinum crucible should leave either no residue at all or only a very faint one; otherwise it is necessary to recrystallize the salt and test again, until the desired degree of purity is obtained.

The determination of the quantity to be dissolved in 1000 c.c. of water is based upon the fact that one molecule of silver nitrate (molecular weight 170) combines with one molecule of sodium chloride (molecular weight 58.5) to form silver chloride and sodium nitrate. As the solution of nitrate of silver shall be of such strength that 1 c.c. corresponds to 0.01 grm. of NaCl, or 1000 c.c. to 10 grms., the quantity to be dissolved in 100 c.c. is found according to the following equation:

$$58.5 : 170 :: 10 : x;\ 58.5\,x = 1700;\ x = 29.059.$$

Theoretically, then, this quantity should be dissolved in 1000 c.c. of water. It is better, however, to dissolve this in a quantity somewhat less than 1000 c.c., such as 900 or 950 c.c., as the silver salt may contain some water of crystallization and the weighed-off quan-

tity not represent the accurate amount required, but less, the correcting of a solution which is too strong being a much simpler matter than that of a solution which is too weak.

To make this correction, or, in other words, to bring the solution to its proper strength, 0.15 gramme of sodium chloride which has been previously dried carefully by heating in a platinum crucible, is accurately weighed off, dissolved in a little distilled water, and further diluted to about 100 c.c. To this solution a few drops of a solution of chromate of potassium are added, and the mixture is titrated with that of silver nitrate.

The nitrate of silver will first precipitate the sodium chloride present, and then combine with the potassium chromate, forming red silver chromate, according to the equation:

$$2AgNO_3 + K_2CrO_4 = Ag_2CrO_4 + 2KNO_3$$

The slightest orange tinge remaining after stirring indicates the end of the reaction. Were the solution of the silver nitrate of the proper strength, exactly 15 c.c. should have been used, as every c.c. represents 0.01 gramme of NaCl. As a matter of fact, less will in all probability be needed, the solution having been purposely made too strong. Its correction then becomes a simple matter, it merely being necessary to determine the degree of dilution required.

Supposing the 29.059 grammes of silver nitrate to have been dissolved in 900 c.c. of water, and that 14.5 c.c. instead of 15 c.c. had been required to precipitate the 0.15 gramme of sodium chloride, it is evident that every 14.5 c.c. of the remaining solution must be diluted with 0.5 c.c. of water. It is, hence, only necessary to divide the number of c.c. of the silver nitrate solution remaining by 14.5; the result multiplied by 0.5 represents the amount of water which must be added in order to bring the solution to the required strength. Hence the rule for the correction of a solution which has been found too strong:

$$C = \frac{N \cdot d}{n},$$

in whch C represents the number of c.c. which must be added to the solution remaining; N the total number of c.c. remaining after titration; n the number of c.c. consumed in one titration; and d the difference between the number of c.c. theoretically required and that actually used in one titration.

In the example given the equation would then read:

$$C = \frac{936.5 \times 0.5}{14.5} = 32.29.$$

32.29 c.c. of distilled water are added to the remaining 936.5 c.c., and the strength of the solution tested by a second titration. If the solution be found too weak, it is best to make it too strong, and then to correct, as described.

2. Preparation of the potassium sulpho-cyanide solution: From the equation $AgNO_3 + KSCN = AgSCN + KNO_3$, it is seen that one molecule of silver nitrate (molecular weight 170) combines with one molecule of potassium sulpho-cyanide (molecular weight 97). The quantity of the latter to be dissolved in 1000 c.c. of water is thus found from the following equation:

$$170 : 97 :: 11.6236 : x;\ 170\,x = 11.6236 \times 97;\ x = 6.6.$$

As potassium sulpho-cyanide is extremely hygroscopic, a solution is made which is too strong by dissolving about 10 grammes of the salt in 900 c.c. of distilled water. In order to bring this solution to its proper strength, 10 c.c. of the silver nitrate solution are diluted to 100 c.c., 4 c.c. of nitric acid (specific gravity 1.2) and 5 c.c. of the ammonio-ferric alum solution added, and the mixture titrated with the KSCN solution; the end-reaction is recognized by the production of a slightly reddish color, which persists on stirring. The KSCN solution having been purposely made too strong, it will be found that less than 25 c.c. will be needed in order to precipitate all the silver present. The quantity of water necessary for dilution is ascertained as above according to the formula:

$$C = \frac{N \cdot d}{n}.$$

3. The solution of ammonio-ferric alum is a solution saturated at ordinary temperatures, care being taken to insure the absence of chlorides in the salt, which may be effected, if necessary, by recrystallization.

Method as applied to the urine: 10 c.c. of urine are placed in a small stoppered flask bearing a 100 c.c. mark, diluted with 50 c.c. of distilled water, and acidified with 4 c.c. of nitric acid. From a Mohr's burette 15 c.c. of the standard solution of silver nitrate are added. The mixture is thoroughly agitated and diluted with distilled water to the 100 c.c. mark. The silver chloride formed is filtered off through a *dry* folded filter into a *dry* graduate; 80 c.c. of the filtrate are placed in a beaker, and, after the addition of

5 c.c. of the ammonio-ferric alum solution, titrated with the potassium sulpho-cyanide solution until the end-reaction—*i. e.*, a slightly reddish tinge—is seen. If necessary, two such titrations should be made, the potassium sulpho-cyanide solution being added 1 c.c. at a time in the first, while in the second the total number of c.c. needed to bring about the end-reaction, less 1 c.c., are added at once, and then one-tenth of a c.c. at a time.

The amount of chlorides present in the urine is calculated as follows:

Example: Total quantity of urine 600 c.c.; 6.5 c.c. of the potassium sulpho-cyanide solution were required to bring about the end-reaction in 80 c.c. of the filtrate; this would correspond to 8.125 c.c. for the total 100 c.c. of filtrate, representing 10 c.c. of urine, as is seen from the equation:

$$n : 80 :: x : 100,\ 80\,x = 100\,n,\ x = \frac{100\,n}{80} = \frac{5\,n}{4},$$

in which x represents the number of c.c. corresponding to 100 c.c. of the filtrate, and n the number of c.c. actually used.

These 8.125 c.c. were used in precipitating the remaining c.c. of the silver nitrate solution not decomposed by the chlorides. As 25 c.c. of the potassium sulpho-cyanide solution correspond to 10 c.c. of the silver nitrate solution, the excess of silver solution in c.c. is found from the equation:

$$25 : 10 :: N : x,\ 25\,x = 10\,N,\ x = \frac{10\,N}{25} = \frac{2\,N}{5},$$

in which x represents the excess of silver nitrate solution in c.c., N that of the KSCN solution, as found in the equation above, x in this case being 3.25 c.c.

The difference between the total amount of silver solution employed (*i. e.*, 15 c.c.) and the excess (*i. e.*, 3.25 c.c.) indicates, of course, the number of c.c. necessary for the precipitation of the chlorides in 10 c.c. of urine. In the case under consideration 11.75 c.c. were employed. As 1 c.c. of the silver solution represents 0.01 gramme of NaCl, there must have been present in the 10 c.c. of urine 0.1175 gramme; in 100 c.c., hence, 1.175 grammes, and in the total amount—*i. e.*, 600 c.c. of urine—7.05 grammes.

From these considerations the following short rule results: Instead of first multiplying the number of c.c. of the potassium sulpho-cyanide solution corresponding to 80 c.c. of the filtrate by $\frac{5}{4}$, as seen from the equation above, and the result by $\frac{2}{5}$, in order to find the

number of c.c. of the potassium sulpho-cyanide solution representing the excess of silver nitrate in 100 c.c. of the filtrate, and then deducting the result from 15, it is simpler to multiply by $\frac{1}{2}$ directly and deduct the result from 15, the number of grammes of sodium chloride contained in 1000 c.c. of urine being thus found. This figure is then corrected for the total amount of urine.

Hence the equations, I., $x = 15 - \frac{n}{2}$; II., $1000 : x :: A : Ch$,

or the combined formula $Ch = \frac{A\,(15 - \frac{n}{2})}{1000}$,

in which Ch represents the quantity of chlorides contained in the total amount of urine, A the amount of urine actually passed, n the number of c.c. of the KSCN solution used in the precipitation of the excess of chlorides in 80 c.c. of the filtrate.

So in the above case $Ch = 600\,\frac{(15 - \frac{6.5}{2})}{1000} = 7.05$.

The method described may be employed in the presence of albumin, albumoses, peptones, and sugar; the urine, however, must be fresh, so as to insure the absence of nitrous acid.

Direct Method. If absolute accuracy is not required, the following method may be employed:

Ten c.c. of urine are diluted with distilled water to 100 c.c. and treated with a few drops of a solution of potassium chromate. This mixture is titrated with a one-tenth normal solution of silver nitrate until the end-reaction—*i. e.*, the occurrence of a faint orange tinge, which no longer disappears on stirring—is reached. The number of c.c. used multiplied by 0.01 will indicate the amount of chlorides present in 10 c.c. of urine.

As uric acid, the xanthin bases, hyposulphites, sulpho-cyanides, and pigments are also precipitated by the silver nitrate, the end-reaction is delayed; moreover, unless the urine be very pale, its recognition may be difficult, and the error thus caused quite considerable. This is especially true of febrile urines which contain only a small amount of chlorides.

Should iodides or bromides have been taken, these must first be removed, as the iodide and bromide of silver, which are insoluble in nitric acid, would give too high a value.

To this end the following method, which is a very accurate one,

should be employed, its only disadvantage being the amount of time required.

Estimation of the Chlorides after Incineration (according to Neubauer and Salkowski). The principle of this method is the destruction of all organic material and the subsequent estimation of the chlorides contained in the mineral ash, by one of the methods described. 10 c.c. of urine are evaporated to dryness in a platinum crucible at a temperature slightly below 100° C., after the addition of a little pure, dried carbonate of sodium and from 3 to 5 grammes of potassium nitrate. The addition of the carbonate of sodium converts any ammonium chloride which may be present into sodium chloride; the potassium nitrate merely acts as an oxidizing agent. The residue is now carefully heated at a moderate temperature, allowed to cool, dissolved in distilled water, and accurately neutralized with very dilute nitric acid. In this solution the chlorides are estimated most conveniently according to the second method.

Should iodides or bromides be present, the aqueous solution just referred to is acidified with hydrochloric acid and the iodine and bromine thereby liberated extracted with carbon disulphide. As complete removal of these bodies is, however, only possible in the presence of a nitrite, it is better not to rely upon the presence of any that may have been formed during the process of incineration, but to add a few drops of a solution of potassium nitrite. After extraction the nitrous acid is decomposed by the addition of a little urea. The solution is then neutralized with sodium carbonate; should it be alkaline, dilute acetic acid is added until neutral. In this solution the chlorides are most conveniently estimated according to the second method.

Albumin and sugar, if present, should be removed before the addition of the sodium carbonate and potassium nitrate, if this method is employed, so as to obviate losses from sputtering, which would otherwise occur. Nitrous acid must also be removed for reasons given above.

The Phosphates.

The phosphates occurring in the urine are sodium, potassium, calcium, and magnesium salts of the tribasic acid H_3PO_4, the most important of which, as was pointed out in the chapter on Reaction, is the diacid sodium phosphate NaH_2PO_4, to which the acidity of

the urine is due. It is owing to the presence of this salt in the urine that the calcium phosphate is held in solution; the fact, at least, that calcium and magnesium phosphates are thrown down when the urine is neutralized would point to this conclusion.

The composition of the phosphates is liable to considerable variation, depending upon the degree of acidity of the urine. As would be expected, diacid sodium phosphate and diacid calcium phosphate are present in an acid urine; in an amphoteric urine, in addition to these there are found disodium phosphate, monocalcium phosphate, and monomagnesium phosphate, while in an alkaline urine trisodic phosphate, neutral calcium phosphate, and neutral magnesium phosphate may be present.

The alkaline phosphates normally exceed the earthy phosphates by one-third, and sodium is combined with far the greater amount of phosphoric acid, the potassium salt normally occurring in only very small amounts.

In addition to the mineral phosphates, phosphoric acid is also excreted in combination with glycerine as glycerine-phosphoric acid, which need not, however, be considered in a quantitative estimation, as it is present only in traces.

As in the case of the chlorides, the phosphates are derived from two sources, by far the greater part being derived from the food, while only a small portion is referable to the phosphorus built up in the proteid molecule, be this in the form of a muscle-cell, nerve-cell, red blood-corpuscle, or bone. But just as the percentage of sulphur varies in the different tissues, so also does that of phosphorus vary; nerve-tissue, for example, which is very rich in lecithin and nuclein, yields relatively more phosphorus than muscle-tissue.

Not all the phosphoric acid ingested, however, is excreted in the urine, one-third to one-fourth of the total quantity being eliminated in the feces.

The quantity of P_2O_5 excreted, which normally varies between 2.5 and 3 grammes, is thus largely dependent upon the amount ingested, increasing with an animal and decreasing with a vegetable diet. During starvation the excretion of P_2O_5 is largely increased, in consequence, no doubt, of an increased destruction of bony tissue, which is very rich in the phosphates of the alkaline earths. In accordance with this view, calcium and magnesium are excreted in increased amount during starvation. The relation between the ex-

cretion of P_2O_5 and N, normally 1 : 7, changes, moreover, in such a manner that both the absolute and relative amount of phosphoric acid as compared with the nitrogen increases, leading to the conclusion that in addition to the muscles some other tissue, rich in phosphorus and relatively poor in N, must suffer during the process, the only one that suggests itself being bone.

If at this time food containing phosphorus be again given, a retention will take place in the body, so that the general rule given in the chapter on Chlorides, that increased elimination is followed by a certain degree of retention, and that a previous retention is followed by an increased elimination, seems to hold good for all the mineral acids found in the urine (see also the chapter on Sulphates). An increased elimination is also caused by the ingestion of large quantities of water, which is followed by a certain degree of retention.

Observations made upon the phosphatic excretion during muscular exercise have not given uniform results, apparently depending upon the nature of the food, as a decrease, no effect at all, and an increase have been reported by different observers. Mental exercise appears to cause a diminished excretion of the alkaline phosphates and an increased elimination of the earthy phosphates. The latter also takes place during sleep.

The factors which influence the exact nature of the individual phosphatic salts have been considered in the chapter on Reaction, in which this has been shown to depend upon the alkalinity of the blood, and ultimately upon the quantity of acid set free by the tissues or which has been absorbed during the process of digestion; increased tissue-destruction, of course, likewise causes an increased elimination of phosphates.

Pathologically the total amount of phosphates eliminated in twenty-four hours may either be increased or diminished.

A *diminished* elimination is observed in most cases of acute febrile disease, such as pneumonia, typhoid fever, typhus fever, recurrens, during a paroxysm of intermittent fever, etc., the degree of diminution being usually proportionate to the severity of the disease, reaching its lowest figure as death approaches. Such a state of affairs may, at first sight, appear paradoxical, in view of what has been said above of the effects of tissue-destruction upon the elimination of phosphates. It is necessary, however, to distinguish sharply between an increased production and an increased elimination, a

retention of the phosphates actually set free from the tissues, analogous to the retention of chlorides before noted, in all probability taking place. It has been supposed that the phosphates set free during the process of tissue-destruction are utilized in the building up of new leucocytes, an increase in which is actually noted in some of the diseases mentioned.

A *diminished* excretion of phosphates is, however, not always observed, and an increased elimination, on the other hand, may occur in certain cases. In fatal cases this condition may even persist until the time of death. It is very difficult to give a satisfactory explanation of this fact at the present time. The phenomenon, in typhoid fever at least, appears to be connected with the intensity of the nervous manifestations, and Robin concludes that here an increased elimination during the fastigium is an unfavorable omen, while an increase during defervescence warrants a favorable prognosis. A similar decrease in the phosphates has also been observed in pulmonary phthisis associated with high fever.

Very interesting and important is the diminished excretion of phosphates associated with acute and, to some extent also, with chronic nephritis, amyloid degeneration of the kidneys, and the anæmias, in which an actual insufficiency on the part of the kidneys in the elimination of these salts appears to exist.

A diminished, or, at least, no increased excretion is seen in certain diseases of the bones, such as osteomalacia, although an increase in the *earthy* phosphates has been noted. This may depend upon either a retention or an elimination through other channels. The *earthy* phosphates especially are found in greatly diminished amount, or may even be absent altogether in certain cases of nephritis. A similar condition is observed in acute and chronic rheumatism.

During attacks of hysteria major, in contradistinction to epilepsy, in which an increased elimination takes place, the phosphates are diminished, the degree of diminution being generally proportionate to the intensity of the attack, increasing again together with the other urinary constituents with the subsequent increase in the diuresis. The data regarding the phosphatic elimination in nervous and mental diseases are, on the whole, very scanty and by no means uniform. In chronic lead-poisoning a diminution to one-third of the normal quantity may occur. Very low figures have been noted in Addison's disease, in acute yellow atrophy, in

which even a total absence may occur, and in certain cases of hepatic cirrhosis.

An *increased* elimination of phosphates, on the other hand, amounting in some cases to 7 or even to 9 grammes in the twenty-four hours, has been described under the name of *phosphatic diabetes*, the patient presenting various symptoms commonly seen in diabetes mellitus, sugar, however, being usually absent. Whether or not phosphatic diabetes is a disease *sui generis* is not as yet certain.

In true diabetes mellitus a curious relation has been found to exist between the elimination of sugar and of phosphates, the quantity of the latter rising and falling in an inverse ratio to the amount of sugar. In diabetes insipidus a slight increase is at times found.

Corresponding to the phosphatic retention observed in acute febrile diseases an increased elimination is noted during convalescence. In meningitis, especially in cerebro-spinal meningitis, an increase occurs in the course of the disease.

Recently an increase to 7 grammes was noted in a case of pseudo-leukæmia, in which the number of red corpuscles fell from 2,200,000 to 800,000 in four days, and in which, to judge from the very careful observations made, there could be no doubt that the high degree of phosphaturia, which was limited to the alkaline phosphates, was referable to this source. In a case of leukæmia also an increase to 7 grammes was observed on the day preceding death; commonly, however, the increase is but slight in this disease.

While it is apparent that important conclusions cannot be drawn, on the whole, from a knowledge of the absolute phosphatic elimination, unless it be from a study of the relation existing between the excretion of the alkaline and earthy phosphates, a study of the *relative phosphatic excretion* seems to promise more valuable results. According to Zülzer, a certain amount of the phosphates and of the nitrogen is referable to the destruction of albuminous material, so that the relation between the phosphoric acid and the nitrogen must be a constant one. Another portion, however, is derived from lecithin, one of the most important constituents of nerve-tissue, containing more phosphorus than the albuminous molecule. Whenever, then, the lecithin-containing tissues are more involved in the general metabolism than under normal conditions, this relation will no longer be a stable one.

This relation which exists between the elimination of nitrogen

and phosphoric acid has been termed the *Relative Value* of phosphoric acid.

The relative value of phosphoric acid in the urine has been calculated as varying from 17 to 20, that of the blood being 3, of muscle-tissue 12.1, of brain 44, of bone 426 to 430. This value supposes the absolute value to vary between 2 and 3 grammes *pro die*. It is found according to the following equation:

$$N : P_2O_5 :: 100 : x, \text{ and } x = \frac{100 \cdot P_2O_5}{N},$$

in which N indicates the amount of nitrogen actually observed, P_2O_5 the amount of phosphoric acid in the same specimen of urine, and x the amount of P_2O_5 corresponding to 100 grammes of N. By observing this relative value a much better idea may be formed of the processes taking place in the body in disease than from a mere expression of the absolute phosphatic value.

In acute febrile diseases the relative as well as the absolute diminution of the phosphates has been ascribed, as mentioned above, to their retention, they being possibly utilized in the building up of white blood-corpuscles. In the course of these diseases oscillations in the relative value are frequently observed, and an increased relative amount would be explained by assuming a transformation of leucocytes rich in phosphorus into red corpuscles, which are relatively poor in phosphorus, resulting in a liberation of P_2O_5. During convalescence the relative as well as the absolute value again rises.

In accordance with these considerations a diminished relative excretion of phosphoric acid should be expected in all cases associated with a notable elimination of pus-corpuscles through other channels, as in pneumonia, for example, or a storing away of the same, as in cases of empyema. The facts observed are in accord with this view.

A relative decrease has further been noted in the various forms of anæmia, conditions of cerebral excitation, and especially preceding an attack of epilepsy. In progressive paralysis following syphilis the relative value, at first low, rises greatly after the administration of potassium iodide, while the excretion of the earthy phosphates is lessened. In chronic cerebral affections, delirium tremens, and acute hydrocephalus a relative decrease has been noted. In mania, during the period of excitement, both the alkaline and earthy phosphates are found increased, while during the stage of

depression, as also in melancholia, the alkaline phosphates are found in diminished and the earthy in increased amount. On the other hand, an increase in the relative value has been noted in apoplexy (amounting to 34.3 in one case two days after an attack), brain-tumors, tabes, arthritis deformans (30), pernicious anæmia (23.8–58), etc.

Of drugs potassium bromide appears to diminish the absolute amount of phosphoric acid. Cocaine and quinine cause a decrease, and salicylic acid an increase. A relative decrease is produced by the cerebral excitants, such as strychnine, small doses of alcohol, phosphorus, valerian, cold baths, salt-water baths, etc. An opposite effect is produced by the cerebral depressants, such as chloroform, morphine, chloral, large doses of alcohol, potassium bromide, mineral and vegetable acids, prolonged cold baths, Turkish baths, low temperature.

As is apparent from the data given, our knowledge concerning the excretion of phosphoric acid is as yet in its infancy, and the causes producing variations in its amount very obscure. It is quite apparent, nevertheless, that a detailed study, especially of the relative excretion of phosphoric acid, would, in all probability, lead to highly important results, permitting an insight into the metabolism of the individual body-tissues, as it were. In this connection the observations of Edlefsen, on the relation existing between the destruction of leucocytes and the excretion of P_2O_5, deserve especial mention.

Practical data as to diagnosis and treatment can, however, not yet be formulated.

Tests for the Phosphates in the Urine. The test for the detection of the phosphates occurring in the urine depends upon the precipitation of phosphoric acid by means of ferric chloride as ferric phosphate, which is insoluble in cold acetic acid, according to the equation:

$$2NaH_2PO_4 + Fe_2Cl_6 = Fe_2(PO_4)_2 + 2NaCl + 4HCl,$$

or

$$2Na_2HPO_4 + Fe_2Cl_6 = Fe_2(PO_4)_2 + 4NaCl + 2HCl.$$

The same result may be accomplished by the addition of a solution of uranyl nitrate, giving rise to the formation of uranyl phosphate, which is also insoluble in acetic acid, according to the equation:

$$Na_2HPO_4 + 2UO.NO_3 = 2NaNO_3 + (UO)_2HPO_4,$$

or

$$NaH_2PO_4 + UO.NO_3 = NaNO_3 + UO.H_2PO_4.$$

Test: A few c.c. of urine are acidified with a few drops of acetic acid, and treated with a few drops of a solution of ferric chloride (one part of the officinal solution to ten parts of water), when the occurrence of a yellowish-white precipitate will indicate the presence of phosphates.

If a solution containing an acid phosphate of the alkalies be treated with an alkaline hydrate, the diacid alkaline phosphate is transformed into the monacid salt, according to the equation:

$$NaH_2PO_4 + NH_4OH = NaNH_4HPO_4 + H_2O.$$

This is further changed into the normal salt, as represented in the equation:

$$3NaNH_4HPO_4 + NH_4OH = Na_3PO_4 + (NH_4)_3(PO_4)_2 + H_2O.$$

As the monacid and neutral salts are both readily soluble, the solution remains clear. If at the same time, as in the urine, a soluble diacid phosphate of the alkaline earths be present, this is likewise transformed into the monacid, and finally into the neutral salt; the latter, however, being insoluble, is thrown down:

$$\text{I. } Ca(H_2PO_4)_2 + 4NH_4OH = Ca(NH_4)_2(PO_4)_2 + 4H_2O.$$
$$\text{II. } 3Ca(NH_4)_2(PO_4)_2 = Ca_3(PO_4)_2 + 2(NH_4)_3PO_4.$$

Test for the earthy phosphates: About 10 c.c. of urine are rendered alkaline with ammonia, when the occurrence of a flocculent precipitate will indicate their presence.

Test for the alkaline phosphates: After having removed the earthy phosphates from 10 c.c. of urine, as just described, the clear filtrate is acidified with acetic acid and tested with ferric chloride, or uranyl nitrate, as shown above.

The alkaline phosphates may also be detected by treating the ammoniacal filtrate with a few drops of *magnesia mixture* (1 part of crystallized magnesium sulphate, 2 parts of ammonium chloride, 4 parts of ammonium hydrate, and 8 parts of distilled water), when ammonio-magnesium phosphate, which is almost insoluble in ammonium hydrate, will be thrown down, the reaction taking place between the monacid or neutral sodium phosphate and the magnesium sulphate, according to the equation:

$$Na_2HPO_4 + MgSO_4 + NH_4OH + NH_4Cl = MgNH_4PO_4 + NH_4Cl + Na_2SO_4 + H_2O.$$

Quantitative Estimation of the Total Amount of Phosphates

Principle: When a solution of disodium phosphate, acidified with acetic acid, is treated with a solution of uranyl nitrate, or uranyl

acetate, a dirty-looking, white precipitate of uranyl phosphate is thrown down, which is formed according to the equation given above.

It is apparent that the quantity of P_2O_5 can be estimated accurately if the solution of uranyl nitrate or acetate be of known strength.

Solutions required :

1. A solution of uranium nitrate of such strength that 20 c.c. shall correspond to 0.1 gramme of P_2O_5.
2. A solution containing acetate of sodium and acetic acid.
3. Tincture of cochineal.

Preparation of these solutions :

1. From the equation :

$$2UO.NO_3 + Na_2HPO_4 = (UO)_2HPO_4 + 2NaNO_3$$

it is apparent that 2 molecules of uranium nitrate combine with 1 molecule of disodium phosphate to form uranium phosphate and sodium nitrate. The molecular weight of uranium nitrate being 318 and that of disodium phosphate 142, it is seen that 636 parts by weight of the former combine with 142 parts by weight of the latter.

As 20 c.c. of the solution of uranium nitrate correspond to 0.1 gramme of P_2O_5, 1000 c.c. must be equivalent to 5 grammes of P_2O_5. In 142 parts by weight of disodium phosphate there would be present 71 grammes of P_2O_5, equivalent to 636 parts by weight of uranium nitrate. The quantity of the latter, then, to be dissolved in 1000 c.c. of water would be found from the equation: 636 : 71 : : x : 5; and x = 44.78.

44.78 grammes of uranium nitrate are weighed off and dissolved in about 900 c.c. of water, the solution being purposely made too strong for reasons pointed out in the chapter on Chlorides. In order to bring this solution to its proper strength it is necessary to titrate with the uranium solution a solution of disodium phosphate of such strength that every 50 c.c. shall contain 0.1 gramme of P_2O_5, or 1000 c.c. 5 grammes. The molecular weight of $Na_2HPO_4 + 12H_2O$ being 358, this amount of disodium phosphate in grammes is equivalent to 179 grammes of P_2O_5; the quantity of P_2O_5 corresponding to 5 grammes, in terms of $Na_2HPO_4 + 12H_2O$, is found from the equation : 358 : 179 : : x : 5; and x = 10. Ten grammes of pure, dry, and non-deliquescent Na_2HPO_4 are dissolved in 1000 c.c. of distilled water. If non-deliquescent disodium phosphate be

not at hand, about 12 grammes of the salt are dissolved in 1000 c.c. of distilled water; of this solution 50 c.c. are evaporated in a weighed platinum dish, and the residue gently heated, the disodium phosphate being thereby transformed into sodium pyro-phosphate, $Na_4P_2O_7$, according to the equation:

$$2Na_2HPO_4 = Na_4P_2O_7 + H_2O.$$

The molecular weight of $Na_4P_2O_7$ being 266, this corresponds to 142 grammes of P_2O_5.

If the solution were of the correct strength—*i. e.*, containing 0.1 gramme of P_2O_5 in 50 c.c. of water—the residue should weigh 0.1873 gramme, as is seen from the equation: 142 : 266 : : 0.1 : x; and x = 0.1873. Supposing, however, the residue to weigh 0.1921 gramme, it is manifest that the solution is too strong, and must be diluted, the degree of the dilution being determined according to the equation : 0.1873 : 1000 : : 0.1921 : x; and x = 1025; *i. e.*, 1000 c.c. of the solution made must be diluted to 1025 c.c. to make it of the proper strength.

In the case given 50 c.c. were used; the 950 c.c. are then diluted with the amount of water found from the equation : 1000 : 1025 : : 950 : x; and x = 953.75. Having thus obtained a solution of disodium phosphate of such strength that every 50 c.c. shall contain 0.1 gramme of P_2O_5, this solution is titrated with the uranium solution which has been made too strong, in order to determine the amount of water that must be added to the latter. To this end a Mohr's burette is filled with the uranium solution; 50 c.c. of the disodium phosphate solution are treated with a few drops of the tincture of cochineal and 5 c.c. of the acetic-acid mixture (see below). This mixture is heated in a beaker and, as soon as the boiling-point has been reached, titrated with the uranium solution until a trace of a greenish color is noticed in the precipitate which does not disappear on stirring. This point having been accurately determined by means of a second titration, the number of c.c. of distilled water with which the remaining solution must be diluted is determined according to the formula: $C = \frac{N.d}{n}$, in which C represents the number of c.c. which must be added, N the number of c.c. remaining after the test-titrations, n the number of c.c. consumed in one titration to bring about the end-reaction, and d the difference between the number of c.c. used in one titration and that theoretically required.

The amount of distilled water necessary for dilution is now added and the solution again tested, when 20 c.c. will correspond to 0.1 gramme of P_2O_5.

2. The acetic-acid mixture consists of about 100 grammes of acetate of sodium dissolved in distilled water, and 100 c.c. of a 30 per cent. solution of acetic acid, the whole being diluted to 1000 c.c.

3. Tincture of cochineal. This may be prepared as follows: A few grammes of cochineal granules are digested at ordinary temperatures with 250 c.c. of a mixture of 3 volumes of water and 1 volume of 94 per cent. alcohol. The solution is then decanted and ready for use. The residue may be utilized in the preparation of a fresh supply of the tincture.

Application to the urine: 50 c.c. of clear, filtered urine are treated with 5 c.c. of the acetic-acid mixture, the object being to transform any monacid sodium phosphate present into diacid sodium phosphate, and to neutralize any nitric acid that may be formed during the titration, as otherwise the nitric acid would cause a partial solution of the precipitated uranyl phosphate. A few drops of the tincture of cochineal are added, when the mixture is heated to the boiling-point, and titrated as directed above, two titrations being usually required.

The results are then calculated as follows: Supposing 15 c.c. of the uranium solution to have been used, the corresponding amount of P_2O_5 contained in 50 c.c. of urine is found from the equation: $20 : 0.1 : : 15 : x$; and $x = 0.075$. The percentage-amount would, hence, be $0.075 \times 2 = 0.15$. Supposing the total amount of urine to have been 2000 c.c., the elimination of P_2O_5 would correspond to 3 grammes.

The presence of sugar and albumin does not interfere with this method.

Separate Estimation of the Earthy and Alkaline Phosphates. If the alkaline and earthy phosphates are to be determined separately, the total amount of P_2O_5 is estimated in one portion of the urine, while the P_2O_5 in combination with the alkaline earths is determined in another, as follows:

Two hundred c.c. of filtered urine are made strongly alkaline with ammonium hydrate and set aside, covered, for several hours, when the earthy phosphates thus precipitated are collected upon a filter, washed with dilute ammonia (1 : 3), and then transferred to a beaker, with the aid of a little water containing a few drops of acetic

acid, by perforating the filter. They are then dissolved with as little acetic acid as possible, diluted to 50 c.c. with distilled water, and titrated with the uranium solution as described. The difference between the total amount of P_2O_5 and the amount thus obtained is the quantity of alkaline phosphates present.

Removal of the Phosphates from the Urine. Whenever it is necessary to remove the phosphates from the urine in the course of an analysis, as is frequently the case, the urine is rendered alkaline by the addition of the hydrate of an alkaline earth and precipitated with a soluble calcium or barium salt. The phosphates may also be precipitated by means of neutral or basic acetate of lead, in which case the excess of lead is removed by means of sulphurated hydrogen or dilute sulphuric acid.

The Sulphates.

The sulphuric acid found in the urine is derived essentially from the albuminous material which is constantly broken down in the body, only a very small portion of the inorganic sulphates excreted being referable to the mineral constituents of the food. As was pointed out in the chapter on Reaction, sulphuric acid is constantly produced in the body, and, coming into contact with the so-called neutral phosphates present in almost all the tissues, transforms these into acid phosphates taking up the alkali thus set free, according to the equation:

$$2Na_2HPO_4 + H_2SO_4 = 2NaH_2PO_4 + Na_2SO_4,$$

both appearing in the urine. The alkaline carbonates, derived from the organic salts ingested by a process of oxidation, are also attacked by the sulphuric acid.

As the amount of food ingested is gradually diminished a point is reached when the body most tenaciously holds any alkaline salts that may still be present, and a new source for the neutralization of the acid is found in the ammonia, which would otherwise have been transformed into urea.

While the greater portion of the sulphuric acid excreted in the urine is found in the form of mineral sulphates, about one-tenth of the total amount may be shown to be in combination with aromatic substances belonging to the oxy-group, most important among these being the salts of phenol, indoxyl, and skatoxyl.

Indoxyl and skatoxyl, as will be shown later on, are derived from indol and skatol, which, together with phenol, are formed during

the process of intestinal putrefaction, their amount increasing and decreasing with the degree of putrefaction, and hence serving as a direct index of its intensity.

The mineral sulphates have been termed preformed sulphates, in contradistinction to the others, which are known as conjugate or ethereal sulphates. In the following pages the former will be designated by the letter A, the conjugate sulphates by the letter B, and the total sulphates as A + B.

The amount of A + B excreted in the twenty-four hours by a normal individual varies between 2 and 3 grammes, the ratio of A to B being as 10 : 1.

From what has been said it is apparent that the elimination of sulphates through the urine is largely dependent upon the degree of albuminous decomposition taking place in the tissues and fluids of the body, and hence to a certain extent upon the quantity of proteid material ingested, the mineral sulphates occurring in such small amount in the food as scarcely to affect the quantity excreted. Secondarily, the degree of intestinal putrefaction plays a *rôle*. The excretion of A + B is thus increased by a diet rich in animal proteids; the time after a meal, however, at which such an increase can be demonstrated varies greatly, depending essentially upon the time necessary for digestion. With a vegetable diet, on the other hand, the total sulphates will be found in diminished amount. During starvation, A + B is, of course, also diminished, this diminution affecting A especially, but in some cases B may be considerably increased.

Our present knowledge regarding the excretion of sulphates is very meagre, as may be seen from the following data: An increase in the elimination of the total sulphates is observed, as would be anticipated, in all cases in which an increased tissue-destruction is taking place, as in the acute febrile diseases. It must be remembered, however, that here the quantity excreted is not always greater than during convalescence, the diet remaining the same. Here, as elsewhere, in urinary studies, it is always necessary to distinguish between a relative increase and an absolute decrease. In pneumonia and acute myelitis the highest figures have been observed, the increased elimination during the febrile period being especially marked:

	Fever diet.		Full diet.
	Fever.	No fever.	No fever.
Pneumonia . . .	3.51 g.	1.47 g.	2.25 g.
Acute myelitis . . .	2.62 g.	1.52 g.	2.33 g.

During convalescence the excretion of the sulphates is diminished, a retention analogous to that of the chlorides and phosphates taking place. In contradistinction to the latter salts, it is in all probability not the mineral matter proper that is demanded by the body, but the sulphur-containing albuminous material.

A considerable elimination of A + B has also been observed in leukæmia, in which an average of 2.46 grammes is excreted, as compared with 1.51 grammes by a healthy individual receiving the same amount and kind of food. In one case of acute leukæmia 5.8 grammes were eliminated on the day preceding death. In diabetes mellitus, diabetes insipidus, œsophageal carcinoma, progressive muscular atrophy, pseudo-hypertrophic paralysis, and eczema an increased elimination has likewise been observed, while in chronic renal diseases a diminished excretion is the rule.

A study of the elimination of the *conjugate sulphates* and of the relation existing between A and B in disease is still more important than that of the total sulphates; but in both cases the data available at the present time are very scanty, and further observations are urgently needed.

The conjugate sulphates, as would be expected, are increased in all cases of increased intestinal putrefaction. In coprostasis the result of carcinoma the ratio of the preformed to the conjugate sulphates, normally 10, may diminish enormously. In one case, reported by Kast and Baas, it fell to 2, to rise again to 7 to 8, and finally to 9.5 to 15 after an artificial anus had been established. The author has observed a drop to 1.5 in a case of volvulus of ten days' standing. Biernacki found an increase in the elimination of conjugate sulphates amounting to from 0.15 to 0.5 gramme *pro die* in cases of chronic parenchymatous nephritis, going hand in hand apparently with a decrease in the secretion of hydrochloric acid by the stomach, the normal amount, according to his observations, being from 0.1973 to 0.2227 gramme. In one case B fell from 0.4382 to 0.1505 during the administration of hydrochloric acid, to increase again to 0.4127 upon its discontinuance.

In accord with these observations are those of Wasbutzki and Kast, the former finding an increased elimination of B in cases of intense bacterial fermentation taking place in the stomach, hydrochloric acid being either totally absent or present in greatly diminished amount, while a diminished elimination was observed in cases of intense torular fermentation, hyperchlorhydria existing at the

same time. In the absence of hydrochloric acid, a normal or even a slightly diminished amount was observed in cases of intense acid fermentation, lactic and butyric acids being present in large quantities.

By neutralizing the gastric juice with large doses of sodium bicarbonate Kast was able to bring about a marked increase in the elimination of B, the ratio A : B having fallen from 10.3–16.1 to 2.9–6.1.

Personal observations have led the author to the same conclusion, so that the following rules may be formulated :

1. A diminution in the secretion of hydrochloric acid is accompanied by an increased degree of intestinal putrefaction.

2. An increase in the secretion of hydrochloric acid is usually accompanied by a decrease in the degree of intestinal putrefaction.

3. The degree of intestinal putrefaction may be measured directly by the elimination of the conjugate sulphates.

(See also the chapter on the Aromatic Bodies.)

In obstructive jaundice the excretion of B was likewise found to be increased, returning to the normal as soon as the permeability of the biliary passages had again become established, while the total sulphates were found in diminished amount in cases of non-obstructive jaundice.

In cases of diarrhœa A + B, as well as B, is diminished, while A : B is increased.

Of drugs, large doses of morphine, potassium bromide, sodium salicylate, and antifebrin appear to cause an increased elimination of the total sulphates, while alcohol slightly diminishes the excretion.

Most important are the observations which have established a diminished excretion of the conjugate sulphates following the ingestion of the terpenes and camphor, Karlsbad and Marienbad water, which latter two, however, at first cause an increase. Kefir, in doses of from 1 to 1.5 liters *pro die*, has proved a most excellent remedy with which to check intestinal putrefaction. Injections of tannic acid and of a saturated solution of boric acid appear to produce but little effect, unless the dose be so large as to cause symptoms of poisoning.

The points of practical interest in connection with the elimination of the sulphates may be summarized as follows, and are concentrated in the elimination of the conjugate sulphates:

1. An increase in the conjugate sulphates in a general way points

to increased intestinal putrefaction, the direct cause for which must, according to our present knowledge, be sought in a total anachlorhydria, or at least a hypochlorhydria of the gastric juice, associated with intense bacterial fermentation, provided that lactic acid and butyric acid are not present in large amounts; an obstruction to the flow of bile and intestinal obstruction may, however, produce the same result.

2. A diminution in the quantity of conjugate sulphates, on the other hand, may be referable to hyperchlorhydria associated with torular fermentation, ulcer of the stomach forming an exception, in which, notwithstanding the fact that conjugate sulphates are frequently eliminated in increased amount, hyperchlorhydria usually exists.

3. In cases of diarrhœa the absolute as well as the relative quantity of A + B and B is diminished while A : B becomes greater.

Tests for the Sulphates in the Urine. The detection of the preformed and the combined sulphates in the urine depends upon the fact that the sulphates of the alkalies are precipitated by barium chloride as insoluble barium sulphate, according to the equation:

$$K_2SO_4 + BaCl_2 = BaSO_4 + 2KCl.$$

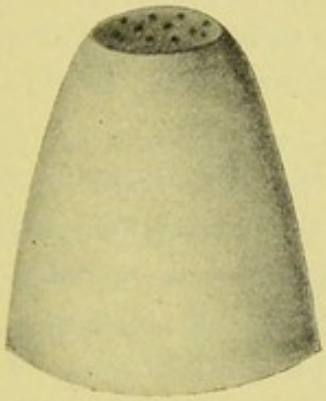
In the urine the addition of barium chloride at the same time causes a precipitation of the phosphates, which must be kept in solution by the addition of an acid, acetic acid being employed for this purpose whenever the presence of the preformed sulphates is to be demonstrated; hydrochloric acid is inadmissible, as it would cause the decomposition of the conjugate sulphates and set free the H_2SO thus held.

To test for the preformed sulphates a few c.c. of urine, strongly acidified with acetic acid, are treated with a few drops of a solution of $BaCl_2$, when in their presence a cloud or a white precipitate, referable to the formation of $BaSO_4$, will form.

To test for the conjugate sulphates, 25 c.c. of urine are treated with about the same volume of an alkaline barium chloride mixture (2 volumes of a solution of barium hydrate and 1 volume of a solution of barium chloride, both saturated at ordinary temperatures) and filtered after a few minutes, the preformed sulphates as well as the phosphates being thus removed. The filtrate is then strongly acidified with hydrochloric acid and boiled, when the occurrence of a precipitate will be referable to conjugate sulphates.

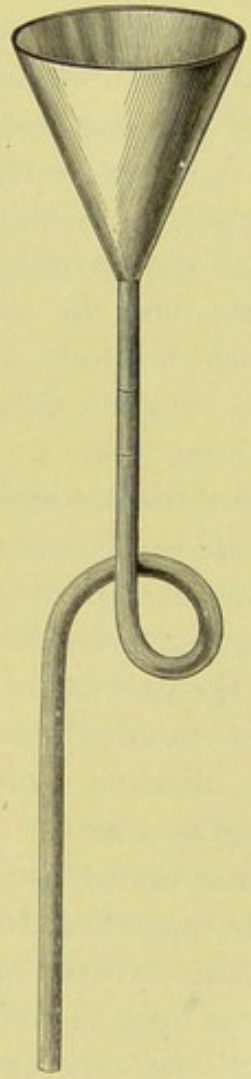
Quantitative Estimation of the Sulphates. The principle of the method employed is the same as that just described, the preformed sulphates contained in the urine forming an insoluble precipitate of $BaSO_4$ when treated directly with $BaCl_2$, while the combined sulphates do so only after having been decomposed by the addition of strong hydrochloric acid and the application of heat. In order to estimate the amount of preformed and conjugate sulphates in the urine it is best to determine the total sulphates in one portion, and the combined sulphates in another, the difference between the two giving the preformed sulphates.

FIG. 77.



A Gooch filter.

FIG. 78.



A suction-funnel.

QUANTITATIVE ESTIMATION OF THE TOTAL SULPHATES. One hundred c.c. of clear, filtered urine are treated with 8 c.c. of hydrochloric acid (specific gravity 1.12) and heated to the boiling-point, when 20 c.c. of a saturated solution of $BaCl_2$ are added. The mixture is kept on the water-bath until the $BaSO_4$ has thoroughly settled down and the supernatant fluid appears clear; this usually requires about half an hour. The precipitate is now filtered off, a Schleich and Schüll filter, or, still better, a Gooch filter (Fig. 77), provided with a close-fitting plug of asbestos, being employed, the whole having been previously dried and weighed. Care should be taken never to allow the filter to become dry, and small amounts of hot water must be added to the last c.c. remaining, the final traces being placed upon the filter with the aid of a rubber-tipped glass rod. The precipitate is washed with boiling water until a specimen

of the washings is no longer rendered cloudy, even on standing for a few minutes, on the addition of a drop of dilute sulphuric acid. Gum-like substances, as well as pigments, are removed by washing with hot alcohol (70 per cent.), and then filling the filter two or three times with ether. A suction-apparatus is necessary, and in the absence of a special pump a simple glass tube bent upon itself may be employed (Fig. 78).

If a paper filter has been used, it is placed in a weighed platinum or porcelain crucible and ignited. The ash is then heated, at first moderately, and almost completely covered with the lid. It is then heated, only half covered, from five to seven minutes, until the contents of the crucible are white. The crucible when cooled is placed in a desiccator and weighed, the difference between the first and the second weight giving the weight of the $BaSO_4$ obtained from 100 c.c. of urine.

A reduction of some of the $BaSO_4$ usually takes place during the process of combustion, owing to the presence of organic matter, so that the weight of the $BaSO_4$ obtained is actually too low. This error may be corrected in the following manner: The $BaSO_4$ is washed into a small beaker with a small amount of water, colored red by a few drops of an alcoholic solution of phenolphthalein, and titrated with a one-tenth normal solution of sulphuric acid until the red color has disappeared. Every c.c. of the one-tenth normal solution corresponds to 0.004 gramme of $BaSO_4$, so that the actual amount of $BaSO_4$ contained in 100 c.c. of urine is ascertained by adding the figure thus found to that obtained by weighing (see below).

Quantitative Estimation of the Conjugate Sulphates. One hundred c.c. of clear, filtered urine are mixed with 100 c.c. of an alkaline solution of $BaCl_2$ (see above), 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 acidified with dilute hydrochloric acid and brought to the boiling-point. It is kept upon the boiling water-bath until the $BaSO_4$ formed has settled and the supernatant fluid is clear. The precipitate is filtered off, washed, dried, and weighed, as described above. The $BaSO_4$ thus obtained multiplied by 2 and deducted from the amount found according to the first method indicates the amount referable to the preformed sulphates. 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 express-

ing the amount of H_2SO_4, SO_3, or S, corresponding to 1 gramme of $BaSO_4$, is found according to the following equations:

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

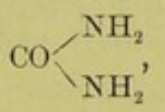
232.82 : 97.82 : : 1 : x, and x = 0.42015. ∴ 1 gramme of $BaSO_4$ = 0.42015 gramme of H_2SO_4.

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

To calculate results it is only necessary to multipy 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.

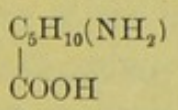
Urea.

Urea is by far the most important nitrogenous constituent of the urine, representing under normal conditions 85 to 86 per cent. of the total amount of nitrogen eliminated by the kidneys. Chemically it may be regarded as carbamide—*i. e.*, as the amide of carbonic acid—and represented by the formula:

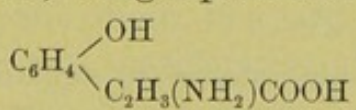


being thus a comparatively simple substance, and the question naturally suggests itself, In what relation does urea stand to the highly complex albuminous molecule from which it is derived? Numerous hypotheses have been offered to explain this most difficult problem, and, although we are in possession of a number of very suggestive data, an ultimate answer to the question cannot be given at the present time.

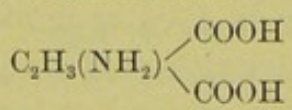
When albumin is treated with strong acids or alkalies, leucin, tyrosin, and asparaginic acid are formed, bodies which belong to the group of amido-acids, being represented by the formulæ:



Leucin.

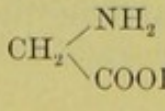


Tyrosin.



Asparaginic acid.

These bodies were regarded by Schultzen and Nencki as intermediary products in the formation of urea. As a matter of fact, it was shown that leucin, asparaginic acid, and glycocoll,



which latter can be obtained under similar conditions from connective tissue, osseous and gelatinous tissue, are transformed, to a large extent at least, into urea within the body. An analogous formation of urea was hence supposed to occur, the transformation of amido-acids into uric acid occurring in birds being regarded as supporting this view, uric acid in birds corresponding to urea in mammals. The manner of the transformation of amido-acids into urea in the body is unknown. It is conceivable that cyanic acid (CONH), for example, may be produced as an intermediary product, the formation of urea resulting from an interaction between 2 molecules of CONH in *statu nascendi*, according to the equation:

$$CONH + CONH + H_2O = CO\begin{matrix}NH_2\\NH_2\end{matrix} + CO_2.$$

A transformation of the amido-acids into the ammonium salts of the fatty acids standing next in order in the downward scale may also be imagined. This change being produced by a process of oxidation, the salts of the fatty acids would then be transformed into ammonium carbonate and this again into urea.

In the case of glycocoll such a process would be represented by the following equations:

$$\text{I.}\quad \underset{\text{Amido-acetic acid.}}{CH_2.NH_2.COOH} + 2O = \underset{\text{Ammon. formate.}}{HCO_2.NH_4} + CO_2$$

$$\text{II.}\quad \underset{\text{Ammon. formate.}}{2H.CO_2.NH_4} + 2O = \underset{\text{Ammonium carbonate.}}{(NH_4)_2CO_3} + H_2O + CO_2$$

$$\text{III.}\quad (NH_4)_2CO_3 = CO\begin{matrix}NH_2\\NH_2\end{matrix} + 2H_2O.$$

The possible formation of urea from ammonium carbonate in the body has been demonstrated by v. Schroeder and Salomon, who observed a fair production of urea when blood containing ammonium carbonate or ammonium formate was allowed to flow through isolated livers of dogs.

Other hypotheses have been offered to explain the mode of formation of urea, such as its production from ammonium carbonate, formed directly from albuminous material without the intermediate occurrence of amido-acids.

According to Drechsel, the amido-acids are transformed into carbamic acid, 2 molecules of the latter uniting to form urea, carbonic acid, and water:

$$CO\begin{matrix}NH_2\\OH\end{matrix} + CO\begin{matrix}NH_2\\OH\end{matrix} = CO\begin{matrix}NH_2\\NH_2\end{matrix} + CO_2 + H_2O.$$

On the other hand, it is possible that urea is not always formed in the same manner, and the possibility of its formation from kreatin and xanthin bases cannot be altogether excluded. It is also conceivable that urea may under certain conditions be produced in a different manner by different organs.

Numerous experiments have been made in order to ascertain definitely in what organ or organs urea is formed during health, and special attention has been directed to the kidneys, the muscular tissue, and the liver.

Opposed to the assumption that urea is formed in the kidneys are the facts that after extirpation of these organs an accumulation of urea is observed in the blood and tissues of the body, and that experiments analogous to those made with still living livers furnished a negative result.

The same result has been reached as far as the muscular tissue of the body is concerned, although the curious fact that more urea is found in these organs than in the blood of nephrectomized animals, in the typhoid stage of cholera Asiatica, etc., has so far not been explained. Under normal conditions, however, urea has not been demonstrated in the muscles.

There remain then for consideration the large glandular organs of the body, especially the liver and spleen, in which urea is always demonstrable. In the former organ the transformation of ammonium carbonate and the ammonium salts of the fatty acids has been conclusively established. The facts that possible antecedents of urea, such as leucin, have been observed in the absence of urea in the urine, in cases of acute yellow atrophy, and that an increase in the eliminaton of ammonia goes hand-in-hand with a diminished excretion of urea in certain diseases of the liver, also speak strongly in favor of the hepatic origin, to a large extent at least, of urea.

Before going on to a consideration of the quantitative excretion of urea in health and disease it will be well to form an idea of its ultimate sources. To this end the theory of Pettenkofer should be recalled, according to which albuminous material exists in the body in two different forms—*i. e.*, as organized albumin—which is built up in the form of tissues of the body, and as unorganized albumin, or circulating albumin, which must be regarded, in a manner, as a

reserve, to be used in tissue-repair, to be broken down if not used, and to be replaced by the proteids ingested with the next meal. It may, hence, be said that, as in the case of the mineral constituents of the urine, the urea found in the urine is referable on the one hand to the proteids of the food, and on the other to the proteids of the body-tissues. It is clear then that the elimination of urea will continue during starvation.

It has been stated that 84 to 86.6 per cent. of all the nitrogen eliminated in the urine is found in the form of urea, the remaining 13.4 per cent. being excreted as uric acid, hippuric acid, kreatinin, xanthin bases, etc. It might, hence, be supposed that an accurate idea of the degree of tissue-destruction could be formed from a quantitative estimation of urea. This, however, is not the case, especially in pathologic conditions, as the quantitative relation existing between the excretion of urea and the remaining nitrogenous constituents is subject to wide variations. In acute yellow atrophy, for example, as pointed out above, urea may disappear entirely from the urine, the nitrogen being eliminated in the form of other compounds. Whenever it becomes desirable then to gain an accurate insight into the degree of proteid-destruction or proteid-assimilation—in other words, into the nitrogenous metabolism—taking place in the body, it is necessary to resort to a quantitative determination of the total amount of nitrogen excreted by the kidneys, the quantity found being conveniently expressed in terms of urea. At the same time it is customary to express the amount of proteid tissue destroyed as muscle-tissue, this serving as a fair type of body-tissue in general.

As 100 grammes of lean muscle-tissue contain about 3.4 grammes of nitrogen, corresponding to 7.286 grammes of urea, 1 gramme of the latter is equivalent to 13.72 grammes of muscle-tissue. It is, hence, only necessary to multiply the quantity of urea eliminated in the twenty-four hours, corresponding to the total amount of nitrogen found, by 13.72, in order to form an idea of the extent of albuminous destruction taking place in the body. If accurate results are to be obtained, it also becomes necessary to determine the amount of nitrogen eliminated in the feces, a knowledge of the quantity in the food ingested being, of course, presupposed.

With all these data given the nitrogenous metabolism of the body can be accurately controlled.

Example: A patient eliminated 50 grammes of urea in twenty-

four hours; these 50 grammes correspond to 50 × 13.72—*i. e.*, 686 grammes of lean muscle-tissue; he ingested, on the other hand, an amount of nitrogenous material corresponding to only 10 grammes of urea, equivalent to 10 × 13.72—*i. e.*, 137.2 grammes of muscle-tissue. The difference between the amount ingested and that excreted in this case—*i. e.*, 548.8 grammes—must be referable to the destruction of organized albumin.

The valuable results of such a study in different cases, and the insight that can thus be obtained into the metabolic processes taking place in the body, are apparent, but such studies are, unfortunately, greatly neglected.

When the amount of nitrogen eliminated is equivalent to that ingested, *nitrogenous equilibrium* is said to exist. A healthy person may be said to be approximately in this condition.

It has been pointed out that during starvation urea is still eliminated from the body, although in diminished amount. The question now arises, What happens if at this time an amount of nitrogenous food is given which corresponds exactly in amount to that eliminated? Under such conditions an increased elimination of nitrogen takes place, all of the nitrogen ingested, in addition to that resulting from a breaking down of tissue, being excreted. The amount of nitrogen referable to the latter source, however, is somewhat less than that eliminated in the total absence of food. Unless starvation has been pushed too far, the body accommodates itself to the amount of food thus given and nitrogenous equilibrium is restored. If more food be allowed, an increased elimination results, again leading to a condition of nitrogenous equilibrium, different levels, so to speak, being possible. This is well illustrated by comparing the condition of the poorly nourished North German laboring population with that of the well-fed merchants, the excretion of urea in the former amounting only to 17.5 to 33.5 grammes of urea, and in the latter to 30 or even 40 grammes.

It is apparent, then, that the elimination of urea, and of nitrogen in general, is subject to great variations, depending upon the amount ingested and *that* resulting from tissue-destruction, which in turn is largely influenced by the body-weight. A statement in figures expressing the daily elimination of urea and of nitrogen would, hence, be of very little value, especially in pathologic conditions, in which the amount of nitrogen ingested is frequently very small. The elimination of nitrogen should hence always be compared with

the amount ingested, for which purpose the tables of König will be found most convenient. At the same time it must be remembered that not all the nitrogen taken into the body as food undergoes resorption, and that a variable amount, which in disease may be considerable, is eliminated with the feces, so that in accurate work this nitrogen also must be taken into account. In order to obviate the tedious estimation of nitrogen in the feces it has been proposed to determine the standard amount of urea which should appear in the urine of a healthy person with different forms of diet. Such experiments, of course, presuppose the control-person to be in a condition of nitrogenous equilibrium, which, from what has been said above, is readily accomplished, the human body adapting itself with ease to different forms of diet. In private practice, however, such a procedure would be difficult, and here approximate results can be obtained by a parallel estimation of the chlorides. In health the elimination of the chlorides may be placed at about one-half of the urea. Whenever the nitrogen resulting from tissue-destruction is in excess of that referable to the proteids ingested this relation between the excretion of chlorides and urea will be disturbed, the tissues of the body containing but very little sodium chloride. Whenever the amount of urea is in excess of the normal amount of chlorides, as indicated above, an increased tissue-destruction may be inferred, and *vice versa*. If, on the other hand, the chlorides are present in diminshed amount, the conclusion may be drawn that a retention of albumins is taking place in the body, a condition which is frequently observed during the convalescence from acute febrile diseases.

An *increase in the amount of urea*, and, as a matter of fact, of all the nitrogenous constituents, is observed especially in the acute febrile diseases, notwithstanding the diminished ingestion of nitrogenous material, and is due to the greatly increased tissue-destruction. An excretion of 50 grammes or more of urea is here frequently observed. Formerly it was thought that the fever itself was responsible for this increased elimination of urea; but this view became untenable when it was shown that the excretion of urea in the beginning of a febrile attack is not at all proportionate to the height of the temperature, reaching its highest point only when the fever has been continuous for several days. Still larger amounts, moreover, may be eliminated when the fever is abating. Similar observations have since been repeatedly made. An increased elimination of

nitrogen may be noted in almost every case of ague preceding the onset of the fever. The latter, therefore, cannot be the only factor which causes the increased excretion of urea, and it has been suggested that the cells of the body have lost the power of taking up nitrogen. The question, however, whether this is dependent upon the increase in temperature or the action of certain toxic substances circulating in the blood, or both, must still be regarded as unanswered.

The large increase in the elimination of nitrogen in febrile diseases is especially striking in those forms which end by crisis. This is notably the case in pneumonia, in which it may persist for two or three days after the occurrence of the crisis. This assumption of an underlying insufficiency on the part of the cells furnishes a very satisfactory explanation for the continued increased elimination of urea. An increase beyond the amount eliminated during the febrile stage is possibly owing to a certain degree of retention analogous to that occurring in the case of the mineral constituents of the urine.

The only exception to the rule that the excretion of urea is increased in acute febrile diseases is, apparently, acute yellow atrophy, in which the excretion of urea is not only greatly diminished, but may altogether cease, its place being taken by other nitrogenous bodies, and notably *leucin* and *tyrosin*.

Among afebrile diseases in which an increased elimination of urea has been noted must be mentioned the ordinary forms of diabetes mellitus, in which the highest figures have been obtained, viz., 150 grammes or more *pro die*. The observation is, in all probability, largely explained by the ingestion of excessive amounts of food by such patients, but carefully conducted experiments seem to show that a not inconsiderable portion of the urea is directly due to increased tissue-destruction. The interesting cases described by Hirschfeld, which will be considered later on, form an exception to this rule.

An increase is also observed in dyspnœic conditions, and particularly in pneumonia, being most marked on the day following the greatest difficulty in breathing. These observations, however, are not free from objections, as an increase has also been noted in conditions of apnœa.

A moderate increase has been found in cases of pernicious anæmia, in severe cases of leukæmia, scurvy, minor chorea, and paralysis

agitans. Observations made in cases of hystero-epilepsy have given rise to conflicting results. It is claimed, on the one hand, that the excretion of urea is diminished following the convulsive seizures of a hystero-epileptic nature, in contradistinction to an increased elimination following true epileptic attacks.

In cases of functional albuminuria associated with an increased elimination of uric acid or oxalic acid, or of both, as well as in numerous cases of gastro-intestinal disease, the author has observed an increased elimination of urea, and believes that in the treatment of these diseases a systematic study of the excretion of nitrogen is of fundamental importance.

Of drugs, an increased elimination is produced by coffee, caffein, morphine, codeia, ammonium chloride, sodium and potassium chloride, carbonate of lithia, the ingestion of large amounts of water, etc. The data concerning the action of quinine, salicylic acid, cold baths, etc., are very conflicting. A large increase has been observed in cases of phosphorus-poisoning.

Electricity also appears to exert a marked influence upon the excretion of urea, producing an increased elimination.

The *diminished elimination of urea* observed in certain diseases of the liver, notably in acute yellow atrophy, carcinoma, cirrhosis, and even in Weyl's disease, is of especial interest, being in perfect accord with the theory that the liver is the main seat of the production of urea.

As has been stated, urea may altogether disappear from the urine in acute yellow atrophy and also in Weyl's disease, notwithstanding the frequently not inconsiderable degree of fever. In cirrhosis, hyperæmia of the portal system has been thought to cause the diminution, which may be further increased in some cases by the occurrence of ascites. In short, the factors which may be regarded as causative in the production of a diminished elimination of urea in hepatic diseases may be summarized under the following headings:

1. Destruction of the hepatic parenchyma.
2. A diminished velocity of the flow of blood through the liver.
3. Insufficient excretion of bile, and coincident digestive disturbances.

Whenever there is disease affecting that portion of the renal parenchyma which is especially concerned in the elimination of urea, a diminished amount will, of course, be met with in the urine, and carefully conducted observations upon the excretion of the various

urinary constituents would undoubtedly be of considerable value from a diagnostic as well as a therapeutic stand-point. As the glomeruli of the kidneys are mainly concerned in the elimination of water and salts from the blood, and as the striated epithelium of the convoluted tubules appears to provide for the excretion of urea, the elimination of a fair amount of the latter with a diminished elimination of salts, the phosphates being here of especial interest, as they are derived to a large extent from albuminous material, would point more particularly to glomerular disease. On the other hand, a fair excretion of phosphates and a diminished excretion of urea would be indicative of tubular disease. Whenever the glomeruli and tubuli contorti are equally diseased an insufficient elimination of both phosphates and urea will be observed.

While, as a rule, the excretion of urea is greatly increased in diabetes mellitus, certain cases which have been elaborately described by Hirschfeld must be excepted. His researches have established beyond a doubt that the resorption of nitrogenous material from the intestines may be very much below normal, and with it the elimination of urea. Upon these grounds he has advocated the recognition of a distinct form of diabetes, which is characterized by a comparatively rapid course, the occurrence of colicky abdominal pains before or at the onset of the diabetic symptoms proper, the existence of pancreatic lesions in a certain proportion of cases, a more moderate degree of polyuria, etc.

In mental diseases a diminished excretion of urea has been observed in melancholia and in the more advanced stages of general paresis, while an increase is associated with the increased digestion of food during the first stage of profound dementia.

Following epileptic, cataleptic, and hysterical seizures, as well as in pseudo-hypertrophic paralysis, a decrease has been noted by some observers.

The diminished excretion found in Addison's disease has also been regarded as being of nervous origin.

All forms of chronic, non-progressive anæmia are associated with a decrease, as are also osteomalacia, impetigo, lepra, chronic rheumatism, etc. In chronic lead-poisoning the elimination of urea may be greatly diminished.

Of the influence of drugs in bringing about a diminished excretion of urea but little is known.

In conclusion, the relation existing between phosphatic excretion

and that of nitrogen should be especially noted, and the reader is referred to that chapter.

Properties of Urea. Urea crystallizes in two forms, viz., in long, fine white needles, if rapidly formed, or in long, colorless, quadratic rhombic prisms when allowed to crystallize gradually from its solutions.

At 100° C. it begins to show signs of decomposition, at 130° to 132° C. it melts, and when heated still further it is decomposed into cyanic acid and ammonia, of which the former is immediately transformed into its polymeric compound, cyanuric acid, the reaction which takes place being represented by the equations:

$$\text{I.} \quad CO\begin{matrix}NH_2\\NH_2\end{matrix} = CONH + NH_3.$$

$$\text{II.} \quad 3CONH = C_3O_3N_3H_3.$$

Biuret is formed as an intermediary product during this decomposition, 2 molecules of urea yielding 1 molecule of ammonia and 1 molecule of biuret, as represented in the equation:

$$CO\begin{matrix}NH_2\\NH_2\end{matrix} \quad CO\begin{matrix}NH_2\\NH\end{matrix}$$
$$= + NH_3.$$
$$CO\begin{matrix}NH_2\\NH_2\end{matrix} \quad CO\begin{matrix}\\NH_2\end{matrix}$$

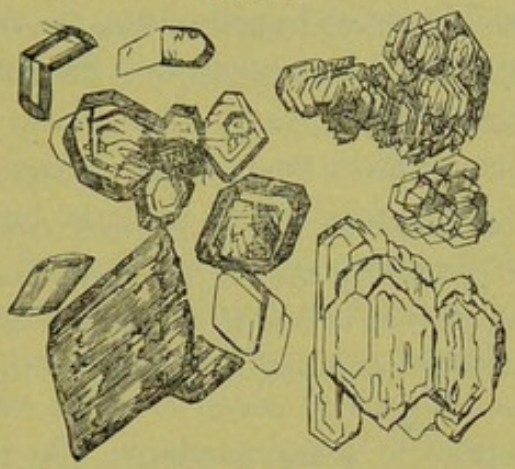
As this substance, which may be obtained by dissolving the residue remaining after all the ammonia has been driven off by careful heating, yields a beautiful reddish-violet color when a drop or two of a very dilute solution of sulphate of copper is added to its solution alkalinized with sodium hydrate, this reaction may be employed as a test for the detection of urea (*Biuret Test*).

Urea is readily soluble in water, fairly so in alcohol, and insoluble in anhydrous ether and benzol. The aqueous solution of urea is neutral in reaction, but combines with acids, bases, and salts to form molecular compounds.

Of special interest are the compounds of urea with nitric acid, oxalic acid, and mercuric nitrate. Urea nitrate, $CON_2H_4.HNO_3$, crystallizes in two different forms: in thin rhombic or six-sided colorless plates, which are frequently observed arranged like shingles one on top of the other when rapidly formed (Fig. 79), while larger and thicker rhombic columns or plates are obtained if the process of crystallization is allowed to proceed more slowly. Urea nitrate

is readily soluble in distilled water, while in alcohol and water containing nitric acid it dissolves with difficulty. Upon heating it evaporates without leaving a residue. Urea oxalate, $CON_2H_4\ C_2H_2O_4$,

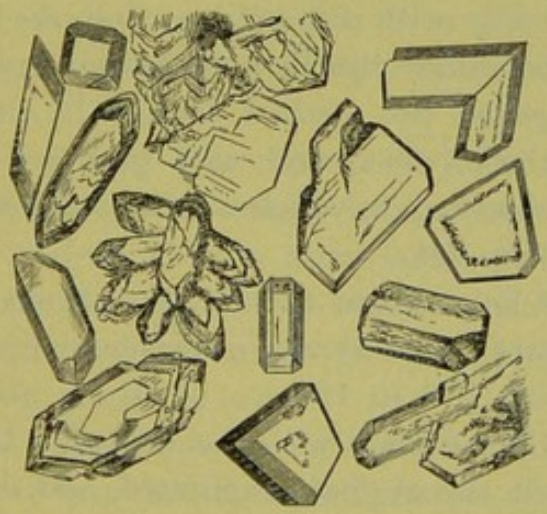
FIG. 79.



Nitrate of urea crystals. (KRUKENBERG, after KÜHNE.)

crystallizes in rhombic or six-sided prisms or plates (Fig. 80), which are less soluble in water than the nitrate; in alcohol and water containing oxalic acid it is only imperfectly soluble. With mercuric nitrate urea forms three different compounds, according to

FIG. 80.



Oxalate of urea crystals. (KRUKENBERG, after KÜHNE.)

the concentration of the two solutions, viz., $(CON_2H_4)Hg_2(NO_3)_4$, $(CON_2H_4).Hg_3(NO_3)_6$, and $(CON_2H_4)_2.Hg(NO_3)_2 + 3HgO$. The latter compound is of special importance, as Liebig's quantitative estimation of urea is based upon its formation. It results when a

2 per cent. solution of urea is treated with a dilute solution of mercuric nitrate, the reaction taking place according to the equation:

$$2CON_2H_4+4Hg(NO_3)_2+3H_2O=[2(CON_2H_4)_2\,Hg(NO_3)_2+3HgO]+6HNO_3.$$

Very important is the behavior of urea when treated with a solution of sodium hypochlorite or hypobromite, the most usual method of estimating urea being based upon this reaction, which may be represented by the equation:

$$CON_2H_4 + 3NaOBr = 3NaBr + 2N + CO_2 + 2H_2O.$$

In the chapter on Reaction it was pointed out that urine when exposed to the air gradually undergoes ammoniacal fermentation, and that this decomposition is due to the action of a non-organized ferment, ammonia being liberated, according to the equation:

$$CO\begin{matrix}NH_2\\NH_2\end{matrix} + H_2O = 2NH_3 + CO_2.$$

The same decomposition may be effected by heating a watery solution of urea in a sealed tube to 100° C.

It might be supposed that an accurate estimation of urea could be made by adding a solution of the ferment, which can readily be obtained, to a known quantity of urine, and then determining the amount of ammonia liberated, 34 parts of the latter corresponding to 60 parts of urea. Unfortunately the complete decomposition of urea is obtained only with difficulty, so that the method is a very tedious one. The same objection, although to a less degree, can also be urged against the method commonly employed, viz., the hypobromite method (which see), as 1 gramme of urea does not yield 372.7 c.c. of nitrogen, which would be theoretically required, but at the most only 354.3 c.c.

Separation of Urea from the Urine. From 50 to 100 c.c. of urine are evaporated to a syrupy consistence upon a water-bath, and extracted with 100 to 150 c.c. of strong alcohol, by rubbing up the residue while still hot with the alcohol. Upon cooling, the mixture is filtered, the alcohol evaporated, and the residue treated with pure cold nitric acid. Urea nitrate then separates out either immediately or on standing. After twenty-four hours the crystalline mass is collected upon a muslin filter, well strained, and freed from any liquid by placing it upon plates of clay. It is then dissolved in hot water, and the solution, if strongly colored, gently warmed with animal charcoal. This solution is neutralized with

barium carbonate, and rendered alkaline with barium hydrate. The urea nitrate is thus decomposed, barium nitrate and urea being formed:

$$2CON_2H_4.HNO_3 + BaCO_3 = 2CON_2H_4 + Ba(NO_3)_2 + H_2O.$$

The barium is now removed by passing a stream of CO_2 through the solution and filtering off the precipitate. The filtrate is evaporated until any barium nitrate still remaining crystallizes out. This is removed by decantation, when upon further evaporation the urea crystallizes out, and may be dried between layers of filter-paper and recrystallized from 95 to 98 per cent. alcohol. The crystals thus formed may now be subjected to further tests. To this end a few drops of an aqueous solution are added to a few c.c. of a sodium hypobromite solution, when in the presence of urea bubbles of gas will be given off. With a solution of sodium hypochlorite the same result may be obtained, but in this case the evolution of gas only takes place upon the application of heat. The formation of biuret may also be demonstrated by carefully melting a few of the crystals in a test-tube, dissolving the residue, when cool, in a little water, and alkalinizing the solution with a little sodium hydrate; upon the addition of a drop or two of a dilute solution of sulphate of copper a beautiful reddish-violet color, owing to the presence of biuret, will develop.

The addition of oxalic or nitric acid to a solution of urea will give rise to the formation of urea nitrate and oxalate, as described above.

This latter test may very conveniently be made under the microscope. A drop of the concentrated solution is placed upon a slide and covered, and a drop of pure nitric acid added from the side. Crystals of urea nitrate will then be seen to separate out, and may be recognized by their characteristic shingle-like arrangement (see Fig. 79).

When a urine is very rich in urea the mere addition of nitric acid will cause a more or less abundant precipitation of urea nitrate, and with this simple test an idea may even be formed of the amount present pro liter. An appearance of hoar-frost is thus only noted when not less than 25 grammes are present to the liter, while the formation of spangles of urea nitrate requires the presence of at least 45 grammes, and a heavy sediment is noted only when 50 grammes or more are present.

Quantitative Estimation of Urea. The only method which will be considered in detail is the one based upon the decomposition of urea into carbon dioxide and nitrogen in the presence of sodium hypobromite, which reaction takes place according to the equation:

$$CON_2H_4 + 3NaOBr = NaBr + CO_2 + 2H_2O + 2N.$$

The carbon dioxide thus formed is absorbed by an excess of sodium hydrate added to the hypobromite solution, while the nitrogen is set free, and can be suitably collected and measured, whence the determination of the corresponding amount of urea becomes a simple matter.

The only solution that is necessary is one of sodium hypobromite containing an excess of sodium hydrate. A 30 per cent. solution of the latter should be kept on hand and the sodium hypobromite solution prepared when required. To this end 70 c.c. of the sodium hydrate solution are diluted with 180 c.c. of water and treated with 5 c.c. of bromine in a bottle provided with a ground-glass stopper, the mixture being thoroughly shaken until every trace of free bromine has disappeared. Heat is evolved during this process, and the mixture should not be used until cold. The sodium hypobromite solution, if kept in a perfectly dark and cool place, may be preserved for a week or two. The reaction which takes place between the sodium hydrate and the bromine may be represented by the equation:

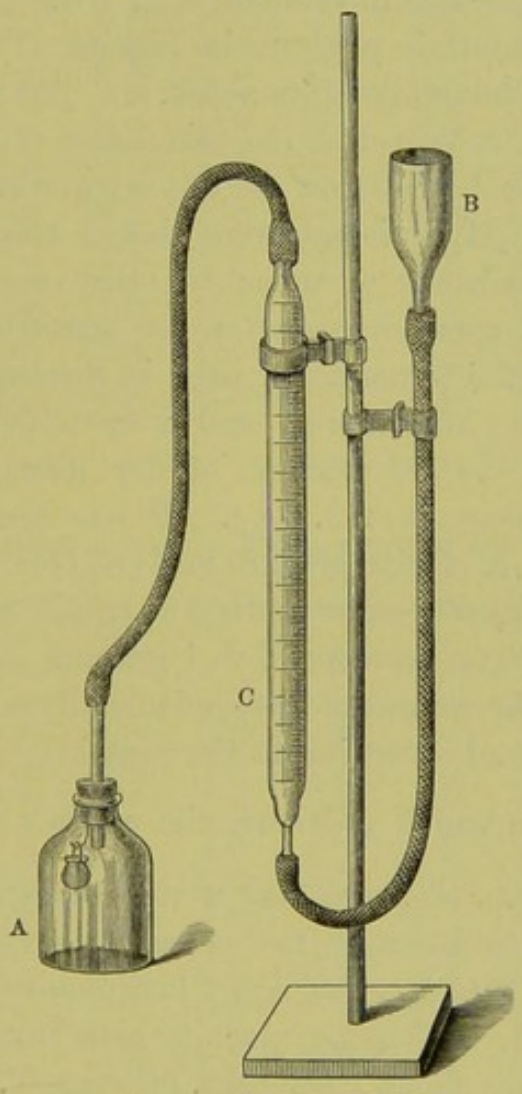
$$2NaOH + 2Br = NaBr + NaOBr + H_2O.$$

Various forms of apparatus, termed *ureometers*, have been suggested for the estimation of urea by this method. One which the author has found very satisfactory is represented in Fig. 81. It consists essentially of a burette, C, with an ascending rubber tube attached to the reservoir B, which can be raised or lowered as required for the purpose of equalizing the pressure, after the collection of the gas in the burette. A descending tube leads to a wide-mouthed bottle, A, containing the hypobromite solution. This is closed by a tightly fitting rubber stopper, to which a loop of platinum-wire is attached carrying a little bucket made of glass or porcelain, which can be swung from its support by inclining the bottle.

Method: The rubber stopper is removed from the bottle A, and water poured into B until the system BCA is filled to such an

extent that the water-level is visible in B above the point where the rubber tube is attached. About 25 to 30 c.c. of the hypobromite solution are then placed in the bottle A, 5 c.c. of urine into the little bucket, and this attached to the wire loop. The stopper is then carefully adjusted and the water in B and C brought to the same level, when the first reading is taken. A is then inclined until the little bucket drops into the liquid below. The nitrogen which is liberated collects in the burette C, the water falling in C

FIG. 81.



The author's ureometer.

and rising in B. After twenty to thirty minutes the pressure in C is equalized by lowering B until the water in both tubes has reached the same level. The second reading is then taken, the difference between the two indicating the volume of nitrogen liberated from 5 c.c. of urine at the temperature of the water in CB, which, as well as the barometric pressure, should be previously noted.

As the volume of gases is greatly influenced by the temperature, the barometric pressure, and the tension of the aqueous vapor, it becomes necessary, in order that the results reached shall be comparable with those obtained by other observers, to reduce the volume of nitrogen actually noted to a certain standard. This has been placed at 0° C. and 760 mercury millimetres pressure, in the absence of moisture. This correction is made according to the following formula: $V = \frac{v.\,(B—T)}{760.(1 + 0.00366.t)}$, in which V represents the corrected volume of the gas in terms of c.c., v the volume actually observed, B the barometric pressure in Hgmm., T the tension of the aqueous vapor at the temperature noted, t. The volume of nitrogen observed being thus corrected, the calculation of the corresponding amount of urea is based upon the following considerations: From the formula CON_2H_4 it is apparent that 2 atoms of nitrogen are contained in 1 molecule of urea; in other words, that 28 parts by weight of nitrogen correspond to 60 parts by weight of urea. The equivalent of 1 gramme of urea is then found according to the equation: 60 : 28 : : 1 : x, and x = 0.46666. The volume corresponding to 0.4666 gramme of dry nitrogen at 0° C. and 760 Hgmm. pressure is 372.7 c.c. It has been found, however, that only 354.3 c.c. of nitrogen are evolved from 1 gramme of urea at best, when the hypobromite method is employed. Knowing that 354.3 c.c. of nitrogen correspond to 1 gramme of urea, the amount of urea to which the volume of nitrogen actually observed is referable would then be found according to the equation: 1 : 354.3 : : x : y, and $x = \frac{y}{354.3}$, in which y denotes the number of c.c. of nitrogen evolved from 5 c.c. of urine, and x the corresponding amount of urea. In order to ascertain the percentage-amount of urea, it is only necessary to multiply the figure just obtained by 20.

Precautions: 1. The urine must be free from albumin. 2. It should contain only about 1 per cent. of urea—*i. e.*, not more than 0.05 gramme in 5 c.c., corresponding to 17.715 to 20 c.c. of nitrogen. Whenever a greater amount is noted, therefore, the urine is diluted to the proper degree, allowance being made in the calculation.

In ordinary clinical work the barometric pressure, as well as the tension of the aqueous vapor, may be ignored, and in the tables appended the corresponding amount of urea may be directly read off at the temperatures 5°, 10°, 15°, 20°, 25°, and 30° C.

Urea. Table for a Temperature of 5° C.

	1	1/10	2/10	3/10	4/10	5/10	6/10	7/10	8/10	9/10
1	1.32	1.45	1.58	1.71	1.85	1.98	2.11	2.24	2.37	2.51
2	2.64	2.77	2.90	3.03	3.17	3.30	3.43	3.56	3.69	3.83
3	3.96	4.09	4.22	4.36	4.49	4.62	4.75	4.88	5.02	5.15
4	5.28	5.41	5.54	5.68	5.81	5.94	6.07	6.20	6.34	6.47
5	6.60	6.73	6.87	7.00	7.13	7.26	7.39	7.53	7.66	7.79
6	7.92	8.05	8.19	8.32	8.45	8.58	8.71	8.85	8.98	9.11
7	9.24	9.38	9.51	9.64	9.77	9.90	10.04	10.17	10.30	10.43
8	10.56	10.70	10.83	10.96	11.09	11.22	11.36	11.49	11.62	11.75
9	11.89	12.02	12.15	12.28	12.41	12.55	12.68	12.81	12.94	13.07
10	13.21	13.34	13.47	13.60	13.73	13.87	14.00	14.13	14.26	14.39
11	14.53	14.66	14.79	14.92	15.06	15.19	15.32	15.45	15.58	15.72
12	15.85	15.98	16.11	16.24	16.38	16.51	16.64	16.77	16.90	17.04
13	17.17	17.30	17.43	17.57	17.70	17.83	17.96	18.09	18.23	18.36
14	18.49	18.62	18.75	18.89	19.02	19.15	19.28	19.41	19.55	19.68
15	19.81	19.94	20.08	20.21	20.34	20.47	20.60	20.74	20.87	21.00
16	21.13	21.26	21.40	21.53	21.66	21.79	21.92	23.06	22.19	22.32
17	22.45	23.59	22.72	22.85	22.98	23.11	23.25	23.38	23.51	23.64
18	23.77	23.91	24.04	24.17	24.30	24.43	24.57	24.70	24.83	24.96
19	25.10	25.23	25.36	25.49	25.62	25.76	25.89	26.02	26.15	26.28
20	26.42	26.55	26.68	26.81	26.94	27.08	27.21	27.34	27.47	27.60
21	27.74	27.87	28.00	28.13	28.27	28.40	28.55	28.66	28.79	28.93
22	29.06	29.19	29.32	29.45	29.59	29.72	29.85	29.98	30.11	30.25
23	30.38	30.51	30.64	30.78	30.91	31.04	31.17	31.30	31.44	31.57
24	31.70	31.83	31.96	32.10	32.23	32.36	32.49	32.62	32.76	32.89
25	33.02	33.15	33.29	33.42	33.55	33.68	33.81	33.95	34.08	34.21
26	34.34	34.47	34.61	34.74	34.87	35.00	35.13	35.27	35.40	35.53
27	35.66	35.80	35.93	36.06	36.19	36.32	36.46	36.59	36.72	36.85
28	36.98	37.12	37.25	37.38	37.51	37.64	37.78	37.91	38.04	38.17
29	38.31	38.44	38.57	38.70	38.83	38.97	39.10	39.28	39.36	39.49
30	39.63	39.76	39.89	40.02	40.15	40.29	40.42	40.55	40.68	40.81

Urea. Table for a Temperature of 10° C.

	1	1/10	2/10	3/10	4/10	5/10	6/10	7/10	8/10	9/10
1	1.31	1.43	1.56	1.69	1.82	1.95	2.08	2.21	2.34	2.47
2	2.60	2.73	2.86	2.99	3.12	3.25	3.38	3.51	3.64	3.77
3	3.90	4.03	4.16	4.29	4.42	4.55	4.68	4.81	4.94	5.07
4	5.20	5.33	5.46	5.59	5.72	5.85	5.98	6.11	6.24	6.37
5	6.50	6.33	6.76	6.89	7.02	7.15	7.28	7.41	7.54	7.67
6	7.80	7.93	8.06	8.19	8.32	8.45	8.58	8.71	8.84	8.97
7	9.10	9.23	9.36	9.49	9.62	9.75	9.88	10.01	10.14	10.27
8	10.40	10.53	10.66	10.79	10.92	11.05	11.18	11.31	11.44	11.57
9	11.71	11.84	11.97	12.10	12.23	12.36	12.49	12.62	12.75	12.88
10	13.01	13.14	13.27	13.40	13.53	13.66	13.79	13.92	14.05	14.18
11	14.30	14.44	14.57	14.70	14.83	14.95	15.09	15.22	15.35	15.48
12	15.60	15.74	15.87	16.00	16.13	16.26	16.39	16.52	16.65	16.78
13	16.91	17.04	17.17	17.30	17.43	17.56	17.69	17.82	17.95	18.08
14	18.21	18.34	18.47	18.60	18.73	18.86	18.99	19.12	19.25	19.38
15	19.51	19.64	19.77	19.90	20.03	20.16	20.29	20.42	20.55	20.68
16	20.81	20.94	21.07	21.20	21.33	21.46	21.59	21.72	21.85	21.98
17	22.11	22.24	22.37	22.50	22.63	22.76	22.89	23.02	23.15	23.28
18	23.41	23.54	23.67	23.80	23.93	24.06	24.19	24.32	24.45	24.58
19	24.72	24.85	24.98	25.11	25.24	25.37	25.50	25.63	25.76	25.89
20	26.02	26.15	26.28	26.41	26.54	26.67	26.80	26.93	27.06	27.19
21	27.32	27.45	27.58	27.71	27.84	27.97	28.10	28.23	28.36	28.49
22	28.62	28.75	28.88	29.01	29.14	29.27	29.40	29.53	29.66	29.79
23	29.92	30.05	30.18	30.31	30.44	30.57	30.70	30.83	30.96	31.09
24	31.22	31.35	31.48	31.61	31.74	31.87	32.00	32.13	32.26	32.39
25	32.52	32.65	32.78	32.91	33.04	33.17	33.30	33.43	33.56	33.69
26	33.82	33.95	34.08	34.21	34.34	34.47	34.60	34.73	34.86	34.99
27	35.12	35.25	35.38	35.51	35.64	35.77	35.90	36.03	36.16	36.29
28	36.42	36.55	36.68	36.81	36.94	37.07	37.20	37.33	37.46	37.59
29	37.73	37.86	37.99	38.12	38.25	38.38	38.51	38.64	38.77	38.90
30	39.03	39.16	39.29	39.42	39.55	39.68	39.81	39.94	40.07	40.20

Urea. Table for a Temperature of 15° C.

	1	1/10	2/10	3/10	4/10	5/10	6/10	7/10	8/10	9/10
1	1.28	1.41	1.53	1.66	1.79	1.92	2.04	2.17	2.30	2.43
2	2.56	2.69	2.81	2.94	3.07	3.20	3.33	3.46	3.58	3.71
3	3.84	3.97	4.10	4.22	4.35	4.48	4.61	4.74	4.87	4.99
4	5.12	5.25	5.38	5.50	5.63	5.76	5.89	6.02	6.14	6.27
5	6.40	6.53	6.60	6.79	6.91	7.04	7.17	7.30	7.43	7.55
6	7.68	7.81	7.94	8.07	8.19	8.32	8.45	8.58	8.71	8.83
7	8.96	9.09	9.22	9.35	9.48	9.60	9.73	9.86	9.99	10.12
8	10.24	10.37	10.50	10.63	10.76	10.88	11.01	11.14	11.27	11.40
9	11.53	11.65	11.78	11.91	12.04	12.17	12.29	12.42	12.55	12.68
10	12.81	12.93	13.06	13.19	13.32	13.45	13.57	13.70	13.83	13.96
11	14.09	14.22	14.34	14.47	14.60	14.73	14.86	14.98	15.11	15.24
12	15.37	15.50	15.62	15.75	15.88	16.01	16.14	16.26	16.39	16.52
13	16.65	16.78	16.91	17.03	17.16	17.29	17.42	17.55	17.67	17.80
14	17.93	18.06	18.19	18.31	18.44	18.57	18.70	18.83	18.95	19.08
15	19.21	19.34	19.47	19.60	19.72	19.85	19.98	20.11	20.24	20.36
16	20.49	20.62	20.75	20.88	21.00	21.13	21.26	21.39	21.52	21.64
17	21.77	21.90	22.03	22.16	22.29	22.41	22.54	22.67	22.80	22.93
18	23.05	23.18	23.31	23.44	23.57	23.69	23.82	23.95	24.08	24.21
19	24.34	24.46	24.59	24.72	24.85	24.98	25.10	25.23	25.36	25.49
20	25.62	25.74	25.87	26.00	26.13	26.26	26.38	26.51	26.64	26.77
21	26.90	27.03	27.15	27.28	27.41	27.54	27.67	27.79	27.92	28.05
22	28.18	28.31	28.43	28.56	28.69	28.82	28.95	25.07	29.20	29.33
23	29.46	29.59	29.72	29.84	29.97	30.10	30.23	30.36	30.48	30.61
24	30.74	30.87	31.00	31.12	31.25	31.38	31.51	31.64	31.76	31.89
25	32.02	32.15	32.28	32.41	32.53	32.66	32.79	32.92	33.05	33.17
26	33.30	33.43	33.56	33.69	33.81	33.94	34.07	34.20	34.33	34.45
27	34.58	34.71	34.84	34.97	35.10	35.42	35.35	35.48	35.61	35.74
28	35.86	35.99	36.12	36.25	36.38	36.50	36.63	36.76	36.89	37.02
29	37.15	37.27	37.40	37.53	37.66	37.79	37.91	38.04	38.17	38.30
30	38.43	38.55	38.68	38.81	38.94	39.07	39.12	39.32	39.45	39.58

Urea. Table for a Temperature of 20° C.

	1	1/10	2/10	3/10	4/10	5/10	6/10	7/10	8/10	9/10
1	1.26	1.38	1.51	1.63	1.76	1.89	2.01	2.14	2 26	2.39
2	2.52	2.64	2.77	2.90	3.02	3.16	3.27	3.40	3.53	3.65
3	3.78	3.91	4.03	4.16	4.28	4.41	4.54	4 66	4.79	4.91
4	5.04	5.17	5 29	5.42	5.54	5.67	5.80	5.92	6.05	6.17
5	6.30	6.43	6.55	6 68	6.81	6.93	7.06	7.18	7.31	7.44
6	7.56	7.69	7.81	7.94	8.07	8.19	8.32	8.44	8 57	8.70
7	8.82	8 95	9.08	9.20	9.33	9.45	9.58	9.71	9.83	9.96
8	10.08	10 21	10.34	10.46	10.59	10.71	10.84	10 97	11.09	11.22
9	11.35	11.47	11.60	11.72	11.85	11.98	12.10	12.23	12.35	12.48
10	12.61	12.73	12.86	12.98	13.11	13.24	13.36	13.49	13.61	13.74
11	13.87	13.99	14.12	14.25	14.37	14.50	14.62	14.75	14.88	15.00
12	15.13	15.25	15.38	15.51	15.63	15.76	15.88	16.01	16.14	16.26
13	16.39	16.52	16.64	16.77	16.89	17.02	17.15	17.27	17.40	17.52
14	17.65	17.78	17.90	18.03	18.15	18.28	18.41	18.53	18.66	18.78
15	18.91	19.04	19.16	19.29	19.42	19.54	19.67	19.79	19.92	20.05
16	20 17	20.30	20.42	20.55	20.68	20.80	20.93	21.05	21.18	21.31
17	21.43	21.56	21.69	21.81	21.94	22.06	22.19	22.32	22.44	22.57
18	22.69	22.82	22.95	23.07	23.20	23.32	23.45	23.53	23.70	23.83
19	23.96	24.08	24.21	24.33	24 46	24.59	24.71	24.84	24.96	25.09
20	25.22	25.34	25.47	25 59	25.72	25.85	25.97	26.10	26.22	26.35
21	26.48	26.60	26.73	26.86	26.98	27.11	27.23	27.36	27.49	27.61
22	27.74	27.86	27.99	28.12	28.24	28.37	28.49	28.62	28.75	28.87
23	29.00	29.13	29.25	29.38	29.50	29.63	29.76	29.88	30.01	30.13
24	30 26	30.39	30 51	30.64	30.76	30.89	31.02	31.14	31.27	31.39
25	31.52	31.65	31.77	31.90	32.03	32.15	32.28	32.40	32 53	32.66
26	32.78	32 91	33.03	33.16	33.29	33.41	33.54	33 66	33.79	33.92
27	34.04	34.17	34.30	34.42	34.55	34.67	34.80	34.93	35.05	35.18
28	35 30	35.43	35.56	35.68	35.81	35.93	36.06	36.19	36.31	36.44
29	36.57	36.69	36.82	36 94	37.07	37.20	37.32	37.45	37.57	37.70
30	37 83	37.95	38.08	38.20	38.33	38.46	38.58	38.71	38.83	38.96

Urea. Table for a Temperature of 25° C.

	0	1/10	2/10	3/10	4/10	5/10	6/10	7/10	8/10	9/10
1	1.24	1.36	1.49	1.61	1.73	1.86	1.98	2.11	2.23	2.35
2	2.48	2.60	2.73	2.85	2.97	3.10	3.22	3.35	3.47	3.59
3	3.72	3.84	3.97	4.09	4.22	4.34	4.46	4.59	4.71	4.84
4	4.96	5.08	5.21	5.33	5.46	5.58	5.70	5.83	5.95	6.08
5	6.20	6.33	6.45	6.57	6.70	6.82	6.95	7.07	7.19	7.32
6	7.44	7.57	7.69	7.81	7.94	8.06	8.19	8.31	8.43	8.50
7	8.68	8.81	8.93	9.06	9.18	9.30	9.43	9.55	9.68	9.80
8	9.92	10.05	10.17	10.30	10.42	10.54	10.67	10.79	10.92	10.04
9	11.17	11.29	11.41	11.54	11.66	11.79	11.91	12.03	12.16	12.28
10	12.41	12.53	12.65	12.78	12.90	13.03	13.15	13.27	13.40	13.52
11	13.65	13.77	13.89	14.02	14.14	14.27	14.39	14.52	14.64	14.76
12	14.89	15.01	15.14	15.26	15.38	15.51	15.63	15.76	15.88	16.00
13	16.13	16.25	16.38	16.50	16.63	16.75	16.87	17.00	17.12	17.26
14	17.37	17.49	17.62	17.74	17.87	17.99	18.11	18.24	18.36	18.49
15	18.61	18.74	18.86	18.98	19.11	19.23	19.36	19.48	19.60	19.73
16	19.85	19.98	20.10	20.22	20.35	20.47	20.60	20.72	20.84	20.97
17	21.09	21.22	21.34	21.47	21.59	21.71	21.84	21.96	22.09	22.21
18	22.33	22.46	22.58	22.71	22.83	22.95	23.08	23.20	23.33	23.45
19	23.58	23.70	23.82	23.95	24.07	24.20	24.32	24.44	24.57	24.69
20	24.82	24.94	25.06	25.19	25.31	25.44	25.56	25.68	25.81	25.93
21	26.06	26.18	26.30	26.43	26.55	26.68	26.80	26.92	27.05	27.17
22	27.30	27.42	27.55	27.67	27.79	27.92	28.04	28.17	28.29	28.41
23	28.54	28.66	28.79	28.91	29.04	29.16	29.28	29.41	29.53	29.66
24	29.78	29.90	30.03	30.15	30.28	30.40	30.52	30.65	30.77	30.90
25	31.02	31.15	31.27	31.39	31.52	31.64	31.77	31.89	32.01	32.14
26	32.26	32.39	32.51	32.63	32.76	32.88	33.01	33.13	33.25	33.38
27	33.50	33.63	33.75	33.88	34.00	34.12	34.25	34.37	34.50	34.62
28	34.74	34.87	34.99	35.12	35.24	35.36	35.49	35.61	35.74	35.86
29	35.99	36.11	36.23	36.36	36.48	36.61	36.73	36.85	36.98	37.10
30	37.23	37.35	37.47	37.60	37.72	37.85	37.97	38.09	38.22	38.24

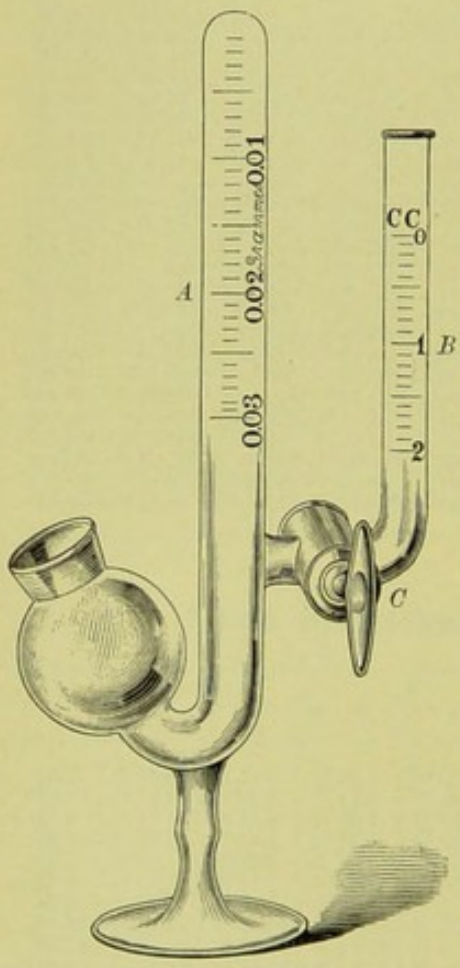
Urea. Table for a Temperature of 30° C.

	0	1/10	2/10	3/10	4/10	5/10	6/10	7/10	8/10	9/10
1	1.22	1.34	1.46	1.58	1.71	1.83	1.95	2.07	2.19	2.32
2	2.44	2.56	2.68	2.80	2.93	3.05	3.17	3.29	3.41	2.54
3	3.66	3.78	3.90	4.03	4.15	4.77	4.39	4.51	4.64	4.76
4	4.88	5.00	5.12	5.25	5.37	5.49	5.61	5.73	5.86	5.98
5	6.10	6.22	6.35	6.47	6.59	6.71	6.83	6.96	7.08	7.20
6	7.32	7.44	7.57	7.69	7.81	7.93	8.05	8.18	8.30	8.42
7	8.54	8.67	8.79	8.91	9.03	9.15	9.28	9.40	9.52	9.64
8	9.76	9.89	10.01	10.13	10.25	10.37	10.50	10.62	10.74	10.86
9	10.99	11.11	11.23	11.35	11.47	11.60	11.72	11.84	11.96	12.08
10	12.21	12.33	12.45	12.57	12.69	12.82	12.94	12.06	13.18	13.30
11	13.43	13.55	13.67	13.79	13.92	14.04	14.16	14.28	14.40	14.53
12	14.65	14.77	14.89	15.01	15.14	15.26	15.38	15.50	15.62	15.75
13	15.87	15.99	16.11	16.24	16.36	16.48	16.60	16.72	16.85	16.97
14	17.09	17.21	17.33	17.46	17.58	17.70	17.82	17.94	18.07	18.19
15	18.31	18.43	18.56	18.68	18.80	18.92	19.04	19.17	19.29	19.41
16	19.53	19.65	19.78	19.90	20.02	20.14	20.26	20.39	20.51	20.63
17	20.75	20.88	21.00	21.12	21.24	21.36	21.49	21.61	21.73	21.85
18	21.97	22.10	22.22	22.34	22.46	22.58	22.71	22.83	22.95	23.07
19	23.19	23.32	23.44	23.56	23.68	23.81	23.93	24.05	24.17	24.29
20	24.42	24.54	24.66	24.78	24.90	25.03	25.15	25.27	25.39	25.51
21	25.65	25.76	25.88	26.00	26.13	26.25	26.37	26.49	26.61	26.74
22	26.86	26.98	27.10	27.22	27.35	27.47	27.59	27.71	27.83	27.96
23	28.08	28.20	28.32	28.45	28.57	28.69	28.81	28.93	29.06	29.18
24	29.30	29.42	29.54	29.67	29.79	29.91	30.03	30.15	30.28	30.40
25	30.52	30.64	30.77	30.89	31.01	31.13	31.25	31.38	31.50	31.62
26	31.74	31.86	31.99	32.11	32.23	32.35	32.47	32.60	32.72	32.84
27	32.96	33.09	33.21	33.33	33.45	33.57	33.70	33.82	33.94	34.06
28	34.18	34.31	34.43	34.55	34.67	34.79	34.92	35.04	35.16	35.28
29	35.41	35.53	35.65	35.77	35.89	36.02	36.14	36.26	36.38	36.50
30	36.63	36.75	36.87	36.99	37.11	37.24	37.36	37.48	37.60	37.72

Of the other forms of apparatus, the ureometers devised by Doremus, Green, Marshall, Hüffner, and Squibb may be mentioned.

The latest modification of Doremus' apparatus is certainly most convenient, and can be highly recommended. Its general construction is seen in Fig. 82. A small amount of urine is poured into B while the stopcock (C) is closed. This is then opened for a moment and again closed, so as to fill its lumen. The tube (A) is washed out with water and filled with the hypobromite solution. The tube (B) is filled with urine, when 1 c.c. or less, if the urine is concentrated, is allowed to mix with the hypobromite solution in A. After all bubbles of gas have disappeared the reading is taken. The degrees marked upon the tube indicate directly the number of grammes or grains of urea contained in the amount of urine employed.[1]

FIG. 82.



Doremus' ureometer.

Green's apparatus (Fig. 83) consists of a tube graduated in c.c., and blown out at the bottom into a wider portion, holding about 50 to 60 c.c. The bulb is provided with a side-tube, into which a bent funnel-tube can be inserted for the purpose of equalizing the pressure. The side-tube having been detached, the apparatus is filled with sodium hypobromite solution, when 2 c.c. of urine, diluted if necessary, are introduced by means of a graduated and bent pipette. After all bubbles of gas have disappeared the funnel-tube is inserted into the side-opening and filled with hypobromite solution until the level in both tubes is the same. The volume is then noted, corrected, and the corresponding amount of urea calculated as described.

[1] Instead of employing the solution described on page 336, it is sufficient to fill the long arm of the tube with a solution containing 100 grammes of caustic soda dissolved in 250 c.c. of distilled water, and to add 1 c.c. of bromine and a sufficient amount of water to fill the bend of the tube.

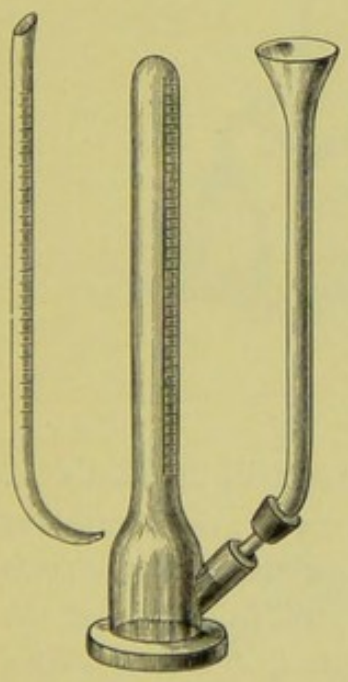
Marshall's apparatus is a conveniently modified form of Green's, and is used in the same manner (Fig. 84).

Hüffner's apparatus is excellent (Fig. 85). It consists of a small bulb, A, of 5 c.c. capacity, which is separated from a larger bulb, C, holding about 100 c.c., by a well-oiled glass stopcock. The upper end of C is drawn out to such an extent that the eudiometer D, which is about 30 cm. long, 2 cm. wide, and divided into fifths of c.c., can be passed over it for a short distance. The bowl E, fitted over C by means of a cork, serves to hold a portion of the hypobromite solution.

The exact capacity of A and of the lumen of the stopcock must be separately determined for each instrument.

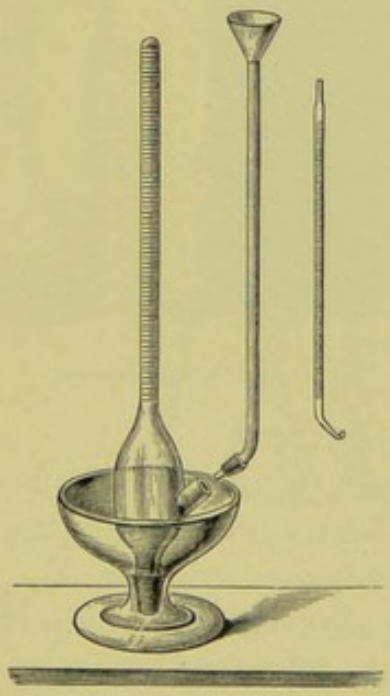
Method: The bulb A and the lumen of the stopcock are filled with urine which has been diluted, if necessary. The stopcock having been closed, C is washed out carefully with distilled water and filled with the hypobromite solution until the liquid in the

FIG. 83.



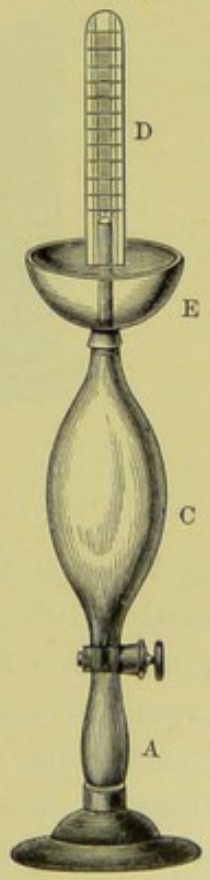
Green's ureometer.

FIG. 84.



Marshall's ureometer.

FIG. 85.



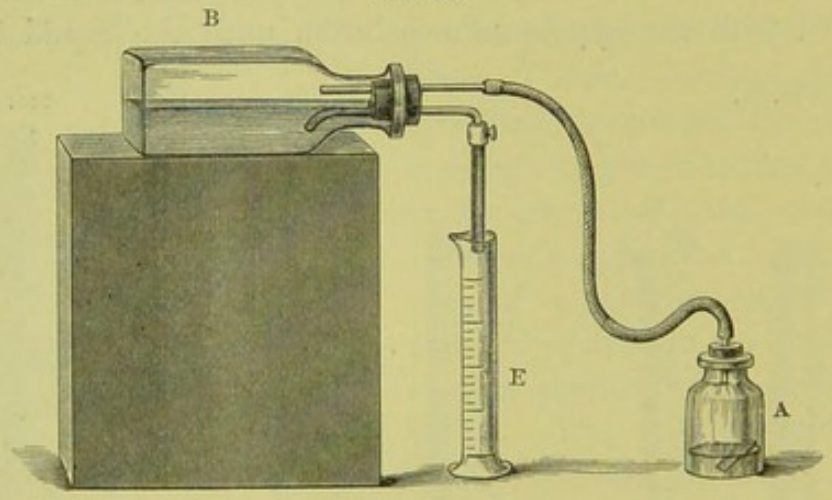
Hüffner's ureometer.

dish stands several cm. above the mouth of C. The eudiometer is next filled with the same solution and carefully submerged in the liquid contained in the dish, adjusted over the mouth of C. The

urine in A is then allowed to mix with the hypobromite solution very gradually by opening the stopcock. After all bubbles of gas have disappeared the eudiometer is transferred to a cylinder filled with water and thoroughly immersed. After twenty to thirty minutes the level of the liquid in the tube and that of the outside water are equalized and the reading taken. The temperature of the water being likewise noted, the volume of the gas is corrected and the corresponding amount of urea calculated.

Squibb's method: This method, like that of Doremus, may be highly recommended to the practitioner for its simplicity. The apparatus (Fig. 86) consists of two ordinary medicine-bottles, A and B, A being the one in which the nitrogen is evolved. B is closed by a doubly perforated rubber-stopper, a straight tube pass-

FIG. 86.



Squibb's ureometer.

ing through the upper aperture and connecting with the bottle A. Another tube, bent downward and carrying a clamp, as seen in the figure, leads to a graduated cylinder, E. B contains a sufficient amount of water for the bent tube to dip into; 25 to 30 c.c. of the hypobromite solution, and a small tube containing 5 c.c. of urine, diluted if necessary, according to the specific gravity, are placed in A, the clamp at E being closed. The rubber-stopper is now firmly inserted and E opened, when a few drops of water, which may be disregarded, will escape. The graduated cylinder is then placed beneath the outflow-tube and the bottle A inclined. The nitrogen collecting in B displaces its own volume of water, which flows out

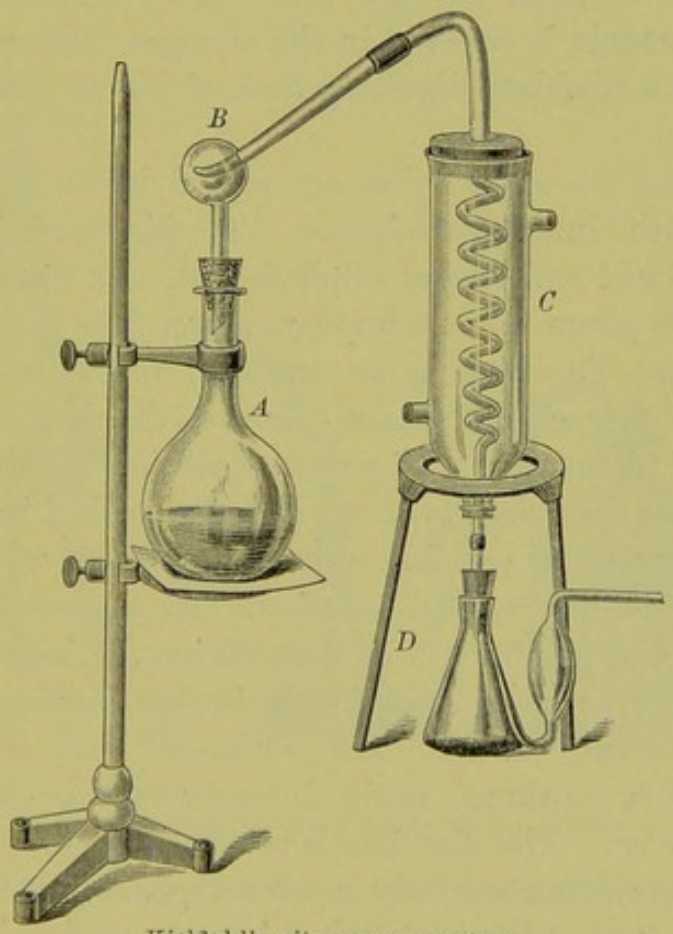
and is collected in E, whence the corresponding amount of urea may be calculated.

It should be mentioned that sodium hypobromite liberates nitrogen, not only from the urea, but also from the other nitrogenous constituents of the urine; the error thus incurred, however, appears just to counterbalance the deficit in the amount of nitrogen obtained, corresponding to 1 gramme of urea.

Estimation of Nitrogen. For the purpose of estimating the total amount of nitrogen in the urine, the method of Kjeldahl or that of Will-Varrentrapp is most conveniently employed.

Kjeldahl's method: Principle: The organic material of the urine is decomposed by means of sulphuric acid, when all the nitrogen

FIG. 87.



Kjeldahl's nitrogen apparatus.

which is not present in combination with oxygen is transformed into ammonia. After adding sodium hydrate in excess this is then distilled off and received in a known quantity of titrated acid, the excess being retitrated with sodium hydrate. In this manner the amount of ammonia and the corresponding quantity of nitrogen is

ascertained, it being remembered that 17 grammes of ammonia correspond to 14 grammes of nitrogen.

Reagents required:

1. Gunning's mixture. This consists of 15 c.c. of concentrated sulphuric acid, 10 grammes of potassium sulphate, and 0.5 gramme of copper sulphate.

2. A solution of sodium hydrate containing 270 grammes in the liter (sp. gr. 1.243).

3. Pulverized talcum or granulated zinc.

4. A one-fourth normal solution of sulphuric acid.

5. A one-half normal solution of sodium hydrate.

Apparatus required (see Fig. 87). This consists of a retort of about 750 c.c. capacity (A), which is connected with a Kjeldahl distilling tube (B), and through this with a Städeler's condenser (C). The ammonia is received in the nitrogen bulb at D.

In addition a Kjeldahl digesting flask of 200 to 300 c.c. capacity is required.

Method: 5 or 10 c.c. of urine are placed in the digesting flask and treated with Gunning's mixture. To this end it is best to add the sulphuric acid and copper sulphate first, to heat until sulphuric acid vapors are given off in abundance, and then to add the potassium sulphate. The heating is continued until the solution has become entirely clear and almost colorless, the flask being inclined to an angle of about 45°. Vigorous ebullition should be avoided.

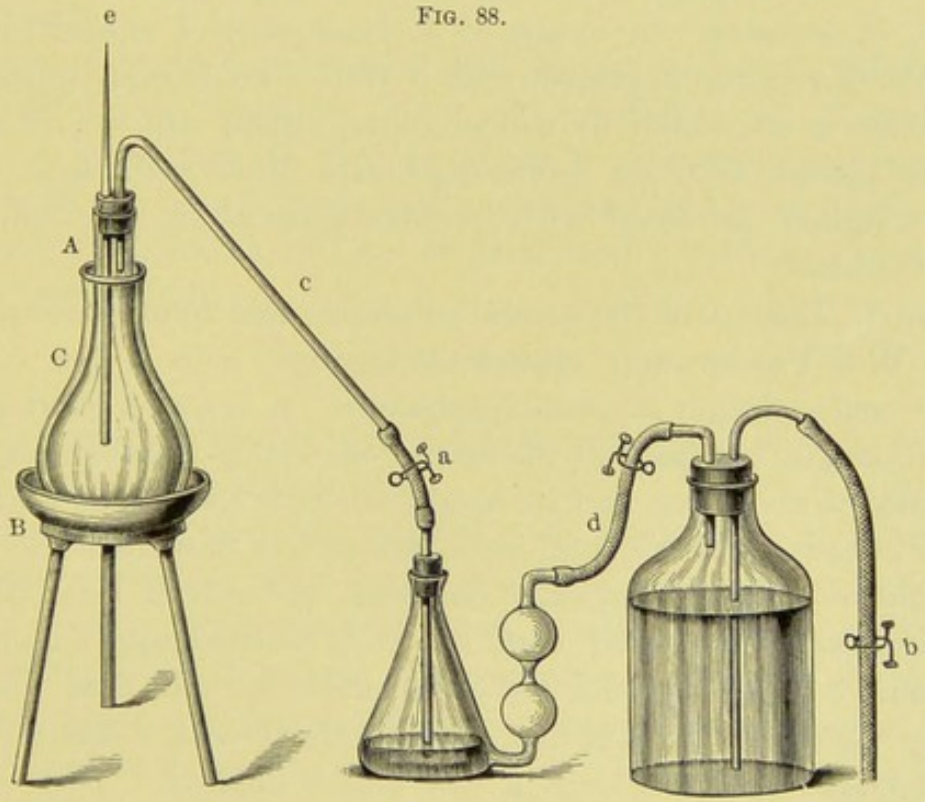
Upon cooling the contents of the flask are washed into the retort, using as little water as possible, and slowly treated with a moderate excess of the sodium hydrate solution. As a general rule, 40 c.c. for every 5 c.c. of sulphuric acid are sufficient. A little pulverized talcum or a few pieces of granulated zinc are finally added, when the retort is connected with the condenser, and the distillation begun. This is continued until about two-thirds of the solution have passed over. The distillate is received in the nitrogen bulb, which should contain a carefully measured quantity of the one-fourth normal solution of sulphuric acid. As a general rule, 30 c.c. are sufficient. As soon as the distillation is completed the condenser is disconnected, washed out with a small amount of distilled water, and the washings added to the distillate. After the addition of a few drops of tincture of cochineal, the excess of sulphuric acid is then retitrated with the one-fourth normal solution of sodium hydrate, and the amount found deducted from the 30 c.c. used.

The titration should be continued until every trace of yellow has disappeared and a pure rose-color is obtained. The difference multiplied with 0.0035 will then indicate the amount of nitrogen present in the 5 or 10 c.c. of urine. The corresponding amount of urea is found by multiplying this figure with 20.

As Kjeldahl's method presupposes a thorough knowledge of chemical technique, it is well to make at least two parallel estimations in every case.

Will-Varrentrapp's method, as modified by Seegen-Schneider. Principle: If nitrogenous organic material is heated in intimate contact with soda-lime, all the nitrogen is given off in the form of ammonia, which is collected in a known quantity of acid; the excess

FIG. 88.



Apparatus for the determination of nitrogen.

not used in the neutralization of the ammonia is then determined by titration with a solution of sodium hydrate of known strength. The amount held by the ammonia is thus ascertained, and from it the corresponding amount of nitrogen, it being remembered that 17 grammes of ammonia correspond to 14 grammes of nitrogen.

Reagents required: 1. A quantity of thoroughly fused calcic soda, which, while still hot, should be placed in a well-stoppered bottle, where it may be kept ready for use for a long time.

2. A normal solution of sulphuric acid.
3. A normal solution of sodium hydrate.

Apparatus required: As is apparent from the preceding diagram (Fig. 88), the apparatus consists of a Kjeldahl digesting flask, A, provided with a long neck (10 to 12 cm. long), of about 100 c.c. capacity, which is placed in a copper crucet, B, and imbedded in sand. The crucet is placed upon a pipe-stem triangle over the flame. The neck of the flask is surrounded by a hood of copper or tin plate, C, moulded to the flask and reaching not higher than 1.5 cm. below the rubber-stopper. The latter is doubly perforated, a tube *e* drawn out to a point and closed at the free end passing through one aperture and extending about half-way down the flask, while the second passes through the other opening. This second tube, *c*, is connected by means of a short piece of rubber-tubing, upon which a clamp is placed, with a Will-Varrentrapp apparatus. The latter is connected by rubber-tubing, upon which a clamp is likewise placed, with an aspirating-bottle filled with water, into which a siphon, provided with a rubber-tube at its free end, dips to the bottom.

Method: Ten c.c. of the normal sulphuric-acid solution are placed in the Will-Varrentrapp apparatus together with a few c.c. of a 1 per cent. solution of phenolphthalein. A layer of sand about 1 cm. in height is placed in the crucet, the clamp *a* closed, and the flask filled to about one-half its height with the soda-lime, when the hood is adjusted and 5 c.c. of urine allowed to flow upon the soda. The rubber-stopper is quickly adjusted, the rubber tube having been previously connected with the Will-Varrentrapp apparatus. The clamp *a* is now opened, the crucet filled up with sand, and the heating begun. This is at first done carefully with a small flame, but increased gradually until a full heat is applied. This is continued for one-half to three-quarters of an hour. When drops of moisture are no longer visible in the tube *c*, or when the evolution of gas has entirely ceased, the rubber-tube of the aspirating-bottle *d* is slipped on to the Will-Varrentrapp apparatus, the clamp *b* slightly opened, the tip of *e* broken off, and air allowed to pass slowly through the entire system for a quarter of an hour, when the flame is extinguished. The Will-Varrentrapp apparatus is then detached, and its contents titrated with the normal solution of sodium hydrate.

The number of c.c. of the sodium hydrate solution employed is

deducted from 10 (the number of c.c. of the normal sulphuric-acid solution, 1 c.c. of the latter being equivalent to 1 c.c. of the former), the difference giving the number of c.c. of the normal sulphuric-acid solution neutralized by the ammonia evolved from 5 c.c. of urine. This number multiplied by 20 will then represent the number of c.c. required to neutralize the ammonia contained in 100 c.c. of urine. As 1000 c.c. of the normal solution of sulphuric acid correspond to 17 grammes of ammonia or 14 grammes of nitrogen, the number of c.c. of the sulphuric-acid solution corresponding to 100 c.c. of urine will be found from the equation: 1000 : 14 : : x : y, and $y = 0.014\ x$, in which x represents the number of c.c. required to neutralize the amount of ammonia evolved from 100 c.c. of urine and y the corresponding amount of nitrogen—*i. e.*, the percentage of nitrogen.

If the nitrogen is to be calculated in terms of urea, this is done according to the equation: 1000 : 30 (= 14N) : : x : y, and $y = 0.03\ x$ = percentage of urea, in which x represents, as above, the number of c.c. of sulphuric acid neutralized by the ammonia, viz., nitrogen, contained in 100 c.c. of urine, and y the urea corresponding to this amount.

Uric Acid.

Uric acid was formerly regarded as an antecedent of urea, but this view has now been abandoned.

In the case of birds the researches of Minkowski, v. Schroeder, and others seem to point to an origin of uric acid analogous to that of urea in mammals. A great decrease in the elimination of this substance has thus been observed after extirpation of the liver in geese, which was associated with a corresponding increase in the excretion of ammonia and of lactic acid. In mammals uric acid is apparently derived from nuclein by a process of dissociation, and the spleen has recently been suggested as the most probable seat of its formation. As a matter of fact, an increased elimination has been observed in cases of splenic hypertrophy, which disappeared again, as the size of the organ returned to the normal, under the administration of quinine. The observations of Horbaczewski, moreover, who noted a decided new formation of uric acid when blood of calves and splenic pulp were allowed to stand in contact in the presence of oxygen, appear to render the splenic origin of this substance still more probable. The leucocytes are thought to

be especially concerned in this transformation, and, as a matter of fact, it is known that the amount of uric acid is increased in cases of splenic leukæmia and during the process of digestive leucocytosis. The origin of uric acid from nuclein is also well shown in the fact that the ingestion of food containing much nuclein, such as thymus gland, leads to an increased elimination, while during a milk-diet minimal amounts only are excreted.

Uric acid, which is almost insoluble in water, is held in solution in the urine in consequence of the presence of disodium phosphate, which transforms it into the readily soluble neutral disodium urate, according to the following equation:

$$2Na_2HPO_4 + C_5H_4N_4O_3 = 2NaH_2PO_4 + C_5H_2Na_2N_4O_3.$$

Should uric acid be present in larger amount, the disodium urate gives up part of its sodium, acid monosodium urate resulting, which, being soluble with difficulty, is thrown down in concentrated urines as a sediment. The reaction taking place is represented by the following equation:

$$C_5H_4N_4O_3 + C_5H_2Na_2N_4O_3 = C_5H_3NaN_4O_3 + C_5H_3NaN_4O_3.$$

Should a still greater amount of uric acid be present, this is thrown down as such.

The normal amount of uric acid excreted in the twenty-four hours may be said to vary between 0.2 and 1 gramme, being influenced to a certain extent by the character of the food, a diet rich in nitrogenous material increasing the amount of uric acid, while a diminished elimination of uric acid results from a diet free from nitrogen. It is also influenced by the amount of exercise taken, diminishing during rest and increasing with muscular activity. In addition, there are certain individual peculiarities, of the nature of which, however, practically nothing is known. Hence it has always been held that it is impossible in many cases to state definitely whether the amount of uric acid excreted by an individual is normal or not, as the tolerance on the part of the body of this substance varies greatly in different persons.

The relation normally existing between the excretion of uric acid and of urea has been placed at between 1 : 50 and 1 : 60, but is inconstant, especially in pathologic conditions, in which the relative amount of uric acid may be greatly increased. It is impossible, however, at the present time to furnish a satisfactory explanation of the variations in the excretion of uric acid observed in patho-

logic conditions, and but little more, in fact, can be done than to enumerate the various diseases in which such variations have been observed.

In febrile diseases, as typhoid fever, pneumonia, pleurisy, pericarditis, etc., the excretion of uric acid appears to be quite constantly increased.

Very interesting and suggestive are the data obtained in cases of true leukæmia, in which a daily excretion of from 1 to 5 grammes is frequently observed. The relation existing between the elimination of uric acid and of urea may here vary from 1 : 45 to 1 : 19, or even 1 : 12. In a few cases of pseudo-leukæmia a like increase has been noted. In one case which the author had occasion to study for about three weeks the actual amount eliminated varied between 0.256 and 0.957 gramme, while the relation between it and urea varied from 1 : 64 to 1 : 22. In general it may said that the elimination of uric acid is increased in all splenic diseases. In pernicious anæmia the uric acid was found to be normal or increased. In dyspeptic disturbances the uric acid is frequently increased. In hepatic cirrhosis the relation of uric acid to urea has been found to vary from 1 : 19 to 1 : 33, while the amount of the former varied between 0.5 and 2 grammes.

An increased elimination of uric acid, forming a disease *sui generis*, as it were, must also be noted, constituting the so-called uric-acid diathesis, in which an enormous increase in the elimination of this substance appears to constitute the only objective symptom. Patients thus afflicted are the subjects of profound hypochondriasis and lose flesh rapidly.

Da Costa has recently described a condition which is characterized by the existence of certain nervous symptoms, such as listlessness, fatigue upon slight exertion, headache, despondency, giddiness, and sleeplessness, associated with the elimination of a trace of albumin and of large amounts of uric acid, oxalic acid, or of both. Cardiac hypertrophy and other cardiac lesions of Bright's disease were conspicuously absent. The specific gravity in such cases is always high, varying between 1.022 and 1.036. The quantity of urine is about normal. The author has noted a considerable increase in the amount of urea in such cases.

The excretion of uric acid in gout has been the subject of numerous investigations, and while the causes producing the variations here observed are still a matter of great uncertainity, a diminished

elimination in the chronic state of the disease, especially marked immediately preceding the occurrence of exacerbations, as well as an increased elimination during and immediately after an attack, may be regarded as indisputable facts. A resorption of the uric acid deposited in the form of tophi, in consequence of an increased degree of alkalinity of the blood, has been urged as the cause of acute attacks, the headaches and mental depression observed at these times being explained by the sudden flooding of the system, as it were, with uric acid. Whether or not we are dealing with a process of increased production or of diminished elimination of this substance in gout remains as yet to be decided.

In diabetes a diminished amount of uric acid is usually found. Cases may be seen, however, in which, associated with a diminution in or an entire absence of sugar, there occurs a most marked increase in the amount of uric acid, amounting in some cases to 3 grammes *pro die*. To this condition the term *diabetes alternans* has been applied.

In the ordinary forms of anæmia and chlorosis the amount of uric acid is quite constantly diminished. So also in chronic interstitial nephritis, chronic lead-poisoning, progressive muscular atrophy, and pseudo-hypertrophic paralysis.

Very interesting and suggestive is the increased elimination observed in acute articular rheumatism, returning to normal or even becoming subnormal with approaching convalescence.

Fats and cane-sugar cause an increased elimination of uric acid. With a vegetable diet much less is excreted than with an animal diet. In a case cited by Bunge, 0.253 gramme was thus noted with the former diet, as compared with 1.398 grammes with the latter.

It is, consequently, necessary to order for a patient the subject of the so-called uric-acid diathesis a diet containing as small an amount of nitrogenous material, particularly of animal origin, as possible. Foods rich in alkaline salts are indicated, such as potatoes, the more acid fruits, and berries. Cheeses should be avoided, being rich in albumins and very poor in alkaline salts. The reverse, of course, holds good when for any reason an increased elimination of uric acid appears advisable, the main factor to be considered in each case being the degree of alkalinity of the blood. Recently it has been shown that enormous amounts of uric acid are excreted under a diet rich in nucleins, thymus having been employed in the cases observed.

Of drugs, salicylic acid and its salts, as well as disodium phosphate, increase the elimination of uric acid. Alkalies, on the other hand, are indicated when an excessive excretion exists, and the same may be said of potassium iodide, quinine, antipyrin, thallin, etc.

Steam baths cause a most decided increase, amounting in some cases to twice or thrice the normal amount, the increase often persisting for several days.

Properties of Uric Acid. Chemically uric acid is closely related to urea on the one hand, and to the xanthin-bases on the other. Its relation to urea is quite clear, if it be remembered that oxidizing agents transform uric acid into urea or into substituted ureas, such as allantoin and alloxan, which latter is closely related to parabanic acid, or oxalyl urea, and barbituric acid, or malonyl urea.

The relation existing between these various substances is seen in the following equations, and it will be observed that uric acid, like the xanthin-bases, contains an alloxan and a urea radicle. Uric acid plus xanthin-bases are hence also spoken of as alloxur bodies, and the relation existing between the elimination of uric acid-nitrogen and the alloxur bases-nitrogen has recently attracted much attention:

1. $\underset{\text{Uric acid.}}{C_5H_4N_4O_3} + H_2O + O = \underset{\text{Allantoin.}}{C_4H_6N_4O} + CO_2$

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

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

The relation existing between uric acid and the xanthin-bases is seen from the following formulæ:

Hypoxanthin	$C_5H_4N_4O$
Xanthin	$C_5H_4N_4O_2$
Uric acid	$C_5H_4N_4O_3$
Guanin	$C_5H_5N_5O$

As a matter of fact, it is possible to produce xanthin and hypoxanthin from uric acid by a process of reduction.

Uric acid forms a white, crystalline powder which is almost insoluble in cold water (1 : 14,000), difficultly soluble in boiling water (1 : 1800), and insoluble in alcohol and ether. In concentrated sulphuric acid it readily dissolves, but is precipitated upon dilution

with water. In aqueous solutions of the alkaline carbonates and hydrates it dissolves with the formation of acid—viz., neutral—salts, as represented in the following equations:

$$C_5H_4N_4O_3 + Na_2CO_3 = C_5H_3Na\,N_4O_3 + NaHCO_3.$$
$$C_5H_4N_4O_3 + 2Na\,OH = C_5H_2Na_2N_4O_3 + H_2O.$$

In the urine the amount of water present would not be sufficient to hold the uric acid in solution, this being accomplished by the disodium phosphate, as pointed out above.

Uric acid is found in the urine in the form of sodium, potassium, and ammonium salts, traces of calcium and magnesium compounds being possibly also present. These salts may be decomposed by the addition of a sufficiently large quantity of a stronger acid, such as hydrochloric acid, when uric acid is set free:

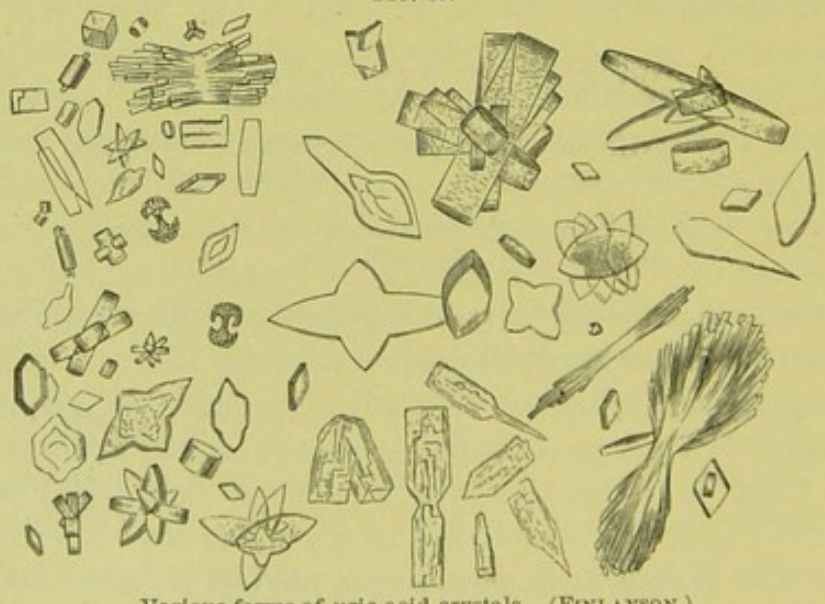
$$C_5H_2Na_2N_4O_3 + 2HCl = C_5H_4N_4O_3 + 2NaCl.$$

If, on the other hand, the amount of acid added be insufficient, the acid salt is thrown down:

$$C_5H_2Na_2N_4O_3 + HCl = C_5H_3NaN_4O_3 + NaCl.$$

All these salts are difficultly soluble, and are, hence, precipitated whenever the urine is markedly acid or concentrated, and also when

FIG. 89.



Various forms of uric-acid crystals. (FINLAYSON.)

it is exposed to a low temperature. This holds good particularly for the acid salts, notably the ammonium compound.

Uric acid that has separated out from the urine spontaneously may occur under a great variety of forms (Fig. 89), of which the

so-called whetstone-form is the most characteristic (see Sediments). When obtained from its alkaline solutions by the addition of hydrochloric acid it usually forms small rhombic plates, which taper markedly toward their ends, being often club-shaped.

Of the compounds which uric acid forms with the heavy metals, the silver salt is especially important. When a solution of uric acid in ammonia is treated with an ammoniacal solution of silver nitrate the solution remains clear. If, then, calcium chloride, sodium chloride, or magnesia mixture be added, a precipitate is formed which contains the uric acid in combination with the silver.

Tests for Uric Acid. About 200 c.c. of filtered urine are treated with 10 c.c. of hydrochloric acid and set aside in a cool place for twenty-four to forty-eight hours. The uric acid which has separated out is then collected on a filter and subjected to further tests:

1. *Murexid test.* A few crystals are dissloved by means of a few drops of concentrated nitric acid, with the application of heat, upon a porcelain plate, such as the cover of a crucible. The nitric acid is then carefully evaporated, when a yellowish-red spot will be found to remain. Upon cooling a drop of ammonia is placed upon this spot, when in the presence of uric acid a beautiful purplish-red color will develop, owing to the formation of ammonium purpurate (murexid). If now a drop of sodium hydrate solution be added, the color will change to a reddish-blue, which disappears upon heating, thus differing from the somewhat similar xanthin reaction.

2. *Copper test.* A few crystals are dissolved in sodium-hydrate solution and treated with a few drops of Fehling's solution. Upon the application of heat white urate of copper separates out, while red cuprous oxide appears if a relatively large amount of copper sulphate be present, a point to be remembered in testing for sugar.

3. When treated with sodium hypobromite solution uric acid gives up about 47 per cent. of its nitrogen.

Quantitative Estimation of Uric Acid.

Hopkins' Method. This method is destined soon to replace the more complicated procedures which have hitherto been employed in the clinical laboratory (see below), as it is much simpler and at the same time just as accurate as the older method of Ludwig-Salkowski and that of Haycraft.

Principle: The method is based upon the observation that ammo-

nium biurate is altogether insoluble in solutions of ammonium chloride. If, then, a specimen of urine be saturated with ammonium chloride, the various urates are transformed into ammonium biurate and precipitated as such. The salt is then decomposed with hydrochloric acid and the uric acid estimated, either gravimetrically or volumetrically, as described below.

Method: 100 c.c. of urine are treated with 30 grammes of finely powdered and chemically pure ammonium chloride. The mixture is thoroughly shaken and set aside for from two to three hours, care being taken to stir it from time to time. It is then passed through a small filter and the precipitate washed two or three times with a saturated solution of ammonium chloride. With the aid of a little boiling water the salt is washed from the filter and decomposed by the addition of 5 c.c. of a 25 per cent. solution of hydrochloric acid. This solution is evaporated until crystals of uric acid begin to separate out. These may then be collected on a dried and weighed filter and washed successively with water, 90 to 94 per cent. alcohol, absolute alcohol, and finally with ether. The water used in washing should be collected separately and 0.0048 gramme added to the weight of uric acid obtained for every 10 c.c. used.

More convenient, according to the writer's experience, and just as accurate, is the volumetric estimation of the uric acid as suggested by Hopkins. To this end the uric acid is collected on a glass-wool or asbestos filter and treated as described above. The precipitate, together with the glass-wool or asbestos, is then placed in a beaker and the uric acid dissolved in as small an amount of a 30 per cent. solution of sodium carbonate as possible with the aid of heat. Upon cooling this solution is diluted with water to 100 c.c., treated with 20 c.c. of concentrated sulphuric acid, and titrated, while warm, with a one-twentieth normal solution of potassium permanganate until the rose-red color which at first appears upon the addition of each drop no longer disappears on stirring. As 1 c.c. of the permanganate solution corresponds to 3.61 milligrammes of uric acid, the amount of the latter contained in 100 c.c. of urine is found by multiplying the number of c.c. used with 3.61.

Haycraft's Method. This method is based upon the precipitation of uric acid with an ammoniacal silver solution and magnesia mixture, 1 molecule of silver corresponding to 1 molecule of uric acid. As the amount of silver thus precipitated can be determined

by titration with a solution of potassium sulpho-cyanide, the corresponding amount of uric acid is readily found.

Solutions required: 1. An ammoniacal silver solution. 2. An ammoniacal magnesia mixture. 3. A one-fiftieth normal solution of nitrate of silver. 4. A one-fiftieth normal solution of potassium sulpho-cyanide.

Preparation of these solutions:

1. The ammoniacal silver solution is prepared by dissolving 26 grammes of nitrate of silver in distilled water, adding enough ammonia to redissolve the brown precipitate of oxide of silver first formed; distilled water is then added in sufficient amount to make the total quantity 950 c.c. This solution is brought to its proper strength by titrating a known amount of sodium chloride as described elsewhere. Each c.c. then contains 0.026 gramme of nitrate of silver, equivalent to 0.00216 gramme of silver.

2. The ammoniacal magnesia mixture is prepared by dissolving 100 grammes of crystallized magnesium chloride in a sufficient amount of water, to which a cold saturated solution of ammonium chloride is added in excess, and enough strong ammonia to impart a decided odor. Should the mixture not be perfectly clear, still more ammonium chloride solution is added. The solution is then diluted with water to 1 liter.

3. The one-fiftieth normal solution of nitrate of silver is prepared by dissolving 3.4 grammes of silver nitrate in 950 c.c. of distilled water, the degree of further dilution being determined as described elsewhere.

4. To prepare the one-fiftieth normal solution of potassium sulpho-cyanide, about 2 grammes of the salt are dissolved in 950 c.c. of water and the solution brought to the required strength, so that 1 c.c. shall correspond to 1 c.c. of the silver solution.

For filtering the uric acid a perforated platinum cone is placed in a small funnel and packed with a fine layer of glass-wool, upon which in turn a layer of finely scraped asbestos is placed, this having been thoroughly washed out in very dilute hydrochloric acid and subsequently with distilled water until every trace of chlorine has disappeared, the asbestos forming, as it were, a mould of the cone.

Method: Five c.c. of the ammoniacal silver solution are mixed with 5 c.c. of the ammoniacal magnesia mixture. Ammonia is then added until the solution is clear, when it is poured into

50 c.c. of urine. As soon as the precipitate has settled the supernatant liquid is filtered through the filter prepared as described, with the aid of a suction-pump. About 4 grammes of sodium bicarbonate in coarse pieces are now placed upon the filter and the precipitate added, the sodium bicarbonate serving the purpose of aiding filtration by loosening the precipitate. This is now washed free from chlorine and silver by means of ammoniacal water, using the suction-pump, until the precipitate appears broken in places, then without the pump, using this only at last to remove the last drops of liquid. Test for silver with very dilute hydrochloric acid, and for chlorine with a solution of nitrate of silver and nitric acid. The precipitate thus obtained is dissolved on the filter by means of 20 to 30 per cent. nitric acid. The nitric acid must be free from nitrous acid. This is accomplished by allowing it to stand in contact with pure urea until all evolution of gas has ceased. The filter is washed with very dilute nitric acid and then with distilled water, until this no longer shows an acid reaction. The solution thus obtained is titrated with the one-fiftieth solution of potassium sulpho-cyanide, using ammonio-ferric alum as an indicator. As every c.c. of this solution indicates 0.00216 gramme of silver, and as 1 molecule of silver indicates 1 molecule of uric acid—*i. e.*, 108 grammes of silver 168 grammes of uric acid—0.00216 gramme of silver, corresponding to 1 c.c. of the potassium sulpho-cyanide solution, represents 0.00336 gramme of uric acid.

Ludwig-Salkowski Method. This method should be employed whenever special accuracy is required.

Principle: A solution of uric acid in sodium carbonate when treated with a solution of nitrate of silver, after a previous addition of an excess of ammonia, gives rise to a flaky, gelatinous precipitate containing uric acid, sodium, and silver, which is very difficultly soluble. From this the silver may be removed, and the compound of uric acid and sodium decomposed by means of hydrochloric acid.

Method: Two hundred and fifty c.c. of urine are treated with 50 c.c. of ammoniacal magnesia mixture (see above) for the purpose of removing the phosphates. The magnesia mixture is employed for the reason that the compound of uric acid with magnesium and silver formed later on is not decomposed as easily as the sodium or the potassium compound, which would occur if the urine were only precipitated with ammonia. The mixture is then immediately

filtered, as otherwise a little magnesium urate would be precipitated; 250 c.c. of the filtrate, corresponding to 200 c.c. of urine, are measured off as soon as possible and treated with a few c.c. of a 3 per cent. solution of nitrate of silver. If the precipitated silver chloride formed in the beginning does not disappear on stirring, a little more ammonium hydrate is added. A flaky precipitate falls next, which is allowed to settle. In order to test whether enough of the silver nitrate solution has been added, a few c.c. of the supernatant fluid are acidified with nitric acid. If a distinct cloudiness appears, referable to silver chloride, enough has been added. Otherwise the few c.c. that were employed for this test are rendered alkaline again with ammonia, poured back, and more silver solution added until the required amount has been reached. The liquid is then rapidly filtered through a folded filter of rather loose paper, a feather or rubber-tipped glass rod being used for the purpose of removing all the precipitate from the beaker. The precipitate is washed until a specimen of the washings is no longer rendered turbid by nitric acid, and only faintly so by the addition of a drop of silver solution. The filter with the precipitate is next placed in a wide-mouthed flask containing about 200 c.c. of distilled water, and the mixture thoroughly shaken. Sulphuretted hydrogen is then passed through the mixture, which is thoroughly shaken from time to time. It is then brought to the boiling-point and rendered distinctly acid by means of a few drops of hydrochloric acid, when the sulphide of silver and the paper are *rapidly* filtered off, as otherwise there will be an admixture of sulphur to the uric acid. The contents of the filter are washed a few times with hot water. Filtrate and washings are quickly evaporated to a few c.c., to which a few drops of hydrochloric acid are added, and then set aside in a cool place for twenty-four hours. Occasionally it happens that upon the addition of the hydrochloric acid a cloudiness appears, due to an admixture of sulphur. In such a case the dried uric acid must be washed with carbon disulphide. Otherwise the uric acid that has separated out is directly collected on a dried and weighed filter and washed successively with water, 90 to 94 per cent. alcohol, and finally with absolute alcohol and ether. The water used in washing should be collected separately, and 0.0048 gramme added to the weight of the uric acid obtained for every 10 c.c. used.

Precautions: 1. Rapidity in working is most essential.

2. Very concentrated urines must be diluted one-half before commencing the test.

3. If the specific gravity of the urine be low, it should be concentrated to a specific gravity of about 1.020.

4. If the urine show a sediment of uric acid, this should be separately collected and weighed, and the weight obtained added to the final result.

5. Any albumin present should be previously removed.

6. If sugar be present in the urine, about 500 to 1000 c.c. are treated with a solution of neutral acetate of lead, filtered, and the filtrate precipitated with mercuric acetate. The precipitate thus formed, which consists essentially of mercuric urate, is filtered off after having stood for twelve to twenty-four hours, first washed with and later suspended in water. The mercury is removed by means of sulphuretted hydrogen, the suphide of mercury filtered off, and the filtrate collected and set aside. The precipitate itself is thoroughly boiled with water and again filtered, the washings thus obtained being added to the filtrate set aside, as just described. The total amount of fluid is then evaporated to a small volume and acidified with hydrochloric acid, when the uric acid will separate out and may be treated as previously directed.

The Old Method of Heintz. The following method, although inaccurate, may be employed when the necessary solutions required for more accurate working are not at hand:

Principle: The urates contained in the urine are decomposed by means of hydrochloric acid, the uric acid formed being set free.

Fig. 90.



Watch-crystals. (W. Simon.)

Method: Two hundred c.c. of urine are treated with 10 c.c. of strong hydrochloric acid and set aside in a cool place for forty-eight hours. The crystals of uric acid which have been deposited by that time are collected on a small filter that has been dried at a temperature of 110° to 115° C., and carefully weighed, using a cut-feather or a rubber-tipped glass rod to remove all the crystals from

the bottom and sides of the vessel, portions of the filtrate being used to bring the last traces upon the filter. The crystals are then washed with cold water, care being taken to collect the washings separately, until a specimen no longer becomes cloudy when treated with a few drops of nitrate of silver and nitric acid. Funnel and filter are then dried in the hot-air bath at a temperature of 110° to 115° C., and the filter finally dried to a constant weight at the same temperature. The filter is most conveniently dried between watch-glasses (Fig. 90), two of these being employed, one placed inside the other during the process of drying, while one is covered by the other and held in position by a spring during the process of weighing. The weight of the glasses and clamp, as well as that of the filter, is deducted from the total weight, the difference indicating the weight of the uric acid contained in 200 c.c. of urine. As the uric acid, however, is slightly soluble in acidified urine and acidified water, a loss will always arise if this method be employed. If but 30 c.c. of water are used during the process of washing, however, the loss will practically be counterbalanced by the weight of the coloring-matter which is carried down by the crystals. It has been estimated, furthermore, that for every 10 c.c. of water used beyond the amount indicated the addition of 0.0045 gramme to the weight obtained will make up for the loss of uric acid thus resulting.

While this method may be employed for clinical purposes, it must be remembered that at times only a portion of the uric acid, or none at all, separates out. Its absence should not, however, be inferred under such conditions, as its presence may be demonstrated by alkalinizing the acid filtrate and treating this with a solution of nitrate of silver, when a considerable precipitation may occur, referable to the presence of uric acid. A test such as this should always be made, and if a considerable cloudiness be obtained, recourse should be had to one of the methods indicated above.

In addition to the precautions given the following should be noted:

Urines rich in uric acid should be warmed after the addition of the hydrochloric acid until the cloudiness which occurs upon the addition of the reagent owing to the presence of acid urates has disappeared. If a sediment or cloudiness, due to urates, be noted in the urine, it should be warmed, and if necessary a small amount of alkali added, before the addition of the hydrochloric acid.

Hippuric Acid.

Hippuric acid is a constant constituent of normal urine, 0.1 to 1 gramme being excreted in the twenty-four hours. That it is derived to some extent at least from albuminous material is proved by the fact that its elimination is not suspended during starvation or during the administration of a purely albuminous diet. The manner in which hippuric acid is formed in the body-economy, however, has not been definitely ascertained. *In vitro* it may be obtained from glycocoll and benzoic acid, according to the equation:

$$\begin{array}{l} C_6H_5 \\ | \\ COOH \end{array} + \begin{array}{l} CH_2NH_2 \\ | \\ COOH \end{array} = \begin{array}{l} CH_2NH \\ | \\ COOH \end{array} - C_6H_5CO + H_2O$$

Benzoic acid. Glycocoll. Hippuric acid.

It has been shown that phenyl-propionic acid, which differs from benzoic acid by the group C_2H_4, and which latter may be regarded as phenyl-formic acid, is produced during the process of intestinal putrefaction, the relation between the two bodies being seen from the formulæ:

$$\begin{array}{l} H \\ | \\ COOH \end{array} \rightarrow \begin{array}{l} C_6H_5 \\ | \\ COOH \end{array} \qquad \begin{array}{l} CH_3 \\ | \\ CH_2 \\ | \\ COOH \end{array} \rightarrow \begin{array}{l} CH_2.C_6H_5 \\ | \\ CH_2 \\ | \\ COOH \end{array}$$

Formic acid. Phenyl-formic acid. Propionic acid. Phenyl-propionic acid.

Phenyl-propionic acid is then absorbed into the blood and there, according to our present ideas, transformed into phenyl-formic acid, or benzoic acid. The latter coming into contact with glycocoll, which is probably produced during the process of intestinal putrefaction also, an interaction between the two substances occurs, hippuric acid resulting, as shown in the above equation. This view is supported by the fact that phenyl-propionic acid, just as benzoic acid, when introduced into the circulation of certain animals, reappears in the urine as hippuric acid. The final proof of the possible synthesis of hippuric acid from glycocoll and benzoic acid in the body has been furnished by Bunge and Schmiedeberg, who obtained this substance when arterialized blood containing glycocoll and sodium benzoate was allowed to pass through isolated kidneys of dogs.

Not all the hippuric acid eliminated, however, is referable to albuminous material, but a considerable portion is derived from benzoic acid, or its derivatives, which latter, contained in many of

the fruits eaten as food, are transformed into hippuric acid in the body. Among those which are particularly rich in these substances there must be mentioned the red bilberry, prunes, coffee-beans, reines-claudes, etc., and in all cases in which an increased elimination of hippuric acid is observed the possibility of this source must always be taken into account.

As to the seat of this synthesis there appears to be some uncertainty, it not appearing to be the same in all animals. In the dog and the frog the kidneys, according to the researches of Bunge and Schmiedeberg, must be regarded as the principal and possibly the only organs in which this process occurs. As Salomon, however, has demonstrated the presence of hippuric acid in the muscles, liver, and blood of nephrectomized rabbits, there must be, in the herbivora at least, other organs concerned in its production.

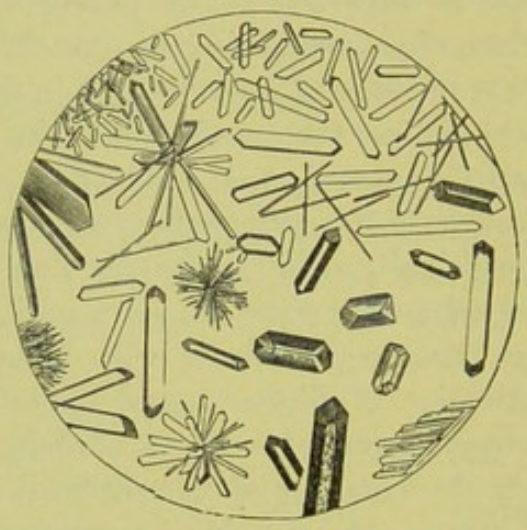
Very little is known of the pathologic variations in the excretion of hippuric acid, principally owing to the fact that suitable methods for its quantitative estimation were unknown until recently. It is an interesting fact that, in accordance with Bunge's experiments in dogs, the elimination of hippuric acid appears to be entirely suspended in cases of acute as well as chronic parenchymatous nephritis following the ingestion of benzoic acid, this reappearing unchanged in the urine. In amyloid degeneration a marked diminution in its amount has likewise been demonstrated. Large quantities of hippuric acid, on the other hand, have been noted in acute febrile diseases, hepatic diseases, diabetes mellitus, chorea, etc. The data, however, are insufficient to warrant any definite conclusions at the present time.

Properties of Hippuric Acid. Chemically, hippuric acid must be regarded as benzoyl-amido-acetic acid, $C_9H_9NO_3(C_6H_5.CONH.CH_2COOH)$. It crystallizes in long rhombic prisms when allowed to separate from its solutions gradually, while it forms long needles if crystallization takes place rapidly and the amount is small (Fig. 91). In water and ether it is soluble with difficulty, while it dissolves readily in alcohol and in aqueous solutions of the hydrates and carbonates of the alkalies, forming salts, from which the acid may again be separated and caused to crystallize out upon the addition of a stronger acid.

When hippuric acid or one of its salts is evaporated to dryness with concentrated nitric acid and the residue heated, the odor of bitter almonds is noticed, due to the formation of nitro-benzol.

When boiled with hydrochloric acid or dilute sulphuric acid it is decomposed into glycocoll and benzoic acid. A similar decomposition is effected during the process of putrefaction, and hence no hippuric acid is found in decomposing urine, *benzoic acid* taking its place. The latter is always found in the urine together with hippuric acid, but has no clinical significance. In large amounts it has recently been found in a case of diabetes. It crystallizes in lustrous laminæ or needles, the former presenting ragged edges and

FIG. 91.



Hippuric-acid crystals.

resembling somewhat plates of cholesterin. It is difficultly soluble in cold water, but easily soluble in ether, alcohol, and solutions of the alkaline carbonates and hydrates, forming salts with the latter.

Hippuric acid in the urine occurs in combination with sodium, potassium, calcium, and magnesium.

Quantitative Estimation of Hippuric Acid. The following method, which may be employed for the quantitative estimation of hippuric acid, although very tedious, must also be employed when it is desired to test for its presence.

Principle: Hippuric acid readily dissolves in solutions of the alkaline hydrates and carbonates, forming salts. These are decomposed by means of a stronger acid, when the hippuric acid which separates out is collected and weighed.

Method: Five hundred to one thousand 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 (90 to 95 per cent.),

taking about half of the quantity 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 acidified with acetic acid, in order to liberate the lactic acid, and extracted with at least five times its own volume of alcoholic ether (1 part of alcohol to 9 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 other constituents 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 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 again extracted with ether. The remaining solution is evaporated to a few c.c., when the hippuric acid will separate out on standing. The crystals are dried on plates of plaster-of-Paris, 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 indicated above.

Hofmeister's Method. Two hundred to three hundred c.c. of urine are evaporated in a glass dish to one-third of the original volume, treated with 4 grammes of disodium phosphate to transform the acid into its sodium salt, and the mixture evaporated to a syrupy consistence. The residue is treated with burnt gypsum, dried thoroughly, and pulverized together with the dish. The powder is extracted in a Soxhlet apparatus with freshly rectified petroleum-ether (boiling-point 60° to 80° C.) for forty-six hours, and then for six to ten hours with pure ether (free from water and alcohol). After distilling off the ether, the residue is dissolved in boiling water and decolorized with animal charcoal, the latter being subsequently thoroughly washed with boiling water; the solution and washings are evaporated to about 1 or 2 c.c. at a temperature of from 50° to 60° C., and set aside to crystallize. The crystals of hippuric acid are finally washed with a few drops of water and ether, and weighed.

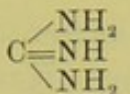
Kreatin and Kreatinin.

Numerous observations point to kreatin, which is constantly present in muscle-tissue, as being in all probability the immediate and constant antecedent of kreatinin, so that two sources of this body must be recognized, viz., the muscle-tissue of the body and the muscle-tissue ingested as food. Beyond this, however, practically nothing is known, and as the artificial production of kreatinin from albuminous material has so far never been accomplished, it is hardly warrantable to venture an hypothesis as to its mode of formation in the body.

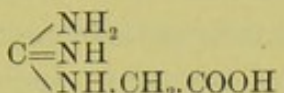
Kreatinin is a constant constituent of the urine, about 1 gramme being daily excreted by a healthy adult. Pathologically variations in this amount have been observed, but the data so far obtained possess little value, and before drawing any conclusions from facts chemically observed it is necessary to take into account the quantity of meat ingested by the individual, as a meat-diet will increase the amount of kreatinin, while this will be diminished by a milk-diet. If then in patients affected with acute febrile diseases, such as pneumonia, typhoid fever, etc., a large increase is observed, the patient being at the same time upon a milk-diet, an increased destruction of muscle-tissue may be inferred. A decrease would logically be expected to occur during convalescence from such diseases. In the various forms of anæmia, marasmus, chlorosis, phthisis, etc., a diminished amount is observed.

The transformation of kreatin into kreatinin has been supposed to take place in the kidneys, a view which accords with the greatly diminished excretion of kreatinin in well-advanced cases of chronic parenchymatous nephritis. In progressive muscular atrophy, in pseudo-hypertrophic paralysis, and in progressive ossifying myositis a diminution has been noted.

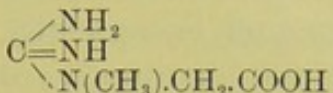
Properties of Kreatin and Kreatinin. Chemically kreatin may be regarded as a methyl derivative of glycocyanin, which latter is guanidin in which one NH_2 group has been replaced by glycocoll. Kreatinin, on the other hand, is the methyl derivative of glycocyanidin, which differs from glycocyanin only in the absence of 1 molecule of water, so that kreatinin is kreatin minus 1 molecule of water, both being derivatives of guanidin. The relation between the various bodies is as follows:



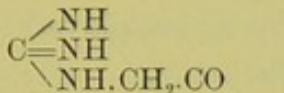
Guanidin.



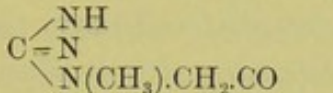
Glycocyanin.



Kreatin.



Glycocyanidin (glyccocyanin minus water).

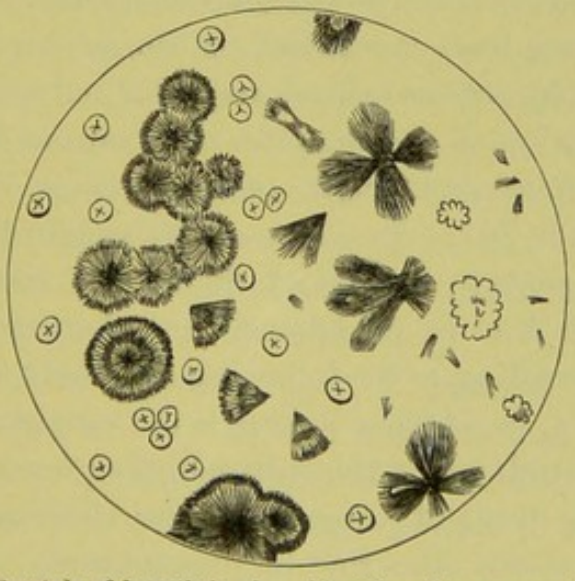


Kreatinin (kreatin minus water).

Kreatinin crystallizes without water of crystallization in colorless, glistening prisms. At times, when the crystals are not well developed, it also appears in the form of whetstones. It is readily soluble in hot and also quite soluble in cold water and hot alcohol, but more difficultly so in cold alcohol and ether.

It forms salts with acids and double salts with some of the salts of the heavy metals. Among these may be mentioned kreatinin hydrochloride, $C_4H_7N_3O.HCl$, which is easily soluble in water and crystallizes in the form of transparent prisms or rhombic plates. Most important is the compound of kreatinin with zinc chloride

FIG. 92.



Crystals of kreatinin-zinc chloride. (SALKOWSKI.)

$(C_4H_7N_3O)_2.ZnCl_2$ (Fig. 92). This is produced when a watery or alcoholic solution of kreatinin is treated with chloride of zinc. The crystalline form of this compound depends greatly upon the purity of the kreatinin solution. When obtained from alcoholic extracts of the urine it occurs in the form of varicose conglomerations which often adhere firmly to the walls of the vessel. If the solution of

kreatinin be perfectly pure, however, it is seen in the form of fine needles grouped together in rosettes or sheaves. Kreatinin-zinc chloride is very difficultly soluble in water and insoluble in alcohol. This compound is especially important, as upon its formation and properties the quantitative estimation of kreatinin in the urine is based. Nitrate of silver and mercuric chloride cause a precipitation of kreatinin, and may, therefore, also be employed for the purpose of obtaining the substance from the urine.

Test for Kreatinin in the Urine. A few c.c. of urine are treated with a few drops of a very dilute solution of sodium nitroprusside, and then drop by drop with a dilute solution of sodium hydrate, when the urine in the presence of kreatinin assumes a ruby-red color, which is particularly well seen in the lowest portion of the tube. This color disappears after a few minutes, and is replaced by an intensely yellow color, which, on warming with glacial acetic acid in pure solutions, gives rise to a green color (*Weyl's test*). The presence of albumin or sugar does not interfere with the reaction.

Quantitative Estimation of Kreatinin in the Urine. Principle: When an alcoholic extract of the urine is treated with an alcoholic solution of zinc chloride, kreatinin-zinc chloride separates out, which, as has been mentioned, is almost insoluble in alcohol. Knowing the molecular weight of kreatinin and kreatinin-zinc chloride, the calculation of the amount of kreatinin becomes a simple matter. The molecular weight of kreatinin is 113, that of kreatinin-zinc chloride 362. In 362 parts by weight of the latter there are, hence, 226 parts by weight of the former, so that the amount of the kreatinin may be calculated from the weight of kreatinin-zinc chloride according to the following equation: 362 : 226 : : y : x, and $x = 0.6243y$, in which y indicates the weight of the kreatinin-zinc chloride found, and x the corresponding amount of kreatinin. The phosphates must, of course, first be eliminated, as insoluble zinc phosphate would otherwise be precipitated.

Method: In 240 c.c. of urine the phosphates are first removed by rendering the urine alkaline with milk of lime and then adding calcium chloride as long as a precipitate forms. If the volume now be less than 300 c.c., water is added to that amount. The mixture is filtered after having been allowed to stand for one-qaurter to one-half hour, and washed with a little water; 250 c.c. of the mixture are then measured off, slightly acidified with dilute hydrochloric

acid so as to prevent any transformation of kreatinin into kreatin during the long process of evaporation. This amount is evaporated on a water-bath to a syrupy consistence, and then thoroughly mixed with 20 to 30 c.c. of absolute alcohol. The mixture is poured into a stoppered flask provided with a 100 c.c. mark, and after thoroughly rinsing out the evaporating-dish with absolute alcohol the washings are also placed in the bottle and absolute alcohol added to the 100 c.c. mark. The bottle is thoroughly shaken and set aside in a cool place for twenty-four hours, the mixture being agitated from time to time. It is now filtered and rendered slightly alkaline with a drop or two of sodium carbonate solution, as kreatinin hydrochloride is not precipitated by chloride of zinc. The reaction, however, should be only *faintly* alkaline, as otherwise zinc oxide will be precipitated. The mixture is now slightly acidified with acetic acid. Eighty c.c., corresponding to 160 c.c. of urine, are treated with 10 to 15 drops of an alcoholic solution of zinc chloride, prepared by dissolving the salt in 80 per cent. alcohol and diluting with 95 per cent. alcohol to a specific gravity of 1.2. The mixture is then well stirred and set aside in a cool place for two or three days. The crystals, which are usually deposited upon the sides of the vessel in the form of wart-like masses, are then collected upon a dried and weighed filter, always using portions of the filtrate to bring the crystals completely upon the filter. These are washed with a small amount of 90 per cent. alcohol until the washings are without color and give only a slight opalescence when treated with a drop of nitrate of silver solution. The crystals are finally dried at a temperature of 100° C., and weighed. By multiplying the weight thus found by 0.6243 the amount of kreatinin is obtained.

Precautions: 1. Albumin and sugar, if present, must first be removed. In diabetic urines it is best, after having removed the sugar by fermentation, to take one-fifth of the total quantity eliminated in twenty-four hours, and to evaporate this to about 300 c.c. before removing the phosphates.

2. The weighed material should be examined microscopically to see whether notable quantities of sodium chloride be present. Should such be the case it is necessary to determine the amount of zinc present and to estimate the kreatinin from this. To this end the alcoholic solution containing the kreatinin-zinc chloride is evaporated to dryness after the addition of a little nitric acid. The residue is incinerated, extracted with water, washed, dried, fused, and finally weighed.

As 100 parts of kreatinin-zinc chloride correspond to 22.4 parts by weight of zinc oxide, the corresponding amount of the compound is found according to the following equation: 22.4 : 100 : : y : x, and x = 4.4642, in which y represents the amount of zinc oxide found, and x the corresponding amount of kreatinin-zinc chloride. By multiplying the number thus ascertained by 0.6243 the corresponding amount of kreatinin is found.

3. Instead of doing this the precipitate in the alcoholic solution may be examined microscopically before filtering, and if sodium chloride crystals be found, providing that the kreatinin-zinc chloride crystals adhere to the sides of the vessel, the sodium chloride may be dissolved in a little water and poured off.

4. If the crystals of kreatinin-zinc chloride adhere very firmly to the sides of the vessel, so that their removal would be incomplete, it is perhaps best to dissolve them in a little hot water, to evaporate to dryness, and to weigh the kreatinin compound directly.

5. If the urine shows an alkaline reaction, it is best to acidify with sulphuric acid and to boil for half an hour before removing the phosphates, so as to transform any kreatin that may be present into kreatinin, when the examination should be continued as described.

The Xanthin Bases.

The xanthin bases which have been found in the urine are: xanthin, heteroxanthin, paraxanthin, hypoxanthin, guanin, adenin, and carnin. The relation existing between these bodies is seen from their formulæ:

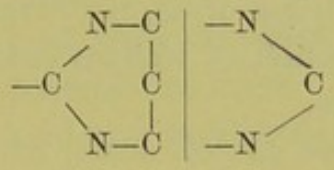
Hypoxanthin	$C_5H_4N_4O$
Xanthin	$C_5H_4N_4O_2$
Heteroxanthin	$C_5H_3(CH_3)\,N_4O_2$
Paraxanthin	$C_5H_2(CH_3)_2N_4O_2$
Adenin	$C_5H_5N_5$
Guanin	$C_5H_5N_5O$
Carnin	$C_7H_8N_4O_3$

Like uric acid, they are undoubtedly derived from nuclein, as follows:

Nuclein . . . { Albumin.
{ Nucleinic acid { Phosphoric acid.
{ Adenin.
{ Guanin.
{ Xanthin.
{ Hypoxanthin.

Individually the xanthin bases are of little interest. In splenic leukæmia hypoxanthin is usually found in increased amount. Xanthin, as such, has been found in urinary sediments, and a few cases are on record where calculi were observed, consisting of almost the pure substance. The reactions by means of which xanthin may be recognized will be described in the chapter on Sediments.

Conjointly, the xanthin bases are spoken of as alloxur bases, as they all contain an alloxan as well as a urea radicle,



Alloxan radicle. Urea radicle.

joined together in a characteristic manner.

Of late, the elimination of nitrogen in this form, as compared with the total amount of nitrogen and that excreted as uric acid, has occupied the attention of numerous investigators. The entire subject, however, is in a somewhat chaotic condition as yet, and the time has not arrived where it would be admissible to draw definite conclusions from the work accomplished. It must be admitted, moreover, that the method of Krüger and Wulff, which has been almost exclusively employed in the estimation of the alloxur nitrogen, is by no means free from objections. The values obtained are usually much higher than those reached with the silver method of Salkowski, and the latter has recently shown that other nitrogenous constituents are also precipitated with Krüger's method.

As Salkowski has not as yet published his new method, that of Krüger-Wulff only will here be considered.

Method of Krüger-Wulff. The method is based upon the observation of Krüger that copper sulphate and sodium bisulphite will completely precipitate uric acid and the alloxur bases in the urine, and these only.[1] In the precipitate the amount of nitrogen is then determined. In a second portion of urine the uric acid is estimated and the corresponding amount of nitrogen deducted from the total quantity. The difference will then indicate the amount of nitrogen in the form of alloxur bases (B). As an equal mixture of 100 parts of xanthin, hypoxanthin, paraxanthin, heteroxanthin, carnin, and guanin, moreover, contains 36.295 per cent. of nitrogen, the quan-

[1] This statement is denied by Salkowski.

tity of B in terms of this mixture, which corresponds to the amount of B-nitrogen found, is readily determined according to the equation:

$$36.295 : 100 :: x : y, \text{ and } y = \frac{100\,x}{36.295}, \textit{ i.e.}, y = x\ 2.755,$$

where x represents the amount of B-nitrogen found and y the corresponding amount of alloxur bases.

Reagents required:

1. A 50 per cent. solution of sodium bisulphite.
2. A 13 per cent. solution of copper sulphate.
3. A 10 per cent. solution of barium chloride.
4. Gunning's mixture.

Method: One hundred c.c. of urine, which must be free from albumin, are brought to the boiling-point and treated with 10 c.c. of the bisulphite, and immediately after with 10 c.c. of the copper solution. The mixture is allowed to boil for a moment, when the originally white precipitate turns brown. Five c.c. of the barium solution are then added in order to facilitate the sedimentation of the precipitate and its filtration. After two hours' standing the precipitate is collected on a folded filter, of Swedish paper, measuring about 10 to 12 cm. in diameter, and washed with boiled water, cooled to a temperature of 60° C. Filling the filter five times is sufficient.

The moist filter is placed in a Kjehldal digesting flask of 150 c.c. capacity, and treated with Gunning's mixture (see p. 346). For practical purposes it is best to treat the moist filter first with the sulphuric acid and copper sulphate, and to heat the mixture until fumes of sulphuric acid are given off in abundance. The potassium sulphate is then added. After heating for an hour or two longer —*i. e.*, until the liquid has become entirely clear and almost colorless—the residue is further treated as described on p. 346. As the method is by no means simple and requires considerable skill, at least three parallel estimations should be made and the average figure taken.

The uric acid is best estimated according to Hopkins' method. One gramme corresponds to 0.33 gramme of nitrogen.

The calculation of the amount of B-nitrogen and of alloxur bases is then conducted as described above. The average amount of B-nitrogen and alloxur bases eliminated in the twenty-four hours in health amounts to 0.0481 and 0.1325 gramme respectively. The relation of uric acid nitrogen to B-nitrogen varies between 2.1 : 1 and 7.6 : 1.

Oxalic Acid.

The origin of oxalic acid in normal urine appears to be twofold, one portion being referable to vegetable food ingested, the other originating in the body in a manner not definitely understood at the present time. It is quite probable, however, that this latter portion is derived, to some extent at least, from uric acid through a process of oxidation, a view which is supported by the artificial production of *oxaluric* acid from uric acid, the former being likewise a constant constituent of the urine. Oxaluric acid is readily decomposed into oxalic acid and urea, as is seen from the following equations:

1. $C_5H_4N_4O_3 + O + H_2O = C_4H_2N_2O_4 + CON_2H_4$
   Uric acid. Alloxan. Urea.

2. $C_4H_2N_2O_4 + O = CO\begin{<}NH.CO \\ NH.CO\end{>} + CO_2$
   Alloxan. Parabanic acid.

3. $CO\begin{<}NH.CO \\ NH.CO\end{>} + H_2O = \begin{matrix}CO—NH—CONH_2 \\ CO.OH\end{matrix}$
   Parabanic acid. Oxaluric acid.

4. $\begin{matrix}CO—NH—CONH_2 \\ CO.OH\end{matrix} + H_2O = \begin{matrix}CO—OH \\ CO—OH\end{matrix} + CO\begin{<}NH_2 \\ NH_2\end{>}$
   Oxaluric acid. Oxalic acid. Urea.

Oxalic acid may also result from an incomplete oxidation of carbohydrates.

From a pathologic standpoint the study of the excretion of oxalic acid is of decided importance. Care should, however, be taken in the interpretation of the results reached by a chemical examination, as many vegetables are capable of producing an excessive excretion of this acid. Among these may be mentioned tomatoes, spinach, carrots, celery, string-beans, asparagus, apples, grapes, etc.

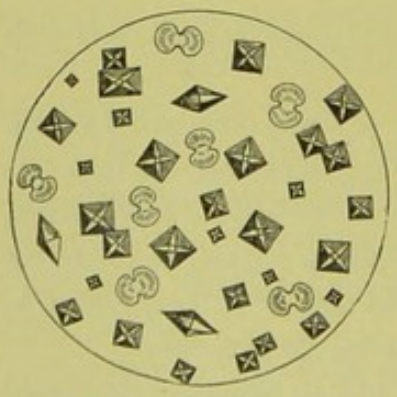
Gastro-intestinal disturbances are very apt to cause an increased elimination of oxalic acid, probably in consequence of a defective digestion and subsequent oxidation of carbohydrates, the so-called nervous oxaluria being probably of this origin. Very interesting is the form of oxaluria observed in cases of transient albuminuria, described by Senator and confirmed by v. Noorden and others. To this class the so-called *Albuminuria and Bright's Disease of Uric Acid and of Oxalic Acid* of Da Costa in all probability also belongs.

In the chapter on Phosphates it was shown that in diabetes mellitus a certain relation appears to exist at times between the excretion of sugar and phosphates, these bodies increasing and decreasing in an inverse relation to each other. A similar condition is also noted in the excretion of uric acid. In the case of oxalic acid such a vicarious elimination, as it were, is likewise not infrequently observed, and may at times be very pronounced, indicating the existence of a probable relation between carbohydrates and oxalic acid.

The *oxalic acid diathesis*, or *idiopathic oxaluria*, must finally be considered. In this condition there is associated with a definitely recognizable increased production a temporary retention, followed by an increased elimination of oxalic acid, notwithstanding the fact that a perfectly normal diet—*i. e.*, one not especially rich in oxalic-acid-containing constituents—may be taken. There can thus be no doubt of the occurrence of abnormal metabolic processes in the body. These are probably similar to those giving rise to diabetes mellitus, there being, as it were, a suspended oxidation in diabetes and an insufficient oxidation in the idiopathic oxaluria, the relation between the two diseases being further shown by the vicarious elimination of oxalic acid in diabetes.

Properties of Oxalic Acid. Oxalic acid occurs in the urine as calcium oxalate, CaC_2O_4, being held in solution by the diacid sodium phosphate. It can, hence, be precipitated by diminishing the acidity of the urine by the addition of a little ammonia, or by allowing it to stand exposed to the air. Calcium oxalate, when allowed to crystallize out slowly, occurs in the form of well-defined, strongly refractive octahedra, the well-known envelope forms resulting, in which the principal axis of the crystals is placed at right angles to the plane of the microscopic slide (Fig. 93).

FIG. 93.



Calcium oxalate crystals.

Calcium oxalate may always be recognized by its characteristic crystals, its insolubility in acetic acid, and its solubility in hydrochloric acid. When strongly heated it is decomposed into calcium oxide, carbon dioxide, and carbon monoxide, according to the equation:

$$CaC_2O_4 = CaO + CO_2 + CO.$$

The quantity excreted in the twenty-four hours varies from faint traces to 20 milligrammes. It must be remembered here that *an increased or diminished excretion of oxalic acid cannot be determined by a microscopic examination of the sediment, as numerous crystals of oxalate of calcium may be seen when a quantitative estimation actually shows a diminution of the normal amount, and* vice versa.

Tests for Oxalic Acid. For the detection of calcium oxalate it is frequently only necessary to examine the sediment of the urine after twenty-four to forty-eight hours, but, as has been pointed out, no oxalate crystals may be found even when an abnormally large amount can be demonstrated by chemical methods. In such cases it is usually possible to bring about the crystallization of the salt by carefully neutralizing the urine with a little ammonia. Should this procedure not lead to the desired result, it is best to proceed by a method which may at the same time be employed for its quantitative estimation.

Quantitative Estimation of Oxalic Acid. Principle: The oxalate of calcium occurring in the urine is held in solution by the diacid sodium phosphate. If this be removed by means of calcium chloride and ammonia, the calcium oxalate is precipitated. By heating this strongly it is transformed into calcium oxide.

As 56 parts by weight of calcium oxide correspond to 128 parts by weight of calcium oxalate, the amount of the latter can be readily calculated according to the equation: 56 : 128 : : y : x, and $x = 2.2857y$, in which y indicates the amount of calcium oxide found in a given amount of urine, and x the corresponding amount of calcium oxalate. As 1 molecule of oxalic acid, moreover, corresponds to 1 molecule of calcium oxalate, the amount of the former can be found from that of the latter according to the equation: 128 : 90 : : y : x, and $x = 0.703y$, in which y represents the amount of calcium oxalate found, and x the amount of the corresponding acid.

Method: A large amount of urine (600 to 1000 c.c.), after having been treated with a small amount of an alcoholic solution of thymol, so as to guard against putrefactive processes, is treated with calcium chloride and ammonia added in excess in order to remove the diacid sodium phosphate which holds the oxalic acid in solution. During this process the oxalate of calcium is thrown down together with the phosphates. The precipitate is then carefully treated with an

amount of acetic acid just sufficient to dissolve it. As calcium oxalate is insoluble in acetic acid, it gradually separates out. To this end the mixture is allowed to stand for twenty-four hours, the addition of the thymol preventing the development of bacteria. At the end of this time the calcium oxalate is filtered off through a small filter. It is then washed with a small amount of water and dissolved with a few drops of hydrochloric acid, any uric acid that may have separated out being left behind. The filtrate is then treated with a small amount of very dilute ammonia, so as to render the solution *slightly* alkaline. After standing for twenty-four hours the calcium oxalate will have separated out, and is collected upon a small filter, the weight of the ash in this being known. After washing with water the contents of the filter are dried and incinerated in a crucible, heating strongly for about twenty minutes, whereby the oxalate is transformed into the oxide. From the weight of this the corresponding amount of oxalic acid is readily calculated according to directions previously given.

Albumins.

The albumins which may be met with in the urine are: Serum-albumin, serum-globulin, albumoses (peptones), hæmoglobin, nucleo-albumin, fibrin, and histon. Of these, serum-albumin is the most important from a clinical standpoint, and whenever in the following pages the term albuminuria is employed it should be remembered that serum-albuminuria is meant.

Serum-albumin. The question whether or not serum-albumin occurs normally in the urine—*i. e.*, under conditions strictly physiologic in their nature—has been much disputed, it being claimed by some that traces may temporarily be met with in many individuals, particularly after severe muscular exercise, cold baths, mental labor, severe emotions, during menstruation, digestion, etc. This so-called *physiologic albuminuria* mostly occurs in young adults, and is usually, if not always, of brief duration, the urine, it is claimed, being otherwise normal—*i. e.*, of normal amount, appearance, specific gravity, and composition, and free from abnormal morphologic constituents, such as casts, red corpuscles, leucocytes, and epithelial cells. The persons examined must, furthermore, be entirely free from subjective or objective abnormalities.

The existence of a physiologic albuminuria, on the other hand, is denied, and the occurrence of serum-albumin at least regarded as

pathologic in every case. The author has never been able to convince himself of the presence of serum-albumin in the urine under strictly physiologic conditions, and it has already been pointed out elsewhere that severe muscular and mental labor, severe mental emotions, cold baths, etc., can hardly be regarded as physiologic stimuli for all persons. The albuminuria so often observed during the first days of life, at which time sediments of uric acid and urates, mucus, epithelial cells from the different portions of the urinary tract, and even casts may also be seen, constituents which in adults would rightly be regarded as abnormal, has also been brought forward in support of the theory of a physiologic albuminuria. There can be no doubt, however, that this form of albuminuria is referable to the profound changes that take place in the circulatory system after birth, and to some extent perhaps also to the well-known uric-acid infarctions so frequently seen in the kidneys of the newly born, so that it would probably be better and more in accord with the teachings of pathology to regard this albuminuria as abnormal.

The more closely the subject of the so-called physiologic albuminuria is studied the more improbable does its physiologic nature appear, and a more detailed study of the metabolic processes, it may be confidently asserted, will untimately lead to the conclusion that *the presence of albumin in every case is a pathologic phenomenon.*

The association of an increased elimination of urea and uric acid with albuminuria in apparently healthy individuals was noted twenty-five years ago, but received comparatively little attention. More recently, Da Costa, in a paper entitled "The Albuminuria and Bright's Disease of Uric Acid and Oxalic Acid," pointed out the existence of albuminuria associated with lithuria and oxaluria. Personal observations have led the author to look upon this form of albuminuria as being of common occurrence, and while in almost every case the albumin can be caused to disappear from the urine by proper diet and exercise, there can be no doubt that if neglected granular atrophy may ultimately result.

An albuminuria may at times be observed in anæmic children and adolescents, and particularly in masturbating boys of the mouth-breathing type, but it can hardly be regarded as physiologic. The same may be said of the albuminuria of pregnancy and parturition.

The course which these various forms of what should be termed

functional albuminuria, in which the amount of albumin rarely exceeds 0.1 per cent., may take, is very interesting. The elimination of albumin may thus be quite *transitory* on the one hand, as when following severe muscular exercise, cold baths, and the like. It may, however, also last for several days or even weeks, and be followed by a disappearance of the albumin for a variable length of time, and again by its reappearance and continuance for days and weeks. The term *intermittent albuminuria* has been applied to this latter type. At times the albuminuria may follow a definite course, disappearing and reappearing with such regularity that it has not improperly been styled *cyclic albuminuria.* In this form the albumin generally disappears from the urine during the night, or during a prolonged rest in bed, reappearing during the day, the erect posture apparently favoring its reappearance ; the term *postural albuminuria* has hence also been suggested for this form. Osswald, who made a careful study of cyclic albuminuria in Riegel's clinic, regards its occurrence as distinctly pathologic, and as indicating the existence of nephritis. Remembering the importance of the subject, it may not be out of place to enumerate the reasons which led Osswald to this conclusion:

1. The patients generally come to the physician complaining of certain definite symptoms which are the same as those noted in cases of true nephritis. At times, however, no complaints are made, because the patients have reasons for concealing these (as in examinations for life-insurance), or because they are for the time being absent.

2. The subjective complaints, as well as the anæmia so frequently observed in such cases, generally disappear, together with the albumin, under suitable treatment, to reappear when the anæmia again becomes marked.

3. In many a history of an antecedent nephritis, the result of scarlatina or diphtheria, may be obtained, as in three cases of Heubner, in fourteen cases out of twenty described by Johnson, etc. In some also a direct transition from an acute nephritis to the cyclic form of albuminuria has been noted. Where this was not possible the history of an acute infectious disease or an angina, that had been overlooked in the clinical history, must be regarded as a possible cause.

4. The absence of morphologic elements, especially tube-casts, does not negative a nephritis. A large number of cases, how-

ever, have recently been observed in which casts were repeatedly found.

5. A cyclic albuminuria may be observed in many cases of chronic nephritis.

6. Marked organic abnormalities (such as heart-lesions) need not be demonstrable, as they may be absent for a long period of time or may be unrecognizable.

Senator's statement, that the existence of a physiologic albuminuria is proved by the fact that the morphologic constituents of the primitive nubecula contain albumin, requires no further criticism, and should be regarded as a misconstruction of the main point at issue—a mere sophism—and Posner's observations, in view of the researches of Malfatti, which tend to show that the body obtained by Posner was not serum-albumin, but a nucleo-albumin, may now be regarded as erroneous.

In conclusion, it may safely be said that a transitory, intermittent, and cyclic albuminuria is not infrequently observed in apparently healthy individuals, but that the facts so far brought forward do not warrant the assumption that such forms of albuminuria are physiologic.

It would lead too far to enter into a detailed consideration of the various causes that have from time to time been suggested as an explanation of the fact that albumin does not occur in the urine under normal conditions. There can be no doubt, however, that the integrity of the epithelial lining of the glomeruli and the convoluted tubules must be regarded as the principal factor which prevents the albumin of the blood from passing into the urine. When the readiness with which the glandular structure of the kidney responds to any abnormal stimulation is considered, it is easily understood how an albuminuria may be evoked in many different ways. Aside from acute and chronic inflammatory processes in the widest sense of the word, an albuminuria may be the result of circulatory disturbances in the kidneys of whatever kind—*i. e.*, the result of anæmia, as well as of hyperæmia. In many and perhaps the majority of cases in which what Bamberger terms a *hæmatogenous albuminuria* occurs, we have direct evidence of the existence of circulatory disturbances, as in cases of uncompensated valvular lesions, weak heart, emphysema, hepatic cirrhosis, etc. In other cases, however, the existence of such disturbances can only be surmised, and the question whether or not, for example, the albumin-

uria observed in the various infectious diseases is referable to circulatory abnormalities, or to a direct irritative action of microbic poisons upon the renal parenchyma, must still remain an open one.

From personal studies in connection with the functional albuminuria of Da Costa, it seems not unlikely that in many cases in which obscure circulatory disturbances are supposed to exist and made responsible for an existing albuminuria, this is referable rather to the strain thrown upon the kidneys by the continued elimination of abnormally large quantities of organic material, the quantity of water being at the same time proportionately small.

If it be remembered, furthermore, that injuries affecting certain portions of the brain are followed by albuminuria, and that such may be artificially produced by a *piqure*, analogous to the glycosuric *piqure* of C. Bernard, still another factor is given which may possibly enter into the causation of albuminuria.

Obstruction to the outflow of urine from the kidneys has also experimentally been shown to lead to albuminuria, an observation with which clinical experience is in perfect accord.

Finally, an abnormal composition of the blood may at times cause albuminuria.

In passing on to a more detailed study of the various pathologic conditions in which an elimination of albumin may be noted, an attempt will be made to classify the various forms of albuminuria in accordance with the more general considerations set forth above. It should be remembered, however, as already indicated, that it may be very difficult, if not impossible, to assign one single cause to a given clinical case, as several factors may at the same time be concerned in the production of the albuminuria.

1. *Functional albuminuria.* Under this heading may be comprised the various forms of "physiologic" albuminuria which have already been considered.

2. *The albuminuria associated with organic diseases of the kidneys;* viz., acute and chronic nephritis, renal arterio-sclerosis, amyloid degeneration of the kidneys.

In acute nephritis, albuminuria, usually of considerable intensity, is a constant and most important symptom. The amount eliminated is generally proportionate to the intensity of the disease, but varies within fairly wide limits, generally from 0.3 to 1 per cent., corresponding to a daily excretion of from 5 to 8 grammes. Much larger quantities, it is true, are at times excreted, but it may be

definitely stated that the daily loss of albumin seldom exceeds 20 grammes.

In chronic parenchymatous nephritis the elimination of albumin is likewise constant, and the amount excreted in severe cases may even exceed that observed in the acute form. An elimination of from 15 to 30 grammes, viz., 1.5 to 3 per cent. by weight, is frequently observed.

In the ordinary form of chronic interstitial nephritis the elimination of albumin is, as a general rule, slight, rarely amounting to more than 2 to 5 grammes *pro die.* At the same time it is not unusual to meet with an apparent absence of albumin, if the more common tests (see below) be employed. If it be remembered that very often the diagnosis of the disease is directly dependent upon the demonstration of the presence or absence of the albumin, the necessity of *frequent* examinations and the employment of more delicate tests, particularly of the trichloracetic-acid test, as well as of a microscopic examination is at once apparent. This is of even more moment in the renal arterio-sclerosis of Senator, in which albumin by the ordinary tests is probably not demonstrable in the majority of cases, and in which even the trichloracetic-acid test *may* not be of service, and casts absent.

Amyloid degeneration of the kidneys, in the absence of inflammatory processes, is accompanied by a condition of the urine closely resembling that observed in the ordinary form of chronic interstitial nephritis. A total absence of albumin, however, is less frequently noted, while an amount varying between 1 and 2 per cent. is not at all uncommon. It will be shown later on that in this condition considerable amounts of serum-globulin are excreted in addition to the serum-albumin; larger amounts, in fact, than are generally observed in this form of chronic renal disease, so that Senator suggests that such a relation, in the absence of an acute nephritis or an acute exacerbation of a chronic nephritis, may be of a certain diagnostic value.

3. *Febrile albuminuria.* That albuminuria may occur in almost any one of the various febrile diseases is a well-known fact, but it is important to remember that, while such an albuminuria may at times be referable to a true nephritis developing in the course of or during convalescence from an acute febrile disease, such is the exception, and not the rule. Under this heading only that form will be considered which is not associated with distinct changes

affecting the renal parenchyma, and which generally appears during the height of the disease only, to disappear again with a return of the temperature to normal limits. As has already been mentioned, it is often very difficult, if not impossible, to assign a definite cause for the occurrence of an albuminuria of this character, and in all probability several factors are in operation at the same time. In the beginning of the disease, when, as a rule, the blood-pressure is increased, the albuminuria may be referable to an ischæmia of the kidneys, as the increased pressure in fever, according to Cohnheim and Mendelson, is largely referable to spasm of the arterioles. Later on, or in the beginning of cases in which especially severe intoxication exists, the blood-pressure may be subnormal, and the albuminuria be due to this cause—*i. e.*, a hyperæmic condition of the kidneys. As a matter of fact, it has been experimentally demonstrated that both anæmia and hyperæmia of the kidney-structure may lead to albuminuria. On the other hand, it is not at all unlikely that the strain thrown upon the kidneys by an excessive elimination of organic material, in the absence of a correspondingly large quantity of water, may produce albuminuria. The author has repeatedly seen the functional albuminuria of the type described by Da Costa disappear during the administration of a diet relatively poor in nitrogen, an increased diuresis being at the same time effected by the consumption of large amounts of water.

In those grave cases of typhoid fever, furthermore, which are characterized by high fever and pronounced nervous symptoms it would appear quite likely that the albuminuria, which in these cases is particularly marked, is referable to a direct influence upon the central nervous system, and in some cases, at least, also dependent upon an irritant action on the part of the microbic poisons circulating in the blood upon the renal epithelium. The character of the albuminuria will largely depend upon the intensity of the intoxication; in other words, upon the amount of bacterial poison present at any one time in the blood.

Notwithstanding the statements to the contrary, albuminuria may be regarded as a constant symptom of typhoid fever, as has been definitely demonstrated by Gubler and Robin. It is difficult to say why other observers found this in only a comparatively small percentage of cases, but it is not unlikely that this was owing to a lack of uniformity in methods, it being presupposed also that observations of this kind can only be decided by *daily* examina-

tions. According to Robin, the trace of albumin which is at times observed during the first week of the disease is an albumose, while later on serum-albumin is quite constantly found, the amount increasing with the intensity of the morbid process, the highest figures being reached in fatal cases. The more severe the disease the earlier does albumin appear in the urine, it being remembered, however, that reference is had only to those cases in which distinct renal changes are not demonstrable. Toward the termination of the fastigium the amount of albumin generally undergoes a certain diminution, and may even disappear entirely. This diminution, however, is only temporary, and in severe cases the albumin again increases in amount during the period of the great variations in the temperature. In light cases an increased elimination also takes place at this stage, but is soon followed by a decrease, after which time only traces can be demonstrated in the urine. In some also it disappears entirely, but it is rare, according to Robin, to meet with cases in which a trace at least does not reappear during convalescence.

In light cases the albuminuria rarely persists longer than the fifth or eighth day of convalescence, and Robin even goes so far as to say that a relapse may frequently be predicted if the albuminuria does not disappear at this time. A limited number of personal observations have borne out the correctness of this view, and in one case in which a relapse occurred as late as the fifteenth day of convalescence traces of albumin could be demonstrated during the entire period. In severe cases, on the other hand, the albumin persists for a variable length of time, rarely disappearing before the tenth day of convalescence. At times an increase is seen during convalescence, where only traces have previously been observed. It is this form which the French generally speak of as *colliquative albuminuria*. While this form is principally observed in typhoid fever, it is not unusual to meet with it during the convalescence from various other acute diseases. Care must be taken not to confound the albuminuria so frequently seen during the convalescence from typhoid fever, referable to a pyelitis, with the form just described.

From the following table, constructed from data given in Robin's most excellent work on the urine of typhoid fever and other acute infectious diseases which may be associated with a typhoid condition, an idea may be formed of the occurrence of albuminuria, as well as of its degree of intensity in these diseases:

Acute miliary tuberculosis: Albumin much less frequent than in typhoid fever; when present it is rarely found in the abundance so characteristic of the fatal cases of the latter disease.

Pneumonia: Albumin is as uniformly present as in typhoid fever. At times very abundant.

Grippe: Albumin infrequent; present in about 20 per cent. of the cases and only in traces.

Herpetic fever: Albumin never present in large amounts.

Embarras gastrique: Albumin rarely present.

Adynamic enteritis of adults: Albumin almost always present, but usually only in traces

Cerebro-spinal meningitis: Albumin in fairly large amounts.

Vegetative endocarditis: Albumin very abundant in about 14 per cent., evident in 44 per cent., and traces in 42 per cent.

Acute articular rheumatism: Albumin present in about 40 per cent.

Rubeola: Albumin usually absent in light cases, but present in the more severe and complicated forms.

Intermittent fever: Albumin variable.

In conclusion, it may be said that practically every acute febrile disease, even simple follicular tonsillitis, may be accompanied by albuminuria in the absence of definite changes affecting the renal parenchyma. Its occurrence in an individual case is probably dependent, to a very large degree, upon the intensity of the intoxication. While it is generally an easy matter to distinguish between this form of albuminuria and that associated with distinct organic changes in the kidneys, considerable difficulty may at times be experienced, a question which will be dealt with later on.

4. *Albuminuria referable to circulatory disturbances.* To this class belongs the albuminuria so frequently observed in cardiac insufficiency referable to valvular lesions, degeneration of the heart-muscle from whatever cause, disease of the coronary arteries, etc., as well as in cases of impeded pulmonary circulation affecting the general circulation through the right heart, and, finally, in conditions associated with local circulatory disturbances, such as compression of the renal veins by a pregnant uterus, tumors, etc. It has already been pointed out that febrile albuminuria also may, to a certain extent at least, be referable to such causes; *i. e.*, an ischæmia or hyperæmia of the kidneys, produced by an increased or diminished blood-pressure. The albuminuria observed in cases of cholera

infantum, the simpler forms of intestinal catarrh, and in cholera Asiatica particularly, are undoubtedly dependent upon such causes. The occurrence of albuminuria after cold baths, as stated above, is regarded by many as a "physiologic" phenomenon, a view which should be rejected, however, as there can be but little doubt that this form of albuminuria also is referable to circulatory disturbances. The quantity of albumin found under these circumstances varies considerably, but rarely exceeds 0.1-0.2 per cent., unless indeed the disease has advanced to a point where distinct changes in the renal parenchyma have resulted.

5. *Albuminuria referable to an impeded outflow of urine.* Clinically, albuminuria referable primarily to an impeded outflow of urine from the kidneys is probably of more frequent occurrence than is generally supposed, and especially in women, in whom Kelly and others have demonstrated the frequent existence of ureteral stenoses. A complete blocking of the excretory duct, on the other hand, is rarely seen, but may be caused by the impaction of a renal calculus, the pressure of a tumor, or following certain gynæcological operations in which the ureter is accidentally caught in a suture, etc. It has also been suggested that the albuminuria of pregnancy may be due to compression of an ureter, but it is more likely that other factors are here of moment—*i. e.*, compression of the renal arteries, as well as of the veins.

6. *Albuminuria of hæmic origin.* It was formerly quite generally supposed that Bright's disease was dependent upon certain abnormalities of the blood, a view which has not only never been disproved, but which is actually gaining in importance from day to day. According to Semmola, Bright's disease is primarily due to an abnormal power of diffusion on the part of the albumins of the blood, which are elimintaed by the kidneys as waste material. As a result of the excessive amount of work thus done definite renal changes are finally produced. According to his theory, then, the albuminuria is the primary factor in the causation of nephritis, a view which, notwithstanding many assertions to the contrary, has certainly many points in its favor. Should this hypothesis hold good, Senator is correct in asserting that an albuminuria of functional origin, so to speak, must precede the occurrence of the nephritis proper. He appears to doubt the occurrence of a prenephritic albuminuria, however. In this connection it is interesting to note that definite renal changes have actually been observed to follow

an apparently functional albuminuria (Da Costa), demonstrating the possibility of such an occurrence. Further researches, however, are urgently needed in this direction, and Semmola's view, as well as all others so far proposed, can only be regarded as an hypothesis. Even if such blood-changes as those which Semmola suggests should not exist, there can be little doubt that true nephritis is dependent upon an acute or chronic dyscrasia of the blood, either in the sense of an abnormal mixture of the normal elements or of the presence of abnormal constituents, and notably of poisons. The same considerations undoubtedly also apply to various other forms of albuminuria, in so far as these are not the direct result of circulatory disturbances.

Clinically, albuminuria of hæmic origin is observed in various diseases of the blood, such as purpura, scurvy, leukæmia, pernicious anæmia, and also in cases of poisoning with lead and mercury, in syphilis, jaundice, diabetes, following the inhalation of ether and chloroform, etc. The albuminuria associated with an excessive elimination of uric acid and oxalic acid, and, according to personal observations, with an excessive elimination of organic material in general, notably of urea, probably also belongs to this class.

7. *Toxic albuminuria.* It has already been stated that the albuminuria of acute febrile diseases may to a certain extent be referable to a direct irritant action on the part of bacterial poisons upon the renal parenchyma. Poisoning with cantharides, mustard, oil of turpentine, potassium nitrate, carbolic acid, salicylic acid, tar, iodine, petroleum, phosphorus, arsenic, lead, antimony, alcohol, and mineral acids produces albuminuria. In all probability, however, the albuminuria here observed is referable not only to a direct irritant action upon the glandular epithelium of the kidneys, but also to circulatory disturbances.

8. *Neurotic albuminuria.* It is claimed by some that albumin, usually in small amounts, is eliminated in epilepsy after every attack, while others either entirely deny its occurrence under such conditions or regard it as exceptional. In a number of cases in which the author had occasion to examine the urine voided after an attack albumin was usually absent. It must be stated, however, that the seizures in these cases were comparatively mild, and that an examination for semen was unfortunately not made in those cases in which only traces of albumin could be demonstrated. A recent examination of the urine voided by an epileptic, after having

been in the epileptic state for more than forty-eight hours, showed the presence of a small amount of albumin, associated with an enormous elimination of uric acid, as well as a large excess of urea. Semen was absent. A transient albuminuria has also been noted in cases of progressive paralysis, mania, tetanus, delirium tremens, apoplexy, migraine, Basedow's disease, etc.[1]

Although albuminuria may apparently be artificially produced by injuries affecting a certain point in the floor of the fourth ventricle, analogous to the production of glycosuria (see Glycosuria), it would probably be going too far to assume the existence of a certain specific centre, stimulation of which would cause the appearance of albumin in the urine. While the influence of the nervous system in preventing the passage of albumin through the glomeruli under normal conditions is undoubted, it would appear more likely that the albuminuria following injuries to the central nervous system is referable to circulatory disturbances in the kidneys secondary to lesions in the brain, especially in the medulla. The albuminuria observed in certain neurotic individuals, on the other hand, is probably more frequently associated with metabolic abnormalities and of hæmic origin.

9. *A digestive albuminuria* has also been described, but need not be considered in detail. Suffice it to say that it may follow the ingestion of excessive amounts of cheese, eggs—particularly when taken raw—beef, etc. The author has seen albuminuria follow a free indulgence in root beer. It is, of course, difficult to explain such occurrences; but, bearing in mind the fact that albuminuria very often follows the ingestion of such articles almost immediately and before they have actually had time to become absorbed, it is hardly justifiable to refer this form to the existence of a hyperalbuminosis. It would appear more rational in such cases, as Senator has suggested, to think of reflex or vasomotor or trophic changes affecting the kidneys; while in other cases, in which the albuminuria does not follow the ingestion of such articles of food immediately, it is quite probable that this may be dependent upon certain metabolic abnormalities affecting the normal composition of the blood.[2]

[1] Recently the author observed the occurrence of albumin in the urine of a case of cerebral sarcoma.

[2] The albumin which is eliminated after the ingestion of much egg-albumin, however, does not belong to this category.

In the account given of the occurrence of albuminuria and its possible causes reference has been only had to a *purely renal* albuminuria. It should be remembered, however, that the origin of the albumin may often be extremely difficult to determine, as albuminous material, such as blood and pus, may become mixed outside of the glandular portion of the kidneys with what would otherwise have been a perfectly normal urine, and that such an admixture may not only take place in the ureters, the bladder, and the urethra, but even in the pelvis of the kidney.

The term *accidental albuminuria* is applied to a condition in which albuminous material becomes mixed with a urine beyond the kidneys which has been secreted free from albumin, as in cases of cystitis and urethritis, or whenever semen has entered the urine. Such an admixture of pus, blood, lymph, or chyle may, however, occur in the kidneys, when the albuminuria is termed *accidental renal albuminuria*, an example of which is frequently seen in the slight degree of albuminuria referable to pyelitis, during the convalescence from typhoid fever. By a *mixed albuminuria* and a *mixed renal albuminuria*, on the other hand, are meant conditions in which the source of the albumin is twofold, renal and extrarenal in the first instance, parenchymal and extraparenchymal in the second, examples being the albuminuria of cystitis combined with nephritis and pyelonephritis, respectively.

It is manifest, of course, that in every instance in which albumin is found in the urine its origin should be ascertained. While this question is usually readily decided by a microscopic examination of the urine, considerable difficulty may occasionally be experienced. It is a well-known fact that in the urine of females a trace of albumin may frequently be detected which is not due to any existing lesion of the urinary organs, but to an admixture of vaginal discharge, of blood during the process of menstruation, and in married women of semen. Whenever, therefore, doubt is felt as to the origin of the albumin, the specimen for examination should be obtained by the catheter, care being taken previously to cleanse the vulva. In males albumin may be referable to a gonorrhœal urethritis, and only recently a case was observed in which a gentleman, who had been rejected by a life-insurance examiner on account of the presence of albumin in his urine, was discovered to have a free urethral discharge, the albuminuria clearing up on treatment of his gonorrhœa. In such cases it is well to let the patient flush out his

urethra first, and make use of the portion last passed for examination. Very often, however, the conditions are more complex, it being uncertain whether the albumin is due to a cystitis or whether it has come from the kidneys. Here a careful microscopic examination is called for, and will in the majority of instances decide the question. At other times even then we may be left in doubt, when recourse should be had, if at all possible, to catheterization of the ureters. The latter procedure is usually called for in obscure cases of pyuria and of hæmaturia, in which it is necessary not only to ascertain the origin of the pus or blood, but also to determine the kidney from which this has proceeded, and, if one be found to be diseased, the condition of the other.

As far as the *amount of albumin* which may be eliminated in the twenty-four hours is concerned, an excretion of less than 2 grammes may be regarded as insignificant, 6 to 8 grammes as moderate, and 10 to 12 grammes or more as excessive. An excretion of 20 to 30 grammes must be considered as very exceptional. An elimination of more than this amount probably never occurs.

Other albumins which may occur in the urine at times, as already indicated, are serum-globulin, albumoses, viz., peptones, hæmoglobin, fibrin, mucin (nucleo-albumin), and histon.

Serum-globulin. It has been pointed out that serum-globulin is found in the urine together with serum-albumin in large amounts in cases of amyloid degeneration of the kidneys, and, according to Senator, a ratio between the amounts of these two albumins of 1 : 0.8 : 1.4 may be regarded as a fairly constant symptom of this disease, and of some diagnostic importance. There seems to be no doubt, however, that serum-globulin occurs in the urine, although in much smaller quantities than in the disease mentioned, whenever serum-albumin is eliminated, and so far not one case of pure globulinuria has been reported, a fact which is not surprising, as there is no reason why only one albumin present in the blood should pass through the kidneys.

Albumoses (peptones). The presence of albumoses in the urine has frequently been observed, but is probably more frequently overlooked, as the bodies in question are not precipitated upon boiling. The factors which cause their appearance in the urine are probably similar to those noted in connection with peptonuria, and will be presently considered. Suffice it to say that albumoses have been observed in a variety of diseases, such as multiple myelomata of the

bones, dermatitis, intestinal ulceration, liver-abscess, croupous pneumonia, septicæmia, carcinomatous peritonitis, apoplexy, heart-disease, pleurisy, caries, puerperal parametritis, endocarditis, typhoid fever, diphtheria, pyæmia, nephritis, phthisis, measles, scarlatina, leukæmia, urticaria, acute yellow atrophy, various psychoses, etc. Very frequently albumosuria accompanies albuminuria, a condition which has been termed *mixed albuminuria* by Senator. In this connection it is interesting to note that albumosuria may alternate with albuminuria, and precede as well as follow the latter, and in any case in which albumoses are demonstrable in the urine the appearance of albumin should be expected.

Albuminous bodies not coagulable by heat, and in their general behavior resembling peptones, have repeatedly been seen in urines when Hofmeister's method of testing for peptones was employed, and various forms of so-called *peptonuria* have since been described. An elimination of such bodies has been noted in conditions associated with large accumulations of pus within the body, it being supposed that the peptonuria observed in such cases was referable to a disintegration of the pus-corpuscles and a resorption into the blood of the peptone contained in these. This form of peptonuria was hence termed *pyogenic peptonuria.* A *hepatogenic form* has been likewise described in connection with diseases of the liver, notably acute yellow atrophy. It was formerly thought that peptones were retransformed, so to speak, into albumins by the liver, and the occurrence of peptonuria in diseases of this organ was explained by the inability on its part to cause this transformation, the peptones accumulating in the blood and being excreted in the urine. Later researches, however, have shown that the transformation of peptones into albumins takes place in the intestinal mucosa, and that the liver apparently has no part in this process, so that an explanation of this form is still wanting. An *enterogenic form* has been noted in various diseases of the intestinal tract, such as typhoid fever, tubercular ulceration, carcinoma, etc., in which it was supposed that peptone is either directly absorbed from the disintegrating pus, or that the intestine itself has lost the power of causing its transformation into albumin. A *histogenic* or *hæmatogenic* origin was further ascribed to the peptonuria seen in cases of scurvy, various forms of poisoning, during the puerperal period, pregnancy, particularly following the death of the fœtus, in various psychoses, etc. Finally, a *renal* and *vesical* form of peptonuria was

noted in which peptones were formed in albuminous urines either in consequence of the presence of enzymes or the occurrence of putrefaction.

More recently, however, since our conception of the nature of peptones has changed—it being quite generally accepted at the present day that true peptones are not precipitated by ammonium sulphate—investigations have shown that in all cases in which the presence of these bodies had been previously assumed true peptones are actually not present, but that the bodies in question are propeptones or albumoses. *According to Kühne's definition of peptones, a peptonuria hence does not exist.*

In the differential diagnosis of suppurative meningitis a positive *peptone*-reaction in the older sense of the word, according to Senator, speaks strongly in favor of the existence of this disease, a point which at times may undoubtedly be of great importance. In support of this view he cites the case of a young man, the subject of a median otitis of long standing, in which symptoms pointing to a meningitis—viz., fever, headache, and pains in the neck—were present, but in which no "peptonuria" was found to exist, and in which an operation revealed the presence of a cholesteatoma.

A digestive form of albumosuria has recently been announced, where albumoses appear in the urine after their ingestion in large quantities, and it is claimed that this is only observed in cases of ulcerative disease of the intestinal tract. Only a positive result, however, is of value.

Hæmoglobin. Under normal conditions the disintegration of red blood-corpuscles constantly taking place in the body never results in such a degree of hæmoglobinæmia as to be followed by an elimination of hæmoglobin in the urine. Whenever for any reason the destruction of red corpuscles is so extensive, however, that the liver is unable to transform into bilirubin all the blood-coloring matter set free, *hæmoglobinuria* will occur. While these factors, then—*i. e.*, an excessive destruction of the red blood corpuscles and an insufficiency on the part of the liver—must be regarded as explaining every case of hæmoglobinuria, our knowledge of the ultimate causes of such excessive disintegration, as well as the manner in which these operate, is as yet very limited. Formerly the term *hæmatinuria* was applied to this condition. It was shown, however, that the pigment eliminated is in reality not hæmatin, but usually methæmoglobin and only at times hæmoglo-

bin, so that the term hæmoglobinuria is also, to a certain extent, ill chosen.

Most frequently to be observed, perhaps, is the hæmoglobinuria produced by certain poisons, such as potassium chlorate, arseniuretted hydrogen, sulphuretted hydrogen, pyrogallic acid, naphthol, hydrochloric acid, tincture of iodine, carbolic acid, carbon monoxide, etc., and also by morels (Helvella esculenta).

Quite familiar is the hæmoglobinuria observed following transfusion of the blood of animals into man, such as that of the calf and lamb; also the form seen in cases of extensive burns and insolation.

While hæmoglobinuria may occur in the course of any one of the specific infectious diseases, such as scarlatina, icterus gravis, variola hæmorrhagica, typhoid fever, yellow fever, etc., it is said to be especially frequent in cases of malarial intoxication. This view is not accepted by many, Osler, among others, thinking that it has frequently been confounded with malarial hæmaturia. The author has never seen a single instance of malarial hæmoglobinuria, and believes that in our more temperate zones it scarcely ever occurs. Bastianello asserts that it is likewise rare in Italy, more common in Sicily and Greece, and very common in the tropics. According to the same observer, hæmoglobinuria only occurs in infections with the æstivo-autumnal parasite. A hæmoglobinuria due to quinine is likewise said to exist, but apparently never occurs, excepting in patients who are suffering, or who have recently suffered, from malarial fever. In our country this form is rare also. On the other hand, there can be no doubt, to judge from the literature upon the subject, that syphilis may, under certain conditions, be a potent factor in the production of hæmoglobinuria. This appears to be particularly true of cases of so-called paroxysmal hæmoglobinuria, a condition in which bloody urine is voided from time to time, the attacks being frequently preceded by chills and fever, so as closely to simulate malarial fever. Other factors, also, notably cold, appear to be concerned in the production of this form.

The occasional occurrence of hæmoglobinuria in cases of Raynaud's disease, coincident with attacks of an epileptiform character, has been referred to in the chapter on Blood. (See p. 36).

Hæmoglobinuria has been observed in a case of leukæmia complicated by icterus.

Finally, an epidemic hæmoglobinuria has been described as occur-

ring in the newborn, associated with jaundice, cyanosis, and nervous symptoms; of its causation, however, we are still in profound ignorance.

While hæmoglobinuria is fairly uncommon, *hæmaturia* is frequently observed, and will be considered later on, as its recognition is not dependent upon the demonstration of the albuminous body, "hæmoglobin," alone in the urine, but upon the presence of red corpuscles, which in hæmoglobinuria are either absent or present in only very small numbers.

Fibrin. The occurrence of fibrin in the urine presupposes the presence of fibrinogen, a fibrinogenic ferment, and probably also of serum-globulin, and is seldom seen. According to Neubauer and Vogel, the fibrin may occur either as coagulated fibrin or in solution. In the former condition it is at times observed in the form of blood-coagula, when its significance is essentially the same as that of hæmaturia in general, although it must be remembered that the usual form of hæmaturia is not associated with the presence of coagula. Colorless coagula of fibrin are only seen in cases of chyluria or diphtheritic inflammation of the urinary passages. On the other hand, urines containing fibrin in solution are likewise seen but rarely, and are characterized by the fact that fibrinous coagula separate out only on standing, when they usually cover the bottom of the vessel, but may at times change the entire bulk of urine into a gelatinous-looking mass. So far this condition has been observed only in cases of chyluria (which see).

Nucleo-albumin. The question whether or not nucleo-albumin is a normal constituent of the urine is still a matter of dispute. Personal investigations have led the writer to the conclusion that with complicated methods and large amounts of urine—from 5 to 25 liters—it is always possible to demonstrate its presence both under physiologic and pathologic conditions. With the usual tests and smaller amounts of urine, however, negative results only are obtained in strictly normal individuals. Trichloracetic acid, with which Stewart claims to have obtained positive results in every one of the 150 normal urines which he examined, does not precipitate nucleo-albumin, according to the writer's experience, when this is present in normal amounts. *A nucleo-albuminuria, recognizable by the available tests, does not exist under normal conditions.* Even under pathologic conditions nucleo-albumin is by no means always found. Sarzin thus was unable to demonstrate its presence in 200

cases which be examined in Senator's clinic. Citron arrived at similar results, and the writer, after having carefully examined several thousand urines in this direction, obtained positive results in only a very small percentage of cases. Its presence always indicates an increased degree of desquamation in some portion of the urinary tract. It is essentially met with in diseases which directly or indirectly involve the integrity of the epithelial lining of the uriniferous tubules or of the bladder.

It has thus been frequently found in cases of acute nephritis and associated with febrile albuminuria, although its presence even then is not constant. In chronic nephritis it is more frequently absent than present. In cases of renal hyperæmia and cystitis the results are variable. In thirty-two icteric urines Obermayer obtained positive results without exception, and it appears that in leukæmia nucleo-albumin is also quite constantly present. During the administration of pyrogallol, naphthol, corrosive sublimate, tar preparations, arsenic, etc., as well as in cases of poisoning with aniline and illuminating gas, large amounts of the substance may be found.

According to the writer's experience, nucleo-albumin is quite frequently observed in cases of so-called functional albuminuria, and it is not at all uncommon to find that this is still present when serum-albumin and serum-globulin can no longer be demonstrated, even with the trichloracetic-acid test. Nucleo-albuminuria may thus exist independently of the presence of the more common forms of albumin. This observation has also been made by Strauss, who found nucleo-albumin only in several cases of cystitis, in one case of chronic interstital nephritis, and in one case of emphysema pulmonum with renal hyperæmia.

The existence of a hæmatogenic form of nucleo-albuminuria has thus far not been satisfactorily demonstrated.

Histon. Quite recently Kolisch and Burion were able to demonstrate the presence of histon in the urine of a case of leukæmia, an albuminous body which was first dicovered by Kossel in the red blood-corpuscles of the goose, and which was shown to exist in the leucocytes of human blood in combination with the acid leuko-nuclein, constituting the so-called nucleo-histon of Lilienfeld. According to these observers, the substance was always present in their case. The method which they employed in testing for its presence was the following:

The urine of twenty-four hours was first examined for albumin,

and this removed, if present. It was then precipitated with 94 per cent. alcohol, the precipitate washed with hot alcohol and dissolved in boiling water. Upon cooling, the solution thus obtained was acidified with hydrochloric acid and allowed to stand for several hours. During this time a cloudiness, referable to a large extent to uric acid, develops, which is filtered off, when the filtrate is precipitated with ammonia. In addition to certain mineral constituents, histon, if present, is also thrown down. The precipitate is collected upon a small filter and washed with ammoniacal water until the washings no longer give the biuret reaction. It is then dissolved in dilute acetic acid and the solution tested with the biuret test; if this yields a positive result, and if coagulation occurs upon the application of heat, the coagulum being soluble in mineral acids, the presence of histon may be inferred.

It is not clear in what manner the histonuria is produced; so much, however, seems certain, that it is not solely dependent upon the increased destruction of leucocytes.

A histon-like body has also been found in acute peritonitis, following appendicitis, in croupous pneumonia, erysipelas, and scarlatina.

Tests for Albumin. The recognition of the various albuminous bodies which may occur in the urine is based partly upon their direct precipitation and partly upon color-reactions when treated with certain reagents.

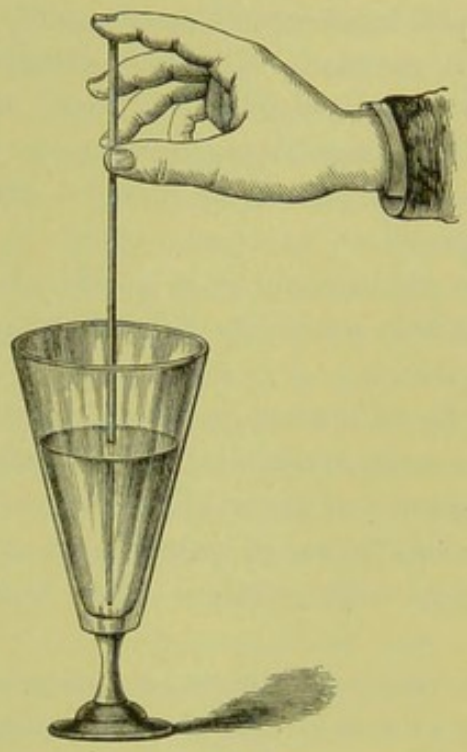
The number of tests which have from time to time been suggested is very large; many of them, after a brief period of use, have been discarded as useless or uncertain, while others have been employed only occasionally and have not received the recognition which they deserved from the fact that simpler tests existed, that they did not possess sufficient delicacy, or that in some instances it was too great. In the following pages no attempt will be made to describe all of these tests, and attention will be directed only to those which are generally used and which clinical experience has proved to be of value, precedence being given to those which have been longest in use. While some of these are applicable for demonstrating the presence of more than one form of albumin, special tests will also be described whereby the various albumins may be individually recognized.

In every case the urine should be carefully filtered, so as to free it from any morphologic constituents, etc., present. To this end it is generally sufficient to pass the urine through one or two layers

of Swedish filter-paper. Frequently, however, a clear specimen cannot be obtained in this manner; it is then advisable to shake the urine with magnesia usta, or to mix it with scrapings of filter-paper, when it is filtered as usual.

Tests for Serum-albumin. *The nitric-acid test.* (Fig. 94.) The value of this test, properly applied, cannot be overestimated, as it is not only simple, but yields an amount of information that can otherwise only be gained with difficulty; information, moreover, which is valuable in many respects. Usually the student is advised to make use of a test-tube partially filled with urine, along the sides of which concentrated, chemically pure nitric acid is allowed to flow, so as to form a layer at the bottom of the tube, when in the presence of serum-albumin a distinct white cloud will appear in the form of a ring at the zone of contact between the two liquids (Heller's test). The pictures thus obtained cannot be compared, however, with those seen when the apparently trivial change is made of using a conical glass of about 2 ounces capacity instead of the test-tube. About 20 c.c. of urine are placed in the glass, and 6 to 10 c.c. of nitric acid added by means of a pipette, which is carried to the bottom of the vessel, when the acid is slowly allowed to escape by diminishing the pressure of the finger upon the tube. When this is carefully done, as in Heller's test, the nitric acid forms a distinct zone beneath the urine. In the presence of albumin the cloud referred to above will be seen, its extent and intensity varying with the amount of albumin present. (Plate X., Fig. 1.) If now the glass be allowed to stand for some time—and if small amounts be present, these only appear on standing—it will be observed that gradually the cloudiness extends upward, the upper border of the albumin-ring, with few exceptions, being at

Fig. 94.



Nitric acid test.

PLATE X.

FIG. 2.



FIG. 4.



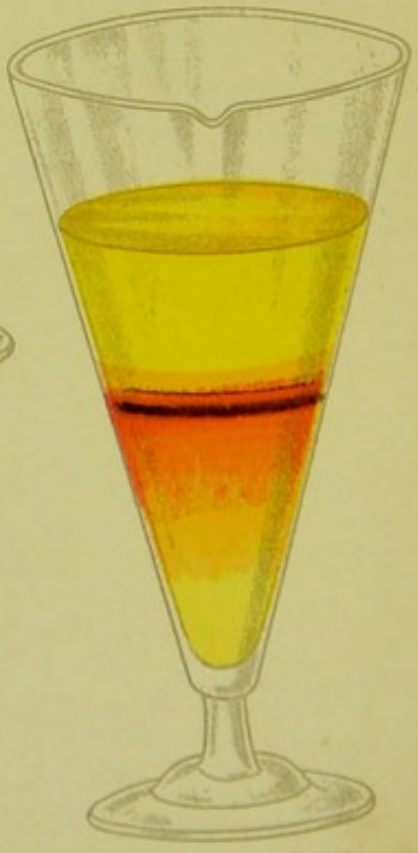
FIG. 1.



FIG. 3.



FIG. 5.



first as well defined as the lower border, when the coagulated albumin may be seen to rise into the supernatant liquid in the form of small, irregular columns. This appearance may possibly be referable to the partial decomposition of uric acid by means of nitric acid, nitrogen and carbon dioxide being set free, which, rising to the surface in the form of small bubbles, carry the nitric acid upward; this coming into contact with albumin in solution then causes the precipitation of the latter. An excess of uric acid, moreover, is indicated by the appearance, within five to ten minutes after the addition of the nitric acid, of a distinct ring in the clear urine about 1 to 2 cm. above the zone of contact, which is similar in appearance to that due to albumin. If this ring (Plate X., Figs. 1, 2, and 3), which has been very appropriately compared to a *holy* wafer, does not appear within five to ten minutes, it may be assumed that the uric acid is present in diminished amount; on the other hand, it is possible to determine the degree of increase by the size of the ring, it being presupposed that the same quantities of urine and of the reagent are employed in every case.

Should more than 25 grammes of urea be contained in a liter of the urine examined, an appearance like hoarfrost will be noted on the sides of the vessel, due to the formation of urea nitrate, while spangles of the same substance only appear in the presence of at least 45 grammes. Should 50 grammes or more of urea be contained in the liter, a dense mass of urea nitrate may be seen to separate out.

DESCRIPTION TO PLATE X.

FIG. 1. The nitric-acid test as applied to the urine: The light, colorless ring in the clear urine above shows a slight increase in the amount of uric acid; the large white band denotes a large amount of albumin, bordering upon a colored ring, referable partly to indican (blue) and partly to urorosein.

FIG. 2. The nitric-acid test as applied to the urine: The light ring in the clear urine above denotes a slight increase in the amount of uric acid. The bluish-black band is referable to an enormous increase in the amount of indican. Taken from a case of ileus.

FIG. 3. The nitric-acid test as applied to the urine: The broad, light band in the clear urine above is referable to an enormous increase in the amount of uric acid. Taken from a case of laparotomy.

FIG. 4. The nitric-acid test as applied to the urine: The color play referable to the presence of bilirubin is shown in a diagrammatic manner.

FIG. 5. The nitric-acid test as applied to the urine: The colored ring is referable to the presence of normal urinary coloring matter.

Biliary urine when treated with nitric acid containing a little nitrous acid shows the color-play referable to the action of nitric acid upon bilirubin (Plate X., Fig. 4), the production of the colors, yellow, green, blue, violet, and red, taking place from above downward, the green color being the most characteristic; in the absence of the latter the presence of biliary pigment may be positively excluded. The presence of albumin is not at all objectionable, as the color-play takes place beneath the albuminous disk.

In normal urine a transparent, colored ring is also obtained, presenting a peach-blossom red, the intensity of which, however, may vary from a faint rose to a pronounced brick color, referable to normal urinary pigment. (Plate X., Fig. 5.) In the presence of urobilin, on the other hand, this ring presents a distinct mahogany color.

Indican is indicated by the appearance of a more or less violet ring (Plate X., Fig. 2) situated above that referable to the normal urinary pigment, its intensity varying with the amount present, from a light blue to a deep indigo-blue, which may color the entire urine when this is shaken.

A cloud at the zone of contact of the two fluids may be referable not only to the presence of serum-albumin, but also of globulin and albumoses (propeptones), while a negative reaction will generally indicate the absence of these bodies. That the uric-acid ring will be mistaken for albumin is hardly likely, if it be recollected that this never first appears at the zone of contact of the two fluids, but always in the uppermost portion of the urine. It is true that urines are occasionally observed in which the separation of uric acid, always in the amorphous form, takes place so suddenly that within a minute or two the entire urinous portion of the mixture is completely clouded, resembling the appearance presented by a highly albuminous urine. Such an excessive elimination of uric acid is quite uncommon, however, and it is to be remembered that with uric acid the cloudiness proceeds from above downward, and never from below upward, as is the case with albumin. Should any doubt be felt, it is only necessary to remove a few c.c. of this cloudy urine by means of a pipette and heat them gently in a test-tube, when the urine will clear up entirely if the precipitate be due to uric acid, while if caused by albumin it will remain or become still more intense. Should the precipitate caused by nitric acid consist of albumoses, this will also clear up entirely, to reappear on

cooling, the fluid at the same time assuming a distinct yellow color. The occurrence of a distinctly yellow color in the urine, moreover, which is only partially cleared upon the application of heat, and be it remembered that a much higher temperature is necessary for the solution of a precipitate referable to albumoses than of one due to urates, will indicate the existence of a mixed albuminuria—*i. e.*, the presence of coagulable albumin and albumoses. Nitric acid may also cause a precipitation of certain resinous bodies, such as those contained in turpentine, balsam of copaiba and tolu, etc. If any doubt be felt, the mixture should be shaken with alcohol, when the precipitate caused by these substances is at once dissolved. The mucinous body—nucleo-albumin—which is at times found in the urine, is also precipitated by nitric acid, but need not occupy our attention at this place. From what has been said it is manifest that the employment of the nitric-acid test in the manner indicated furnishes much valuable information, and the adoption of the method, as described, not only by hospital students, but by general practitioners as well, cannot be too strongly urged.

Boiling-test. A few c.c. of urine are boiled in a test-tube and then treated with a few drops of concentrated nitric acid, no matter whether a precipitate has occurred upon boiling or not. If albumin be present, this will separate out as a flaky precipitate, which consists of serum-albumin frequently mixed with serum-globulin. It is true that albuminous urines will generally yield a preciptate on boiling alone, but it must be remembered that unless the reaction be decidedly acid, a preciptation of normal calcium phosphate may occur owing to the fact that the reaction of the urine upon boiling becomes less acid, probably owing to an escape of the carbonic acid held in solution. In urines presenting an alkaline or amphoteric reaction this is very frequently noted, and might give rise to confusion, as the precipitate due to calcium phosphate very closely resembles that due to albumin. Care must hence be taken to insure a distinctly acid reaction, which is best accomplished by the addition of nitric acid, when a precipitate referable to phosphates is at once dissolved, while one due to albumin remains and may even become more marked. The quantity to be added should usually be equivalent to about 0.05 to 0.1 of the volume of the urine, and under no consideration should the acid be added before boiling, nor should the urine be boiled after its addition, as small amounts of albumin will otherwise be overlooked, owing to the fact

that hot nitric acid dissolves the precipitate to a certain degree. If after the addition of the nitric acid the urine turns a distinct yellow, and if then upon cooling a white precipitate appears, the presence of albumoses may be inferred. Uric acid will probably never cause confusion, as this only separates out upon cooling, and then presents a dark-brown color. As in the case of the nitric-acid test, so also here, a precipitation of certain resins is noted at times, which may, however, be recognized by their solubility in alcohol.

Should acetic acid be used instead of nitric acid, great care must be taken to avoid an excess, as otherwise the albumin will be dissolved. As this danger diminishes the greater the quantity of salts contained in the urine, it is advisable to treat the urine first with a few drops of acetic acid until a distinctly acid reaction is obtained, and then to add one-sixth of its own volume of a saturated solution of sodium chloride, magnesium sulphate, or sodium sulphate, when upon boiling a precipitation of the albumin will take place. Carried out in this manner, the test is absolutely certain and will demonstrate even minimal amounts of albumin.

The potassium ferrocyanide test. A few c.c. of urine are *strongly* acidified with acetic acid (sp. gr. 1.064) and treated with a few drops of a 10 per cent. solution of potassium ferrocyanide, when in the presence of but little albumin a faint turbidity, or, if much albumin be present, a flaky precipitate, is noted, which is best recognized by comparison with a tube containing some of the pure filtered urine, both tubes being held against a black background. Concentrated urines should be previously diluted with water, as propeptones, like serum-albumin and serum-globulin, which may be precipitated in this manner, otherwise remain in solution. Here, also, as in the tests described, the presence of propeptones may be inferred if the precipitate disappears upon boiling, while a partial clearing up, on the other hand, indicates the presence of both albumoses and coagulable albumin.

At times the addition of acetic acid by itself is followed by the appearance of a cloud in the urine, which may be due to urates or to urinary mucin (nucleo-albumin), as already mentioned. In such cases the urine should be refiltered and diluted with water and the test again applied.

v. Jaksch advises the careful addition, by means of a pipette, of a few c.c. of fairly concentrated acetic acid to which a little potassium ferrocyanide has been added, when the albumin, as in Heller's

test, is seen to form a ring at the surface of contact between the two fluids. Instead of potassium ferrocyanide, potassium platinocyanide may also be employed, and has the advantage that the test-solution is colorless.

The trichloracetic-acid test. This test is undoubtedly the most delicate of those so far described, but not so delicate that a trace of albumin, or nucleo-albumin, as has been suggested by some, can be demonstrated in every urine. An experience based upon the examination of several thousand urines with this reagent warrants the author's speaking with a certain amount of confidence upon the subject. Very frequently it is possible with this method to demonstrate albumin in urines in which the more common tests yield negative results, but in which tube-casts may nevertheless be found upon microscopic examination. The test is applied as follows: By means of a pipette, 1 or 2 c.c. of an aqueous solution of the reagent (sp. gr. 1.147) are carried to the bottom of a test-tube containing the carefully filtered urine, so as to form a layer beneath the urine, when, in the presence of albumin, a white ring will be seen to form at the zone of contact between the two fluids, varying in intensity with the amount of albumin present. As far as the test for albumin is concerned, this reagent possesses an advantage over the nitric acid in that the colored rings, so often confusing to the inexperienced, are but rarely observed. Serum-albumin, serum-globulin, and albumoses are thus precipitated, the presence of the latter being recognized, as in the previous tests, by the fact that the precipitate disappears upon boiling, to reappear again upon cooling. A cloud, referable to uric acid, also appears if this be present in excessive amounts, but it is readily distinguished from that caused by albumin by the fact that it disappears upon the application of gentle heat. Furthermore, a previous dilution of the urine guards against this occurrence.

Other tests have also been suggested for the detection of albumin in the urine, such as the metaphosphoric-acid test, the phenol, tannic-acid, and picric-acid tests, that with Tanret's reagent, phosphotungstic and phosphomolybdic acids, and quite recently Spiegler's reagent.

Of these, only the picric-acid and Spiegler's tests will be considered.

Picric-acid test. The picric-acid test is not applicable as a test for albumin as such, and is only mentioned in this connection be-

cause Esbach's quantitative method is based upon it. His reagent is composed of 10 grammes of picric acid and 20 grammes of crystallized citric acid, dissolved in a liter of distilled water. If to this solution albuminous urine be added, the mixture is rendered turbid, and after some time a sediment which consists not only of albumins, but also of uric acid, kreatinin, and other extractives, will form at the bottom of the tube. (See Quantitative determination of albumin.)

Spiegler's test. Spiegler's reagent consists of 8 parts by weight of mercuric chloride, 4 parts of tartaric acid, and 200 parts of water, in which 20 parts of cane-sugar are further dissolved so as to increase the specific gravity of the reagent and permit of its being employed, like Heller's test, in even concentrated urines. One-third of a test-tube is filled with the reagent, and the urine carefully placed above this by allowing it to flow slowly down the side of the tube; in the presence of albumin a sharply defined white ring will be observed where the two liquids are in contact. Peptone gives no reaction, while albumoses are precipitated and may be recognized as indicated above.

Special test for serum-albumin. Should it be desired, for any reason, to demonstrate serum-albumin alone, the urine is rendered amphoteric or faintly alkaline with sodium hydrate, and then saturated with magnesium sulphate in substance, in order to remove any globulin. The filtrate is strongly acidified with acetic acid, when a flaky precipitate, appearing upon boiling, will indicate the presence of serum-albumin.

Very often, as in the examination for sugar, it is necessary to remove any coagulable albumin that may be present, to which end the urine is rendered distinctly acid with acetic acid and boiled. An examination of the filtrate with potassium ferrocyanide, if the amount of acetic acid added was just sufficient, will then yield a negative result (see p. 404).

Quantitative Estimation of Albumin. For the quantitative estimation of albumin a number of methods have been devised, which fact in itself is sufficient to indicate that the majority of these, at least, are unsatisfactory.

Old method by boiling. If only comparative results are to be obtained, the old method of boiling a definite amount of urine, after the addition of acetic acid, and allowing the albumin to settle for twenty-four hours, may be employed. For this purpose Neubauer suggests the use of glass tubes measuring one-half to three-

quarters of an inch in diameter, closed at the lower end with a cork, into which the urine is poured. Ordinary test-tubes answer the purpose perfectly well, but care should be taken that the same quantity of urine be used in every case. These tubes may then be corked and kept for several days for comparison. Of course, the results obtained express only the relative amount of albumin present, and it should be remembered that the errors incurred may amount to as much as 30 or even 50 per cent., when compared with those obtained gravimetrically, owing to the fact that sometimes the albumin separates out in large flakes, and at other times in small flakes, and that the degree of precipitation is also influenced by the specific gravity of the supernatant urine.

Volumetric method of Wassiliew. This method can be strongly recommended for the quantitative estimation of albumin, as it is both simple and accurate.

Ten to twenty c.c. of urine, which are best diluted to 50 c.c. with distilled water, are treated with 2 drops of a 1 per cent. aqueous solution of true yellow and then titrated with a 25 per cent. solution of salicyl-sulphonic acid until a distinct brick-red color is obtained. The number of c.c. employed multiplied by 0.01006 will then indicate the amount of albumin contained in the 10 or 20 c.c. of urine examined. If the urine be alkaline, it should first be slightly acidified with acetic acid.

FIG. 95.



Esbach's albuminimeter.

Esbach's method. For clinical purposes, Esbach's method is the most convenient. As stated above, his reagent is composed of 10 grammes of picric acid and 20 grammes of citric acid, dissolved in 1000 c.c. of distilled water. Special tubes, termed albuminimeters (Fig. 95), are employed which bear two marks, one, *U*, indicating the point to which urine must be added, and one, *R*, the point to which the reagent is added. The lower portion of the tube up to *U* bears a scale reading from 1 to 7. The tube is filled to *U* with the filtered albuminous urine, and the reagent added until the point *R* is reached. The tube is then closed with a stopper, inverted twelve times, and set aside for twenty-four hours. At the expiration of this time serum-albumin, serum-globulin, and peptones, as well as uric acid and kreatinin, will have settled down, when the amount pro mille in grammes may be directly read

off from the scale. A few precautions must, however, be observed in order to obtain as accurate results as possible. The reaction of the urine should be acid, and if such be not the case acetic acid is added. Its specific gravity should, furthermore, not exceed 1.006 or 1.008, the proper density being obtained by diluting with water. The temperature also appears to play an important *rôle*, the reading generally being higher with a low than with a more elevated temperature, 15° C. being best adapted to our purposes.

The differential density method. More accurate results may be obtained with the following method, which is based upon the diminution in the specific gravity of the urine after the removal of all albumin, and its comparison with the specific gravity observed before. To this end the urine is treated with a sufficient amount of acetic acid to insure a complete precipitation of the albumin (see below), when its specific gravity is noted. It is then brought to the boiling-point, care being taken to guard against evaporation by placing the urine in an ordinary medicine-bottle, closing this with a rubber stopper that has been previously boiled in a sodium hydrate solution and washed until free from an alkaline reaction, the stopper being tightly fastened with a cord or wire. Thus prepared, the bottle is kept in boiling water for ten to fifteen minutes, the urine filtered upon cooling, evaporation being again carefully guarded against by filtering into a bottle through a funnel which has been passed through a closely fitting stopper, the funnel being kept covered by a plate of glass, when the specific gravity is again determined, it being best in both cases to use a pyknometer. The decrease in the specific gravity, multiplied by 400, will indicate the number of grammes of albumin contained in 100 c.c. of urine.

Gravimetric method. If special accuracy be required, the amount of albumin must be determined gravimetrically as follows: A certain amount of urine, after having been acidified with acetic acid to such a degree as to insure a complete separation of all albumin, is boiled; the albumin is then filtered off, dried, and weighed. For this purpose, 500 to 1000 c.c. of carefully filtered urine should be available. A specimen of this, if already acid, is placed in a test-tube in boiling water until coagulation takes place, when it is further heated over the free flame and filtered. The filtrate is then tested with acetic acid and potassium ferrocyanide. Should no albumin be thus demonstrable, the entire amount of urine is treated in the same manner and requires no further addition of acetic acid.

If, however, the test yields a positive result, it is apparent that the urine was not sufficiently acid. The entire volume is then treated with a 30 to 50 per cent. solution of acetic acid, drop by drop, the mixture being thoroughly stirred and specimens being tested from time to time, as described. When, finally, the urine remains clear or shows only a faint turbidity, 100 c.c. or less, according to the amount of albumin present, are first heated in boiling water until the albumin begins to separate out in flakes, and then carefully brought to the boiling-point over the free flame. The supernatant urine is now decanted off through a filter, dried at 120° to 130° C., and accurately weighed, when the whole amount of the precipitate is itself brought upon the filter. Any albumin remaining in the beaker is detached from its sides by means of a small glass rod, tipped with a piece of rubber-tubing and collected by the aid of hot water, with which the entire precipitate is now thoroughly washed, until the washings no longer become turbid when treated with a drop of nitric acid and silver nitrate; in other words, until the chlorides have been completely removed. The precipitate is further washed with alcohol and finally with ether to remove any fats that may be present, when it is dried at 120° to 130° C. until a constant weight is reached. If still greater accuracy be required, the dried and weighed precipitate must now be incinerated to determine the amount of mineral ash in combination with the albumin, which is then deducted from the previous weight. The best results are obtained if not more than 0 2 to 0.3 gramme of albumin is contained in the amount of urine employed, so that a smaller quantity than 100 c.c. should be used if a previous test with Esbach's albuminimeter shows a higher percentage.

A glass-wool filter insures a more rapid process of drying—twenty-four to thirty hours; but care must then be had that this is properly prepared, so as to guard against a loss of the wool while washing.

Test for Serum-globulin and its Quantitative Estimation. To test for serum-globulin the urine is rendered alkaline by the addition of ammonium hydrate, any phosphates that may thus be thrown down being filtered off on standing. The urine is then treated with an equal volume of a saturated solution of ammonium sulphate, when the occurrence of a precipitate will indicate the presence of the globulin. Ammonium urate, which may likewise separate out, can always be recognized by its color.

According to Paton, the following test may also be employed: The

urine after having been rendered alkaline with sodium hydrate—any phosphates which may separate out being filtered off—is carefully poured down the side of a test-tube containing a saturated solution of sodium sulphate so as to form a layer above this, when in the presence of serum-globulin a white ring will appear at the zone of contact.

If a *quantitative estimation* of the globulin is to be made, the precipitate thus obtained, after about one hour's standing, is collected on a dried and weighed filter and washed thoroughly with a one-half saturated solution of ammonium sulphate until a specimen of the washings treated with acetic acid and potassium ferrocyanide no longer gives a precipitate. It is then treated as directed in the method employed for the quantitative estimation of serum-albumin.

Tests for Albumoses. It has been pointed out that the albumoses are precipitated in the ordinary tests for serum-albumin, and that a precipitate referable to these bodies will clear up upon the application of heat, to reappear again upon cooling, and that in the presence of nitric acid the fluid will assume a deep yellow color. If, however, coagulable albumin be also present, which is usually the case, this should first be removed by strongly acidifying the urine with acetic acid, adding an equal amount of a saturated solution of sodium chloride and boiling. Should albumoses be present, these will separate out in the filtrate upon cooling. If, furthermore, the *hot* filtrate be rendered alkaline with sodium hydrate, a red color (biuret-reaction) will result upon the addition of a very dilute solution of copper sulphate, added drop by drop. When boiled with *Millon's reagent* a red color is also obtained. This reagent is prepared by dissolving 1 part of mercury in 2 parts of nitric acid of a specific gravity of 1.42 and diluting with 2 volumes of water.

Test for Peptones. That peptones in the sense of Kühne do not occur either in normal or pathologic urines has already been pointed out, and the method to be described has therefore only reference to peptone in the *older sense of the word.* Hofmeister's method is so tedious and time-consuming that the author has substituted Salkowski's modification, which is both accurate and simple, so much so in fact that its general adoption in the clinical laboratory can be strongly recommended.

Fifty c.c. of urine are acidified in a beaker with 5 c.c. of hydrochloric acid, and precipitated with phosphotungstic acid, the mixture being heated over the free flame, when in a few minutes the

precipitate will form a resinous mass which closely adheres to the bottom of the vessel. The supernatant fluid is decanted off, and the mass at the bottom, which now becomes granular, washed twice with distilled water, which is likewise removed by decantation. The precipitate is then covered with about 8 c.c. of distilled water, and treated with 0.5 c.c. of a sodium hydrate solution (sp. gr. 1.16). Upon shaking the beaker the mass will dissolve, the solution assuming a dark-blue color. This is heated on the free flame until the blue color turns to a dirty, grayish-yellow; the solution at the same time becomes turbid, but at times may turn yellow and remain clear. This discoloration may be hastened by the further addition of a few drops of sodium hydrate solution. As soon as this point has been reached, some of the liquid is placed in a test-tube, allowed to cool, and then treated with a very dilute solution of copper sulphate (1 to 2 per cent.), drop by drop, when in the presence of peptones the solution assumes a bright-red color, which may be brought out still more strongly if the specimen is now filtered. If albumin or much mucin be present, these bodies must first be removed (see p. 404 and below); but the quantity of urine employed is so small that the mucin can be usually disregarded. With this method, which occupies only about five minutes, 0.015 gramme of peptones pro 100 c.c. may be demonstrated without difficulty.

Salkowski has recently pointed out that urines which are very rich in urobilin, as in pneumonia, may give rise to the biuret-reaction even when albumoses are absent. The coloring-matter, it is true, may be removed entirely by precipitation with acetate or subacetate of lead, but a portion of the albumoses unfortunately is also carried down, and the substance may thus escape detection when present in only small amounts. He hence suggests that smaller quantities of urine, such as 10 c.c., be employed in the test. The reaction is then not so well marked, but the results are more reliable.

Tests for (Mucin) Nucleo-albumin. The carefully filtered urine is treated in a test-tube drop by drop with an excess of *concentrated* acetic acid, when the occurrence of a turbidity will indicate the presence of nucleo-albumin.

If the urine contain albumin, this must first be removed, simple boiling being sufficient. Dilution of the urine (1 part to 3 of water) should also be practised when any doubt is felt, as urates will then not interfere with the reaction, nor will the urinary salts, if these

be present in large amounts, be so apt to exert a solvent action upon the mucin.

Ott's test may also be advantageously employed. To this end a few c.c. of urine are treated with an equal volume of a saturated solution of common salt, when Almén's solution, consisting of 5 grammes of tannic acid, 10 c.c. of a 25 per cent. solution of acetic acid, and 240 c.c. of 40 to 50 per cent. alcohol, is slowly added. In the presence of nucleo-albumin a precipitate develops at once.

Nucleo-albumin is characterized by its insolubility in acetic acid, in the fact that it is preciptated by magnesium sulphate and that it does not give rise to the formation of a reducing substance when boiled with dilute acids. It is thus readily distinguished from globulin and true mucin, with which it has frequently been confounded. Globulin precipitates are easily soluble in acetic acid, and mucin, when boiled with acids, gives rise to the formation of a reducing substance.

In order to remove nucleo-albumin from the urine this is treated with neutral acetate of lead, an excess of the reagent being carefully avoided. If it is desired to test for peptones, the filtrate is then treated with hydrochloric acid and the process continued as described above.

Tests for Hæmoglobin. The diagnosis of hæmoglobinuria is based upon the demonstration of hæmoglobin, viz., methæmoglobin in the urine in solution, in the absence of red corpuscles, or at least in the presence of only a very small number, so that an examination in the latter direction also is an important factor.

Bloody urine is generally turbid and may vary in color from bright-red to almost black.

Oxyhæmoglobin, as such, can only be recognized by the spectroscope, giving rise to the appearance of two bands of absorption, situated between D and E, as described in the chapter on the Blood.

The urine to be examined spectroscopically should be rendered feebly acid by means of acetic acid, and placed before the open slit of the spectroscope in a test-tube, beaker, or similar vessel, when the two bands of oxyhæmoglobin will be seen either at once or upon carefully diluting with distilled water. If ammonium sulphide be now added, the spectrum of reduced hæmoglobin will be obtained. It must be remembered, however, that more commonly the spectrum of methæmoglobin is seen in cases of hæmoglobinuria.

The following tests, which will also indicate the presence of blood

coloring-matter, cannot be employed to decide the nature of the pigment present, as methæmoglobin and oxyhæmoglobin will both react in the same manner.

Heller's test. Some of the urine to be examined is boiled in a test-tube with caustic potash, when in the presence of blood coloring-matter the precipitate, which consists of basic phosphates, will present a bright-red color. At times, when the urine contains a large amount of coloring-matter (bile-pigment, etc.), it may be difficult to appreciate the color of this sediment; in this case it should be filtered off and dissolved in acetic acid, when if blood-pigment be present the solution becomes red, and the color vanishes gradually upon exposure to the air (v. Jaksch). Instead of this test, the following one may also be advantageously employed, but, in the author's experience, it does not surpass in delicacy that just described.

The guaiacum test. A mixture of equal parts of tincture of guaiacum and oil of turpentine, which has been ozonized by exposure to the air, is allowed to flow carefully along the side of a test-tube upon the urine to be examined in such a manner as to form a distinct layer above the urine, when in the presence of blood-pigment a white ring which gradually turns to blue will be seen to form at the surface of contact.

Test for Fibrin. Fibrin usually occurs in the urine in the form of distinct clots, the nature of which may be determined by thoroughly washing them with water, when they are dissolved by boiling in a 1 per cent. solution of soda or a 5 per cent. solution of hydrochloric acid. Upon cooling, this solution is then tested as for serum-albumin.

Test for histon. (See p. 394.)

Carbohydrates.

The carbohydrates which may occur in the urine are glucose, lactose, maltose, dextrin, levulose, inosit, and animal gum. Of these, glucose alone will be considered in detail in the following pages, as being the only one of clinical interest.

Glucose. The question whether sugar—*i. e.*, glucose—can occur in the urine under normal conditions has been as much discussed as the existence of a physiologic albuminuria, and may now be definitely answered in the affirmative. Külz and Moscatelli, it is true, were unable to demonstrate its presence even in such large

quantities of urine as 200 liters; the methods employed by these observers, however, were not sufficiently accurate, and more recent investigations in Baumann's laboratory leave no doubt as to the existence of a physiologic glycosuria. A trace of glucose is of no clinical significance, being demonstrable only with the most delicate methods; with the tests usually employed a normal urine is apparently free from sugar. Nevertheless, there appears to exist a limit to the assimilation of glucose on the part of the body-economy, the over-stepping of which leads to glycosuria, termed by Claude Bernard "glycosurie alimentaire."

The question now arises, Where does this limit lie? Notwithstanding numerous experiments made in this direction, a definite answer cannot as yet be given, for, while some observers have demonstrated that the ingestion of 200 to 250 grammes of sugar does not lead to glycosuria, sugar has been found by others after the ingestion of only 100 grammes, and Helfereich even claims to have found sugar in the urine of individuals living upon an exclusively vegetable diet.

v. Jaksch states that glycosuria following the ingestion of so small an amount as 100 grammes of chemically pure glucose must be considered as pathologic, an observation with which those of the author accord perfectly. A pathologic *digestive glycosuria* following the ingestion of from 100 to 150 grammes of glucose has been observed by Kraus, Ludwig, and Chvostek in cases of atrophic hepatic cirrhosis, pancreatic cysts, diabetes insipidus, Basedow's disease, and in one case of tachycardia. v. Jaksch, on the other hand, was unable to find sugar, under the same conditions, in the urine of two cases of hyperæmia of the liver, one case of amyloid degeneration, and four cases of hepatic cirrhosis, of which two were of the atrophic and two of the hypertrophic variety. Referring to the contradictory results thus obtained, he regards these as accidental, and thinks it not at all improbable that a more satisfactory classification of hepatic diseases than that now existing could be made on the basis of an artificially produced digestive glycosuria. Negative results were reached in cases of leukæmia, anæmia, nephritis, and tuberculosis; of nervous diseases, in minor chorea, tabes, multiple sclerosis, progressive paralysis, hemiplegia, and cerebral tumors; while mere traces were found in a case of sciatica associated with fatty degeneration of all organs, in one case of morphine-poisoning, and in one of renal tumor. Amounts of glucose large

enough to be quantitatively determined were observed following the ingestion of 100 grammes in one case of cerebral atrophy simulating tumor and associated with renal cirrhosis, in one case of glioma of the corpus callosum, in one of chronic hydrocephalus, in one of cerebral syphilis, and in one of cerebral embolism. Definite conclusions cannot, of course, be drawn from so small a number of observations. It would appear, however, that diffuse cerebral lesions referable to alcohol and syphilis are more likely to give rise to digestive glycosuria than more localized lesions.

A digestive glycosuria has also been observed in febrile diseases, such as pneumonia, typhoid fever, acute articular rheumatism, scarlatina, tonsillitis, etc. The amount of sugar which is found usually varies from 0.5 to 3 per cent.; larger amounts may, however, also be encountered, and one case is on record in which 8 per cent. were present.

The same is observed quite frequently during pregnancy, and in one case recorded by Lanz 29.6 grammes of glucose were found after the administration of 100 grammes. Such figures, however, are rare, and as a general rule less than 3 grammes are found. After confinement the power of assimilation for glucose no longer appears to be subnormal. Finally, it should be mentioned that in diabetes mellitus the sugar may also at times disappear from the urine, its elimination being replaced, as it were, by an excessive excretion of uric acid or phosphates. In such cases a glycosuria may be produced with ease by the ingestion of 100 grammes of glucose, a point which may be of considerable diagnostic value. It is also important to note that the exhibition of such amounts of sugar in *true* diabetes will cause an increased elimination, while this does not appear to occur in the *other forms of glycosuria*.

Aside from the digestive form, just considered, which may be produced in any healthy individual by an over-indulgence in sugars and starches, a *transitory glycosuria*, not artificially produced, is met with under various conditions. A transitory glycosuria, apparently of central origin, is thus noted in connection with lesions affecting the central as well as the peripheral nervous system, such as tumors and hemorrhages at the base of the brain, lesions of the floor of the fourth ventricle, cerebral and spinal meningitis, concussion of the brain, fracture of the cervical vertebræ, tetanus, sciatica; following epileptic, hystero-epileptic, and apopletic seizures, mental shock produced by railroad accidents,

(traumatic neuroses), etc., mental strain and worry, fatigue, and anxiety. Glycosuria following epileptic and apopletic attacks, however, does not appear to be so common as is generally believed. v. Jaksch was unable to demonstrate the presence of sugar in 50 recent cases of hemiplegia, and the author has reached only negative results in a large number of cases of epilepsy, with urines voided within the first few hours following the seizure.

Siegmund noted a transitory glycosuria in 52.38 per cent. of general paretics, in 7.4 per cent. of epileptics, and in 3.77 per cent. of dementia cases, while it was not observed in any other mental diseases.

It is a well-known fact that Claude Bernard experimentally produced a transitory glycosuria by puncturing a certain spot in the floor of the fourth ventricle, the supposed origin of the hepatic vasomotor nerves, and it is not improbable that this neurotic form of glycosuria is due to some direct or reflex influence affecting that portion of the medulla.

The transitory glycosuria which is occasionally observed, particularly during convalescence, in acute febrile diseases, such as typhoid fever, scarlatina, measles, cholera, diphtheria, influenza, and especially malaria, may possibly be referable to the action of ptomaïns or leukomaïns upon this centre, and Seegen reports five cases of malaria with "diabetes" in which *both conditions* disappeared under the administration of quinine.

A glycosuria of toxic origin has been noted in cases of poisoning with curare, chloral hydrate, sulphuric acid, arsenic, alcohol, carbon monoxide, morphine, etc., and even after simple transfusion of normal salt-solution into the blood. Phloridzin, a glucoside obtained from the bark of the root of the apple tree, will likewise cause sugar to appear in the urine, the glycosuria produced, however, being temporary and ceasing with the withdrawal of the drug.

The occurrence of a transitory glycosuria under the conditions above mentioned, which, moreover, may be met with in almost any disease, while interesting from a theoretical standpoint, must, in the majority of instances, be regarded as a medical curiosity only, it being but rarely possible to draw either diagnostic, prognostic, or therapeutic conclusions from its existence.

A *persistent form of glycosuria* is noted in connection with certain lesions of the brain, especially those affecting the floor of the fourth ventricle, and is at times of considerable diagnostic value.

A *continuous elimination of sugar* is noted principally in the complex of symptoms to which the term *diabetes mellitus* has been applied, and it is this condition to which the greatest practical and theoretical interest attaches.

Diabetes mellitus is essentially a persistent form of glycosuria, associated with the occurrence of a more or less intense polyuria and a greatly increased elimination of all the metabolic products normally found in the urine, with the exception of uric acid, which is usually present in diminished amount. In the more advanced cases acetonuria, lipuria, and lipaciduria may also exist. Diabetes, however, is not a persistent form of glycosuria in an absolute sense of the word, since times may occur in the course of the disease when glucose cannot be demonstrated in the urine.

The quantity of sugar excreted may be enormous, and 180 to 360 grammes pro die may be quite frequently observed; but, as stated above, this quantity may diminish to zero under various conditions, such as the occurrence of intercurrent diseases, but often also without any apparent cause, and not infrequently in the condition which has been termed diabetic coma. Some cases are also at times observed in which, from beginning to end, mere traces are eliminated, the total amount of sugar not exceeding a few grammes, while the course of the disease rapidly tends toward a fatal termination, *so that the severity of the pathologic process cannot be measured by the amount of sugar eliminated.* A few years ago the author had occasion to observe a diabetic patient in whom for months a daily examination of the urine never revealed the presence of more than 5 to 10 grammes of sugar per diem, and where death occurred after eighteen months.

At the same time it should be remembered that diabetes cannot be excluded by one or even more negative urinary examinations, and the value of repeating such examinations three or four hours after the exhibition of 100 grammes of glucose, as indicated, cannot be too strongly insisted upon.

Clinicians are in the habit of determining the severity of a case, to a certain extent at least, by the condition of the urine under a diet free from starches and sugars, generally regarding those cases as the more serious in which the glycosuria does not disappear under a diet of this character, a more favorable prognosis being given if the sugar disappears. It should be remembered, however, that there are numerous exceptions to this rule which may hold good in

many instances, and that a light case—*i. e.*, one in which the sugar has disappeared under appropriate dietetic treatment—may suddenly exhibit symptoms seen only in the most severe forms, and succumb to one of the numerous intercurrent maladies, while apparently severe cases may suddenly assume the more benign type.

It may not be out of place in this connection to say a few words regarding the specific gravity of the urine. While usually very high, varying between 1.030 and 1.060, as pointed out in the chapter on Specific Gravity, comparatively low figures are noted at times, such as 1.012, corresponding to a quantity of urine not exceeding 1000 c.c., and implying, of course, a greatly diminished elimination of solids. This is especially marked in those cases described by Hirschfeld, in which, as pointed out in the chapter on Urea, the resorption of nitrogenous material from the digestive tract is below par. Polyuria, a fairly constant symptom of the more common types of diabetes mellitus, is much less pronounced in Hirschfeld's form, and may be altogether absent, although it is true that this may occur in ordinary diabetes also.

The simultaneous occurrence of glycosuria, acetonuria, lipuria, and lipaciduria (which see) is probably always indicative of true diabetes.

It is, of course, impossible to enter here into a detailed consideration of the origin of diabetes. Suffice it to say that a persistent glycosuria, aside from nervous influences, may be referable, on the one hand, to an inability on the part of the liver to transform into glycogen all of the sugar which is carried to this organ, or, on the other hand, to an inability on the part of the muscular system of the body to utilize all the sugar sent to it by the liver, which may have performed its work properly. Accordingly, we may distinguish between a *hepatogenic* and a *myogenic diabetes*. As a matter of fact, cases are seen, usually belonging to the milder form of diabetes, in which the sugar may be temporarily caused to disappear from the urine by muscular exercise, a point which, bearing in mind the deleterious effect which a continuous excessive elimination of solids exerts upon the kidneys, is certainly of great therapeutic interest. On the other hand, again, cases are seen, and unfortunately only too frequently, in which, notwithstanding a total abstinence from carbohydrates and a free indulgence in muscular exercise, the sugar does not disappear from the urine. In such cases it is permissible to speak of a hepatogenic combined with a myogenic diabetes.

Within recent years it has been shown that pancreatic disease is frequently associated with diabetes, and while the number of cases in which no pancreatic lesions were discovered is still too large to warrant the conclusion that disease of this organ is invariably associated with glycosuria, it must still be admitted that lesions of the pancreas are the more frequently met with in diabetes the more closely the organ is examined. It appears to be certain that diabetes *may* be produced by pancreatic disease. As to the manner, however, in which such a result can occur we are as yet in profound ignorance.

Hirschfeld pointed out the fact that, while in the majority of diabetic patients the proteid food ingested is quite satisfactorily utilized, the assimilation of albumin and fats is very much below par in others, and particularly so in cases of diabetes associated with pancreatic disease. (See also Urea.) As yet, observations in this direction are scanty, so that a definite opinion cannot be expressed regarding the utility in diagnosis of investigations similar to those of Hirschfeld. The author had occasion to observe a diabetic patient for some length of time, in whom, notwithstanding that conclusions were reached similar to those of Hirschfeld, the existence of pancreatic disease could not be determined post mortem.

Whether or not a renal and a thyroigenic diabetes also exists, as has recently been suggested, must still remain an open question.

Tests for Sugar. The tests for sugar usually employed in the clinical laboratory depend upon the following properties of sugar:

1. It acts as a reducing agent upon certain metallic oxides, such as copper and bismuth, in the presence of alkalies (Fehling's, Trommer's, Böttger's, and Nylander's tests).

2. In the presence of yeast (saccharomyces cerevisiæ) it undergoes fermentation, with the formation of alcohol, carbonic acid, succinic acid, glycerine, and a number of other bodies, such as amyl alcohol, etc. (fermentation test).

3. With phenylhydrazin sugar forms an insoluble crystalline compound—phenylglucosazon.

4. Solutions of glucose turn the plane of polarized light to the right, from which property glucose has also received the name *dextrose*.

In every case the urine should first be tested for the presence of albumin, which should be removed by boiling.

Trommer's test. A few c.c. of urine are strongly alkalinized in

a test-tube with sodium hydrate solution, and then treated with a 5 per cent. solution of sulphate of copper, added drop by drop, until the cupric oxide formed is no longer dissolved. The mixture is carefully heated, when in the presence of sugar a yellow precipitate of cuprous hydroxide is formed, which will gradually settle to the bottom as a red sediment of cuprous oxide.

It is important to note that while sugar, unless present in mere traces, can readily be detected in this manner, other substances are or may be present in the urine, such as uric acid, kreatin and kreatinin, allantoin, nucleo-albumin, milk-sugar, pyrocatechin, hydrochinon, and bile-pigment, which may likewise reduce cupric oxide. Following the ingestion of benzoic acid, salicylic acid, glycerine, chloral, sulphonal, etc., reducing substances also appear in the urine. These may, it is true, be generally disregarded, if care be taken *not to boil* the urine after the addition of the copper sulphate, as the precipitation of cuprous oxide in the presence of sugar takes place before this point is reached, and the result should be regarded only as positive if precipitation occurs in this manner. Unfortunately, however, the test, when thus applied, yields negative results, or results which are doubtful if mere traces only of sugar are present, so that it cannot be utilized, as a rule, in the study of transitory or digestive glycosuria.

Fehling's test. This is a modification of the test just described, and can only be recommended with the same restrictions.

Two solutions are employed, which must be kept in separate bottles, the one containing 34.64 grammes of crystallized copper sulphate dissolved in 500 c.c. of distilled water, and the other 173 grammes of the tartrate of potassium and sodium and 125 grammes of potassium hydrate dissolved in 500 c.c. of distilled water. Equal parts of these two solutions, mixed in a test-tube and diluted with four times as much water, are boiled and a small amount of urine is added. In the presence of sugar a precipitate of the yellow hydroxide of copper or of red cuprous oxide will be produced, *care being taken only to warm, but not to boil the solution after the addition of the urine.*

Not infrequently it will be observed that upon standing, when no precipitation has occurred previously, the blue color of the mixture changes to an emerald-green, the solution at the same time becoming turbid. Such a phenomenon should not be referred to the presence of sugar, it being in all probability due to

the action of other reducing substances, such as those mentioned above.

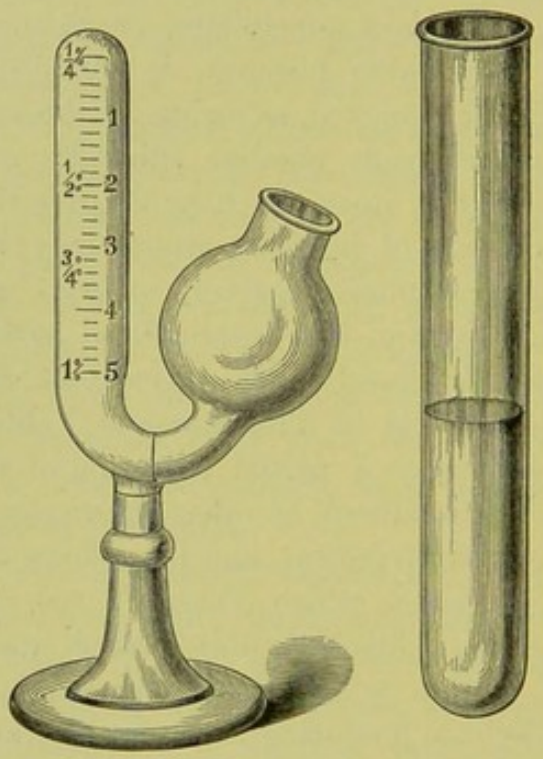
Böttger's test with Nylander's modification. A few c.c. of urine are treated in the proportion of 11 : 1 with *Almén's solution.* This is prepared by dissolving 4 grammes of the tartrate of potassium and sodium, 2 grammes of the subnitrate of bismuth, and 10 grammes of sodium hydrate in 90 c.c. of water, heating the solution to the boiling-point and filtering upon cooling, when it should be kept in a colored-glass bottle. The mixture of urine and Almén's fluid is thoroughly boiled, when in the presence of sugar a grayish, dark-brown, and finally a black precipitate, consisting of bismuthous oxide, BiO_2, or of metallic bismuth, is obtained. Albumin, if present, must first be removed, as owing to the sulphur contained in the albuminous molecule alkaline sulphides could be formed upon boiling, and acting upon the bismuth give rise to the formation of black sulphide of bismuth, which may be mistaken for metallic bismuth. Rhubarb-pigment, as well as melanin and melanogen (which see), and free sulphuretted hydrogen must also be absent, as misleading results will otherwise be obtained.

Nylander's test, as that of Trommer and Fehling, is, however, not without objections, as a partial reduction of the subnitrate of bismuth may also be produced by other substances, such as kairin, tincture of eucalyptus, turpentine, and large doses of quinine. The author observed a urine in which Fehling's test yielded a positive result, and in which a blackish discoloration was observed with Nylander's test, but in which the fermentation-test failed completely. The substance producing these results was *glycosuric acid.*

Fermentation-test. A small piece of ordinary compressed yeast is shaken with some of the suspected urine and a test-tube filled with the mixture, to which some mercury is added. The tube is then inverted into a vessel containing mercury and allowed to stand in a warm place (22°–28° C.). If sugar be present, fermentation will occur in the course of twelve hours, and the carbon dioxide formed rise to the top of the tube, gradually expelling more and more of the urine or mercury, as the amount of the gas increases. It is easy to demonstrate that the gas thus formed is actually carbon dioxide by introducing a small piece of caustic soda into the urine, when, owing to absorption of the carbon dioxide, the liquid will again rise in the tube. Very convenient for this purpose also are the saccharimetric tubes of Einhorn (Fig. 96), which are employed

as just described, a little mercury being poured into the bent limb to guard against an escape of gas. As the yeast itself, however, may give rise to the formation of a little gas in the absence of sugar, it will always be well to make a control-test with normal urine; *i. e.*, to prepare a similar tube with normal urine mixed with yeast, and to allow this to stand at the same temperature. If a positive result be thus obtained, there can be no doubt as to the presence of a fermentable substance in the urine, which may

FIG. 96.



Einhorn's saccharimeter.

not be glucose, however, as other carbohydrates, such as lactose, maltose, and levulose, will likewise undergo fermentation. Still, if large amounts of gas be obtained and if Trommer's test also yields a positive result, it will be fairly safe to regard the substance present as glucose.

Phenylhydrazin test. Six to eight c.c. of urine are treated with two pinches of phenylhydrazin hydrochlorate and 3 parts of acetate of sodium, and warmed until the salts have been dissolved, a little water being added if necessary. The tube is then placed in boiling water for twenty to thirty minutes, and then suddenly plunged into cold water. If sugar be present in moderate amounts, a bright

PLATE XI.



Phenyl-Glucosazon Crystals obtained from a Diabetic Urine.

yellow crystalline deposit will at once be thrown down, and partly adhere to the sides of the tube. But even in the presence of mere traces a careful microscopic examination will reveal the presence of crystals of phenylglucosazon. These are highly characteristic (Plate XI.), and cannot be mistaken for any other substance. They are seen singly or arranged in bundles and sheaves, composed of very delicate bright-yellow needles which are insoluble in water.

This test, properly applied, is undoubtedly not only the most delicate, but at the same time the most reliable, as no other substances which may be present in the urine, excepting maltose and certain pentoses, will give rise to the formation of an osazon. Hence, whenever any doubt is felt as to the nature of a substance reacting in a positive manner with the reagents described above, recourse should be had to this test. It has been stated that maltose forms an exception; this, however, will never become embarrassing, as the microscopic appearance of maltosazon crystals differs from that of the phenylglucosazon. The melting-point of phenylglucosazon, 205° C., moreover, is about 15° higher than that of the maltosazon—190°–191° C. To determine this point it is necessary to filter off the osazon, and, after washing with water, to dissolve it upon a filter by means of a little hot alcohol. From this alcoholic solution it is reprecipitated by water, when it may be collected and dried over sulphuric acid. The melting-point is then determined according to the usual methods.

The pentosazons can be readily distinguished from glucosazon by their melting-points.

The amount of lactose which may be found in the urine is far too small to give rise to the formation of an osazon when the test is directly applied to the urine.

Polarimetric test. Glucose turns the plane of polarized light to the right, but the same may be said of maltose, the degree of polarization of which is even more intense, so that it may be impossible to state in a given case whether such rotation is referable to a large quantity of glucose or to a smaller quantity of maltose. The latter substance, however, occurs in the urine but rarely, and may be recognized not only by the microscopic appearance of its osazon, but also by the fact that its power of reduction is increased in the presence of sulphuric acid and by the application of heat.

An error which may further arise with the employment of the polarimetric method is referable to the fact that if glucose be

present in only small amounts, while the urine contains large quantities of β-oxybutyric acid, the latter turning the plane of polarized light to the left, it may happen that the rotation in this direction will neutralize or even overcome any rotation to the right due to glucose. In such cases, however, the urine will react in a positive manner with the other reagents described, and the fermented urine will, moreover, turn the plane of polarization still more strongly to the left, indicating the presence of a dextrorotatory substance, and in all probability of glucose.

The delicacy of this method varies considerably with the instrument employed; the figures given below were obtained with the apparatus of Lippich, which yields the best results.

(For a description of this method see the Quantitative Estimation of Sugar by Means of the Polarimeter.)

TABLE SHOWING THE DELICACY OF THE TESTS DESCRIBED.

Trommer's test	0.0025 per cent.
Fehling's test	0.0008 "
Nylander's test	0.025 "
Fermentation-test	0.1–0.05 "
Phenylhydrazin test	0.05–0.001 "
Polarimetric test	0.025–0.05 "

TABLE SHOWING THE BEHAVIOR OF THE VARIOUS FORMS OF SUGAR WHICH MAY OCCUR IN THE URINE TOWARD THE TESTS DESCRIBED.

	Trommer's, viz., Fehling's test.	Nylander's test.	Fermentation-test.	Phenylhydrazin test.	Polarimetric test.
Glucose,	Positive reaction.	Positive reaction.	Positive reaction	Positive reaction; Melting-point 205° C.	Rotation toward the right.
Levulose,	Positive reaction.	Positive reaction.	Positive reaction.	Same osazon obtained as with glucose, only more rapidly.	Rotation toward the left.
Maltose,	Positive reaction.	Positive reaction.	Positive reaction.	A maltosazon is formed; melting-point 190–191° C.	Rotation toward the right.
Lactose,	Positive reaction.	Positive reaction.	No reaction, or only a very faint one.	No reaction in the concentration in which it may occur in the urine; melting-point 200° C.	Rotation toward the right; increased by boiling with a 2-5 p.c. solution of sulphuric acid.
Laiose,	Positive reaction: on boiling only 1.2–1.8 per cent more is obtained than by the polarimeter.	Positive reaction.	No reaction.	With phenylhydrazin a yellowish-brown, non-crystallizable oil is obtained.	No reaction or rotation toward the left.

Clinically, it is unimportant to search for minute traces of sugar, such as may be found in every normal urine, and the reader is referred to special works on physiologic chemistry for a consideration of the methods generally employed.

Quantitative Estimation of Sugar. The methods used in the quantitative estimation of sugar are essentially based upon the qualitative tests described.

Fehling's method. Fehling's solution, prepared as described above, is of such strength that the copper contained in 10 c.c. is completely reduced by 0.05 gramme of glucose. If then urine is carefully added to this quantity until complete reduction takes place, the amount of sugar contained in a given specimen of urine can be readily calculated according to the following equation:

$$y : 0.05 :: 100 : x, \text{ and } x = \frac{5}{y},$$

in which y indicates the number of c.c. of urine required to reduce the 10 c.c. of Fehling's solution, and x the amount of sugar contained in 100 c.c. of urine.

As the best results are only obtained if from 5 to 10 c.c. of urine are used in one titration, it is usually necessary to dilute the urine to the required degree, in the determination of which the specific gravity may serve as a guide. As a general rule, urines of a specific gravity of 1.030 should be diluted five times, and if the density be still higher, ten times. To be certain that the proper degree of dilution has been reached, 5 c.c. of Fehling's solution are treated with 1 c.c. of the diluted urine, a little caustic soda and distilled water being added to make in all about 25 c.c. This mixture is thoroughly boiled, and if the fluid still remains blue another 1 c.c. of diluted urine added, and so on until the last two tests differ by 1 c.c. of urine, the last c.c. added causing a separation of cuprous oxide. In this manner the percentage of sugar may be approximately determined. Albumin, if present, must first be removed by boiling.

Ten c.c. of Fehling's solution, diluted with 40 c.c. of water, are placed in a porcelain dish and boiled. While boiling, the diluted urine is added from a burette, 0.5 c.c. at a time, when, as a rule, the precipitated cuprous oxide will rapidly settle, so that gradually a white bottom may be seen through the blue fluid, the color of which becomes less and less intense upon the further addition of urine until, finally, the solution is almost colorless. When this point is

reached the urine is added only drop by drop, until the decolorization is complete. The degree of dilution multiplied by 5 and the result divided by the number of c.c. of diluted urine employed will then indicate the percentage-amount of sugar. In the following table the percentage results corresponding to the number of c.c. of undiluted urine employed will be found:

SUGAR.—*Quantity of glucose pro liter corresponding to the number of cubic centimeters used for the complete reduction of* 10 *centimeters of Fehling's solution.*

	1	1/10	2/10	3/10	4/10	5/10	6/10	7/10	8/10	9/10
1	50.00	45.44	41.68	38.46	35.70	33.32	31.24	29.40	27.76	26.30
2	25.00	23.80	22.72	21.72	20.84	20.00	19.22	18.50	17.84	17.24
3	16.66	16 00	15.62	15.14	14.15	14.28	13.88	13.50	13.14	12.82
4	12.50	12.18	11.90	11.62	11.36	11.10	10.86	10.62	10 40	10.20
5	10.00	9.80	9.60	9.42	9.24	9.08	8.92	8.76	8.62	8.50
6	8.32	8.18	8.06	7.92	7.80	7.68	7.56	7.44	7.34	7.24
7	7.14	7.04	6.94	6.86	6.78	6.66	6.56	6.48	6.40	6.32
8	6.24	6.16	6.08	6.02	5.94	5.88	5.80	5.74	5.68	5 60
9	5.54	5.48	5.42	5.36	5.30	5.24	5.20	5.16	5 12	5.06
10	5.00	4.94	4.90	4.82	4 78	4.76	4.70	4.66	4 62	4.58
11	4.54	4.50	4.46	4.42	4.38	4.34	4.30	4.26	4.22	4.20
12	4.16	4.14	4.12	4 08	4.04	4.00	3.98	3.96	3.92	3.86
13	3.84	3.80	3.78	3.76	3.74	3.70	3.68	3.66	3.62	3.58
14	3.56	3.54	3.52	3.48	3.46	3.44	3.42	3.40	3.36	3.34
15	3.32	3.32	3 28	3.26	3.24	3.22	3.20	3.18	3.16	3.14
16	3 12	3.10	3 08	3.04	3.04	3.02	3.00	2.98	2.96	2.94
17	2.94	2.92	2.90	2.88	2.86	2.84	2 82	2.82	2.80	2.78
18	2 76	2.76	2.74	2.72	2·70	2.70	2 68	2.64	2.64	2.64
19	2.62	2.62	2.60	2.60	2.58	2.56	2 56	2.54	2.52	2.52
20	2.50	2.50	2.48	2.48	2.44	2 42	2.42	2.40	2.40	2.38
21	2.38	2.36	2.34	2.34	2.32	2.32	2.30	2.30	2.28	2 28
22	2.26	2.26	2.24	2.24	2.22	2.22	2.20	2.20	2.18	2.18
23	2.16	2.16	2.14	2.14	2.12	2.12	2.12	2.10	2.10	2.10
24	2.08	2.08	2.06	2.06	2.06	2.04	2.04	2.02	2.02	2.02
25	2.00	1 98	1.98	1.96	1.96	1.96	1.94	1.94	1.92	1 92
26	1.92	1.92	1.90	1.90	1.88	1.88	1.88	1.86	1.86	1 86
27	1.84	1.82	1.82	1.82	1.82	1.80	1.80	1.80	1.80	1.80
28	1.78	1 76	1.74	1.74	1.74	1.74	1.74	1.74	1.74	1 72
29	1.72	1.70	1.70	1.70	1.70	1.68	1.68	1.68	1.68	1.66
30	1.66	1.66	1.65	1.64	1.63	1.62	1.62	1.62	1 62	1.62

Unfortunately, it is difficult as a general rule to determine exactly the point when all the copper has been reduced; *i. e.*, the point at which the blue color has entirely disappeared. When it is thought that this has been reached, about 1 c.c. should be filtered through thick Swedish filter-paper, and the filtrate, which must be absolutely clear, acidified with acetic acid and treated with a drop or two of a solution of potassium ferrocyanide. If unreduced copper be still present in the solution, a brown color will result, indicating that sufficient urine has not been added. But if, on the other hand, no brown discoloration be noted, it is possible that the desired point has already been passed, when the titration should be repeated. At times the precipitate will not settle at all, and even pass through

the filter, so that it is almost impossible to determine the end of the reaction. In such cases the following procedure, suggested by Cause, will be found serviceable:

Ten c.c. of Fehling's solution are diluted with 20 c.c. of distilled water and treated with 4 c.c. of a $\frac{1}{2}\frac{1}{0}$ per cent. solution of potassium ferrocyanide. While boiling, the diluted urine is now added drop by drop, until the blue color has entirely disappeared, a precipitate not appearing at all with this method.

In order to obtain reliable results, however, the Fehling's solution must be prepared with great care and its strength determined. This may be done in the following manner: 0.2375 gramme of crystallized cane-sugar, pure and dried at 100° C., is dissolved in 40 c.c. of distilled water to which 22 drops of a $\frac{1}{1}\frac{1}{0}$ per cent. solution of sulphuric acid have been added. This solution is kept upon a boiling water-bath for an hour, when it is allowed to cool and diluted to 100 c.c. with distilled water. Twenty c.c. of this solution will then contain exactly 0.05 gramme of glucose, corresponding to 10 c.c. of Fehling's solution, if this be of the required strength. If too strong, so that 21 c.c., for example, of the sugar solution are required to obtain a complete reduction of the copper, the strength of Fehling's solution may be determined according to the equation: $20 : 0.05 : : 21 : x$, and $x = 0.0525$. If too weak, on the other hand, so that 19 c.c., for example, are required, its strength is similarly determined: $20 : 0.05 : : 19 : x$, and $x = 0.0475$. If necessary, the solution may of course be brought to the exact strength in the manner indicated elsewhere, by first making it too strong and then ascertaining the required degree of dilution.

The following method, suggested by Knapp, is said to be better than that of Fehling, as daylight is not necessary, as it is applicable even in cases in which the amount of sugar is small, as the solution keeps for a long while, and as it is simpler.

The principle of the method depends upon the observation that the cyanide of mercury in alkaline solutions is reduced to metallic mercury in the presence of sugar. The solution which is required should contain 10 grammes of chemically pure, dry cyanide of mercury and 100 c.c. of a solution of sodium hydrate (sp. gr. 1.145) to the liter. Twenty c.c. of this solution correspond to 0.050 gramme of glucose.

Knapp's method. Twenty c.c. of the solution are placed in a small retort and diluted with 80 c.c. of water. If we have reason

to suppose that the urine contains less than 0.5 per cent. of sugar, 40 to 60 c.c. are sufficient. The solution is then heated to the boiling-point, when the diluted urine (see below) is added, at first 2 c.c. at a time, then 1 c.c., 0.5 c.c., 0.2 c.c., and 0.1 c.c., as the final point is approached. After every addition the solution is boiled for one-half minute. As the end-reaction is approached the solution begins to become clear, and the mercury, together with the phosphates, settles to the bottom. The final point is determined by placing a drop of the supernatant fluid upon a piece of clean, white Swedish filter-paper, and holding this first over a bottle containing concentrated hydrochloric acid and then over one containing a saturated solution of sulphuretted hydrogen. If all the cyanide of mercury has not been reduced, a yellow spot will result, the color of which becomes the more manifest if it be compared with one which has not been exposed to the action of the sulphuretted hydrogen. As soon as the mercury has been entirely reduced the reading is taken.

Example: Supposing that 15 c.c. of urine have been required, the corresponding amount of sugar is then found according to the following equation, 20 c.c. of Knapp's solution requiring 0.05 gramme of sugar for its reduction:

$$15 : 0.05 :: 100 : x;\ 15x = 5, \text{ and } x = 0.333 \text{ per cent.}$$

Precautions: 1. Albumin must first be removed.

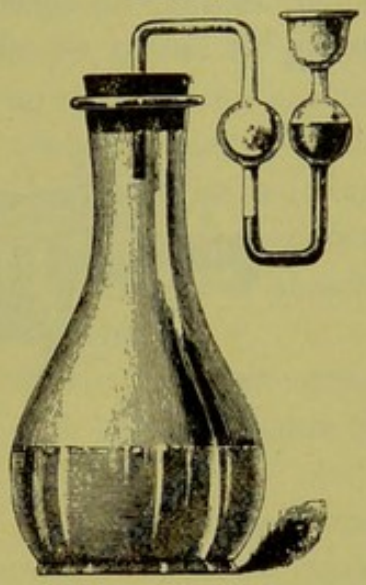
2. The urine should not contain more than 0.5 to 1 per cent. of sugar. The urine is hence diluted, if necessary, as with Fehling's method.

Differential density method. This method is very useful in clinical work, and should be preferred to the more uncertain titration with Fehling's solution, unless considerable experience has been acquired with this method.

The specific gravity of the urine is accurately ascertained by means of a pyknometer, or a hydrometer accurately graduated to four decimals and provided with a thermometer indicating tenths of a degree. The temperature at which the specific gravity is taken should be that for which the hydrometer has been constructed, the urine being heated and cooled to the desired degree. 100 to 200 c.c. are then set aside in a flask, after the addition of some yeast which has been washed free from mineral material, loosely stoppered or provided with an arrangement like the one shown in the accompanying figure (Fig. 97). After twenty-four hours, if but

little sugar be present, or forty-eight hours, if there be much, the specific gravity is again determined under the precautions given after having filtered the urine. The difference in the specific gravity is then multiplied by 230, an empirical factor which has been found by dividing the amount of sugar ascertained by titration or polarization with the difference in the density of the urine after fermentation, the result indicating the percentage of sugar. The process may be hastened if to every 100 c.c. of urine, 2 grammes of tartrate of potassium and sodium and 2 grammes of diacid-sodium phosphate be added with 10 grammes of compressed yeast, and the mixture allowed to stand at a temperature of from 30° to 34° C. If but little sugar be present, two to three hours will be sufficient.

FIG. 97.



Flask for the approximate estimation of sugar by fermentation. (V. JAKSCH.)

That portion of the urine in which the specific gravity is determined before fermentation should really be treated in the same manner. It will suffice, however, to add 0.022 to the specific gravity found, to make up for the increase that should otherwise be observed in the second specimen owing to the addition of the salts.

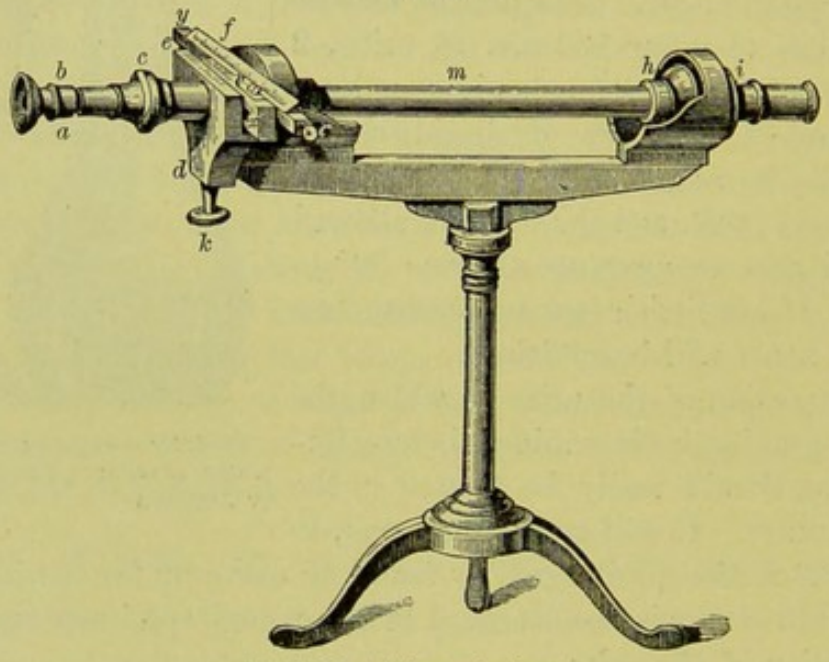
In every case the urine must be perfectly fresh, as fermentation will generally begin spontaneously even after standing a short time.

Einhorn's method. This will answer very well for ordinary purposes. Two especially constructed and graduated saccharimetric tubes (Fig. 96) are used, one of which is filled with a mixture of the suspected urine and yeast, and the other with normal urine and yeast, as a control. The tubes are then set aside at a temperature of from 30° to 34° C., when the percentage-amount of sugar in the urine is read off from the column of the carbon dioxide present. Should the second tube also show a small amount of gas, the figure corresponding to this amount is deducted from the first.

Polarimetric method. For this purpose the saccharimeter of Soleil-Ventzke is very convenient (Fig. 98). This consists essentially of a Nicol's prism, *a*, which may be rotated about the axis of the apparatus; a second Nicol's prism at *d*; vertically placed compensating prisms, consisting of dextro-rotatory quartz at *e*, which may be

moved horizontally by means of a rack-and-pinion adjustment, this being turned by a milled head at *k*, so that light can pass through a thicker or thinner layer of the dextro-rotatory quartz. At *f* there is a plate of gyro-rotatory quartz cut perpendicularly to the optical axis, covering the entire field of vision; at *h* biquartz plates of Soleil, and at *i* an Iceland-spar crystal; *b c* represents a small telescope, by means of which the biquartz plates can be accurately

FIG. 98.



Soleil-Ventzke's saccharimeter.

focussed. When the compensation-prisms of this apparatus are in a certain position, the gyro-rotation of the plate *f* will be exactly compensated and the two halves of the field of vision present the same color, while the zero of the scale *x* will coincide with the zero of the vernier *y*, arranged on the upper surface of the compensators. Any change in this position produced by turning the screw *k* will cause the appearance of a different color in each half of the field of vision. If now, with a zero-position, an optically active dextro- or gyro-rotatory substance be interposed, the color of each half of the field of vision will become altered, but may be equalized again by changing the position of the compensators, the degree of change necessary to produce this result constituting an index of the power of rotation of the solution interposed in the tube *m*.

Soleil-Ventzke's apparatus is constructed in such a manner that if a solution of glucose be employed, the length of the tube *m* being

10 cm., every entire line of division on the scale will indicate 1 per cent. of sugar.

The tube of the saccharimeter should be carefully washed out with distilled water, and at least once or twice with the filtered urine, when it is placed on end upon a flat surface, and filled with the urine to such a degree that this forms a convex cup at the end. The little glass plate is now carefully adjusted, so as to guard against the admission of bubbles of air. The metallic cap is then placed in position, care being taken to avoid undue pressure. The examinations are made in a dark room, an ordinary lamp being used, and several readings taken, until the differences do not amount to more than one-tenth or two-tenths per cent. The tubes should be thoroughly cleansed *immediately* after the experiment.

In every case the filtered urine should be free from albumin, and, if markedly colored, previously treated with neutral acetate of lead in substance and filtered.

If it be desired to demonstrate only the presence of sugar, the compensators are first brought to the zero-position. If now, upon the interposition of the tube filled with urine, a difference in the color of the two halves of the field of vision be noted, the presence of an optically active substance in the urine may be assumed, and if at the same time the deviation be to the right, the presence of glucose is rendered highly probable, while a deviation to the left will generally be referable to levulose or β-oxybutyric acid. Indican, peptones, cholesterin, and certain alkaloids, it is true, also turn the plane of polarization to the left, but as a rule these substances need not be considered, cholesterin occurring but rarely, while indican in diabetic urines is usually present in only small amounts, and a concurrence of sugar and peptones has not as yet been observed. Lactose and maltose, which also turn the plane of polarization to the right, may be distinguished from each other and from glucose by the phenylhydrazin test. Levulose turns the plane of polarization to the left. Oxybutyric acid is practically always associated with the presence of glucose, and may be recognized by allowing the urine to undergo fermentation, when the filtered urine will become distinctly gyro-rotatory.

Comparatively little interest, from a clinical point of view, attaches to the occurrence of other forms of sugar in the urine.

Lactose. Lactose may be found in the urine near the end of gestation, but more especially in nursing-women in whom the flow

of milk is impeded, owing to the existence of mastitis, for example. It has also been stated that lactosuria occurs in nursing-women who have well-developed breasts, in the absence of any obstruction, and that the *good qualities* of a wet-nurse are indicated by a copious and persistent elimination of milk-sugar. Its presence may be inferred if a positive result is obtained with Trommer's and Nylander's tests, while the phenylhydrazin and fermentation tests give negative results, although an osazon can be obtained from the pure substance, and although this undergoes a certain form of alcoholic fermentation.

Lemaire, who has recently investigated this subject, found that the urine of nineteen women examined in this direction apparently contained no sugar during the last twelve days preceding confinement (Trommer's and Nylander's test), while a positive reaction was obtained with Trommer's reagent in two cases, and with Nylander's reagent in thirteen cases after confinement. The phenylhydrazin test was negative in all nineteen before and positive after confinement, *when this was directly applied to the substance, isolated according to Baumann's method.* The percentage varied between 0.013 and 0.438 per cent., and appeared to be uninfluenced by the act of nursing.

Levulose. Levulose is occasionally found in diabetic urines together with glucose, its presence being often indicated by the fact that a polarimetric examination shows a deviation to the left or none at all, while the other tests for sugar indicate the presence of a reducing substance.

Maltose. Maltose together with glucose was found in the urine of a patient supposedly the subject of pancreatic disease, associated with an acholic condition of the stools. Its recognition is practically dependent upon the formation of its osazon and a determination of the melting-point of the latter.

Dextrin. In one case of diabetes dextrin appeared to take the place of glucose. It may be recognized by the fact that upon the application of Fehling's test the blue liquid first becomes green, then yellow and sometimes dark brown.

Laiose. Laiose occurs at times in the urine of diabetic patients. It is essentially characterized by the fact that by titration with Fehling's solution from 1.2 to 1.8 per cent. more sugar is indicated than by the polarimetric method.

Pentoses. To judge from recent observations, traces of pentoses, viz., xylose, arabinose, and rhamnose, may be found in every urine.

Large quantities were first observed by Salkowski and Jastrowitz in the urine of a morphine habitué, where the pentosuria alternated with glycosuria. A similar case was reported by Reale, and Külz and Vogel found large quantities in diabetes. Such urines reduce Fehling's solution, and give rise to the formation of an osazon when treated with phenylhydrazin. The osazon, however, can be readily distinguished from that obtained from glucose, maltose, or lactose, etc., by the melting-point. The fermentation-test is negative. Arabinose and rhamnose turn the plane of polarized light to the right, while xylose remains indifferent. When present in notable amounts they are readily detected with *Tollens' reagent:* To this end phloroglucin is dissolved in 5 to 6 c.c. of concentrated hydrochloric acid by the aid of heat, so that a slight excess is present. This solution is divided into two equal parts and allowed to cool. To one portion 0.5 c.c. of the urine to be examined is added, and to the other an equal amount of normal urine of the same specific gravity. Both specimens are placed in a beaker containing boiling water, when in the presence of pentoses a deep red color will first be observed at the top, which gradually extends throughout the mixture, while the normal specimen scarcely changes in color. In the presence of 0.1 per cent. a positive reaction is still obtained, which is especially marked if the urine has been previously decolorized with animal charcoal. After dilution with an equal volume of water the coloring-matter may be extracted with amyl alcohol.

Animal gum. Animal gum, according to modern researches, is a constant constituent of normal urine, but of no clinical interest.

Inosit. Inosit does not occur normally in the urine, but may be demonstrated after the ingestion of large amounts of water. Pathologically it has been found in cases of diabetes insipidus and in albuminuria, but is of no especial interest.

Urinary Pigments and Chromogens.

In considering the subject of urinary pigments it is necessary to differentiate sharply between such pigments as occur preformed in the urine and others that only appear upon the addition of certain reagents which have the power of decomposing their chromogens. Until quite recently this subject was in a most confused condition, and even now our knowledge can only be regarded as rudimentary; for, notwithstanding the fact that numerous investigations have been made with a view to determine the source of the color of normal

urine, this problem is not even yet definitely solved, and it is only possible to say at the present time that urochrome and possibly a certain indoxyl derivative are to some extent responsible for the normal color of the urine.

Under normal conditions urochrome and uroerythrin, to which latter the red color of urate sediments is due, are the only known pigments occurring preformed in the urine, while indigo-red and indigo-blue, derived from indoxyl sulphate and indoxyl glycuronate, may be artificially produced. Pathologically, on the other hand, various other pigments may be found, occurring in the urine either free or in the form of chromogens. Among the former may be mentioned hæmoglobin, methæmoglobin, hæmatin, hæmatoporphyrin, urorubrohæmatin, urofuscohæmatin, urobilin, the biliary pigments and melanin, while abnormal chromogens are seen following the ingestion of certain drugs, such as santonin, senna, rheum, iodine, etc., as also in cases of poisoning with carbolic acid, creosote, etc. The occurrence of some of these substances, such as the various forms of blood-pigment, the biliary pigments, and indigo, viz., indican, is of considerable clinical interest, while others again are only of minor importance.

Normal Pigments. *Urochrome.* To the presence of this pigment, which appears to be identical with the *normal urobilin of MacMunn*, but which should not be confounded with the *pathologic urobilin of Jaffé*, the normal yellow color of the urine appears to be due to a certain extent. It is undoubtedly derived from bilirubin, which in turn is referable to the hæmatin and hæmoglobin of the blood and results from the bilirubin secreted into the intestinal tract by a process of oxidation, and not of reduction, as is generally stated. Such a transformation, according to our present knowledge, may, however, also occur directly, without the intervention of bilirubin, as urochrome is found in the urine of dogs in which the bile is prevented from entering the intestinal tract by the establishment of a biliary fistula. An increased amount is similarly found in cases in which resorption of large extravasations of blood is taking place in the body—in short, whenever an increased destruction of red corpuscles is noted; while under the opposite circumstances—*i. e.*, in conditions associated with a definite formation of red corpuscles, as in certain forms of anæmia, chronic parenchymatous nephritis, diabetes, diseases of the bone-marrow, etc.—it occurs in diminished amount.

In order to obtain urochrome from normal urine this is acidulated with 1–2 grammes pro liter of dilute sulphuric acid, filtered, and saturated with ammonium sulphate in substance, when the flakes which are found in an excess of the salt are dried and treated with warm, slightly ammoniacal absolute alcohol, the pigment being obtained upon evaporation of the alcohol. An alcoholic solution of urochrome, like the urobilin of Jaffé, exhibits a beautiful greenish fluorescence when treated with ammonia and a few drops of a solution of zinc chloride, but, unlike the latter substance, its acidulated alcoholic solutions present a broad band of absorption at "F," extending more to the left than to the right of this line, while the remainder of the spectrum at the same time is absorbed to the right end from a point somewhat to the left of "G."

Uroerythrin. Uroerythrin is the pigment which imparts the red color to crystals of uric acid and urate sediments. In pathologic conditions it is seen especially in cases of hepatic insufficiency, in which the liver, owing to a greatly increased destruction of red corpuscles, is unable to transform all the blood-pigment which is carried to it into bile-pigment, and also where an absolute insufficiency on the part of the hepatic cells exists, so that the organ is not even capable of causing the transformation of a *normal* amount of hæmoglobin. Uroerythrin is thus seen in notable quantities in cases of pneumonia, malarial fever, erysipelas, spinal curvature, hepatic cirrhosis, carcinoma of the liver, etc. Chemically, its close relation to hæmoglobin, hæmatoidin, and bilirubin is seen from the following analyses of the various pigments:

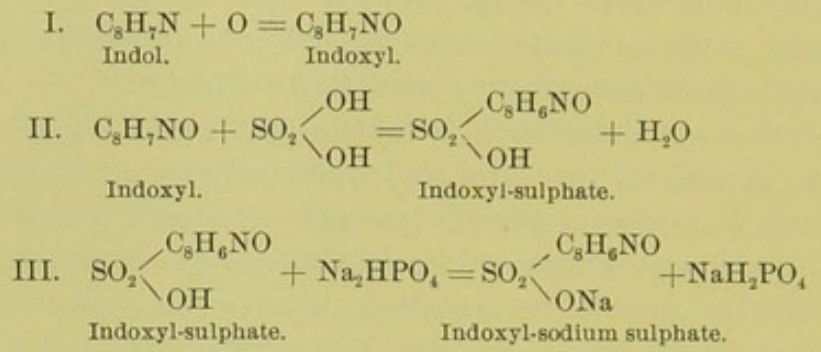
	C	H	N	O	S	Fe
Hæmoglobin,	53.85	7.32	16.17	.....	0.39	0.43
Hæmatoidin,	65.05	6.37	9.51	.....	.....	.....
Bilirubin,	67.83	6.29	9.79	16.79	.....	.....
Uroerythrin,	62.51	5.79	31.70		.....	.....

When present in large amounts uroerythrin is readily recognized by the salmon-red color which it imparts to urinary sediments. Otherwise it is best to precipitate the urine with neutral acetate of lead, barium chloride, or a similar reagent, when in the absence of uroerythrin a milky-white precipitate is obtained, a pale rose-colored sediment indicating the presence of the pigment in appreciable amounts, a more pronounced rose-color being produced by large quantities. In every case at least ten to fifteen minutes should be

allowed to elapse before forming a definite conclusion, so that the sediment may have abundant time to settle.

Normal Chromogens. The chromogens occurring in normal urine are indican, urohæmatin, and an unknown chromogen which yields urorosein when treated with mineral acids.

Indican. It has already been pointed out (see Sulphates) that the indol formed during the process of intestinal putrefaction is oxidized to indoxyl in the blood; this, entering into combination with sulphuric acid, is eliminated in the urine as sodium or potassium indoxyl-sulphate, or indican, as represented by the equations:



Formerly it was thought that indican was also formed within the tissues of the body in the absence of putrefactive organisms (this view having been held especially by Salkowski). Further researches, however, have demonstrated beyond a doubt that micro-organisms are always concerned in the production of indican, and that in health the large intestine is its only source. Thus, Baumann, who succeeded in absolutely disinfecting the intestinal tract in a dog by means of large doses of calomel, observed that all traces of indican, as also of phenol and paracresol, disappeared from the urine. According to Senator, moreover, indican does not occur in the urine of newly born infants which have not as yet received nourishment. This observation is a strong point in favor of Nencki's teachings that indol is a specific product of albuminous putrefaction in the presence of organized ferments, as putrefiable substances are present, but no putrefactive organisms. Tuczek's observations on abstinence from food in cases of insanity, in which indican was only observed in the urine when albumins, though in minimal amounts, were ingested, also speak very strongly against Salkowski's theory. Finally, it has been demonstrated that in cases in which an artificial anus is established near the distal end of the ileum the conjugate sulphates disappear almost entirely from the urine, while they reappear in normal

amount as soon as the connection between the small and large intestines has been re-established.

The amount of indican normally eliminated in the urine varies somewhat with the character of the diet, Jaffé having found 6.6 milligrammes in 1000 c.c. of urine as an average of eight observations. The largest quantities excreted in health are found after a liberal indulgence in animal food, particularly the so-called red meats, while the smallest amounts are observed during a milk or kefir diet. By means of the latter article, indeed, the greatest diminution in the degree of intestinal putrefaction may be effected in man. In pathologic conditions an increased elimination of indican is observed:

1. In all cases associated with an increased degree of intestinal putrefaction. As there appears to be little doubt that this is largely regulated by the acidity of the gastric juice, an increased indicanuria, according to personal observations, is encountered when anachlorhydria or hypochlorhydria exists. It has been pointed out elsewhere that it is possible to form a fairly accurate idea of the amount of free hydrochloric acid in the gastric juice by an examination of the urine in this direction. Large quantities of indican are thus eliminated in cases of carcinoma of the stomach, and exceeded only by those observed in cases of ileus, so that this symptom, in the author's estimation, is one of considerable value in differential diagnosis, and one, moreover, which has not as yet received the attention which it undoubtedly deserves. Exceptions to this rule are at times, though rarely, met with, for which it is, however, impossible to account definitely at the present time. Large quantities of indican are also observed in cases of acute, subacute, and chronic gastritis, of whatever origin. In the course of personal observations in this direction the author was struck with the curious phenomenon that in cases of ulcer of the stomach, notwithstanding the simultaneous occurrence of hyperchlorhydria, an increased elimination of indican, contrary to what is usually seen in hyperchlorhydria, referable to other causes, is quite constantly found. Possibly the existence of muscular atony noted in those cases may serve to explain this apparent incongruity, but it is as yet impossible to offer a satisfactory explanation of the phenomenon. Remembering the origin of indican, and the relation which the amount eliminated bears to the degree of intestinal putrefaction, it will be unnecessary to enumerate the long list of diseases in which an increased indicanuria has

been observed, as it will be found that in the majority of these cases the indicanuria is merely an index of the condition of the gastric juice.

2. It should be noted that in cases in which the peristaltic movements of the *small* intestine have become impeded, as in ileus, acute and chronic peritonitis, an increased elimination of indican will invariably take place, no matter what the state of the gastric juice may be. In such conditions, indeed, and especially in ileus, the largest quantities are observed, a point which may be of *decided* value in differential diagnosis, as diseases of the large intestine alone are *never* associated with an increase in the amount of indican. *In simple, uncomplicated constipation increased indicanuria is not seen,* and should an examination in such cases reveal the presence of more indican than normal, it will be safe to assume the existence of disease elsewhere, and especially of the stomach.

3. As albuminous putrefaction can also take place within the body, an increased indicanuria is observed in cases of empyema, putrid bronchitis, gangrene of the lungs, etc.; but while in the conditions mentioned above the indol-producing organisms appear to be especially active, the elimination of phenol in the latter condition may be more pronounced at times than that of indican. Bearing in mind the points here set forth the author cannot agree with others in saying that the study of indicanuria possesses no importance from a clinical standpoint; he maintains, on the other hand, that *an examination of the urine in this direction is at least as important as the testing for albumin and sugar, and that points of decided importance, not only in diagnosis, but also in prognosis and treatment, can thus be gained.*

When indican is treated with hydrochloric acid it is decomposed into sulphuric acid and indoxyl; should an oxidizing substance be present at the same time, indigo-blue, the blue coloring-matter of the urine, results:

$$\underset{\text{Potassium indoxyl sulphate.}}{2C_8H_6NKSO_4} + 2O = \underset{\text{Indigo-blue.}}{C_{16}H_{10}N_2O_2} + 2HKSO_4$$

Indigo-blue in small amounts may be found free in the sediment of almost every decomposing urine, usually occurring in the form of small, amorphous granules, and more rarely in crystalline form. Urines, however, have also been observed which were blue when passed, or which turned blue, as a whole, upon standing. Such a

phenomenon must be regarded as a medical curiosity. The blue pigment which may be obtained from urines has been variously described as Prussian-blue, urocyanin, cyanourin, Harnblau, uroglaucin, choleraic urocyanin, but has been ultimately shown to be indigo-blue, derived from a colorless mother-substance present in every urine to a greater or less extent, which has been named indican, and which has been shown to be identical with the uroxanthin of Heller and Thudichum's choleraic urocyaninogen.

Test for indican. Unfortunately the methods which so far have been proposed for the purpose of quantitatively determining the amount of indican in the urine are not only inaccurate, excepting, perhaps, the spectroscopic method devised by Müller, but, what is more, are too lengthy and complicated to be of value to the practising physician. As a consequence the observations made by almost all observers are based upon an approximative estimation only. For practical purposes such a method, particularly the one to be presently described, is sufficient, the degree of increase which interests us of course, more particularly being judged fairly accurately thereby, as is quite generally admitted by those who have employed this method, and have compared the same with the results obtained with the more complicated ones mentioned.

The most convenient method is a modification of that of Jaffé, suggested by Stokvis :

The urine of twenty-four hours is carefully collected and a specimen taken for examination. A few c.c. of urine are mixed with an equal amount of concentrated hydrochloric acid, and 2 or 3 drops of a strong solution of sodium hypochlorite, calcium hypochlorite, or common saltpeter, and 1–2 c.c. of chloroform added. The mixture is thoroughly agitated and set aside. The indigo which has been set free in this manner is taken up by the chloroform, coloring this blue to a greater or less extent, the degree of increase as compared with the normal being determined by the intensity of the color. Albumin need not be removed. Bile-pigment, which interferes with the reaction, is removed by means of a solution of subacetate of lead carefully added in order to avoid an excess. Urines presenting a very dark color may be cleared in the same manner. Potassium iodide, which, if present, will, owing to the liberation of free iodine, color the chloroform more or less of a carmine, must also be removed. For the sake of comparison, it is well to employ the

same quantities of urine and reagents in every case, marked tubes being very convenient for this purpose.

In this connection it may be said that the author has found this method to be at the same time a fairly sensitive test for albumin, the mixture of hydrochloric acid and urine upon the addition of the oxidizing agent presenting a well-marked cloudiness on the surface of the liquid, which gradually extends downward.

Urohæmatin. Urohæmatin appears to be the chromogen of the red pigment of the urine, and is very likely closely related to indoxyl. Little, however, is known of its chemical composition or of its mode of formation. In all probability the red pigment which may be obtained from this substance is identical with other red pigments which have been described from time to time as occurring in the urine, such as that of Scherer, the urrhodin of Heller, the urorubin of Plosz, Schunk's indirubin, Bayer's indigo-purpurin, Giacosa's pigment, and also the indigo-red obtained by Rosenbach and Rosin by careful oxidation of the urine with nitric acid.

Further investigations are necessary before this subject is fully understood, but bearing in mind the probable origin of urohæmatin from indoxyl, it would possibly be best to speak of the red pigment as indigo-red.

The presence of urohæmatin in normal urine—*i. e.*, a chromogen yielding a red pigment when treated with certain reagents—may be demonstrated by shaking urine with chloroform and decanting after several days, when the addition of a drop of hydrochloric acid to the chloroform extract will cause the appearance of a beautiful rose-color, varying in intensity according to the amount of the chromogen present.

In accordance with the view that urohæmatin is an indoxyl derivative, its clinical significance is similar to that of indican (which see). The purplish color so often obtained in the chloroform extract, when Stokvis' modification of Jaffé's indican test is employed, is due to a mixture of indigo-blue and indigo-red. Indican, however, always appears to be present in larger amounts than urohæmatin; and in normal and usually also in pathologic urines a red color is not obtained with the test mentioned. In a few isolated cases of ileus, peritonitis, and carcinoma of the stomach the author found more indigo-red than indigo-blue.

The so-called "Reaction of Rosenbach" is a convenient test for indigo-red when this is present in increased amounts: the boiling

urine is treated drop by drop with concentrated nitric acid, when in the presence of large amounts of indigo-red it will assume a dark Burgundy color, which sometimes takes on a bluish tinge if held to the light. Owing to a precipitation of the pigment the mixture at the same time becomes cloudy, the foam assuming a blue color. In well-marked cases the Burgundy color does not appear to be changed by the further addition of nitric acid, but will sometimes, when 10–20 drops of the acid have been added, suddenly turn from red to yellow. This reaction Rosenbach regarded as symptomatic of various forms of severe intestinal disease associated with an impeded resorption throughout the entire intestinal tract. Ewald likewise noted this reaction in cases of extensive disease of the small intestine, in carcinoma of the stomach, acute and chronic peritonitis, but obtained negative results in carcinoma of the colon, stricture of the œsophagus, chronic diarrhœa, etc. *Rosenbach's reaction should be viewed in the same light as a highly increased elimination of indican;* the author has met with the same in all conditions associated with greatly increased intestinal putrefaction, and, as did Ewald, failed to note the reaction in a few cases of occlusion of the large intestine, in which an increased elimination of indican is likewise never observed.

Uroroseinogen. In addition to indican and urohæmatin still another chromogen, which yields a rose-red pigment when treated with mineral acids, appears to occur in normal urine, although in small amounts. Beyond the fact that the chromogen is no conjugate sulphate, practically nothing is known of its chemical nature. The pigment, which has received the name *urorosein*, or Harnrosa, appears to be identical with Heller's urophain. Urorosein may be best demonstrated by treating 5–10 c.c. of urine with an equal amount of concentrated hydrochloric acid and 1 or 2 drops of a concentrated solution of bleaching-powder, when in the presence of much indican the mixture first assumes a dark-greenish, blackish, or dark-blue color, owing to the formation of indigo. When the mixture is shaken with chloroform the supernatant fluid will exhibit a beautiful rose-color, due to the urorosein. This may then be extracted with amyl alcohol and separated from any other pigment present at the same time by shaking with sodium hydrate, whereby the solution is decolorized. Upon the addition of a drop or two of hydrochloric acid to the alcoholic extract the rose-color will reappear. Such solutions, however, soon become decolorized upon standing. A

rose-red ring, referable to this pigment, is also frequently obtained in pathologic urines when the ordinary nitric-acid test is employed.

While normally urorosein can only be obtained in traces, appreciable amounts are often met with in pathologic conditions associated with grave disturbances of nutrition, as in nephritis, diabetes, carcinoma, and dilatation of the stomach, pernicious anæmia, typhoid fever, phthisis, and at times in profound chlorosis, etc. A vegetable diet also appears to cause an increase in the amount of the chromogen.

Pathologic Pigments and Chromogens. *The blood-pigments.* The blood-pigments proper which may occur in the urine have already been considered (see p. 409), and in this connection it will only be necessary to refer briefly to the occasional presence of hæmatin, urorubrohæmatin, urofuscohæmatin, and hæmatoporphyrin.

Hæmatin is only rarely seen. In order to demonstrate its presence the urine is rendered strongly alkaline with ammonia, filtered, and the filtrate examined spectroscopically, when the spectrum shown in Fig. 6 will be noted, which may be changed into the spectrum represented in Fig. 7 by the addition of ammonium sulphide.

Urorubrohæmatin and *urofuscohæmatin* are two pigments which were observed by Baumstark in the urine of a case of pemphigus leprosus complicated with visceral lepra, and which appear to be closely related to hæmatin. The color of the urine in this case varied between dark red and brownish-red, strongly suggesting the presence of blood. In order to separate out the pigments the urine was dialyzed and the contents of the dialyzer dissolved in sodium hydrate solution. Upon the addition of hydrochloric acid to this solution a brown pigment separated out in flakes, while a second pigment remained in solution, imparting to it a beautiful red color. Upon filtration the acid filtrate was again subjected to dialysis, when the red pigment likewise separated out. The former substance Baumstark termed urorubrohæmatin, and the latter urofuscohæmatin.

Urohæmatoporphyrin has the formula $C_{16}H_{18}N_2O_3$, and is probably closely related to the hæmatoporphyrin resulting from the action of sulphuric acid upon hæmatin. MacMunn found a pigment answering the description of this substance in the urine in cases of rheumatism, Addison's disease, pericarditis, and paroxysmal hæmoglobinuria, which he termed urohæmatin, but which in all probability was hæmatoporphyrin. Le Nobel found the same pigment in two cases

of hepatic cirrhosis and in one case of croupous pneumonia. More recently hæmatoporphyrin has been repeatedly noted in the urine during a long-continued administration of sulphonal, trional, and tetronal, as also in cases of lead-poisoning and intestinal hemorrhages. Clinically its occurrence does not appear to be of any diagnostic significance, and recent researches have shown that in traces at least it is present in every urine. Urines rich in hæmatoporphyrin present an abnormal color, varying from a sherry or port-wine tint to Bordeaux. Albumin in uncomplicated cases is not present, and hæmatoporphyrin itself does not give the albumin reactions. In urines presenting the color just described hæmatoporphyrin may be tested for in the following manner:

Thirty c.c. of urine are treated with an alkaline solution of barium chloride. The precipitate, after having been washed with water and then with absolute alcohol, is extracted with ordinary alcohol acidulated with hydrochloric acid, by rubbing in a mortar. The solution thus obtained will present a reddish color in the presence of hæmatoporphyrin, and its filtrate yield the characteristic spectrum of the latter substance; *i. e.*, four bands of absorption, of which two are broad and dark and two light and narrow. The former alone are characteristic, and frequently the only ones visible. One of these extends beyond "D" into the red portion of the spectrum, while the other is situated between "b" and "F." Of the other two bands, one may be seen between "C" and "D," and the other between "D" and "E," nearer "E" (Fig. 9).

In conclusion it may be said that a chromogen of hæmatoporphyrin also usually occurs in urines containing the free pigment, which probably explains why such urines gradually become darker on standing.

Biliary pigments. Of the four biliary pigments, viz., bilirubin, biliverdin, biliprasin, and bilifuscin, the former alone is met with in freshly voided urines, while the others may form upon standing, being oxidation-products of bilirubin. As this pigment is never found in normal urines, its occurrence may be regarded as an infallible symptom of disease.

In health it will be remembered that *bilirubin*, $C_{16}H_{18}N_2O_3$, formed in the liver from blood-pigment, is eliminated into the small intestine, in which it is transformed into hydro-bilirubin and largely excreted as such in the feces, while a small portion is resorbed into the blood and eliminated in the urine as urochrome or normal urobilin.

Whenever then the outflow of bile into the intestines becomes impeded bilirubin is absorbed by the lymphatics and eliminated in the urine, icterus at the same time resulting.

Among the numerous causes which give rise to *choluria* under such conditions may be mentioned obstruction of the biliary ducts and especially of the common duct, referable to simple swelling of its mucous membrane, as in the ordinary forms of catarrhal jaundice; it may also be due to the presence of a biliary calculus, to parasites, compression of the duct by tumors of the liver, the gall-bladder, the duct itself, and of neighboring structures, particularly the pancreas, stomach, and omentum. Whenever the blood-pressure in the liver is lowered, so that the tension in the smaller biliary ducts becomes greater than that in the veins, choluria likewise results. The icterus occurring under these conditions has been termed *hepatogenic icterus*, in contradistinction to the form observed in cases in which the liver has either totally or partially lost the power of forming bile, owing to the existence of degenerative processes affecting its glandular epithelium, as in cases of acute yellow atrophy, or in which the destruction of red corpuscles is going on so rapidly and so extensively that the organ is incapable of transforming into bilirubin all the blood-pigment which is carried to it. This occurs in pernicious anæmia, malarial intoxication, typhoid fever, poisoning with arseniuretted hydrogen, etc. The *icterus neonatorum* is probably to a certain extent also dependent upon the latter cause. To this form the term *hæmatogenic icterus* has been applied. In such cases the occurrence of bilirubin in the urine can only be explained by assuming that a transformation of blood coloring-matter into bilirubin has taken place in the blood itself or in other tissues of the body. As a matter of fact, it appears to be quite generally accepted that such a transformation *can* actually occur outside of the liver, as the hæmatoidin which may be found in old extravasations of blood seems to be identical with bilirubin. On the other hand, however, the existence of a hæmatogenic icterus is positively denied, especially by Stadelmann. In accordance with his view it may actually be demonstrated that in cases of pernicious anæmia, malaria, etc., the urine does not contain bilirubin, but usually urobilin. In cases of this kind which the author had occasion to examine bilirubin was never found. Further investigations are necessary to settle this question definitely.

Usually the presence of biliary pigment may be recognized by

ocular inspection, as urines which contain this in notable amounts present a color varying from a bright yellow to a greenish-brown. Any morphologic elements which may occur in the sediment are stained a golden-yellow, and the same color is imparted to the foam of the urine, as well as to the filter-paper used in its filtration. At times, however, and particularly in cases in which the icterus is only beginning to appear, the presence of bilirubin is not infrequently overlooked, and urines containing urobilin in large amounts may be similarly mistaken for icteric urines. In doubtful cases, therefore, whether icterus exists or not, but in which the urine presents an intense yellow color, it is necessary to have recourse to chemical tests. A large number of these have been devised for the purpose of demonstrating the presence of bilirubin, all of which are fairly reliable. Only those will be described here which the author has had occasion to employ personally and which deserve especial consideration as being the most delicate.

Smith's test, as modified by Rosin: 5–10 c.c. of urine are placed in a test-tube and treated with 2 or 3 c.c. of tincture of iodine which has been diluted with alcohol in the proportion of 1 : 10, in such a manner that the iodine solution forms a layer above the urine. In the presence of bilirubin a distinct emerald-green ring will be seen to form at the zone of contact. This test can be highly recommended as being the simplest, and is not surpassed in delicacy by any other.

Huppert's test: 10–20 c.c. of urine are precipitated with milk of lime (a solution of barium chloride is, perhaps, still more convenient), and the precipitate, after filtering, brought into a beaker by perforating the filter and washing its contents into the latter with a small amount of alcohol acidulated with sulphuric acid. The mixture is boiled, when in the presence of bilirubin the solution assumes a bright emerald-green color. Huppert's test is as delicate as that of Smith, but not so convenient for the needs of the practising physician.

Gmelin's test, as modified by Rosenbach: The urine is filtered through thick Swedish filter-paper, when the latter is removed and a drop of concentrated nitric acid, which has been allowed to stand exposed to the air for a short time, is placed upon its inner surface. In the presence of bilirubin rings presenting the colors of the rainbow will be seen to form around the nitric acid.

Gmelin's test: The urine is treated with nitric acid, which is carried

to the bottom of the test-tube by means of a pipette, so as to form a layer beneath the urine, when a color-play, as already described (p. 396), will take place at the line of contact between the two fluids, the green color being the most characteristic.

In this connection a few words may also be said of the occurrence in the urine of biliary acids and cholesterin.

Biliary acids. These may be demonstrated in the urine whenever bile-pigment is present, so that their clinical significance is essentially the same as that attaching to bilirubin. Their demonstration is, however, attended with such difficulties that the methods devised for this purpose may well be omitted here (see also p. 196).

Cholesterin. Cholesterin has never been found in icteric urines and is only rarely seen in other pathologic conditions. It has been observed in cases of chyluria, fatty degeneration of the kidneys, diabetes, in one case of epilepsy, and in two cases of pregnancy. v. Jaksch has noted the presence of cholesterin crystals in a urinary sediment in a case of tabes and cystitis. The author found cholesterin crystals in the sediment in a case of acute nephritis. The urine was of a dark amber-color, cloudy, of an acid reaction, and a specific gravity of 1.028. In the sediment numerous hyaline and epithelial casts and some red blood-corpuscles were found. Güterbock described a urinary calculus obtained from the bladder of a woman which consisted almost entirely of cholesterin (see also Feces).

Beginners at times regard the spangles of urea nitrate seen in urines rich in urea, after the addition of nitric acid, as cholesterin, an error which should be guarded against.

Pathologic urobilin. This pigment should not be confounded with the urochrome or normal urobilin described above, to which it is closely related, but from which it may be readily distinguished by means of the spectroscope. Gautier states that pathologic urobilin may be obtained from urochrome by submitting the latter to the action of reducing agents. Like normal urobilin it is derived from the coloring-matter of the blood and bilirubin, merely representing a lower form of oxidation than normal urobilin. It is said to be identical with the *stercobilin* found in the feces. While its occurrence in the urine is essentially a pathologic phenomenon, it is at times also met with in normal urines, and appears to be derived from a special chromogen, *urobilinogen*, from which it may be set free by the addition of an acid. From its frequent occurrence in febrile urines pathologic urobilin has also received the name *febrile*

urobilin. It is, however, also observed in many other conditions, and especially in cases presenting the so-called hæmatogenic form of icterus, from which fact, indeed, and the usual absence of bilirubin at the same time, this form has also been termed "urobilin icterus." In this connection it is interesting to note that, according to v. Jaksch, bilirubin occurs in the blood in almost every case in which urobilin is present in the urine, showing that bile-pigment circulating in the blood is in all probability transformed into urobilin in the kidneys.

Urobilinuria has been observed in certain hepatic diseases; in twelve cases of atrophic and hypertrophic cirrhosis examined, v. Jaksch was able to demonstrate the presence of urobilin in the urine in every instance, a point which at times may be of considerable diagnostic importance, providing that other causes which are known to lead to urobilinuria can be eliminated. The author has observed urobilin in a few cases of hepatic cirrhosis, chronic malaria, and pernicious anæmia, in all of which the skin presented a light icteric hue, and in which bile-pigment was absent from the urine. An examination of the blood was, however, unfortunately not made. Urobilin has also been noted in cases of carcinoma, scurvy, Addison's disease, hæmophilia, retro-uterine hæmatocele, extra-uterine pregnancy, following intracranial hemorrhages, etc.

Urines which are rich in urobilin usually present a dark-yellow color, strongly suggestive of the presence of bilirubin; the foam even in such cases may be colored, making the resemblance between the two pigments still more complete. v. Jaksch further points out that urines containing indican in large amounts often likewise present a very dark-yellow color, a statement with which personal observations are in perfect accord. It is possible that the color in such cases may be due to the presence of humin-substances derived from the indican. In every case a more detailed chemical examination should hence be made. The method suggested by v. Jaksch appears to be more serviceable than that suggested by Gerhardt.

v. Jaksch's test. 10–20 c.c. of urine are submitted to Huppert's test (which see), when in the presence of urobilin in notable quantities the precipitate assumes a brownish-red color, which disappears upon boiling with acidulated alcohol, the liquid at the same time becoming colored a brownish or pomegranate-red. In the presence of only a small amount of the pigment, on the other hand, the liquid is colored only a light reddish tinge.

Gerhardt's test. If the urine contains much urobilin, which the

acid, hydro-para-cumaric acid, para-oxyphenylglycolic acid, oxy-amygdalic acid, and homogentisinic acid. Glycosuric acid is more frequently seen in children than in adults, its presence being apparently due to some such metabolic anomaly as the occurrence of cystin and diamines in the urine, the condition at times occurring in families and persisting for years. Although it has been found in pathologic conditions, viz., in phthisis, and in one case of brain-tumor, no connection appears to exist between any local lesion and the alkaptonuria. Marshall, who was the first to obtain glycosuric acid in a pure form, noted a gradually increasing weakness in his case.

While alkaptonuria is usually a chronic condition, it may also occur as an acute disorder. Boraczewski thus found homogentisinic acid before death in a case of tuberculosis of the lungs and of the peritoneum. As the elimination of indican was much increased in this case, and as the ingestion of tyrosin increased the alkaptonuria, Boraczewski thinks that the alkaptonuria was referable to an increased production of tyrosin.

The presence of such acids may at times give rise to confusion, and a case of alkaptonuria may be mistaken for one of glycosuria, if reliance be placed only upon Fehling's or Trommer's test for sugar. Several years ago the author had occasion to examine a urine containing glycosuric acid, the following note having been made at the time: "The urine presents a dark-brown color, which has developed on standing. Its reaction is acid; the specific gravity 1.028. It reduces Fehling's solution, but does not reduce the subnitrate of bismuth, causing merely a blackish discoloration; the fermentation-test is negative. When Ehrlich's test is applied, a dark-brown color develops on standing for fifteen minutes, while at the end of an hour the urine has turned almost black."

For methods of isolating glycosuric acid, see Neubauer and Vogel's Urinary Analysis.

Blue urines. Blue urines are sometimes seen, the blue color being due to indigo formed from urinary indican, in all probability, within the urinary passages. Their occurrence can be regarded only as a medical curiosity. Formerly, when indigo was employed in the treatment of epilepsy, blue urines were frequently seen. At the present time, where methylene-blue is occasionally used in the treatment of malaria and chyluria, the pigment is found in the urine.

Green urines. Green urines have also been described, the cause of the color of which, however, has not been definitely ascertained.

PLATE XII.



Ehrlich's Diazo-Reaction, as modified by the author. The orange color in the lower portion of the test tube may be obtained in any urine; the dark carmine ring indicates the presence of the reaction in a well-pronounced degree; the colorless zone above is intended to indicate the ammonia that has been added.

Pigments referable to drugs. Certain drugs may also cause changes in the normal color of urine, and in doubtful cases inquiry in this direction should be made. It has been pointed out that carbolic acid, hydrochinon, pyrocatechin, and salol cause the appearance of a dark-brown color, and that after the administration of indigo and methylene-blue blue urines are voided. Santonin, rheum, and senna color urines a bright yellow, so that they may resemble icteric urines in appearance. The yellow color in such cases is changed to an intense red by the addition of an alkali, and if ammoniacal fermentation be going on at the same time in the bladder the patient may believe himself to be suffering from hæmaturia. The red color thus produced is due to the action of the alkali upon chrysophanic acid. When urines containing copaiba are treated with hydrochloric acid a red color results, which changes to violet upon the application of heat. During the administration of potassium iodide, or the use of iodine in any form, a dark mahogany color is obtained when the urine is treated with nitric acid. In doubtful cases Stokvis' modification of Jaffé's test for indican should be employed, when in the presence of an iodide the chloroform assumes a beautiful rose-red color.

For the detection of other drugs and poisons in the urine the reader is referred to special works.

Ehrlich's reaction. In pathologic conditions, and particularly in typhoid fever, a chromogen appears to be present in the urine, which, when treated with a solution of diazo-benzene-sulphonic acid and ammonia, imparts a tint to the urine varying from eosin to a deep garnet-red (Plate XII.). This reaction, which is generally spoken of as Ehrlich's reaction, or the "diazo-reaction," was at one time regarded as pathognomonic of typhoid fever. Subsequent researches have shown, however, that it is also at times met with in other acute febrile diseases, such as scarlatina, measles, malaria, smallpox, pneumonia, etc., and notably in phthisis pulmonalis, in which it is frequently observed, and in which its presence for any length of time may be regarded as a bad omen. Still there appears to be no doubt that its occurrence in doubtful cases may be regarded as pointing to typhoid fever, especially when found between the fifth and the thirteenth day of the disease, and when it disappears later on. The author has studied this question in a large number of instances, and has arrived at the conclusion that, while the reaction may be observed in other diseases as well as in typhoid fever, it is

usually not difficult to distinguish between these and the latter condition, excepting in certain cases of acute miliary tuberculosis. As the reaction, however, is obtained not later than the twenty-second day of the disease, and is usually present as early as the fifth or sixth day in typhoid fever, and while it generally does not appear earlier than the beginning of the third week, and then persists almost to the end in acute tuberculosis, its occurrence may be of decided value in diagnosis in many instances.

Its absence from the fifth to the ninth day in typhoid fever usually indicates a very mild case, excepting in children. This rule, however, is not an invariable one. The author recently observed a case of typhoid fever in which, notwithstanding exceedingly high temperatures (106.5°), the reaction was not obtained before the beginning of the third week, and then persisted for only a few days.

The author cannot agree with v. Jaksch when he states that he "disclaims for this test any clinical importance whatsoever, and that he would enjoin the necessity of avoiding inferences based upon the appearance of the reaction indicated." Nor does he believe that "the color, when obtained, is always due to acetone, and that the diazo-reaction is rather an uncertain indication of that body than a test for anything else," as he has not only been unable to demonstrate this reaction in a large number of cases of diabetes in which acetone was present, but has likewise only occasionally observed acetone in cases of typhoid fever in which a positive result was obtained, notwithstanding a most careful examination.

Since the preparation of chemically pure, crystalline diazo-compounds is a difficult process, Ehrlich made use of the fact that sulphanilic acid when treated with nitrous acid in a nascent state forms diazo-benzene-sulphonic acid, which thus becomes the active principle in the mixture employed.

Other compounds, of course, can also be used, as the meta-amido-benzene-sulphonic acid, the ortho- and para-toluidine-sulphonic acids, etc., but of all these Ehrlich found the common sulphanilic acid the most convenient. Two solutions kept in separate bottles are employed, the one containing 50 c.c. of hydrochloric acid, which is diluted to 1000 c.c. and saturated with sulphanilic acid, the other being a 0.5 per cent. solution of sodium nitrite.

To make the test, 40 c.c. of the sulphanilic-acid solution are taken in a measuring-glass, and treated with 1 c.c. of the sodium-nitrite solution, the mixture being thoroughly shaken. The hydrochloric acid acts

upon the sodium nitrite, forming nitrous acid, which, in a nascent state, forms the diazo-benzene-sulphonic acid by its action upon the sulphanilic acid. Small quantities of the sodium nitrite are used, the absence of any free nitrous acid in the mixture being thus insured; very small quantities of the diazo-benzene-sulphonic acid are at the same time formed, one of the principal requirements in order to insure success in the experiment.

The reaction which takes place is represented as follows:

I. $NaNO_2 + HCl = NaCl + HNO_2$

II. $C_6H_4\begin{cases}NH_2\\SO_3H\end{cases} + HNO_2 = C_6H_4\begin{cases}\diagup\!\!\diagdown N\\SO_3\end{cases} + 2H_2O$

Para-amido-benzene-sulphonic acid. Diazo-benzene-sulphonic acid.

In his original article Ehrlich advises the addition of this mixture in the proportion of 1 : 1 per volume to the urine to be tested. If ammonia be added in excess to the urine thus treated, the color-play presently to be described occurs. In a later communication he has modified this method by mixing 1 volume of urine with from 5 to 6 volumes of absolute alcohol previous to the addition of the sulphanilic-acid mixture, filtering, and then adding the acid mixture to the filtrate.

It is convenient to add about 50 c.c. of absolute alcohol to 10 c.c. of urine, to filter, and then to add to the alcoholic urine, which has become more or less decolorized, the sulphanilic-acid mixture from a burette; 20 c.c. of the latter added to about 30 c.c. of the alcoholic urine are sufficient. The addition of the acid in small quantities, 2 c.c. at a time, for example, followed by thorough shaking of the urine, is at times useful, especially in typhoid fever, when the disease has advanced to a point at which the color-reaction has no longer its original intensity. By the addition of a few drops of ammonia to the final mixture the characteristic color appears in typhoidal urine; this, however, disappears on shaking, and becomes permanent only after an excess of ammonia has been added. A small Erlenmeyer's flask is more convenient for holding the urine than the ordinary test-tube, the exact shade being more apparent by transmitted light. With this modified method most of the author's experiments were performed.

There is a third method, however, which is more convenient, less expensive, and likewise most delicate. A few c.c. of urine are poured into a small test-tube, when an equal quantity of the sulphanilic-acid

mixture is added, the whole being thoroughly shaken; 1 or 2 c.c. of ammonia are then allowed to run carefully down the side of the tube, forming a colorless zone above the yellow urine containing the acid. At the junction of the two a more or less deeply colored ring will be seen, the color of which is readily distinguished, the slightest carmine tinge being shown more readily by contrast with the colorless zone above and the yellow below, than when dealing with a uniform color. *If the mixture be then poured into a porcelain basin containing water, a salmon-red color will be obtained if the reaction be positive, while a yellow or orange color is obtained when negative.* This latter additional test the author has found most valuable in doubtful cases.

As to the color-play which takes place in different urines, it will be observed that in normal, or pathologic, but non-febrile urines, the color of the pure, or alcoholic, urines, when method No. 2 is employed, remains either unaffected or is merely intensified by the addition of the ammonia. A deep orange tint may even be produced in this way, but is of no significance whatsoever, and is easily distinguished from the typical color. Ehrlich records one exception to this rule, namely, that in urines containing biliary coloring-matter an intensely dark, cloudy discoloration occurs at times, which, upon boiling, is changed to an intense reddish-violet color.

In the course of certain experiments another very interesting exception was met with, but it is to be regretted that there is only one observation to record, which the author owes to the kindness of Dr. Ogden, of Milwaukee. The urine in this case contained a substance which reduced Fehling's solution, but did not reduce the subnitrate of bismuth, producing merely a black discoloration; the fermentation-test failed completely. Undoubtedly this was one of the rare instances in which glycosuric acid, first isolated by Marshall (see above), occurred in the urine. When Ehrlich's test was applied to this urine according to the second method, a dark-brown color developed on standing for fifteen minutes, which at the end of an hour turned almost to black. As regards febrile urines, Ehrlich observed an intensely yolk-yellow color, which was even imparted to the foam when method No. 1 was employed, in rare instances of endocarditis ulcerosa, abscessus hepatis, and intermittens; *i. e.*, in diseases associated with well-marked chills.

In typhoid fever—and this is most important—a color varying from that of eosin to a deep garnet develops upon the addition of ammonia. Here method No. 2, and particularly No. 3, were found

very useful, as with these the production of the faintest rose-tint is more readily perceived than when No. 1 is employed, owing to the fact that in the second method we are practically dealing with a primarily colorless solution, and in No. 3, as above stated, we can take advantage of contrasts.

Greene states that if the solution be prepared, such that one part of the sodium nitrite solution is added to 100, instead of the usual 40 parts of the sulphanilic-acid mixture, a positive reaction is never obtained in cases of acute croupous pneumonia and of pulmonary tuberculosis. In septic conditions and in cases of advanced malignant disease, however, a positive reaction may even then be obtained. It is possible that the test may be still further modified, so as to become truly pathognomonic of typhoid fever.

The following table is taken from Dr. Greene's very valuable paper :[1]

	Cases.	Plus.	Minus.
Typhoid fever	10	10	0
Septicæmia	3	0	3
Varicella	1	0	1
Typhoid relapse	2	2	0
Pseudo-relapse	1	0	1
Scarlatina	1	0	1
Phthisis pulmonalis	12	0	12
Lobar pneumonia	3	0	3
Febrile diarrhœas	2	0	2
Pleurisy	2	0	2
Syphilis, second stage	3	0	3
" third stage	2	0	2
Malarial fever	2	0	2
Carcinoma, advanced	2	2	0
Chronic rheumatism	3	0	3
Simple anæmia	1	0	1
Heart disease	4	0	4
Chronic nephritis	6	0	6
Tuberculosis of hip and elbow-joints	1	0	1
Arterio-sclerosis	2	0	2
Cirrhosis of liver	2	0	2
Oxaluria	3	0	3
Gastric ulcer	1	0	1
Acute bronchitis	2	0	2
Chronic constipation	1	0	1
	75		

[1] The Diagnostic Value of Ehrlich's Diazo-reaction : Journal of the American Medical Association, February, 1894.

Conjugate Sulphates. In addition to indoxyl (see Indican), skatoxyl, phenol, paracresol, and pyrocatechin occur in the urine in combination with sulphuric acid.

Skatoxyl. Skatoxyl results from the skatol formed during the process of intestinal putrefaction, as indoxyl is derived from indol, and is partly eliminated in the urine as skatoxyl sulphate. Clinically it is of little interest, as the amount excreted is very small, and it is not necessary here to enter into a further consideration of its chemical properties or modes of detection (see Feces).

Phenol. Phenol, according to Brieger, occurs in only small amounts in human urine, the phenol reactions being largely caused by *paracresol.* Normally only about 0.03 gramme is eliminated in the twenty-four hours, but in pathologic conditions much larger quantities may be found. These conditions are essentially the same as those described under Indicanuria, but it should be remembered that while an increased elimination of indican is usually associated with an increased elimination of phenol, a diminished excretion of the former, in those cases in which the increased degree of intestinal putrefaction is referable to diseases of the stomach, is never, so far as personal observations go, associated with an increased elimination of phenol. In cases, however, in which an increased elimination of conjugate sulphates is due to albuminous putrefaction going on in other parts of the body, as in cases of empyema, pulmonary gangrene, putrid bronchitis, etc., an increased elimination of phenol alone may be noted, the amount of indican being about normal. A greatly increased excretion of conjugate sulphates referable to phenol alone is especially observed in cases of poisoning with carbolic acid or one of its derivatives (see also Indicanuria and Sulphates).

The method employed for the demonstration of phenol in the urine is the same as that used for its quantitative estimation.

Principle: When potassium-phenyl sulphate is treated with hydrochloric acid phenyl sulphate results, which further takes up one molecule of water, giving rise to the formation of sulphuric acid and phenol, according to the following equations:

$$\text{I.}\quad SO_2\begin{matrix}O.C_6H_5\\OK\end{matrix} + HCl = KCl + SO_2\begin{matrix}O.C_6H_5\\OH.\end{matrix}$$

$$\text{II.}\quad SO_2\begin{matrix}O.C_6H_5\\OH\end{matrix} + H_2O = SO_2\begin{matrix}OH\\OH\end{matrix} + C_6H_5.OH.$$

By the action of bromine-water upon phenol a yellowish-white crystalline precipitate of tribromophenol is formed :

$$C_6H_5.OH + 6Br = 3HBr + C_6H_2Br_3.OH.$$

As 331 (molecular weight) parts by weight of tribromophenol correspond to 94 (molecular weight) parts by weight of phenol, the amount of the latter contained in a certain volume of urine is readily determined according to the equation :

$$331 : 94 :: x : y, \text{ and } y = \frac{x \times 94}{331} = 0.28398\ x,$$

in which x indicates the weight of the tribromophenol found in the amount of the urine employed, and y the corresponding quantity of phenol.

Method : 500–1000 c.c. of urine are treated with one-fifth of this amount of dilute hydrochloric acid and distilled as long as a specimen of the distillate is rendered cloudy by the addition of bromine-water (1 : 30), the specimens used for this purpose being carefully preserved. The total quantity of the filtered distillate, together with the specimens which 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. Beyond this point a further addition of bromine-water is beset with danger, as compounds will be formed which contain more bromine, the presence of which would indicate a smaller amount of phenol than that actually contained in the urine. After two or three days the precipitate is collected on a filter which has been dried over sulphuric acid, washed with water containing a trace of bromine, and then dried over sulphuric acid and weighed. The drying over sulphuric acid is necessary, as tribromophenol is fairly volatile, and a vacuum hence inadmissible.

Pyrocatechin. Urines containing pyrocatechin, like those containing hydrochinon (see above), darken upon standing, though presenting a normal color when voided. For the demonstration of these bodies in the urine the reader is referred to special works upon urinary analysis.

Acetone. The amount of acetone which may be found in the urine under normal conditions varies between 0.008 and 0.027 gramme, and is greatly influenced by the character of the diet. Whenever the carbohydrates are withdrawn the quantity rapidly increases, and reaches its maximum about the seventh or eighth day. At this time from 200 to 700 mgrms. may be eliminated in

the twenty-four hours. If, then, carbohydrates are again added to the diet the acetonuria soon disappears. This result is not reached, however, if fats are substituted for the carbohydrates. The acetonuria is greatest when but little albuminous food and no carbohydrates at all are ingested, and during starvation the same amounts are essentially found. There can hence be no doubt that acetone is derived from proteid material, be this in the form of organized or circulating albumin. Increased amounts are accordingly found whenever, as in fevers, the various cachexias, in conditions associated with inanition, etc., large quantities of circulating albumin are broken down, or whenever carbohydrates are not furnished in sufficient amount.

Most important is the diabetic form of acetonuria, and it may be stated as a general rule that the diagnosis of diabetes mellitus is justifiable whenever sugar and notable quantities of acetone are found in the urine. The amount of acetone, moreover, stands in a direct relation to the intensity of the disease, the maximum excretion being usually observed toward the fatal end. Whether or not this form of acetonuria can always be explained upon the basis given above must still remain an open question. There can be no doubt, however, that the threatening symptoms which are so commonly associated with a greatly increased elimination of acetone, will often disappear when carbohydrates are administered in large amounts. It is certain, moreover, that diabetic coma is more apt to occur when the old-fashioned plan of excluding carbohydrates entirely from the dietary of diabetic patients is adopted. Hirschfeld suggests that in every case of diabetes the excretion of acetone be carefully followed, and that large amounts of carbohydrates be administered whenever the acetonuria approaches a dangerous height. With his experience that of the writer agrees entirely.

Among the febrile diseases in which acetonuria has been observed may be mentioned typhoid fever, pneumonia, scarlatina, measles, acute miliary tuberculosis, acute articular rheumatism, and septicæmia. In those of short duration, on the other hand, even if the fever be high, as in acute tonsillitis, intermittent fever, the hectic fever of phthisis, etc., an increased elimination of acetone is rarely observed. In the continued fevers the acetonuria is largely referable to the character of the diet, as carbohydrates are usually excluded entirely, and the writer has repeatedly observed that a return to the normal occurred as soon as sugar was administered in amounts varying from 50 to 100 grammes.

In certain nervous and mental diseases, as in general paresis, melancholia, following epileptic seizures, and in tabes, acetonuria is frequently observed. During the second stage of general paresis increased amounts are indeed quite constantly found, and Hirschfeld is probably correct when he states that the psychotic form of acetonuria is largely referable to improper feeding.

In the primary diseases of the stomach, and notably in carcinoma, acetonuria is quite commonly observed, and it is possible that the acetone in these cases is to some extent, at least, formed in that organ directly from the proteids ingested. The fact that in carcinoma acetone may be observed at a time when marked loss of flesh has not as yet occurred, and that larger amounts of acetone may be found in the stomach than in the urine, is certainly in favor of this view.

The acetonuria following chloroform narcosis is probably referable to an increased destruction of organized albumin. Finally, the possibility of the occurrence of an enterogenic form of acetonuria must be borne in mind. The cases of so-called asthma acetonicum probably belong to this class.

Tests for Acetone. *Legal's test.* This test may be applied to the freshly voided urine, but is not conclusive. Several c.c. of urine are treated with a few drops of a strong solution of sodium-nitroprusside and sodium hydrate, when the mixture will present a red color, which rapidly disappears, and in the presence of acetone is replaced by a purple or violet-red upon the addition of acetic acid. As a rule, it is safer to distil the urine (500–1000 c.c.) after the addition of a little phosphoric acid (1 gramme pro liter), and to employ the first 10–30 c.c. of the distillate for the following tests.

Lieben's test. A few c.c. of the distillate are treated with several drops of a dilute solution of iodo-potassic iodide and sodium hydrate, when in the presence even of traces of acetone a precipitation of iodoform in crystalline form occurs, which may be readily recognized by its odor.

Reynold's test. A few c.c. of the distillate are treated with a small amount of freshly precipitated yellow oxide of mercury. This is prepared by precipitating a solution of bichloride of mercury with an alcoholic solution of sodium hydrate. If acetone be present, a black color, due to the formation of sulphide of mercury, will result in the clear filtrate upon the addition of a few drops of ammonium sulphide.

Quantitative estimation of acetone. For the purpose of estimating the amount of acetone the method of Messinger, as modified by Huppert, is now employed, and greatly to be preferred to the old procedure of v. Jaksch.

Principle: It is based upon the observation of Lieben that acetone gives rise to the formation of iodoform when treated in an alkaline solution with iodine. If, then, a solution of acetone be treated with a known amount of iodine, it is a simple matter to determine the quantity present by retitrating the iodine which 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. Sodium hydrate solution (50 per cent.).
4. A decinormal solution of iodine.
5. A decinormal solution of sodium thiosulphate.

Preparation of the solutions :

1. The decinormal solution of iodine is prepared as described elsewhere.

2. As the molecular weight of sodium thiosulphate—$Na_2S_2O_3 + 5H_2O$—is 248, a decinormal solution of the salt would contain 24.8 grammes to the liter. This quantity is dissolved in about 950 c.c. of distilled water, and brought to the proper strength by titrating a given volume, such as 10 c.c., with a decinormal solution of iodine. A small amount of starch solution is added to the 10 c.c., when the iodine solution is added until the blue color has just disappeared. As 1 c.c. of the thiosulphate solution should correspond to 1 c.c. of the iodine solution, the necessary amount of water which must be added to the former is then determined.

Method: One hundred c.c. 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 have passed over. The distillate is received in a retort which is connected with a ball arrangement filled with water. As soon as seven-eighths of the urine have been distilled over, a small amount of the distillate of the remainder is tested for acetone according to 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 distill until all the acetone has been driven over. The dis-

tillate 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, moreover, 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 a ball arrangement, as described above. The distillate is then treated with a carefully measured quantity of the one-tenth normal solution of iodine —about 10 c.c. for 100 c.c. of urine—and sodium 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 sodium 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 acidified 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 c.c. of starch solution are then added, and the titration continued until the last trace of blue has disappeared. The number of c.c. employed in the titration is finally deducted from the total amount of the iodine solution added and the result multiplied with 0.967. The figure thus obtained will then indicate the amount of acetone contained in the 100 c.c. of urine, in terms of mgrms., as 1 c.c. of the thiosulphate solution is equivalent to 1 c.c. of the iodine solution or to 0.967 mgrm. of acetone.

Diacetic Acid. The occurrence of diacetic acid in the urine must always be regarded as abnormal. Its pathologic significance is identical with that of acetonuria. It is found especially in diabetes, in various forms of digestive disturbance, and in febrile diseases. In the high and continued fevers of childhood it is almost constantly present.

In order to demonstrate the presence of diacetic acid a few c.c. of urine are treated with a strong solution of perchloride of iron, added drop by drop. Should a precipitation of phosphates occur, these are filtered off, when more of the iron solution is added to the filtrate. If now a Bordeaux-red color appears, another portion of the urine is boiled and similarly treated. If in the second test no reaction is obtained, a third portion of the urine should be treated with sulphuric acid and extracted with ether. A positive reaction, when the ethereal extract is tested with perchloride of iron, the color disappearing upon standing for twenty-four to forty-eight hours, will indicate the presence of diacetic acid, particularly if the urine be also rich in acetone.

Oxybutyric Acid. The fact that in some cases of diabetes an excessive elimination of ammonia was observed led to the belief that there must be present an unknown acid; this was finally shown to be β-oxybutyric acid. The occurrence of this acid in the urine of diabetic patients is of great clinical interest, as a probable connection has been established between its presence in the blood and diabetic coma. The latter condition is explained by assuming that the diabetic patient is unable to furnish sufficient quantities of ammonia to neutralize the acids formed in the tissues of the body, the alkalies of the blood being consequently attacked. A prophylactic treatment with alkalies, such as intravenous injections, has hence been suggested in severe cases, with an encouraging degree of success. This, however, is a mere theory, and the fact that a case of diabetic coma has been reported in which the alkalinity of the blood was not diminished, and in which recovery took place without the use of alkalies, renders the correctness of the hypothesis rather doubtful. Possibly the cause of the coma is due to the presence of toxins circulating in the blood, causing an increased tissue-destruction, with a simultaneous formation of acetone and abnormal acids.

The presence of oxybutyric acid may always be regarded as indicating a severe type of the disease, and when associated with marked acetonuria and diaceturia as indicating danger of coma.

The presence of oxybuytric acid may be inferred in diabetic urines if after fermentation a rotation of the plane of polarized light to the left be observed.

Lactic Acid. Sarco-lactic acid is normally absent from the urine, but is met with in pathologic conditions, and particularly in cases of hepatic disease, the liver normally being concerned in the

decomposition of lactic acid and of the lactates that have been ingested with the food.

In order to test for lactic acid the urine is evaporated on a water-bath to a thick syrup and extracted with 95 per cent. alcohol. This is decanted off after twenty-four hours, evaporated to a syrup, acidified with dilute sulphuric acid, and extracted with ether as long as this presents an acid reaction. The ether is then distilled off, and the residue dissolved in water. This solution is treated with a few drops of basic acetate of lead, filtered, the excess of lead removed by means of sulphuretted hydrogen, and the filtrate evaporated to dryness on the water-bath, when the lactic acid will remain behind as a slightly yellowish syrup. This is then dissolved in a little water, the solution saturated with zinc carbonate, and heat applied. Zinc lactate will separate out upon evaporation, and may be recognized by the form of its crystals, viz., small prisms.

Volatile Fatty Acids. The term *lipaciduria* has been applied by v. Jaksch to an increased elimination of volatile fatty acids in the urine which is observed at times in cases of fever, hepatic diseases affecting the proper structure of the liver, leukæmia, both myelogenic and lieno-lymphatic, and in diabetes. Clinically, lipaciduria is of no especial significance. Traces of fatty acids are also found under normal conditions, and are probably formed in the lower segment of the small intestine. The fatty acids which have thus far been isolated from the urine are formic, acetic, butyric, and propionic acid. They may be demonstrated in the same manner as described in the chapter on Feces.

Fat. Under strictly normal conditions the urine contains no fat, while variable amounts may be found in disease. When present in large quantities, so that it is possible to recognize it with the naked eye, the condition is termed *lipuria*. Such cases, however, are rare, and the diagnosis should only be made when it is possible to exclude an accidental contamination of the urine from without. Smaller quantities of fat, recognizable only with the microscope, are much more common, and are indeed quite constantly observed, whenever fatty degeneration of the renal epithelial cells, of pus-corpuscles, or of tumor-particles is taking place in the urinary tract. The fat-droplets may then be found floating in the urine or attached to or imbedded in any morphologic elements that may be present. Lipuria may also occur when abnormally large quantities of fat are circulating in the blood. It is thus observed after the administra-

tion of cod-liver oil in large quantities, following oil inunctions, in cases of fracture of the long bones with extensive destruction of the bone-marrow, in cases of eclampsia, as also in such diseases as diabetes mellitus, chronic alcoholism, phthisis, obesity, leukæmia, in certain mental diseases, in affections of the pancreas and heart, etc.

The term chyluria or galacturia has been applied to a condition in which a turbid urine presenting the macroscopic appearance of milk is excreted. Upon microscopic examination it may be demonstrated that the turbidity in such cases is owing to the presence of innumerable highly refractive globules of fat, which may be removed from the urine by shaking with ether. Of morphologic constituents leucocytes are occasionally encountered in large numbers. Red blood-corpuscles are also seen at times, and when present in large numbers impart a rose-color to the urine. Fibrinous coagula are often observed when the urine has stood for some time, and the entire bulk of urine may even become transformed into a gelatinous mass. Albumin is present in most cases in the absence of other constituents pointing to renal disease, such as tube-casts and renal epithelial cells. Leucin, tyrosin, and cholesterin may at times also be present, particularly the latter. It was formerly quite generally accepted that this condition was due to the presence of the filaria sanguinis hominis; but while filariæ are undoubtedly present in the blood in the majority of instances, and may also be present in the urine, it has been demonstrated that cases occur in which filariasis does not exist, and Götze expressed the opinion that chyluria may be owing to a distinct anatomical lesion affecting the renal parenchyma. Further observations, however, are necessary, in order to clear up not only the etiology of the disease, but also the manner in which fat and albumin enter the urine.

Ferments. Ferments may be demonstrated in every urine both under physiologic and pathologic conditions, but are of little clinical importance, excepting, perhaps, pepsin, which is said to be absent in cases of typhoid fever, carcinoma of the stomach, and possibly also in nephritis. In order to demonstrate its presence a small flake of fibrin is placed in the urine, and after several hours removed to a 2 to 3 p. m. solution of hydrochloric acid. The pepsin, if present, will have become deposited upon the fibrin, and cause the digestion of the latter in the hydrochloric-acid solution. Diastase, a milk-

curdling ferment, and one causing the decomposition of urea into carbon dioxide and ammonia have also been observed.

Gases. Every urine contains a small amount of gases, notably carbon dioxide, oxygen, and nitrogen, which may be withdrawn by means of an air-pump. In pathologic conditions sulphuretted hydrogen is at times also found, constituting the condition known as *hydrothionuria.* It is curious to note in this connection that *indigosuria* has at times been observed to accompany the hydrothionuria. That the latter condition is the result of bacterial activity was shown by Müller, and the simultaneous occurrence of indigo and sulphuretted hydrogen would make it appear that the former arises under the same or similar conditions as the latter. The occurrence of sulphuretted hydrogen, moreover, is of interest, in so far as a retention of the same within the body may exert a toxic action. It is not probable that the presence of sulphuretted hydrogen is due to an abnormal communication between the gut and the urinary passages, and it would appear more likely to be derived from the intestinal tract by a process of endosmosis.

In order to test for sulphuretted hydrogen a strip of filter-paper moistened with a solution of subacetate of lead and sodium hydrate is suspended to a cork, and the tube or vessel containing the urine closed with this, when in the presence of the gas the paper will be colored a gray or black.

Ptomaïns. Toxic substances of a basic nature are found only in traces in normal urines. In pathologic conditions, however, and especially in the acute febrile diseases, such as typhoid fever, pneumonia, pleurisy, and acute yellow atrophy, large amounts may be found, and appear to be identical with those obtained from putrefying albuminous material. Bouchard pointed out that these substances are in all probability formed in the lower portion of the intestinal tract. Diamines, viz., putrescin and cadaverin, have been found in the urine in cases of cholera Asiatica, pernicious anæmia, and in connection with cystinuria. Ptomaïns in notable amounts have also been demonstrated in the urine of maniacs, and the question of autointoxication with substances of this character as an etiologic factor in mental diseases is prominently engaging the attention of alienists at the present time. The whole subject is one of the utmost importance, but, as yet, it must be confessed, wrapped in the deepest obscurity.

In order to demonstrate the presence of ptomaïns in the urine,

the methods suggested by Brieger, Stass-Otto, and Gautier may be employed, of which the author can recommend that of Gautier particularly.

Sediments.

In the chapter treating of the general physical characteristics of the urine it was stated that on standing every urine gradually becomes cloudy, owing to the development of the so-called nubecula, which was shown to consist of a few mucous corpuscles, some pavement epithelial cells derived from the urinary and genital passages, and under certain conditions of a few crystals of uric acid, of oxalate of calcium, or both. It was further pointed out that owing to a diminution in the acidity of the urine on standing, in consequence of an interaction between the neutral urate of sodium and the acid phosphate of sodium, a sediment is thrown down which consists of acid urate of sodium, and at times of free uric acid (see Reaction). Should the reaction of the urine upon being voided be alkaline, however, a condition which may occur physiologically, when it is dependent upon the ingestion of large quantities of vegetables rich in organic salts of the alkalies, but which may also be due to ammoniacal fermentation, those constituents of the urine which are held in solution merely in consequence of the presence of acid sodium phosphate are thrown down. In the latter case the sediment consists essentially of calcium, magnesium, and ammonium salts. Crystals of ammonio-magnesium phosphate, it is true, may also be observed in alkaline urines of the first variety, but are then almost always due to an increased elimination of ammonia, and hence rarely observed in physiologic conditions.

Normally calcium is found only in combination with phosphoric acid and carbonic acid. Of the three possible calcium salts of phosphoric acid—*i. e.*, $Ca_3(PO_4)_2$, $CaHPO_4$, and $Ca(H_2PO_4)_2$—only the former two are found in an alkaline urine, while they may be observed also in specimens which are either neutral or at least but faintly acid. The acid calcium phosphate, $Ca(H_2PO_4)_2$, is seen but rarely in sediments, and its occurrence always presupposes the existence of a high degree of acidity, being precipitated together with uric acid, and under similar conditions. Calcium carbonate, $CaCO_3$, is seen only in neutral or alkaline urines. As soon as ammoniacal fermentation has begun, ammonium salts are, of course, formed, viz., ammonium urate and ammonio-magnesium phosphate.

The following table shows the various mineral constituents which are usually observed in sediments, the reaction of the urine being in every case the all-important factor:

Reaction acid.

Uric acid.
Urate of sodium.
Oxalate of calcium.
Primary calcium phosphate.
Ammonio-magnesium phosphate.

Reaction alkaline (referable to fixed alkalies).

Secondary calcium phosphate.
Tricalcium phosphate.
Calcium carbonate.
Ammonio-magnesium phosphate.

Reaction alkaline (referable to ammonia).

Ammonium urate.
Ammonio-magnesium phosphate.
Tricalcium phosphate.
Calcium carbonate.

In pathologic conditions still other unorganized substances may be observed in urinary sediments, viz., cystin, xanthin, tyrosin, hippuric acid, indigo, urorubin, bilirubin, hæmatoidin, magnesium phosphate, calcium sulphate, cholesterin, leucin, tyrosin, fats, ammonium and magnesium sulphate. Of these cystin, xanthin, hippuric acid, tyrosin, calcium sulphate, bilirubin, hæmatoidin, magnesium phosphate, leucin, and the soaps of magnesium and calcium occur only in acid urines, while indigo, urorubin, and cholesterin are usually found only in alkaline specimens. Before considering these various possible constituents in detail a few words regarding sediments in general and the method to be followed in their microscopic examination may not be out of place.

An idea of the nature of a deposit may often be formed by simple inspection, especially if the reaction of the urine be known.

A crystalline sediment, presenting a brick-red color and appearing to the naked eye like cayenne pepper, observed at the bottom of the vessel, is usually referable to uric acid. On the other hand, a deep red, amorphous deposit occurring in an acid urine will consist essentially of urates, the color in this case, as in the former, being due to uroerythrin. Further proof is hardly required. Should any doubt be felt, however, it will only be necessary to heat the urine, when

the deposit will be seen to dissolve. A white, flocculent sediment in an alkaline urine is usually referable to a mixture of phosphates, carbonates, and alkaline urates, and will dissolve without difficulty upon the addition of acetic acid, while it remains unaffected by heat.

A sediment, consisting of pus, occurring in alkaline urines is frequently mistaken for a phosphatic deposit by the beginner. Aside from a microscopic examination this question may be settled by the addition of a small piece of caustic soda, and stirring, when in the presence of pus the liquid becomes mucilaginous and ropy. If much pus be present, a tough, jelly-like mass will be formed, which escapes from the vessel *en masse* when the urine is poured out. Such a sediment, moreover, does not disappear upon the addition of an acid, and is rendered still more dense upon the application of heat.

Blood, when present beyond traces, may also be recognized.

Reliance should, however, not be placed upon the macroscopic appearance of a sediment to the exclusion of a careful microscopic examination, as those constituents, particularly the morphologic elements of a sediment, which are of more especial importance, can only be demonstrated in this manner. As a general rule, moreover, it may be said that the unorganized elements of a deposit are usually of little clinical interest

Students are frequently in the habit of diagnosing an excessive, normal, or subnormal elimination of one or another urinary constituent from the result of a microscopic examination. This is unwarrantable, and it should always be remembered that no conclusions whatsoever can be drawn in this manner as to the amount actually eliminated, for nothing would be more erroneous, for example, than to infer an excessive excretion, not to speak of an excessive production, of uric acid or oxalic acid from the fact that crystals of these substances are seen in large numbers under the microscope. Again and again are cases observed in which an excessive elimination of uric acid, oxalic acid, or phosphates is diagnosed by mere inspection, and in which a careful chemical analysis shows not only no increase, but even a diminution of the normal quantity.

A urine which is turbid when passed may be examined microscopically at once. As a rule, however, it is necessary to wait until a sediment has formed. The advice is usually given to allow the specimen to settle in a conical glass, to decant off the supernatant fluid as soon as a sufficient deposit has been obtained, and to examine a drop of the latter upon a slide covered with a cover-

glass. This recommendation is a good one, and is usually followed. Not infrequently, however, it is necessary to wait for twenty-four hours or even longer, until a sufficient deposit has formed; but even when the urine is kept covered it will frequently be found that ammoniacal fermentation has taken place, rendering the microscopic examination decidedly unsatisfactory. The urine should hence be kept in a clean and well-stoppered bottle until the desired deposit has formed. A small amount is then removed by means of a *clean* pipette carried down to the sediment with the distal end tightly closed with the finger, care being taken not to allow the urine to *rush* into the tube by suddenly releasing the pressure, but withdrawing only a small amount, just sufficient for an examination. This is then spread over a *clean slide* that has been moistened upon its surface by the breath, when the specimen may be examined at once. *Covering the specimen with a slip is not only unnecessary, but even undesirable, crushing being thus avoided, while at the same time a much larger field is offered to observation at one time. A low power of the microscope should always be employed, and the high power reserved entirely for more detailed examination.*

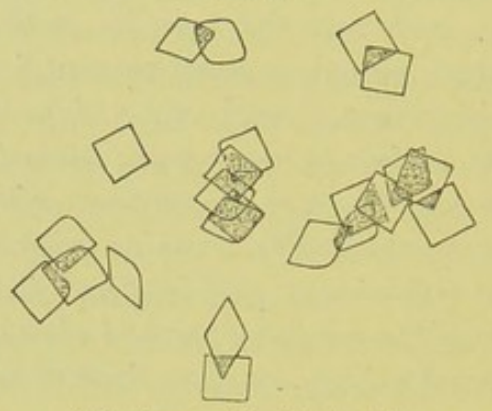
MICROSCOPIC EXAMINATION OF THE URINE.

Of late years the centrifugal machine has been applied to urinary examinations, and whenever it is desired to obtain a deposit at once, or whenever a deposit separates out so slowly as to endanger the integrity of the urine, an apparatus of this kind will be found very convenient. Daland's *hæmatokrit* is furnished with an attachment for this purpose.

Non-organized Sediments. SEDIMENTS OCCURRING IN ACID URINES. *Uric acid.* The form which uric-acid crystals may present in a deposit varies greatly, the most common being the so-called whetstone-form shown in Fig. 89. The crystals may occur singly or arranged in groups. Accidental impurities, such as threads or hairs, are at times covered with such crystals, forming long cylinders. When presenting this form their presence can generally not be determined macroscopically. Very frequently, however, uric acid crystallizes out in the form of large rosettes composed of tube-shaped or long-pointed crystals, presenting a deep-red color, referable to uroerythrin, when they are often visible to the naked eye, forming the well-known *brick-dust sediment* at the bottom of the

vessel. While it is generally stated that uric-acid crystals may always be recognized by their color, varying from a light yellow to a dark brown, the author has repeatedly observed uric acid in sediments, in which the crystals, which in such cases formed small rhombic plates with rounded edges, occurring singly or several joined together, were absolutely devoid of coloring-matter, as far as a microscopic examination went (Fig. 99). Uric-acid "dumb-bells" are also at times observed, and may be mistaken for calcium oxalate.

FIG. 99.



Colorless crystals of uric acid.

A uric-acid sediment is observed in cases in which an increased excretion of uric acid occurs, but it should be remembered that, as a rule, it is not permissible to infer an increased production or elimination from the presence of an abundant deposit of this substance alone. Brick-dust sediments are frequently observed in the urine during cold weather; but it would be erroneous to infer an increased elimination from such an occurrence, as the phenomenon in nine cases out of ten is explained by the fact that uric acid is far less soluble in cold than in warm water. During the summer months, for the same reason, a deposit of uric acid is less frequently observed, although an increased amount may nevertheless be present, being held in solution owing to the higher temperature. The more concentrated the urine and the more uric acid it contains, the more readily will such a deposit occur. Whenever more water is eliminated through other channels than is consumed or at least absorbed from the intestinal mucosa, such deposits will occur, and are hence noted after profuse perspiration, following severe muscular exercise, in acute rheumatism with copious diaphoresis, acute gastritis and enteritis, profuse diarrhœa, during the crisis of pneumonia, par-

ticularly if accompanied by much sweating, etc. In all these conditions, however, an increased elimination of uric acid does not necessarily take place, the all-important factors being the reaction of the urine, its degree of concentration, and the surrounding temperature. On the other hand, uric-acid sediments are frequently observed in cases in which uric acid is actually *eliminated* in increased amounts. From what has been said, however, it is clear that the occurrence of such deposits is usually not of much diagnostic interest.

Should formed concretions of uric acid—*i. e.*, uric-acid gravel—be found in the urine, a direct indication is afforded to diminish the acidity of the urine and to increase the amount of water, so as to guard against the formation of a renal or vesical calculus.

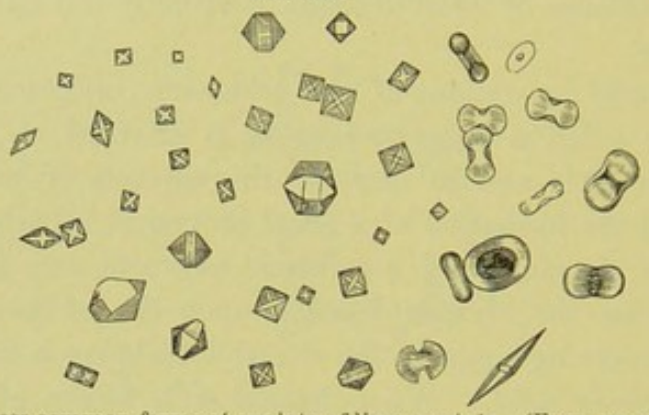
Chemically the nature of a uric-acid sediment may be recognized by the fact that the crystals dissolve upon the addition of sodium hydrate, reappearing again in the rhombic form upon neutralization with hydrochloric acid. When heated with dilute nitric acid the beautiful red color of ammonium purpurate is obtained upon the subsequent addition of ammonia (murexid test), as described elsewhere (see p. 355).

Amorphous urates. Sodium and potassium urates frequently, especially in fevers, form sediments of such density that upon microscopic examination it is almost impossible to discern anything but innumerable amorphous granules scattered over the entire microscopic field in a most irregular manner, and obscuring all other elements that may at the same time be present. Cells or casts that might possibly be discovered will frequently be seen to be studded with these granules. In such cases it is best to heat the urine to a temperature of 50° C., and to filter it as rapidly as possible while still hot, the contents of the filter being subsequently used for microscopic purposes.

Urate sediments are always colored, the tint varying from a dirty brown to a bright brick-red, owing to the presence of uroerythrin. Difficulties can hence never arise in determining the nature of the sediment, as a colored deposit appearing in an acid urine, which dissolves upon the application of heat, cannot be due to anything but urates. If a drop of the sediment, moreover, is treated upon a slide with a drop of hydrochloric acid, some characteristic whetstone-crystals of uric acid will be seen to separate out, while the greater portion will appear in the form of rhombic tablets.

Calcium oxalate. This substance generally appears in urinary sediments in the form of small, colorless, highly refractive octahedra (Fig. 100), which vary greatly in size, some appearing as mere specks even under a comparatively high magnifying power, while others may attain the dimensions of a large leucocyte. Frequently one axis is longer than the other. From the fact that their diagonal

FIG. 100.



Less common forms of oxalate of lime crystals. (FINLAYSON.)

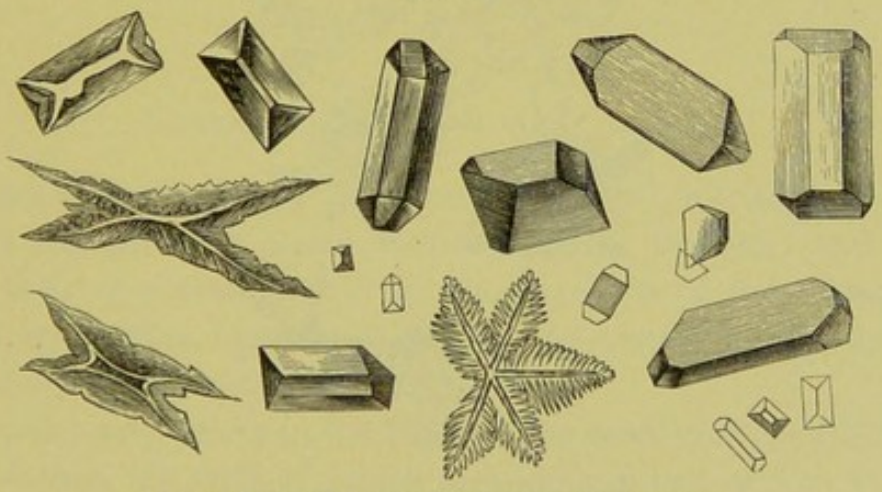
planes are very highly refractive, apparently dividing the superficial plane into four triangles, they have been compared to envelopes, and it is this envelope-form of the crystals which is especially characteristic. In the same specimen of urine so-called dumb-bell forms may be found, which appear to be made up of two bundles of needle-like crystals united in the form of the figure 8. The latter, according to Beale, originate in the uriniferous tubules, and are frequently found adherent to or imbedded in tube-casts. Other forms may also be found, and are shown in the accompanying figure. In this connection the author wishes to draw attention to the occurrence in urinary sediments of curious, highly refractive, more or less angular bodies, which do not present a well-defined crystalline form, and which he is inclined to regard as an amorphous form of calcium oxalate.

While the envelope crystals are highly characteristic and can hardly be mistaken for any other substance, the student may at times confound them with crystals of ammonio-magnesium phosphate. This error may be avoided if it be remembered that the calcium oxalate crystals are never so large as those of the magnesium salt, and that the latter dissolve upon the addition of acetic acid, in which calcium oxalate is insoluble. The distinction from uric acid, if we are dealing with the dumb-bell form, cannot always be made

by mere inspection. A drop of caustic soda should be added, which will dissolve the crystals if these be uric acid, while calcium oxalate remains unchanged. It has been pointed out that under strictly normal conditions a few isolated crystals of calcium oxalate may be found in the primitive nubecula, so that their presence in urinary sediments cannot be regarded as pathologic. After the ingestion of certain vegetables and fruits, notably rhubarb, garlic, asparagus, oranges, or following the continued administration of sodium bicarbonate or the salts of vegetable acids, calcium oxalate crystals may be observed in large numbers; so also in certain diseases, such as diabetes mellitus, catarrhal jaundice, phthisis, emphysema, etc.

As in the case of uric acid, no inference can be drawn from a microscopic examination of the sediment as to the quantity actually eliminated. The frequent occurrence of abundant sediments of this substance may, however, generally be regarded as abnormal, providing that such an occurrence cannot be explained by the nature of the diet. It is very suggestive to note the frequency with which such sediments are observed in certain cases of neurasthenia, associated with a mild degree of albuminuria, as also in various digestive neuroses. Finally, as in the case of uric acid, the possibility of the formation of renal calculi should be borne in mind whenever abundant sediments of calcium oxalate are encountered upon frequent examinations.

FIG. 101.

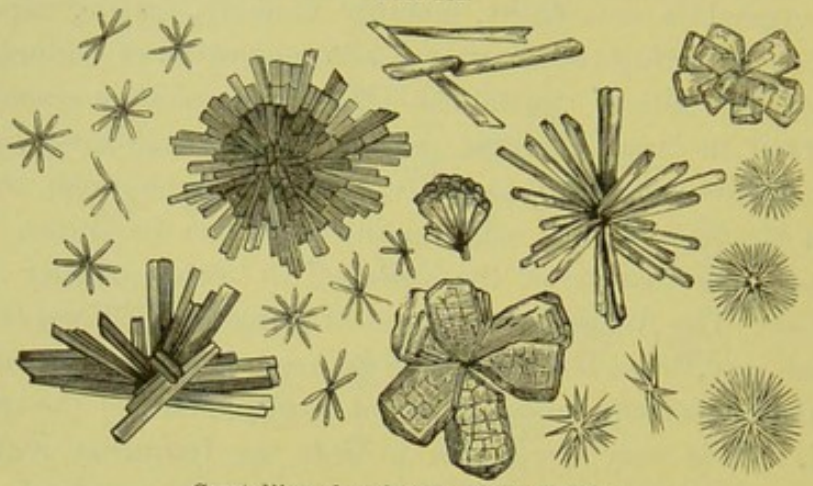


Various forms of triple phosphates. (FINLAYSON.)

Ammonio-magnesium phosphate, usually spoken of as triple phosphate, crystallizes in large prismatic crystals of the rhombic system, and is most abundantly observed in alkaline urines, but is also quite frequently seen in feebly acid specimens. Of the various forms seen, that resembling the lid of a coffin of the old-fashioned type is

the most characteristic. (Fig. 101.) The size which these crystals at times attain is quite considerable; very small specimens, however, also occur which could possibly be mistaken for oxalate of calcium, but from which they are readily distinguished by the ease with which they dissolve in acetic acid, as has already been pointed out.

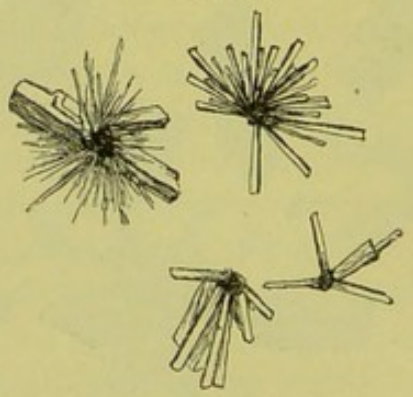
FIG. 102.



Crystalline phosphates. (FINLAYSON.)

Here as elsewhere it should be remembered that no conclusions as to the amount actually eliminated can be drawn from a microscopic examination, and the diagnosis "Phosphaturia" should only be based upon the results of a quantitative anaylsis.

FIG. 103.



Monocalcium phosphate crystals.

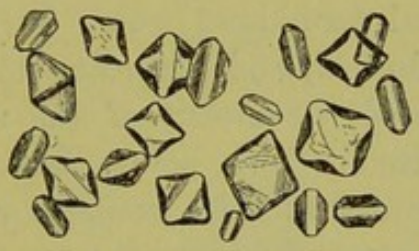
Monocalcium phosphate crystals are rarely seen and only in specimens presenting a highly acid reaction, when uric-acid crystals are also frequently observed in large numbers. The author observed but three cases of this kind, occurring in patients the subjects of functional albuminuria. The urine was highly acid, in one case of

a sp. gr. of 1.036, and on standing deposited a sediment which consisted largely of monocalcium phosphate crystals (Fig. 103), with a considerable number of uric-acid crystals, from which they are readily distinguished by the absence of pigment and their solubility in acetic acid.

Neutral calcium phosphate. These crystals may be found in alkaline, neutral, and feebly acid urines. They are at times of large size, but more commonly acicular, occurring either singly or united together in a star-like manner (Fig. 102). They are colorless, readily soluble in acetic acid, and insoluble in warm water, so that they can be easily distinguished from uric acid.

Basic magnesium phosphate crystals, occurring in the form of large, highly refractive plates (Fig. 104), are at times seen in alkaline, neutral, or faintly acid and highly concentrated urines. They are readily recognized by treating a drop of the sediment upon the slide with a drop of ammonium carbonate solution (1 : 4), when the crystals become opaque and their edges assume an eroded aspect. In acetic acid they dissolve with ease and may then be reprecipitated by means of sodium carbonate.

FIG. 104.



Basic phosphate of magnesia crystals. (V. JAKSCH.)

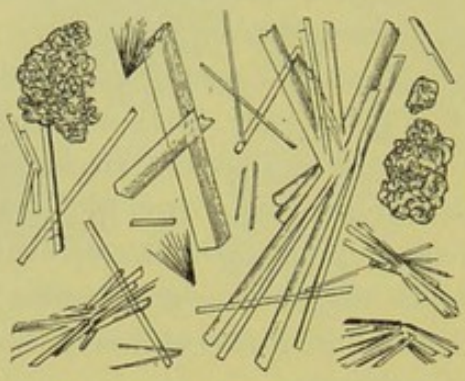
Hippuric-acid crystals have been observed, although rarely, in urinary sediments in acute febrile diseases, diabetes, and chorea, while their occurrence following the ingestion of large amounts of prunes, mulberries, blueberries, or the administration of benzoic acid and salicylic acid is more common.

Hippuric acid occurs in the form of fine needles or rhombic prisms and columns, the ends of which terminate in two or four planes, at times resembling the crystals of ammonio-magnesium phosphate and of uric acid. From the former they may be readily distinguished by their insolubility in hydrochloric acid, and from the latter by the fact that they do not give the murexid reaction when treated with nitric acid and ammonia (see p. 355). In the case of urines rich in hippuric acid, in which this does not appear in the sediment, it is

well to add a small amount of hydrochloric acid, when the crystals will gradually separate out. As yet their presence does not appear to possess any clinical significance.

Calcium sulphate in the form of long, colorless needles or elongated prismatic tablets (Fig. 105), has been observed in urinary sediments in only two cases. In both cases the urine, especially on standing, deposited a milky-looking sediment, the reaction being strongly acid. It may be recognized by its insolubility in acids and ammonia.

FIG. 105.



Calcium sulphate crystals. (V. JAKSCH.)

Cystin, the chemical formula of which is $(C_3H_6NSO_2)_2$, must be regarded as an amido-acid, and, according to the observations of Baumann, as a normal constituent of the urine. The quantity eliminated in the twenty-four hours, however, is very small, amounting to not more than 0.01 gramme pro liter. In urinary sediments cystin is never found under normal conditions, while pathologically its occurrence appears to be intimately associated with the simultaneous formation of certain *diamines*. These, viz., putrescin, cadaverin, and a third diamine, isomeric with the latter, are formed in the intestinal tract, and are eliminated in the urine as well as in the feces. There can be little doubt that the causes which give rise to the formation of the one are also responsible for the presence of the other, and that the occurrence of cystinuria is thus dependent to a large degree at least upon a specific form of intestinal putrefaction. Beyond this, however, practically nothing is known of the relation existing between these bodies.

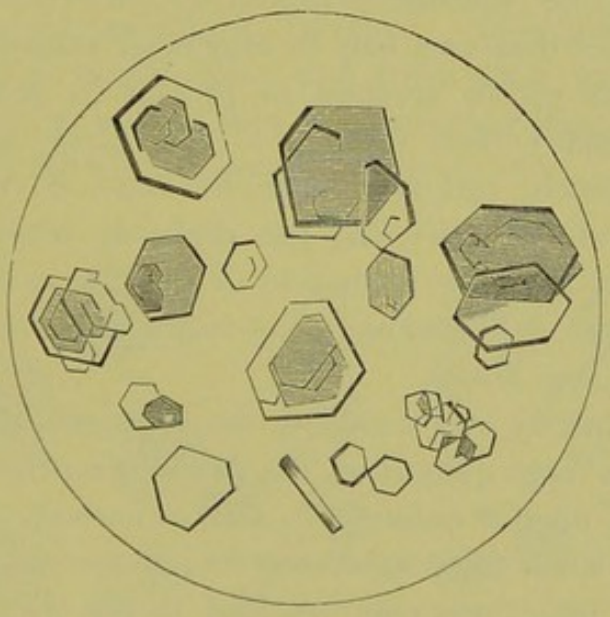
Clinical interest in connection with cystinuria centres in the frequent association of cystin sediments with cystin gravel or calculi, but it is curious to note that the cystinuria, even after removal of the calculus, may persist for years without giving rise to symptoms

denoting the existence of a pathologic process. Cystin concretions and calculi must be regarded as medical curiosities, as not more than fifty cases of this kind have been described.

Urine containing cystin in pathologic amounts may be of normal appearance, reaction, odor, and specific gravity, but is often described as presenting a yellowish-green color, a higher specific gravity than normal, and a curious odor. When undergoing putrefaction a marked odor of sulphuretted hydrogen develops, owing to decomposition of the cystin. When treated with acetic acid, a white, crystalline sediment separates upon standing, which is soluble in ammonia, and from which the crystals usually observed in the sediment of the native urine may be obtained upon evaporating the ammonia.

The appearance of these crystals (Fig. 106), which take the form of small, colorless, hexagonal plates, and are frequently superimposed upon one another, is quite characteristic. If any doubt exist, it should be remembered that uric acid, with certain forms of which cystin might possibly be confounded at first sight, gives the murexid reaction and is insoluble in hydrochloric and oxalic acids, in which cystin dissolves with ease, as also in ammonia, from which the crystals separate out again upon evaporation, as just described.

FIG. 106.



Crystals of cystin spontaneously voided with urine. (ROBERTS.)

Cystin crystals, when tested upon platinum foil, burn with a bluish-green flame without melting.

To determine the amount of cystin, the urine should be treated with an excess of acetic acid, as directed, and the sediment which

forms upon standing filtered off, washed with water, dried over sulphuric acid, and weighed. This method is not very exact, as not all the cystin is obtained, but it is the only one available. Should uric acid be present in the sediment, the cystin must be separated by dissolving it in ammonia. Mucin may be removed by previously adding neutral acetate of lead.

Leucin and tyrosin, which belong to the group of amido-acids, being represented by the formulæ $C_6H_{13}NO_2$ and $C_9H_{11}NO_3$, respectively, are never found in the urine under normal conditions. Their presence, indeed, may be regarded as pathognomonic of acute yellow atrophy of the liver, excepting, perhaps, some rare cases of acute phosphorus-poisoning associated with hepatic atrophy, notwithstanding statements to the contrary, according to which these substances may also be encountered in cases of acute hepatic atrophy due to other causes, in typhoid fever, variola, etc. In two cases of so-called malignant jaundice, in which a most rapidly progressing atrophy of the liver was noted, the author was unable to detect either of these bodies, notwithstanding a most careful chemical examination. In acute phosphorus-poisoning, moreover, leucin and tyrosin are not as a general rule found, so that in the differential diagnosis between this condition and acute yellow atrophy the presence of these bodies may be regarded as indicating the existence of the latter disease. The fact that urea may be altogether absent from the urine in cases of acute yellow atrophy, or present in greatly diminished amount, has already been referred to (see Urea, p. 329), and the elimination of leucin and tyrosin, in its stead, as it were, has been regarded not only as indicating the probable origin of urea from amido-acids, but also the formation of urea, to a large extent, at least, in the liver. The albuminous origin of these substances has also been noted (see Urea).

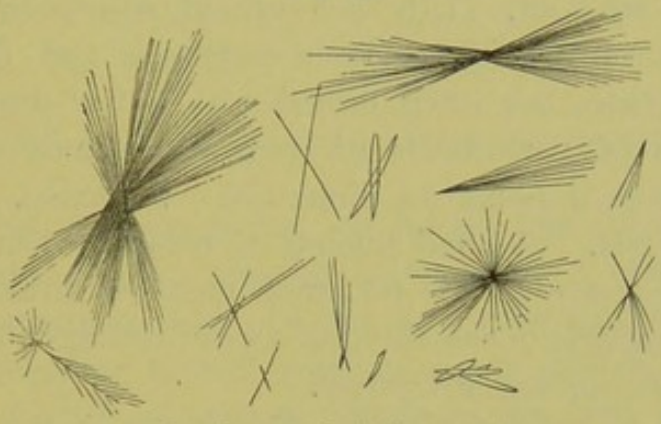
As leucin is hardly ever found in the sediment, and tyrosin only when present in large quantities, the urine in every case should first be concentrated upon a water-bath, and examined on cooling. At times, however, when these substances are present in only very small quantities, this procedure may not lead to the desired end, and in doubtful cases the following method should be employed :

The total amount of urine voided in twenty-four hours is precipitated with basic acetate of lead and filtered, when the filtrate, from which the excess of lead has been removed by means of sulphuretted hydrogen, is evaporated to as small a volume as possible and set

aside for crystallization. The residue thus obtained is then microscopically examined, and if crystals be detected which answer the description of tyrosin and leucin, they should be subjected to further chemical tests.

Tyrosin crystallizes in the form of very fine needles (Fig. 107), which are usually grouped together in sheaves or bundles, crossing each other at various angles. They are insoluble in acetic acid, but soluble in ammonia and hydrochloric acid.

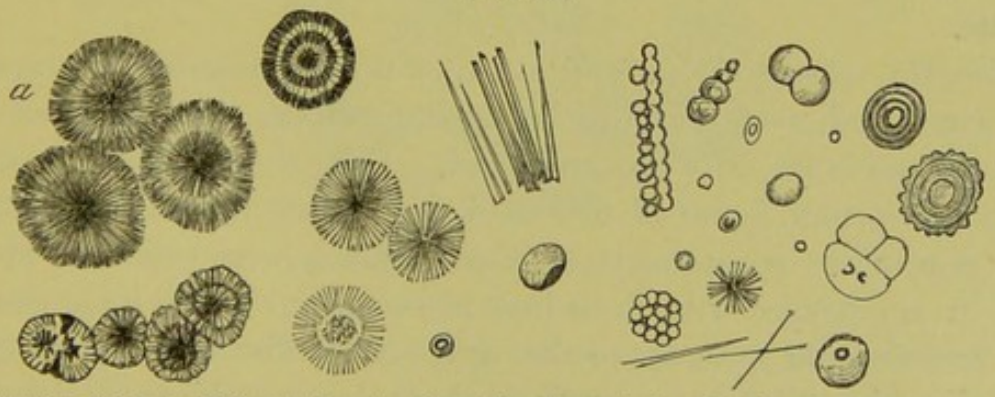
FIG. 107.



Tyrosin crystals. (CHARLES.)

Leucin (Fig. 108) occurs in the form of spherules of variable size, which closely resemble globules of fat, but may be distinguished from these by their insolubility in ether. They present a more or less pronounced brownish color, and upon close examination concentric striations as well as very fine radiating lines can at times be made out, the latter being especially characteristic.

FIG. 108.



Crystals of leucin (different forms). (Crystals of creatinin chloride of zinc resemble the leucin crystals depicted at *a*.) The crystals figured toward the right consist of comparatively impure leucin. (CHARLES.)

If crystals resembling tyrosin and leucin be found, the following procedure should be employed:

In order to separate the leucin from the tyrosin, the residue is treated with a small amount of alcohol, in which leucin is more readily soluble than tyrosin.

Tests for tyrosin. The sediment is filtered off, washed with water, and dissolved in ammonia, to which a little ammonium carbonate has been added. This solution is allowed to evaporate, leaving the tyrosin behind.

Piria's test. A bit of the tyrosin is moistened on a watch-crystal with a few drops of concentrated sulphuric acid, covered, and set aside for half an hour. It is then diluted with water, heated, and while hot saturated with calcium carbonate and filtered. The filtrate is colorless, but when heated with a few drops of a very dilute solution of perchloride of iron, which must be free from hydrochloric acid, it assumes a violet tint (v. Jaksch).

Hoffmann's test. A small amount of tyrosin, when dissolved in hot water and treated, while hot, with mercuric nitrate and potassium nitrite, imparts to the solution a beautiful dark-red color, and yields a voluminous red precipitate.

Tests for leucin. Scherer's test. To test for leucin, this is separated from tyrosin, as described, by the addition of a little alcohol. The alcohol is allowed to evaporate, and a portion of the residue treated upon platinum-foil with nitric acid, when a colorless residue is obtained, which, upon the application of heat and a few drops of a solution of sodium hydrate, forms a droplet of an oily fluid which does not adhere to the platinum.

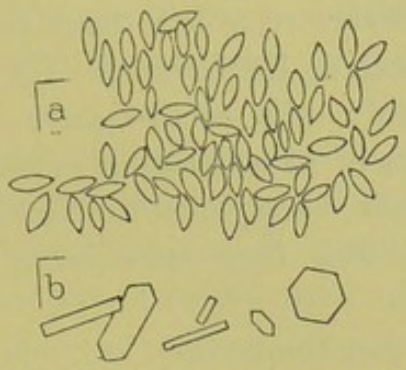
Hofmeister's test. A small amount of leucin dissolved in water causes a deposit of metallic mercury when heated with mercurous nitrate.

Xanthin crystals (Fig. 109) are very rarely observed in urinary sediments, and, as far as can be ascertained, the case observed by Bence Jones is the only one on record. Care should be had not to confound certain forms of uric acid with xanthin, and the author well remembers an instance in which crystals were observed identical in appearance with those here pictured, but which upon chemical examination proved to be uric acid. *The necessity of disregarding the statement generally made that uric-acid crystals found in urinary sediments are invariably colored cannot be insisted upon too strongly.* It has been stated elsewhere that colorless uric-acid crystals may be encountered, and in the case just cited this was observed.

Clinically, xanthin sediments are of interest only in so far as this

substance may give rise to the formation of calculi; in the case observed by Bence Jones attacks of renal colic had occurred several years previously.

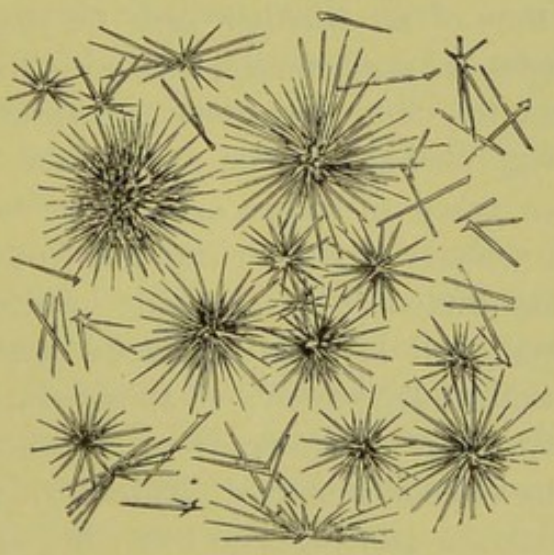
FIG. 109.



a. Crystals of xanthin (SALKOWSKI); b. Crystals of cystin (ROBIN).

Soaps of lime and magnesia. v. Jaksch has pointed out that in various diseases crystals may be found which "closely" resemble tyrosin in appearance, and pictures such crystals (Fig. 110), which from their behavior toward reagents he is inclined to regard as calcium and magnesium salts of certain higher fatty acids.

FIG. 110.



Lime and magnesium soaps. (V. JAKSCH.)

Should any doubt arise, the question may be readily decided by a chemical examination (see tests for tyrosin and fatty acids).

Bilirubin crystals in the form of yellow or ruby-red rhombic plates or needles, as well as amorphous granules, have been seen in the urine in rare cases, but are of no special interest. They are easily soluble in alkalies and chloroform, but not in ether. When treated

upon a slide with a drop of nitric acid, a green ring will be seen to form around them (Gmelin's reaction).

Hæmatoidin crystals, which cannot be distinguished from bilirubin by the microscope, and also resemble the latter chemically to such a degree that Hoppe-Seyler regarded them as practically identical, are almost as rarely seen as the former. They may be found either free or imbedded within cells or tube-casts in cases of scarlatinal nephritis, the nephritis of pregnancy, in granular atrophy and amyloid degeneration of the kidneys, and in carcinoma of the bladder, of which latter condition they have been regarded by some as pathognomonic.

It has been stated that hæmatoidin crystals may be distinguished from bilirubin crystals by the appearance of a transient blue color when treated with nitric acid, but v. Jaksch rightly regards this reaction as of doubtful value, as a blue color is similarly obtained when bile-stained elements of a urinary sediment are treated in this manner.

Fat. When small, strongly refractive globules of fat, which may be readily recognized by their solubility in ether, are observed either floating on top of the urine or held in suspension, it is necessary to ascertain first of all whether such fat may not have been introduced into the urine accidentally, owing to the use of a bottle or vessel not absolutely clean, previous catheterization, etc. The diagnosis "Lipuria" should only be made when all possible precautions have been taken to insure against the *accidental* presence of this substance. Every physician who has frequently occasion to examine urines has undoubtedly met with instances in which fat-globules were found, and in which a careful inquiry showed that these were only accidentally present. Lipuria—*i. e.*, an elimination of fat usually in the form of minute droplets floating in the urine—has been noted in various cachectic conditions, in cases of heart-disease, affections of the pancreas and liver, in gangrene, and pyæmia, associated with diseases of the bones, especially following fractures, in diseases of the joints, etc. Fat has also been observed in the urine following the ingestion of large amounts of cod-liver oil and inunctions with fats and oils.

In cases of fatty degeneration of the kidneys, in Bright's disease, phosphorus-poisoning, etc., minute droplets of fat are seen in the epithelial cells and tube-casts—so minute at times that they appear as mere granules. The true nature of these may be recognized by

their solubility in ether, benzol, chloroform, carbon bisulphide, xylol, etc., and the fact that they are colored black when treated with a 0.5 to 1.0 per cent. solution of osmic acid, and red when a drop of tincture of alcanna is added to the specimen. The occurrence of fat-droplets in the morphologic elements of a urinary sediment should not, however, be regarded as constituting a form of lipuria.

The largest amounts of fat are observed in chyluria, a condition which is usually due to the presence of a distinct parasite in the blood, the filaria sanguinis hominis, or more rarely the distoma hæmatobium, which has been referred to in the chapter on Blood (see Chyluria).

Sediments Occurring in Alkaline Urines. *Basic phosphates of calcium and magnesium.* The most common sediments observed in alkaline urines consist of amorphous phosphates of calcium and magnesium. They are usually as abundant as the urate sediments mentioned, but may be readily distinguished from these by the fact that they do not dissolve upon the application of heat, but readily disappear upon the addition of acetic acid, and are never colored. In this manner it is also easy to distinguish such a sediment from one due to pus, with which it might possibly be confounded at first sight. Upon microscopic examination a drop of the sediment will be seen to contain innumerable transparent granules, scattered over the entire field, closely resembling those of urate of sodium and potassium.

Phosphate sediments are observed, as mentioned elsewhere, whenever the reaction of the urine is alkaline, be this owing to the presence of fixed alkalies or to ammoniacal fermentation.

Ammonium urate is only observed in urines which are undergoing ammoniacal fermentation. Its presence should always call for a careful investigation in order to ascertain whether this has taken place after the urine has been voided or before (see Reaction).

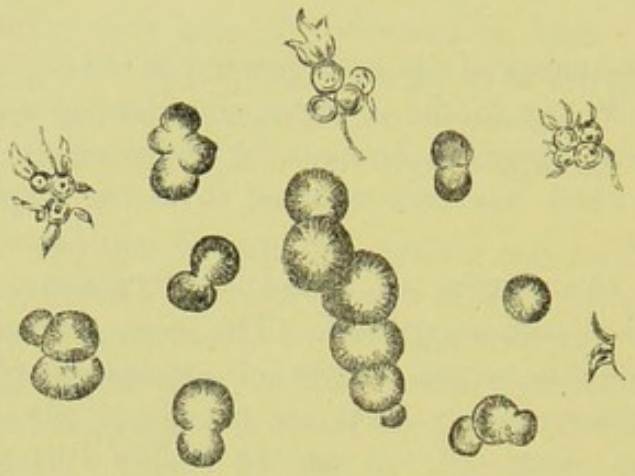
The salt occurs in the form of colored spherical bodies of variable size, which are frequently beset with prismatic spicules, and are not easily mistaken for any other substance which may be present in urinary sediments (Fig. 111). It is characterized, moreover, by its solubility in acetic and hydrochloric acids, and the subsequent separation of rhombic crystals of uric acid.

Magnesium phosphate has been described above (see p. 471).

Ammonio-magnesium phosphate. While the well-known coffin-lid-

shaped crystals are commonly seen in feebly acid urines, as pointed out, ammonio-magnesium phosphate presents a great variety of forms in alkaline urines, especially in specimens undergoing ammoniacal fermentation, those resembling flakes of snow being the most common (see Fig. 101).

FIG. 111.



Ammonium urate crystals.

Calcium carbonate occurs frequently in alkaline urines, appearing under the microscope as minute granules, occurring singly or arranged in masses; dumb-bell forms are also seen (Fig. 112). They may be recognized by the fact that they readily dissolve in acetic acid with the evolution of gas.

FIG. 112.



Calcium carbonate crystals.

Indigo in the form of delicate blue needles (Plate XIII.), arranged in a stellate manner or in plates, visible only with the microscope, is rarely seen, and a specimen, such as the one which v. Jaksch pictures, can only be regarded as a medical curiosity. In an amorphous condition, however, indigo may be met with in almost every stale urine, occurring in the form of small granules, and frequently staining morphologic elements that may be present a distinct blue. Sedi-

PLATE XIII.



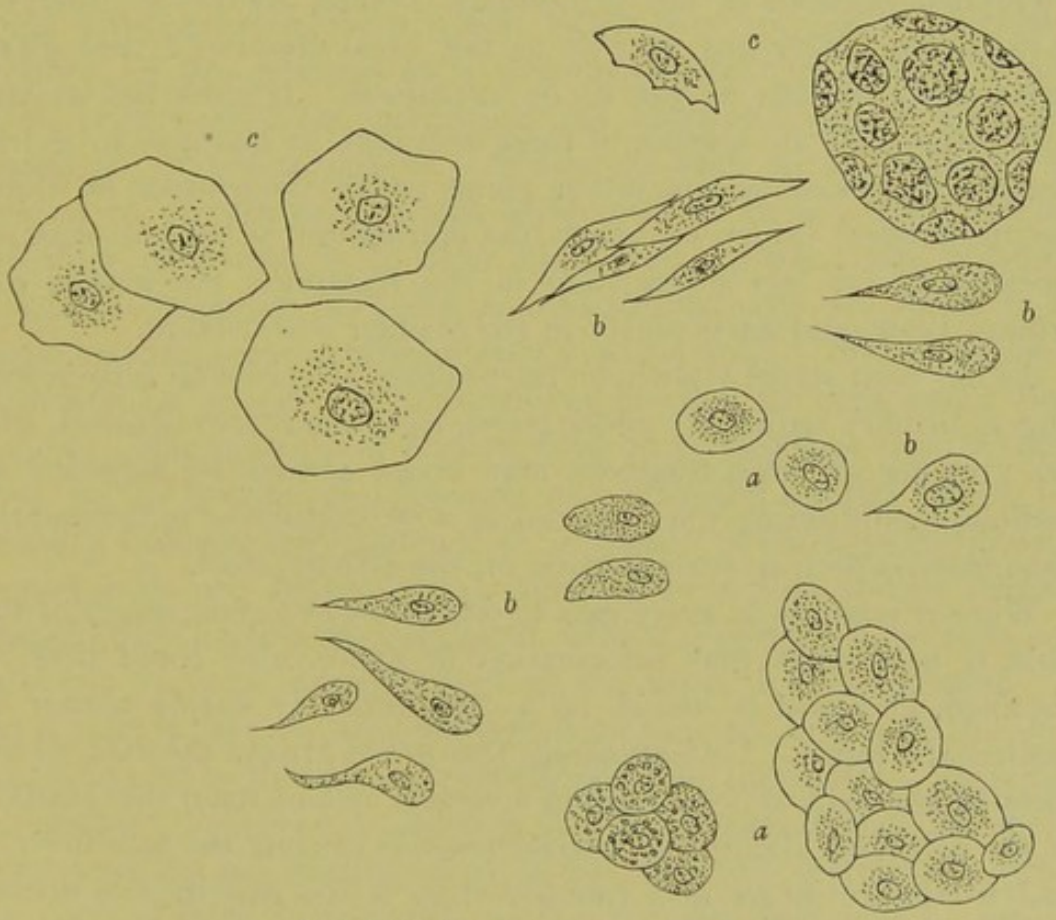
Indigo Crystals from a Urine Rich in Indican, after Standing for Eight Days at Ordinary Temperature. (V. Jaksch.)

ments which present a bluish-black color were already noted at the time of Hippocrates, and have since been described by numerous observers, although the true nature of the coloring-matter has only been determined within the last fifty years. Clinically the occurrence of indigo in the urine is of significance only in so far as renal calculi have been observed which consisted almost entirely of this substance. But little is known of the causes which give rise to the appearance of indigo in the urine, but there can be no doubt that its occurrence is referable to the action of certain micro-organisms upon urinary indican.

Organized Constituents of Urinary Sediments.

Epithelial Cells. (Fig. 113.) Bearing in mind the fact that desquamative processes are constantly going on in the epithelial

FIG. 113.



Epithelium from the urinary passages.
a. Round cells; *b*, conical and caudate cells; *c*, flat cells.

lining of the various cavities and channels of the body, one should expect to find in every urine representatives of the different forms

of epithelium occurring in the urinary organs, from the Malpighian tufts down to the meatus urinarius. To a certain extent this actually happens, and cells apparently derived from the meatus, the urethra, bladder, ureters, and pelvis of the kidneys may be met with in almost every specimen, although it may at times be difficult to refer the individual cells observed to their proper origin. Bizzozero even claims that it is impossible to distinguish between the cells of the bladder and those of the meatus and renal pelvis, while, as a class, they may readily be differentiated in most cases from the cells of the urethra, the ureters, the prepuce of the male and the vulva and vagina of the female. Cells from the uriniferous tubules of the kidneys, on the other hand, are seldom seen in normal urines, and when they do occur it is impossible to determine their exact origin; *i. e.*, the particular portion of the tubule from which they have been detached. Cells presenting the characteristic striated appearance seen in the irregular, and to a less evident degree in the convoluted portions of the uriniferous tubules, are never observed in the urine. This fact, as well as the usual absence of true glandular cells, remains as yet to be explained. It does not appear improbable that the absence of these cells may be referable to a less marked degree of desquamation going on in those parts, in which the mechanical injury to which the epithelium is subject must of necessity be far less severe than in the remaining portions of the urinary tract, and particularly in the bladder and urethra.

As has been stated elsewhere, the number of epithelial cells occurring in urinary sediments under physiologic conditions is small, and the presence of large numbers may hence always be regarded as pathologic, indicating the existence of a circulatory or inflammatory disturbance affecting some portion of the urinary tract.

Were it possible in every case to determine the exact origin of the cells, it is evident that information of great value could thus be obtained, and that it would be a comparatively simple matter to localize the lesion. Unfortunately this is not always possible, as the form of the cells is dependent to a certain extent upon the reaction of the urine, an alkaline or neutral reaction causing the cells to swell and to appear larger and rounder than is the case in acid urines. As has been mentioned, the cellular type is practically the same in the bladder, ureters, and pelvis of the kidneys.

Definite conclusions should hence be drawn only exceptionally from a microscopic examination alone, but there can be no doubt

that in conjunction with other factors and the clinical history the demonstration of a normal or increased number of epithelial cells may frequently be of decided value in a differential diagnosis, and taking these factors into consideration it may even be possible to localize the seat of the lesion. If attention be directed to the structure of the individual cell, and this holds good more especially for the cells derived from the uriniferous tubules, an idea may at times even be formed of the character of the lesion (see below).

Ultzmann recognizes three forms of epithelial cells which may be found in urinary sediments, viz.:

1. Round cells.
2. Conical and caudate cells.
3. Flat cells.

Round cells are usually derived from the uriniferous tubules and the deeper layers of the mucous membrane of the pelvis of the kidneys. In the urine they present a more or less rounded form and are provided with a distinct nucleus, being not much larger than pus-corpuscles, from which latter they may be distinguished readily by the presence of a well-defined nucleus, which in pus-cells becomes distinct only upon the addition of acetic acid, and, moreover, is polymorphous. Whenever such cells are found adhering to urinary casts, which latter may at times consist entirely of these structures, it is clear that they represent the glandular elements proper of the kidneys. As similar cells are found in the male urethra, some confusion may possibly arise. Should albumin, however, be present, the probabilities are that the cells are of renal origin. The presence of such cells in large numbers together with pus, in the absence of tube-casts and albumin, beyond traces, will usually indicate the existence of a simple pyelitis, particularly if round cells are found joined together in a shingle-like manner. Should the pyelitis be associated with a nephritis, tube-casts and albumin in large amounts will at the same time be present. In such cases it may be impossible to determine the origin of the cells, excepting of such that may be adhering to tube-casts. In simple circulatory disturbances affecting the renal parenchyma no special abnormalities can be discovered in the structure of the cells, while in cases of fatty degeneration of the kidneys they will be seen to contain fatty particles in greater or less abundance, so that it may be possible to determine the existence of degenerative processes which may be of inflammatory or non-inflammatory origin. The

same may be said to hold good if the epithelial elements are markedly granular and occur in fragments.

Conical and caudate cells are mostly derived from the superficial layers of the pelvis of the kidneys, and are hence seen especially in cases of pyelitis. Similar cells are also found in the neck of the bladder, and may usually be distinguished from those of the pelvis by the greater length of their processes.

Flat cells may come from the ureters, the bladder, the prepuce of the male, and the vulva and vagina of the female. These cells present the usual characteristics of squamous epithelium, being large, polygonal in form, and provided with a well-defined nucleus, the extra-nuclear protoplasm being only slightly granular. Other more or less rounded forms are also seen which are derived from the deeper layers of the mucosa, but are readily distinguished from the small round-cells of the kidneys proper. Irregular or conical cells, often provided with one or more protoplasmic processes, likewise come from the lower layer of the mucosa of the bladder and ureters.

While the cells of the bladder may thus be confounded with those of the ureters and vagina under the microscope, it is not likely that a vaginitis or vulvitis will be mistaken for a cystitis or a ureteritis. In doubtful cases specimens of urine should be procured by means of the catheter, care first being taken to thoroughly cleanse the vulva. The warped appearance so frequently seen in vaginal epithelial cells, and the fact that these often and indeed usually appear in masses, may further aid in the differential diagnosis.

It has been pointed out by Peyer that the presence of pavement-epithelial cells, together with mucus and leucocytes, in the urine of hysterical and anæmic girls may be regarded as indicating an irritated condition of the genitals, possibly in consequence of masturbation. Bearing in mind the moist and sensitive condition of the vulva of female masturbators, such a view appears plausible.

A ureteritis, notwithstanding the fact that the ureteral cells closely resemble those of the bladder, may be inferred indirectly, the presence of squamous cells in abundance pointing to a cystitis, a small increase in their number to ureteritis. In conclusion, it should be stated that the so-called mucous corpuscles present in every urine are nothing more than the youngest vesical cells.

From what has been said it is clear that, with due precautions and taking other factors into consideration, the discovery of epithelial

cells in large numbers in urinary sediments may be of decided value in diagnosis.

Leucocytes. Leucocytes are only encountered in very small numbers in normal urines. A marked increase should, hence, always be regarded as indicating the existence of disease somewhere in the course of the urinary tract, excepting in females, when their presence may be owing to an admixture of leucorrhœal discharge. In the latter case the source of the pus will generally be recognized by the simultaneous occurrence of pavement-epithelial cells of the vaginal type in correspondingly large numbers. In doubtful cases the urine should always be obtained with the catheter, care first being taken to thoroughly cleanse the vulva.

Occasionally the pus is derived from a neighboring abscess that has opened into the urinary passages.

The amount of pus found in urines may vary considerably. On the one hand, deposits several cm. in height are not at all uncommon, and closely resemble deposits of phosphates in appearance, for which they are indeed frequently mistaken; on the other hand, it may only be possible to discover its presence by means of the microscope, which should be employed in every case.

The appearance of the pus-corpuscles likewise varies in different cases: In acid urines their form is usually well preserved, and in feebly alkaline and neutral specimens it may even be possible to observe amœboid movements when the slide is carefully warmed. In alkaline urines, however, they usually swell up and become opaque, so that it is impossible to discern their nuclei unless they are treated with acetic acid. At other times, and particularly when pus has long remained in the body, as where a neighboring abscess has burst into the urinary passages, it may be almost impossible to make out a nucleus, and in extreme instances nothing but a mass of granular and fatty detritus is encountered.

While with a certain degree of experience it is hardly likely that a distinct sediment of pus will be mistaken for anything else, such as a deposit of phosphates, it should be remembered that if pus be exposed to the action of ammonia, or an ammonium salt, the pus-corpuscles become disintegrated. In such cases, as in cystitis, in which ammoniacal decomposition of the urine is taking place in the bladder, a deposit may be obtained which macroscopically resembles mucus, and in which pus-corpuscles may not even be demonstrable with the microscope. The sediment then escapes as a gelatinous,

slippery mass when the urine is poured from one vessel into another. Under such conditions recourse must be had to certain chemical tests, as a pyuria might otherwise be overlooked. To this end the following procedure, suggested by Vitali, may be employed:

The urine, after having been acidified with acetic acid, is filtered and the contents of the filter treated with a few drops of tincture of guaiacum which has been kept from the light, when in the presence of pus the filter-paper is colored a deep blue.

A solution of iodo-potassic iodide may be employed in less extreme instances. A drop of this solution is added to a drop of the sediment upon a slide, when the pus-corpuscles, owing to the presence of glycogen, are colored a dark mahogany-brown, while epithelial cells, with certain forms of which they might possibly be mistaken, assume a light color.

Donne's pus-test is based upon the fact that the transformation of pus into a gelatinous, mucus-like mass, observed in cases of cystitis, owing to the action of ammonium carbonate, may also be artificially produced by the addition of a small piece of caustic soda and stirring, when in the presence of pus in small amounts the liquid becomes mucilaginous and ropy, while a gelatinous mass is obtained if the pus be abundant.

From a clinical point of view it is most important to establish the source of the pus in every case of *pyuria*. This may at times be difficult, but the following data will be found of great value in a differential diagnosis:

1. In diseases affecting the renal parenchyma the amount of pus, as a rule, is small, except where a large abscess located in the kidney structure proper has suddenly burst into the pelvis of the kidney.

In uncomplicated cases it is a comparatively easy matter to recognize the renal origin of the pus, as other constituents, such as renal epithelial cells, and especially tube-casts, are usually present at the same time, and, as was noted in the case of renal epithelial cells, leucocytes are quite frequently found adhering to the tube-casts, and at times apparently composing these entirely, when they are spoken of as *pus-casts* (see Casts). In nephritis, according to Bizzozero, the number of pus-corpuscles stands in a direct relation to the intensity and acute character of the morbid process, the greatest numbers being found in cases of acute nephritis, while in the chronic forms their number is usually insignificant. Whenever in the course of a

chronic nephritis large numbers of pus-corpuscles appear in the urine, they may be regarded as indicating either an acute exacerbation of the disease or a complicating inflammation of some portion of the urinary tract. In such cases errors may be guarded against by carefully observing the number and character of the epithelial cells present at the same time, when it will often be found that what at first sight appears as an acute exacerbation of a chronic process, judging from the number of pus-corpuscles, is in reality a secondary pyelitis, ureteritis, or cystitis.

In cases of simple renal hyperæmia pus-corpuscles never occur in notable numbers.

2. In pyelitis the amount of pus eliminated may vary considerably, and at times even perfectly normal urine may be voided, probably owing to the fact that the ureter of the affected side, if the disease be unilateral, has become obstructed temporarily, when suddenly large quantities may again appear. The diagnosis of pyelitis is often difficult, and should be based not only upon the condition of the urine, but upon the clinical symptoms, a rule which, of course, holds good in other conditions as well. Very significant is the fact that the urine in pyelitis is usually acid, a point to be remembered in the differential diagnosis between this condition and cystitis, with which pyelitis is quite frequently confounded. A careful examination of the epithelial elements present in the urine may also be of value, and should never be neglected. Bacteria in large numbers are generally present.

When pyelitis is associated with nephritis it may at times be almost impossible to determine the origin of the pus, but if the rule set forth above be remembered, that in chronic nephritis the number of leucocytes is always small, it is not likely that a pyelitis will be overlooked, particularly if the clinical symptoms be taken into consideration.

Matters may become still more complicated when a cystitis is accompanied by a pyelitis or a pyelonephritis. Catheterization of the ureters, the feasibility of which, even in the male, has been clearly demonstrated by the late Dr. James Brown, should be resorted to, and it is highly desirable that this most valuable method of diagnosis should become common property as soon as possible. Fischl regards the presence of cylindrical masses composed of pus-corpuscles, formed in all probability in the papillary ducts, as highly characteristic of pyelitis. In the examination of

a number of cases of this kind the author, however, has never been able to demonstrate their presence.

3. A pyuria referable to ureteritis can hardly be diagnosed from the appearance of the urine, and in suspected cases catheterization of the ureters should be resorted to, which may possibly elicit some information of value.

4. In mild cases of cystitis pus may be altogether absent, while in the more severe forms its presence is constant. In cystitis the largest amounts of pus referable to disease of the urinary organs are observed, exceeded only in those rare conditions in which a neighboring abscess has suddenly discharged itself through the urinary passages.

As the urine in cystitis is usually alkaline, and always so in the more severe forms, the alkalinity being due to ammoniacal fermentation, it may happen, owing to the disintegrating action of ammonium carbonate upon the pus-corpuscles, that these may not even be demonstrable with the microscope, and that a gelatinous, mucoid sediment appears instead, which escapes from the vessel *en masse* when the urine is poured out. Vitali's test for pus (referred to on p. 486) should be employed in such cases.

5. In urethritis pus may be present in the urine in considerable amounts. The source of the pus is recognized by the fact that a drop may be manually expressed from the urethra, particularly in the morning upon awaking. Mucoid gonorrhœal threads—the "Tripperfäden" of the Germans—which are largely composed of pus-corpuscles will almost always be detected in the urine in such cases. In order to distinguish between a simple urethritis and a urethritis complicated with cystitis, the urine should be obtained in two portions and allowed to settle. In simple urethritis affecting the anterior portion of the urethra the first specimen is cloudy, while the second one is clear. If the urethritis, however, has extended to the neck of the bladder, in the absence of cystitis, while the first portion will, of course, be cloudy, the second portion may present a variable appearance, being clear at times and cloudy at others. This phenomenon is explained by the fact that a portion of the pus contained in the posterior portion of the urethra has found its way into the bladder. A cystitis may, however, be excluded by the acid reaction of the second specimen and the fact that the latter is never so cloudy as the first; while in cases of urethritis complicated with a purulent cystitis the second portion

of urine contains at least as much pus as the first, and usually more, owing to the pus, which is heavier than the urine, falling to the floor of the bladder, in which case also the last drops passed will often be found to be pure pus. The reaction of the urine, moreover, will then generally be alkaline.

6. A sudden elimination of large quantities of pus with a urine which up to that time has presented a normal or nearly normal appearance may almost always be referred to the rupture of a neighboring abscess into the urinary passages. Exceptions to this rule have been noted in rare instances in which large amounts of pus suddenly appeared, the origin of which could not be demonstrated upon post-mortem investigation. Whether such a phenomenon, as v. Jaksch suggests, is dependent upon "unusual conditions favoring diapedesis" remains an open question.

Red Blood-corpuscles. The presence of red blood-corpuscles in the urine, constituting the condition usually spoken of as *hæmaturia*, is observed only in pathologic conditions, and is, in contradistinction to hæmoglobinuria (which see), a very common occurrence.

Urine containing blood-corpuscles in notable numbers presents a color which may vary from a bright red to a dark brown, verging upon black. Upon standing a sediment of a corresponding color is obtained in which distinct coagula of variable size are at times seen.

If the urine should contain but a small number of red corpuscles, however, no deviation from its normal appearance will be noted, and the diagnosis of hæmaturia can then only be made with the microscope, which should be employed in every case. The appearance of the red corpuscles varies greatly, being influenced especially by the length of time during which they have been exposed to the action of the urine. In cases of hæmaturia of urethral or vesical origin it will be found that they have mostly retained their normal appearance fairly well, or have become crenated, when they may be recognized without difficulty. Other corpuscles, however, will probably also be seen which are no longer biconcave, but which have become spherical or shruken, and present an irregular outline. In cases, on the other hand, in which the corpuscles have remained in the urine for a longer time, as in hæmaturia of renal origin, the inexperienced will frequently be puzzled by the presence of small bodies of the size of red corpuscles, or somewhat smaller, which are entirely devoid of coloring-matter, and merely appear as faint, transparent rings, often presenting a double contour, and in

which no nucleus can be discovered. These formations are red blood-corpuscles from which the hæmoglobin has been dissolved. They are usually spoken of as blood-shadows. Chemical tests are rarely necessary, but may be employed if any doubt should arise (see p. 409).

Clinically it is, of course, all important to determine the source of the blood. This may at times be accomplished without much difficulty by a urinary examination, but at other times may be almost impossible, when the clinical symptoms and physical signs must be taken into consideration.

1. Hæmaturia of urethral origin, due to urethritis, or traumatism incident to catheterization, for example, is a common event, and readily diagnosed, as in such cases blood either escapes of its own accord from the urethra or may be squeezed out manually. The last portions of the urine voided, moreover, will always be found free from blood, unless the latter is referable to disease of the neck of the bladder, when the blood appears only toward the end of micturition, or at least more markedly then than in the beginning.

2. The diagnosis of vesical hæmaturia is not always easily made. It should be remembered, however, that here the blood-corpuscles present a normal appearance, as has been mentioned, unless ammoniacal fermentation is occurring in the bladder, in which case blood-shadows are seen in large numbers. The blood, moreover, is less intimately mixed with the urine than in cases of renal hæmaturia, so that the corpuscles rapidly settle after the urine has been passed. Blood-clots of an irregular form and considerable dimensions can only be of vesical origin. A careful examination for the presence of any other morphologic constituents which may be observed in urinary sediments, considered in conjunction with the clinical symptoms, will usually lead to a correct diagnosis so far as the seat of the hemorrhage is concerned. Hæmaturia of vesical origin may be due to numerous causes, among which may be mentioned diphtheritic cystitis, ulcers of the bladder caused by calculi and carcinoma, traumatism, the presence of parasites, and, more rarely, rupture of varicose veins in the bladder. In determining the cause of the hemorrhage in a given case more reliance should be placed upon the clinical history than upon the urinary examination.

3. In hæmaturia of ureteral origin characteristic blood-coagula corresponding in diameter and form to the ureters are occasionally seen. Their presence, however, does not necessarily indicate that

the blood has come from the ureters ; more frequently the hemorrhage will be found to be due to disease of the pelvis of the kidney.

4. The diagnosis of hemorrhage into the pelvis of the kidney must be based upon the clinical symptoms taken in conjunction with the results of a urinary examination. In doubtful cases recourse should be had to catheterization of the ureters, when a unilateral hæmaturia may in the majority of cases be regarded as referable to this source.

5. Hæmaturia of purely renal origin is of common occurrence, and may be due to numerous causes, such as a simple hyperæmic condition of the organs, acute nephritis, in which the passage of smoky-looking urine containing blood-corpuscles, usually in large numbers, is quite a constant symptom, and chronic nephritis, in which their number may be taken to indicate the intensity of the morbid process. Hæmaturia may also be due to renal abscess, nephrophthisis, renal carcinoma, and, in rare instances, to aneurism and embolism of the renal artery, thrombosis of the renal vein, etc. In the malignant forms of the acute infectious diseases, such as smallpox, yellow fever, malaria, etc., in scurvy, hæmophilia, and purpura, in leukæmia, filariasis, and distomiasis, renal hæmaturia is common. It is also observed in cases of poisoning with turpentine, carbolic acid, cantharides, etc.

6. An idiopathic form of hæmaturia has also been described, in which hemorrhage from the kidneys occurs without apparent cause. To this form Senator has applied the term "renal hæmophilia." The writer has seen three cases of this kind in which no lesion existed which could be made responsible for the hemorrhage. In all three the attacks of hæmaturia were invariably associated with anachlorhydria, while normal values were found between the attacks. Two of the patients were males and undoubtedly neurasthenics. The third was a hysterical chlorotic female, in which hæmatemesis, pulmonary hemorrhages, and melæna were also at times observed.

Hæmaturia of renal origin is usually recognized without much difficulty, as in such cases tube-casts, bearing red blood-corpuscles, and at times apparently consisting of these altogether, as well as numbers of renal epithelial cells, will usually be found upon careful examination. The blood, moreover, is intimately mixed with the urine, and the individual corpuscles have mostly lost their hæmoglobin and appear as mere shadows. The clinical history should, of

course, always be taken into consideration, and especially in determining the primary cause of the hemorrhage.

Urine containing red blood-corpuscles is always albuminous, so that it may sometimes be difficult to decide in a given case whether the albumin found is due solely to the presence of blood, or whether the hæmaturia is complicated with an albuminuria *per se*. Frequently it is possible to arrive at some conclusion by comparing the amount of albumin with the number of red corpuscles, the presence of a large amount of the former in the presence of only a small number of the latter indicating that the albumin is not altogether due to the blood. At other times it is impossible to gain information in this manner, when the only expedient left is to determine the quantity of albumin and of iron separately, and to ascertain whether the amount of iron found is sufficient to combine with that of the albumin. As a rule, however, the presence of serum-albumin, aside from that contained in the blood of the urine, may be inferred whenever tube-casts are present, although the amount can only be estimated approximately in this manner.

Tube-casts. In various pathologic conditions, and it is claimed even in health, curious formations are seen in the urine, which represent moulds of different portions of the uriniferous tubules. To these the term *tube-casts* or *urinary cylinders* has been applied, and it may be said that there is hardly a subject of greater importance in urinary analysis, from a clinical point of view, than that of *cylindruria;* but it must also be admitted that notwithstanding numerous investigations our knowledge of their nature and mode of formation is still defective, and the same may be said of their clinical significance. The term "tube-casts," however, is not altogether appropriate, as it is only applicable to one great division of such formations—*i. e.*, to those consisting of a uniform, transparent, gelatinous matrix to which other elements, such as epithelial cells, red blood-corpuscles, leucocytes, and salts in a crystalline or amorphous form, may accidentally have become attached—*the tube-casts proper*.

From these what may be termed "pseudo-casts" must be sharply differentiated, a pseudo-cast being characterized essentially by the absence of a uniform matrix. Closely related apparently to the true cast are the so-called cylindroids—band-like formations which resemble the former in appearance, and like these may carry various morphologic elements as well as salts. It is thus necessary to distinguish between true casts, pseudo-casts, and cylindroids. Of these

the true casts are by far the most important and the most common. They may be divided into hyaline and waxy casts, the two forms being readily differentiated by the fact that the former readily dissolve in acetic acid, while the waxy casts are either not affected at all by this reagent, or, if so, at least not so rapidly. The latter, moreover, are more strongly refractive, to which property their waxy appearance is owing; their color is slightly yellow or yellowish-gray, while the hyaline casts are colorless and usually very pale and transparent.

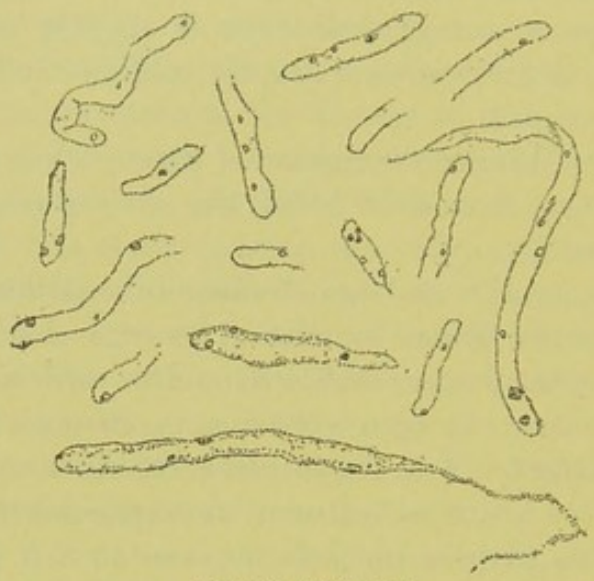
Before giving a detailed description of these various forms it may not be out of place to consider briefly the *mode of examination* that should be employed.

As tube-casts readily undergo disintegration within a comparatively short time in urines containing bacteria even in moderate numbers, a microscopic examination should be made as soon as possible after the urine has been voided—*i. e.*, as soon as a sufficient sediment has formed. The examination should never be delayed longer than twelve hours, unless some antiseptic substance has been added. For this purpose chloroform-water (5–7.5 grammes pro liter) is the most convenient, according to Salkowski, of which 20 to 30 c.c. should be used for every 100 c.c. of urine. The use of the centrifugal machine is, of course, best of all, as a sediment sufficient for microscopic purposes may be obtained in a few minutes. In the text-books on urinary analysis mention is usually made of the difficulty attending the search for hyaline casts, owing to their transparency, and the advice is usually given to color the preparation with a drop of a dilute solution of iodo-potassic iodide, or of some other staining reagent, such as gentian-violet, picrocarmin, methylene-blue, or osmic acid. In the case of the inexperienced it is possible that such a procedure may at times be of value, but, as a rule, it may be doubted whether a student who has been unable to find tube-casts, if the procedure which has been described above be employed—*i. e.*, careful examination, without a cover-glass and with a low power, of a drop of the sediment carefully spread over a slide—will be materially aided by the use of stains. With a high power of the microscope, it is true that tube-casts may be overlooked again and again, not only by the student, but also by those familiar with clinical microscopy: *a high power should, as a rule, only be employed to study details of structure.*

TRUE CASTS. 1. *Hyaline casts.* (Fig. 114.) Upon careful exami-

nation it will be seen that with rare exceptions the matrix of hyaline casts is not *altogether* homogeneous, as small granules may almost always be detected imbedded in or adhering to the matrix. As these granules may occur in greater or less numbers, hyaline casts

FIG. 114.



Hyaline tube-casts.

are spoken of as being finely granular (Fig. 115), coarsely granular, finely dotted, etc. Should true morphologic elements be detected, the casts are termed blood-casts, epithelial casts (Fig. 116), or pus-

FIG. 115.



Granular tube-casts.

casts (Fig. 117). It would be better, however, to add the term hyaline in every instance, so as to distinguish them from pseudo-casts, which consist of three elements entirely, and lack a uniform

matrix. It would thus be proper to speak of hyaline epithelial casts, hyaline blood-casts, etc., and to apply the collective term—compound hyaline casts—to these various subvarieties.

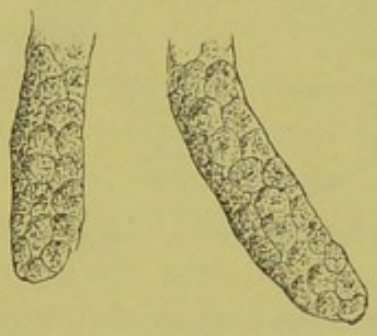
FIG. 116.



Epithelial casts.

The true nature of these various forms can probably always be made out without much difficulty, and even in those cases in which the hyaline matrix is apparently concealed beneath cellular elements it will usually be possible upon closer observation to detect a fine boundary-line at some portion of the structure. Not infrequently the end of the cast will be seen to be more or less distinctly hyaline.

FIG. 117.



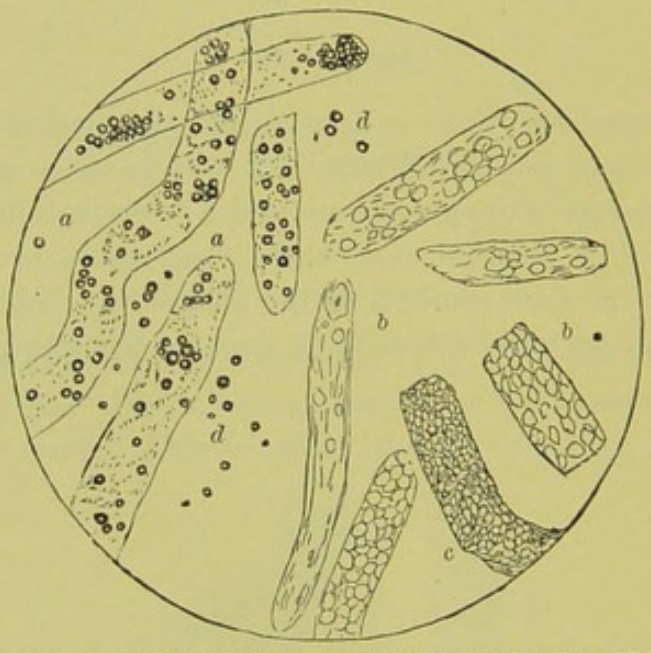
Pus casts.

In others, again, a hyaline zone may be observed along the sides of a central organized thread, so to speak, this being frequently seen in specimens which are very broad and long. Should any doubt, however, arise, a drop of acetic acid is added to a drop of the sediment on the slide; the acid dissolves the hyaline matrix, the organized constituents are set free, and the differential diagnosis between a pseudo-cast and a compound hyaline cast is thus readily established.

The length of hyaline casts may vary greatly. It may scarcely

exceed the breadth, on the one hand, while on the other, although rarely, it may pass through the entire microscopic field. In breadth they vary between 0.01 and 0.05 mm. As a rule, the breadth of a cast is uniform throughout its entire length, but specimens are not infrequently observed in which one end tapers off considerably, and presents a spirally twisted appearance. This may be so marked that the entire cast appears transversely striated. It is generally supposed that this results from the adhesion of one end of the cast to the walls of a tubule the lumen of which it does not fill, the free end becoming twisted in the downward course. A dichotomous branching of one end is also at times seen in very broad hyaline specimens.

FIG. 118.



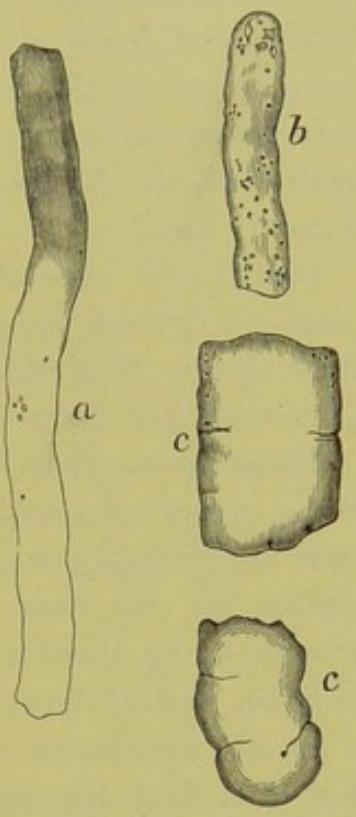
a. Fatty casts. *b* and *c*. Blood-casts. *d*. Free fatty molecules. (ROBERTS.)

"Fatty globules are found upon the surface of granular casts (Fig. 118), but they also form by themselves short, strongly refractive casts, which are often beset all over with needles of fatty crystals. These, however, are not composed exclusively of fat, but probably to some extent of lime and magnesium salts of the higher fatty acids and allied compounds, for they are not all soluble in ether. They have their origin doubtless in fatty degeneration of the renal epithelium" (v. Jaksch).

Granules of melanin, indigo, and altered blood-pigment may also at times be observed in casts; Riedel regards the occurrence of dark brown casts as pathognomonic of fractures.

2. The *waxy* casts (Fig. 119) may be divided into two groups—true waxy casts and amyloid casts; but as the latter are not necessarily indicative of the existence of amyloid degeneration of the kidneys, such a classification is at the present time at least of only theoretical interest. They are readily distinguished from the hyaline casts by the characteristics mentioned above —*i. e.*, their higher degree of refraction, their yellow or yellowish-gray color, and the fact that they are either not attacked at all by acetic acid or only very gradually. As a rule, only small fragments are found, but these are broader and stouter than the stoutest hyaline casts. Waxy casts may also contain cellular elements, crystals, and amorphous mineral matter; but, as a rule, such compound casts are not so frequently observed as are those of the hyaline variety. From the latter they differ furthermore in frequently presenting a cloudy appearance, which in some cases is undoubtedly due to the presence of innumerable bacteria, and it has been suggested that these may be directly concerned in their production.

FIG. 119.



Different forms of waxy casts: *a*. With a coating of urates. *b*. Waxy cast covered with crystals of oxalate of lime. *c*. Fragments of waxy casts. (v. JAKSCH.)

As has just been stated, some waxy casts give the amyloid reaction; *i. e.*, they assume a mahogany color when treated with a dilute solution of iodo-potassic iodide, which turns to a dirty violet upon the addition of dilute sulphuric acid. It should be remembered, however, that this reaction in casts does not necessarily indicate the existence of amyloid disease of the kidneys, as the reaction may be absent on the one hand in this condition, and present on the other where amyloid degeneration does not exist. This curious phenomenon is usually explained by assuming that such casts have remained in the uriniferous tubules for a long time, and have there undergone certain chemical changes analogous to the so-called "amyloid metamorphosis" of old precipitates of fibrin, and it is indeed possible that waxy casts are originally hyaline. Frerichs has pointed out that fibrin which has remained in the uriniferous tubules for a long time becomes denser and yellowish in appearance, which would

explain the fact that these casts are only with difficulty attacked by acetic acid.

Before leaving this subject it should be stated that "cast-like" formations, consisting entirely of amorphous urates, are not infrequently encountered in urines, and according to Leube they may be obtained from any urine, if it be concentrated in a vacuum at a temperature of 37° to 39° C. Students frequently regard such formations as coarsely granular casts, an error which may be guarded against if the characteristics of hyaline casts set forth above be borne in mind.

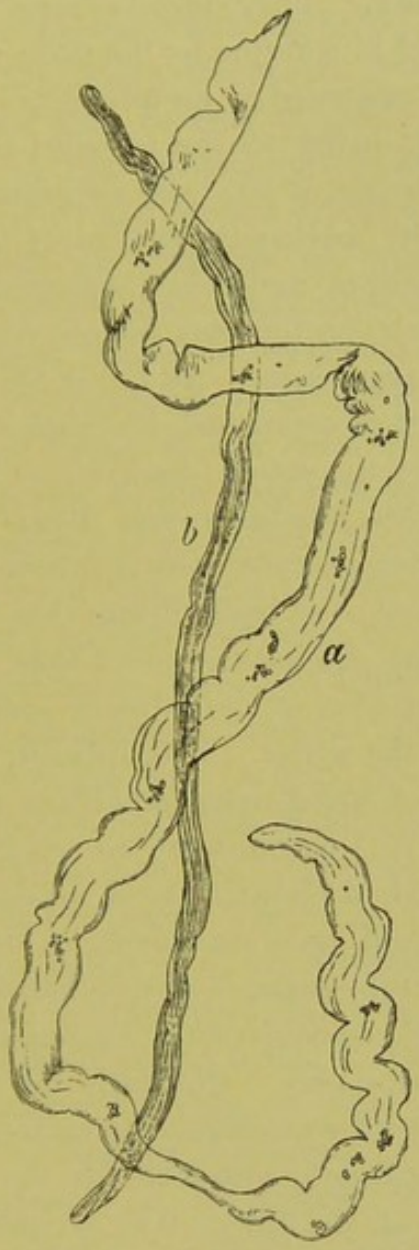
Bacteria (in cases of infectious pyelo-nephritis), hæmatoidin, and granular detritus frequently occur grouped in a cast-like manner; their nature is readily ascertained, as in the case of the so-called urate casts just described.

Pseudo-casts, consisting of epithelial cells or blood-corpuscles and fibrin, are rarely seen in urinary sediments. The epithelial pseudo casts are probably only seen in cases of desquamative nephritis, and, unlike the true casts, are hollow, the epithelium of the uriniferous tubules being thrown off *en masse*. Blood-casts (Fig. 118) consist of fibrin, within the meshes of which red corpuscles, presenting either a normal appearance or occurring as mere shadows, owing to the fact that their hæmoglobin has been dissolved out, will generally be found. They are found whenever extensive hemorrhage has taken place in the renal parenchyma, and are far more frequently seen than the epithelial pseudo-casts. Hyaline casts are probably always met with in urinary sediments in which pseudo-casts are found, and may be readily distinguished from the latter, even when beset with numerous epithelial cells or red corpuscles (see above).

Cylindroids (Fig. 120) resemble hyaline tube-casts somewhat in general appearance, but differ from them in being much larger and band-like. Like tube-casts, they have a uniform breadth, and are often beset with crystals and cellular elements, such as leucocytes, red corpuscles, and epithelial cells. They are easily dissolved by acetic acid, thus differing from the *mucous cylinders* or pseudo-cylinders (Fig. 121), which may be observed in any urine containing mucus in abundance; the latter probably never contain morphologic or mineral constituents, and are never of the same breadth throughout their length. The cylindroids proper are undoubtedly of renal origin and closely related to the true casts; formations are indeed not

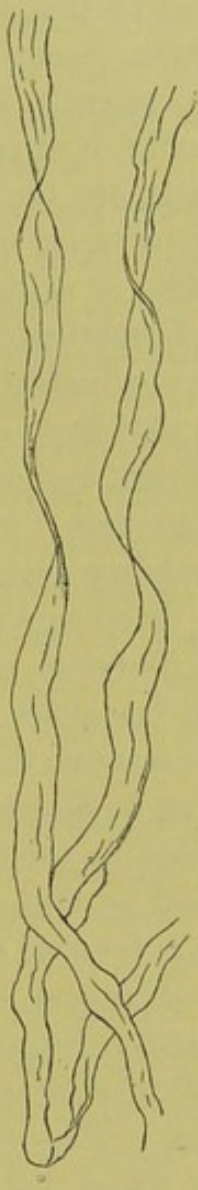
infrequently seen in which a tube-cast terminates in a cylindroid at one or both ends (see Fig. 114).

FIG. 120.



a and *b*. Cylindroids from the urine in congested kidney. (V. JAKSCH.)

FIG. 121.



Mucous cylinders.

FORMATION OF TUBE-CASTS. Several hypotheses have been advanced to explain the formation of tube-casts—reference is here only had to true casts, and not to pseudo-casts, the origin of which is sufficiently obvious—and until recently it was quite generally accepted that these consisted of coagulated albumin which had transuded into the tubules; according to this view a cylindruria would always be indicative of the existence of albuminuria. In Neubauer and Vogel's *Urinary Analysis*, latest edition (ninth), it is stated that "as to the

significance of tube-casts it must be remembered that these, according to our present knowledge, consist of albumin, which coagulates under the influence of the acid reaction of the urine in the renal parenchyma in a peculiar hyaline manner. They merely represent a solidified portion of the albumin held in solution by the urine; their elimination essentially indicates the existence of an albuminuria."

More recently, however, probably owing to the reported absence of albumin in certain cases of cylindruria, it has been suggested that tube-casts are the product of a faulty metamorphosis, or of inflammatory irritation of the renal epithelium, and that a secretion from these cells or a disintegration of their protoplasm occurs, resulting in the formation of cylindroids or true casts. As far as the existence of a cylindruria *sine* albuminuria is concerned, the author must confess that he is very skeptical as to the actual occurrence of such a condition, and he fully agrees with Neubauer and Vogel when they state that "whenever the number of tube-casts is minimal the corresponding amount of albumin may be so insignificant that it may not be demonstrable by means of the ordinary, *coarser* tests." In several thousand examinations a true case of cylindruria *sine* albuminuria has never been observed by the writer. It is difficult, moreover, to imagine that an elimination of blood-casts and others, which, according to Kossler, are "frequently" encountered in urines, can take place in the absence of a coincident elimination of albumin, as is claimed by him, and until further and more convincing evidence is offered in favor of a cellular origin of tube-casts, it may be better to be conservative and to regard cylindruria as equivalent to albuminuria.

Clinical Significance of Tube-casts. Formerly the occurrence of tube-casts in the urine was held to indicate the existence of nephritis. This view has been abandoned, however, for the same reasons which led to the rejection of the theory that albuminuria invariably indicates Bright's disease (see above).

The statement is frequently made in text-books that tube-casts may occur in the urine of perfectly healthy individuals following severe muscular exercise, cold baths, etc.—in short, all stimuli which may cause the appearance of albumin in apparently normal individuals. It has been indicated elsewhere (see Functional Albuminuria), however, that such stimuli should not be regarded as "physiologic" in every instance, and *the presence of tube-casts in the urine similarly should be regarded as a pathologic event.*

It is not necessary in this connection to enumerate the various

pathologic conditions in which cylindruria is observed, these being the same as those which give rise to albuminuria; and just as a *nephrangiogenic albuminuria* is more frequently observed than a *nephritidogenic albuminuria*, so also is the presence of tube-casts in the urine more frequently due to circulatory disturbances in the kidneys than to true nephritis. In every case in which tube-casts occur in the urine it may be assumed that the accompanying albuminuria is, to a certain extent at least, of renal origin.

While the existence of cylindruria is not necessarily associated with definite pathologic alterations of the renal parenchyma, this statement should be restricted to the occurrence of purely hyaline casts when present in only small numbers. A few renal epithelial cells may be found at the same time, occurring either free in the urine or adhering to the casts, but never presenting an atrophic or otherwise altered appearance in the absence of definite renal lesions. The presence of compound hyaline and coarsely granular casts, as well as of waxy and amyloid casts, on the other hand, may probably always be regarded as indicating definite changes in structure, so that, so far as the diagnosis of nephritis is concerned, a microscopic examination of the urine will furnish information far more valuable than the simple demonstration of albumin.

Hyaline casts are those most usually seen—reference is here had only to the purely hyaline or, at least, but faintly granular form—and are found in all conditions in which albuminuria occurs. When present in only small numbers, and particularly when occurring but temporarily in the urine, it may be assumed, in the absence of other symptoms pointing to renal disease, that we are dealing with a mild circulatory disturbance in the kidneys. Renal epithelial cells are absent, or, if present, they are seen in only small numbers and present no special alterations in structure. The albuminuria at the same time is only trifling. If, however, hyaline casts be continuously present in large numbers, and if the amount of albumin exceed a trace, the existence of a nephritis may usually be inferred. In such cases granular casts and compound hyaline casts, particularly the former, will usually also be found, if the nephritis be chronic, while in the acute form the hyaline type will prevail. Should blood-casts be present at the same time, the probabilities are that we are dealing with an acute nephritis, or an acute exacerbation of a chronic process, in which latter case, however, coarsely granular casts will also be present in large numbers.

Waxy casts always indicate a chronic or, at least, a subacute process. The fatty casts described by Knoll and v. Jaksch "are most commonly associated with subacute or chronic inflammations of the kidney of protracted course, with a tendency to fatty degeneration of the renal tissues. Post-mortem examination has shown that they form most frequently in cases of large white kidney. In some cases in which they were present, however, the organ was found to be more or less contracted; but when this was so, it was invariably far advanced in fatty degeneration."

It has been stated that from a careful examination of the renal epithelial cells it is often possible to determine whether an inflammatory process affecting the kidneys is at the same time complicated with degenerative changes. As a matter of fact, the cells found on the tube-casts under such conditions no longer present a normal appearance, but are shrunken and atrophied, and in cases of fatty degeneration of the kidneys studded with fatty granules. Epithelial casts, in the absence of distinct changes affecting the renal parenchyma, are probably never seen.

The occurrence of *pus-casts* presupposes the existence of suppurative inflammation in the kidneys, while the presence of only a small number of leucocytes on hyaline casts may be observed in the ordinary forms of nephritis and particularly in the acute form.

The pathologic significance of the so-called amyloid casts and pseudo-casts has already been considered.

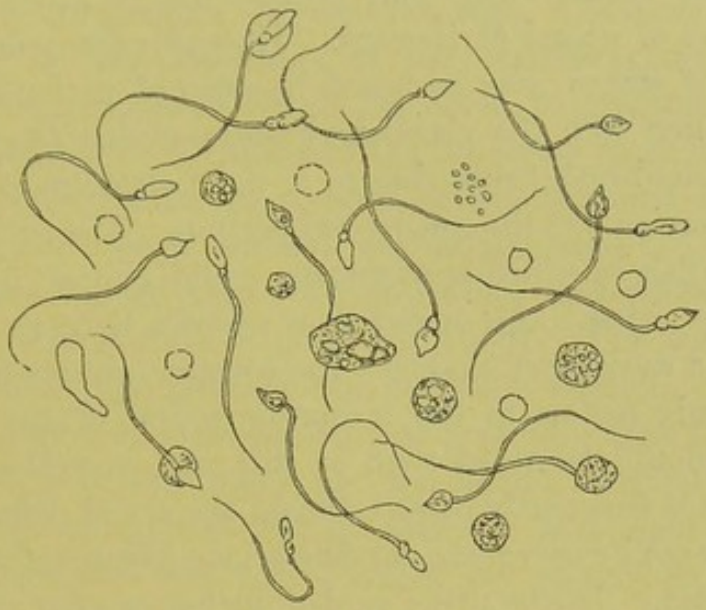
Cylindroids are present whenever hyaline casts are seen in the urine, and have essentially the same import. They are said to occur most frequently in the urine of children.

So far as the constancy with which tube-casts occur in the urine in nephritis is concerned, it is well known that in the chronic interstitial form of the disease they, as well as albumin, are frequently absent for a long time, so that it may only be possible to make the diagnosis from the clinical history and the physical signs. It is a well-known fact, moreover, that pathologic alterations of the kidneys, particularly in men past middle-age, are observed again and again in the post-mortem room, where a previous examination of the urine showed no evidence of the existence of renal disease. In the acute and subacute forms of nephritis as well as in the ordinary parenchymatous form, tube-casts are probably always found, and it would further appear that acute circulatory disturbances

affecting the renal parenchyma quite constantly lead not only to albuminuria, but also to cylindruria.

Spermatoza. Spermatozoa, for a description of which the reader is referred to the chapter on Semen, are frequently observed in the

FIG. 122.



Human spermatozoa.

urines of healthy adults, and are quite constantly met with in the first urine passed after coitus or pollutions, when their presence is, of course, of no significance. (Fig. 122.) Such urines are always cloudy, but it is impossible to recognize the source of the turbidity by simple inspection.

A sediment composed of phosphates is popularly regarded as being due to semen, and no doubt every physician has seen patients —usually sexual neurasthenics—who were greatly alarmed at finding a white deposit in the chamber, and who imagined themselves "sufferers from loss of manhood." The microscope is necessary in every case to determine the presence of spermatozoa.

In females semen is found in the urine whenever the external genitals have been polluted during or after coitus as well as in the exceptional cases in which connection has been effected by the urethra. From a medico-legal standpoint the discovery of spermatozoa in the urine of women may be of the greatest importance, but otherwise is without significance.

In a few instances it is stated that trichomonades have been mistaken for spermatozoa. The writer, however, is convinced that such

an error could only occur if the observer is totally unacquainted with questions appertaining to microscopic research.

In pathologic conditions spermatozoa are not infrequently found in the urine. In cases of severe constipation, owing to pressure of the hard scybalæ upon the seminal vesicles, a partial evacuation of semen may occur, which may or may not be accompanied by a certain degree of sexual excitement. Horowitz has pointed out that a discharge of semen may be noted in cases of periurethral abscess with perforation into the ejaculatory ducts, giving rise to *spermatocystitis*, the condition being due to a tight stricture of the urethra with dilatation beyond the constricted portion. The author observed a case of cystitis in which spermatozoa could almost always be detected in the urine. An operation revealed a tight stricture of the urethra and a sacculated bladder; the constant elimination of semen was apparently owing to the irritating action of the ammoniacal urine. It should be noted that in this case, as well as in those in which semen is frequently passed during the act of defecation in the absence of sexual excitement, no deleterious effects referable to such loss were noted. In the urine voided during or after epileptic and, more rarely, hystero-epileptic seizures, spermatozoa may be found in the urine. Such an event is undoubtedly due to muscular spasm, and is identical in origin with the emission of semen observed so frequently after death, during strangulation, etc.

In certain spinal diseases semen may be found in the urine, and Fürbringer relates a most interesting case in which, following fracture and dislocation of the vertebral column, with partial destruction of the middle dorsal cord, spermatorrhœa associated with partial erection occurred thirty hours later, and continued until death, which took place after three days.

Most important, however, is the loss of semen noted in cases of true *spermatorrhœa* due to venereal excesses or masturbation, when spermatozoa may be found in the urine almost constantly, and the diagnosis indeed will often be dependent upon such an observation.

As far as the question of *sterility* in the male is concerned, reliance should not be placed upon an examination of the urine, but the semen should be obtained as soon as possible after coitus and examined as indicated elsewhere (see p. 532).

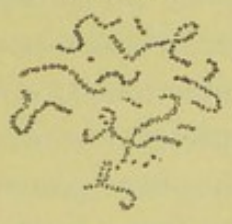
Parasites.. Vegetable Parasites. It has been shown by numerous investigations that bacteria are always present both in the male and female urethra, and that these may *at times* gain entrance to

the bladder. The weight of evidence, however, is in favor of the view that the urine *intra vesicam* is under normal conditions free from micro-organisms, and that any bacteria which may have found their way into the bladder are rapidly killed in healthy individuals. In every urine, on the other hand, that has been exposed to the air, bacteria are always present. Whenever, then, it is desired to determine whether or not the urine of the bladder contains micro-organisms, every precaution should be taken to guard against accidental contamination. To this end the following method should be employed: If the patient be a male, he is instructed to hold his urine until a fairly large amount has accumulated. The glans is then thoroughly washed with soap and water and rubbed off with cotton soaked in bichloride solution (1 : 1000). The fossa navicularis is also thoroughly cleansed with the same solution. The urine is then voided under as great pressure as possible. The first portion (about 100 c.c.) is thrown away, and the second received in a sterilized vessel, when cultures should be made at once, agar or gelatin plates being inoculated with 1 or 2 c.c. of the urine. In the female the vulva is cleansed with soap and water, and the urethral aperture disinfected with bichloride solution. After then washing with sterilized water and drying with sterilized cotton the urine is evacuated through a sterilized metallic or glass catheter and received in a sterilized vessel.

Among the bacteria which may be found in every urine that has been exposed to the air the *micrococcus ureæ* is the only one of interest, as ammoniacal fermentation is largely due to its presence.

When fermentation has commenced it is readily recognized, occurring in almost pure culture upon the surface of the urine, mostly in the form of characteristic chains (Fig. 123). The individual coccus is colorless and quite large, so that it may be mistaken by the beginner for a blood-shadow.

FIG. 123.



Micrococcus ureæ.

It is a common error to infer from the occurrence of ammoniacal decomposition very soon after micturition that this process has already begun in the bladder. It should be remembered that urine may undergo fermentation, particularly in warm weather, shortly after having been voided, and especially if the vessel employed is not absolutely clean and the urine has been allowed to stand exposed to the air. The diagnosis of ammoniacal fermentation in the bladder

should hence only be made when the presence of ammonia can be demonstrated in the urine immediately upon being voided.

The urinary *sarcina* which is at times met with is smaller than that found in the gastric contents, but otherwise presents the same appearance. Its presence is of no clinical interest.

Under pathologic conditions various pathogenic bacteria may be eliminated through the urine. Their presence may always be regarded as indicating the existence of some definite alteration of the renal parenchyma, but it should be remembered that this need not necessarily be in the sense of a nephritis. Pyogenic cocci are especially prone to settle in the kidneys and give rise to focal inflammations, but even without these they frequently pass into the urine. In all forms of infectious nephritis an abundant elimination of bacteria may probably always be observed. v. Jaksch states that in erysipelas the bacteriuria and nephritis disappear together with the cessation of the disease. In various suppurative processes taking place in the body it has been found that the specific bacteria which were frequently observed in the urine disappeared within twenty-four to thirty-six hours after the evacuation of the pus. Most interesting observations have been recently made by Engel in various cases of nephritis. Thirty-one cases were examined. In sixteen he found the staphylococcus pyogenes albus and aureus, in eight pyogenic streptococci, in four the tubercle bacillus, in one the typhoid bacillus, in five the bacillus coli communis, while negative results were obtained in only two instances. In the same series, moreover, he found a pyogenic coccus in seventeen cases, which was larger than the known forms, which could be stained according to Gram's method, and which did not liquefy gelatin. Intravenous injection of large quantities of the organism produced nephritis in rabbits.

In pneumonia and pneumococcus infections in general the diplococcus pneumoniæ may be found, and in erysipelas and streptococcus infections streptococci. Fairly constant is the presence of the bacillus coli communis in cases of pyelonephritis, where it is usually found in pure culture, but is at times associated with the staphylococcus pyogenes aureus and the proteus Hauser. In some instances the latter organism has also been found in pure culture. The typhoid bacillus has been repeatedly observed in the urine of typhoid patients.

Actinomyces kernels may be observed in the urine when the disease has attacked the genito-urinary tract or when they have found their way into the urine from other organs.

Very important is the fact that in tubercular disease affecting the urinary organs *tubercle bacilli* may be found in the urine. The search for these, however, is frequently fruitless and always tedious. In suspected cases, and particularly in those in which a careful examination of the lungs has yielded negative results, an attempt should be made to find the organism in the urine.

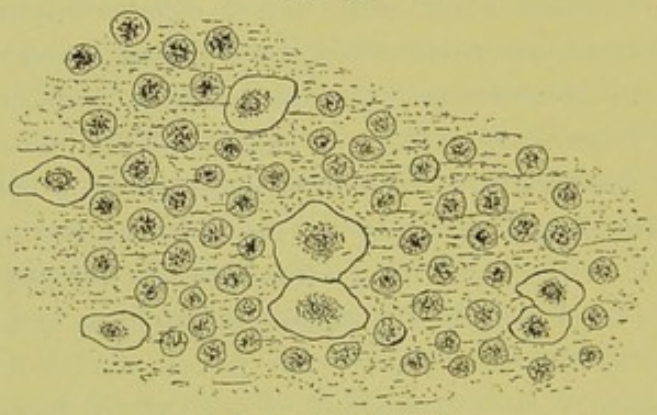
Grethe's method. To this end the urine is best centrifugated, the supernatant fluid removed by means of a pipette, and cover-slips prepared. After having been fixed, by being passed through the flame of a Bunsen burner, the specimens are stained with a concentrated alcoholic solution of fuchsin under the application of heat, washed off in water, and counterstained with a concentrated alcoholic solution of methylene-blue at the temperature of the room. The excess of the stain is removed by washing with water, when the preparations are dried between filter-paper and mounted in a drop of cedar oil. The tubercle bacilli will thus be colored red, while all other morphologic elements that may be present, including the *smegma bacilli*, are stained blue. The usual methods of staining for tubercle bacilli should not be employed when urinary deposits are to be examined, as the smegma bacilli, which may be found in females as well as in males, are stained in the same manner. At the Charité of Berlin the examination is conducted upon the slide, when larger amounts of the sediment may, of course, be examined at one time. Cover-glasses are not necessary. A drop of oil of cedar is placed directly upon the specimen and a $\frac{1}{12}$-immersion lens employed.

Very frequently it is necessary to prepare a large number of cover-glass specimens, but, as stated above, even then the search may be without result, notwithstanding the existence of a tubercular lesion. In such an event it will be best to inject a few drops of the sediment into the anterior chamber of the eye of a rabbit, the urine being obtained under bacteriologic precautions, and to watch for the development of miliary tubercles in the iris. Isolated tubercle bacilli have also been found in the urine in cases of acute miliary tuberculosis, so that their presence not necessarily indicates the existence of tuberculosis of the urinary organs. If, however, definite symptoms of renal disease exist at the same time, the diagnosis of renal tuberculosis will probably always be justifiable.

In this connection it may not be out of place to refer to the gonococcus of Neisser, which may now be considered as pathog-

nomonic of gonorrhœal infection. The organism (Plate XIV.) occurs in the form of small, oval, or round granules, usually grouped in twos and fours, so as to resemble a German biscuit or the figure 8, enclosed within pus-corpuscles and epithelial cells, although they may also occur free in the pus obtained from the urethra, in the vaginal discharge, or more rarely free in urinary sediments, as in cases of complicating prostatitis, peri-urethritis, etc. In making a diagnosis account should only be taken of specimens which are enclosed in cellular elements, as these alone can be regarded as characteristic. They are best stained with Loeffler's methylene-blue solution (see p. 109). In cases of urethritis it is only necessary to receive a small drop of the discharge upon a cover-glass and to spread this out in as thin a layer as possible; after drying the preparation is passed through the flame of a Bunsen burner three or four times and stained with a drop of the methylene solution without the application of heat. The excess of coloring-

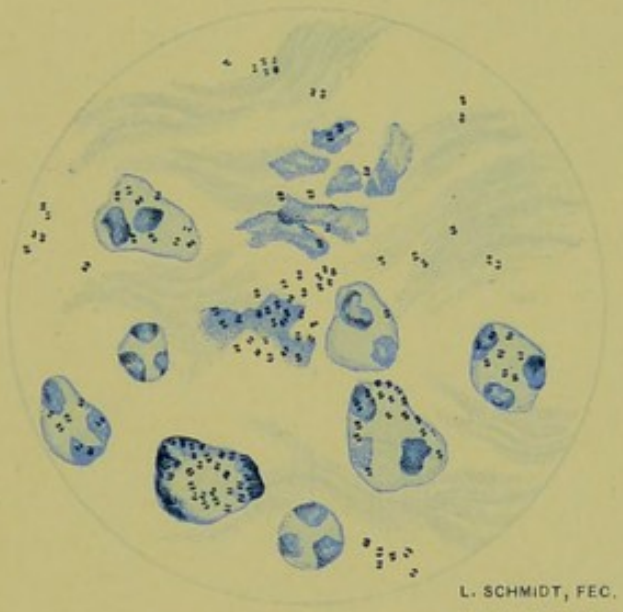
FIG. 124.



A gonorrhœal thread.

matter is removed by rinsing the specimen in water, when it is dried between layers of filter-paper, mounted in a drop of water, and examined with an oil-immersion lens, although with a little practice reliable results can also be obtained with a lower power. In doubtful cases, and especially in women and children, cultures should be made, as the organism may at times be confounded with the pseudo-gonococci, which are quite frequently present both in the diseased and normal urethra of males and females. The organism grows best in a mixture of human blood-serum and nutrient agar (1 : 2 or 3 parts). The surface-colonies are pale, grayish, translucent, finely granular, with finely notched borders. In bouillon and blood-serum mixed it forms a membrane, while the fluid remains

PLATE XIV.



Urethral Discharge from a Case of Gonorrhœa, showing Gonococci Enclosed in Pus Corpuscles, and Lying Free in the Discharge. Stained with Methylene Blue. (Personal Observation.)

clear. Like the pseudo-gonococci, it cannot be stained according to Gram's method.

In conclusion, reference should be made to the occasional occurrence of *bacteriuria* of a non-pathogenic form. Such cases are very rare, and the diagnosis of *idiopathic bacteriuria*, as this form may be termed, should only be made if every possible source of contamination of the urine can be definitely excluded. According to Schottelius, this condition is not associated with any pathologic lesion.

Urines containing bacteria in large numbers are always cloudy, and usually present an acid reaction when voided unless a cystitis exists at the same time. Attention will be directed to their presence by the fact that such specimens cannot be cleared by simple filtration.

Yeast-cells in large numbers are only seen in urines containing sugar. Whenever a chemical examination has not been made their demonstration will be of importance as suggesting the possible existence of diabetes.

Moulds are usually seen in old diabetic urines after alcoholic fermentation has taken place, but may also occur, though far less frequently, upon the surface of putrid urines that have contained no sugar.

Animal Parasites. The organism which Hassal saw in a urine that had been "freely exposed to the air" and was alkaline, and which he termed Bodo urinarius, was in all probability an infusorial monad and of no pathologic significance. Salisbury was the first to point out that the "trichomonas vaginalis" of Donné may at times occur in the bladder, but gave no detailed account of his cases. Künstler, Marchand, Miura, and Dock then reported cases in which flagellate protozoa were found, and modern research leaves no doubt that the organisms described by these observers are identical with the trichomonas of Donné. In Miura's case the habitat of the parasite was the urethra, and an examination of the patient's wife revealed the presence of similar organisms in the vagina. Künstler's case was one of pyelitis following cystotomy. Marchand's patient had a fistula in the perineum following suppuration in the pelvis of unknown origin; cystitis did not exist. Dock's case was associated with hæmaturia. Within the last year the writer likewise found a trichomonas in the urine of a female patient occurring in the practice of Dr. W. M. Lewis, of Baltimore. The case was one of cholelithiasis. The urine contained blood in fairly

large amount. Evidence of cystitis and nephritis did not exist. The number of the parasites was small.

Bälz observed numerous amœbæ in the turbid urine of a girl the subject of phthisis, which he described as being of larger size than the amœba coli. Ciliated infusoria have also been found in the urine in isolated cases.

The ova of distoma hæmatobium and the filaria sanguinis hominis are at times found in the urine, their elimination being usually accompanied by hæmaturia and chyluria. Echinococcus hooklets and fragments of cysts may also be found, and in rare instances ascarides find their way into the urinary passages when a fistulous opening exists between the rectum and the bladder. Bothriocephalus linguloides, Leuckart, was found in the urine in one case occurring in Eastern Asia. Eustrongylus gigas is likewise found very rarely. Moscato records one case in which chyluria existed at the same time.

Tumor-particles. Tumor-particles are so rarely seen in the urine that a detailed account of their occurrence may be omitted, particularly so as it is seldom possible to base the diagnosis of tumor upon the presence of fragments in the urine, the clinical history and the physical signs being usually sufficient to reach a satisfactory diagnosis.

Foreign Bodies. Among foreign bodies which may be found in the urine may be mentioned particles of fat, fibres of silk, linen, and wool, etc.; in short, material the presence of which is owing to the use of unclean vessels for the reception of the urine. Fecal matter may be passed per urethram; such an occurrence, of course, always indicates the existence of an abnormal communication between the bowel and the urinary passages, especially the bladder. Hair derived from a dermoid cyst may similarly be found. In hysteria foreign bodies of almost any kind may be shown the physician as having been passed in the urine, such as hair, teeth, fish-bones, wood, etc., and even snakes and frogs. The author had occasion to examine "gravel" "passed" from time to time by an hysterical patient in large amounts, "every attack being accompanied by the most agonizing pains shooting down into the lower abdomen;" the gravel upon examination proved to be mortar, obtained from the cellar of the patient's house.

CHAPTER VIII.

TRANSUDATES AND EXUDATES.

DEFINITION.

In health the so-called serous cavities of the body contain but very little fluid, and quantities sufficient for analytical purposes can normally only be obtained from the pericardial sac. In pathologic conditions, on the other hand, large accumulations of fluid may be observed not only in the serous cavities, but also in the areolar connective tissue, beneath the skin, and beneath the muscles. When due to circulatory disturbances, a hydræmic condition of the blood, or an insufficient elimination of water through the kidneys, such accumulations of fluid are spoken of as *transudates*, while the term *exudates* is applied to similar accumulations of inflammatory origin.

Clinically, it is frequently difficult to distinguish between transudates and exudates, and large ovarian, pancreatic, and hydatid cysts, as well as cystic kidneys, may at times be mistaken for ascites. In such cases a careful chemical and microscopic examination of the fluid in question may be of decided value. Very frequently, moreover, it is possible *only* in this manner to determine the true nature of the disease, and the importance of freely using the trocar and the aspirating-needle in diagnosis cannot be too strongly advocated.

TRANSUDATES.

General Characteristics.

Transudates are usually serous in character, when they present a light-straw color; at times, however, owing to an admixture of blood, they have a reddish tinge, and are then spoken of as sanguineous; in rare instances they are chylous.

The Specific Gravity.

The specific gravity varies somewhat according to the origin of the fluid, but is usually lower than that of serous exudates occurring in the same cavities, one of the most important points of difference between the two kinds of fluid. Thus, in acute pleurisy the specific gravity of the exudate is usually higher than 1.020, and in chronic

pleurisy, if an accumulation of pus exists at the same time, higher than 1.018, and even reaching 1.030. In transudates into the pleural cavity, on the other hand, referable to circulatory disturbances, for example, as in cases of hepatic cirrhosis or cardiac insufficiency, the figures obtained are usually lower than 1.015. Transudates of peritoneal origin similarly present a specific gravity varying between 1.005 and 1.015, while that of exudates frequently reaches 1.030.

As the chemical composition, in so far as the mineral constituents and extractives are concerned, is practically the same in both classes of fluid, the difference in the specific gravity appears to be essentially due to the amount of albumin present, viz., serum-albumin and serum-globulin. It may be demonstrated, as a matter of fact, that exudates contain far more albumin than transudates, the amount varying between 4 and 6 per cent. in the former as compared with 1 and 2.5 per cent. in the latter. The largest amounts of albumin in transudates are found in those of pleural origin, while in œdema not more than 1 per cent. is usually present.

In the table below, taken from Reuss, the relation between the percentage-amount of albumin and the corresponding specific gravity is shown. Reuss suggested the following formula for the purpose of determining from the specific gravity the amount of albumin in transudates and exudates:

$$E = \frac{3}{8}(S - 1000) - 2.8,$$

in which "E" indicates the percentage-amount of albumin and "S" the specific gravity, taken by means of an accurate urinometer.

Specific gravity.	Albumin.	Specific gravity.	Albumin.
1.008	0.2	1.019	4.3
1.009	0.6	1.020	4.7
1.010	1.0	1.021	5.1
1.011	1.3	1.022	5.5
1.012	1.7	1.023	5.8
1.013	2.1	1.024	6.2
1.014	2.5	1.025	6.6
1.015	2.8	1.026	7.0
1.016	3.2	1.027	7.3
1.017	3.6	1.028	7.7
1.018	4.0		

The following table shows the percentage-amount of albumin obtained by Runeberg in ascitic fluid under various pathologic conditions:

	Average.	Maximum.	Minimum.
Hydræmia (Bright's disease, tuberculosis, etc., with amyloid degeneration)	0.21	0.41	0.03
Portal stasis (referable to hepatic cirrhosis or stenosis)	0.97	2.68	0.37
General venous stasis (referable to organic heart disease)	1.67	2.30	0.84
Carcinoma of the peritoneum (complicated with carcinoma of the stomach).	3.51	5.42	2.70
Chronic peritonitis (one case complicated with heart disease)	3.71	4.25	3.36

The fact, moreover, that transudates do not coagulate spontaneously in the absence of blood may further serve to distinguish these from exudates, in which a coagulum is frequently observed after having stood for twenty-four hours. But not much reliance should be placed upon this point of difference, as exudates likewise do not always coagulate, and clotting of transudates in the presence of blood may already take place within the body.

The Chemistry of Transudates.

An idea of the chemical composition of the various forms of transudates may be formed from the following tables, taken from Hoppe-Seyler and Hammarsten, the figures corresponding to 1000 parts by weight of fluid, and the specimens being taken from one individual:

	Pleura.	Peritoneum.	Œdema of the feet.
Water	957.59	967.68	982.17
Solids	42.41	32.32	17.83
Albumin	27.82	16.11	3.64
Ethereal extract	14.59	5.27	0.50
Alcoholic extract		10.94	3.71
Aqueous extract			1.10
Inorganic salts			9.00
Errors of analysis			0.12

Analysis of Hydrocele Fluid.

Water	938.85
Solids	61.15
Fibrin (formed)	0.59
Globulins	13.52
Serum-albumin	35.94
Ethereal extract	4.02
Soluble salts	8.60
Insoluble salts	0.66
Sodium chloride	6.19
Sodium oxide	1.09

Sugar and uric acid in small amounts are also, as a rule, found in transudates, and in one case of hepatic cirrhosis Moscatelli succeeded in demonstrating the presence of allantoin.

Microscopic Examination.

Upon microscopic examination only a few isolated leucocytes and endothelial cells derived from the serous surfaces and undergoing fatty degeneration are seen. In cases in which the transudates have been confined for a long time in one of the serous cavities plates of cholesterin are frequently found. These appear to be especially abundant in hydrocele fluid.

EXUDATES.

Exudates may be serous, sero-fibrinous, sero-purulent, purulent, putrid, hemorrhagic, chylous, or chyloid, terms which do not require further definition.

The purulent, sero-purulent, and putrid forms are manifestly of inflammatory origin, while it may at times be difficult to decide the true nature of serous, sero-fibrinous, and sero-sanguineous fluids. In such cases the points of difference already described between transudates and exudates should be borne in mind, and will, when taken in conjunction with the physical signs and the clinical history, generally lead to a correct diagnosis of the origin of the fluid.

Serous Exudates.

Serous exudates are clear, of a light-straw color, and present a specific gravity usually exceeding 1.008. After standing, a white, fibrinous coagulum is generally formed. Upon microscopic examination some red corpuscles, which are probably referable to the puncture, polynuclear leucocytes, and endothelial cells undergoing fatty degeneration are found. Such exudates, as indicated, differ from the corresponding transudates in presenting a higher specific gravity, and in the fact that clotting is observed in transudates only in the presence of blood. Exudates, however, do not invariably coagulate, and too much importance should hence not be attached to this point.

Hemorrhagic Exudates.

Hemorrhagic exudates are essentially sero-fibrinous in character, the exact color depending upon the amount of blood-pigment present. Microscopic examination reveals the presence of a large number of red corpuscles, polynuclear leucocytes, and endothelial cells. Cholesterin-crystals may also at times be seen, though rarely in very large numbers. When numerous, attention is readily drawn to them, during the macroscopic examination of the fluid, by the peculiar glistening appearance of its surface.

Tuberculosis. As hemorrhagic exudates are most commonly observed in cases of tuberculosis and of carcinoma of the lungs and pleura, the specimen should be carefully examined for tubercle bacilli and cancer-cells. In every case it will be best to subject portions of the fluid to centrifugation and to examine the sediment thus obtained. Usually tubercle bacilli are not found, even when tuberculosis of the pleura exists. If in such cases culture-experiments likewise prove negative and cancer-cells are not found, the diagnosis of probable tuberculosis will nevertheless be warrantable.

Cancer. The diagnosis of cancer should be based upon the demonstration of cancer-cells in the fluid. The physician, however, is warned not to mistake endothelial cells for cancer-cells. The diagnosis should hence only be made when large epithelial cells of variable form, measuring at times 120 μ in diameter, are found in large numbers, especially when arranged in groups, unless, indeed, cancerous nodules presenting the characteristic alveolar structure are at once found. Quincke has drawn attention to the occurrence of large numbers of fat-droplets, which may attain a diameter of from 40 μ to 50 μ in the fluid in cases of neoplasm. At times these fat-droplets are so small and numerous as to give a *chylous* appearance to the exudate. At other times a similar appearance is due to the presence of minute albuminous granules, which may be readily distinguished from the former by their insolubility in ether. The occurrence of numerous fatty-acid crystals arranged in groups should likewise be regarded as favoring the diagnosis of carcinoma. It is also claimed by Quincke that carcinoma probably exists if a marked glycogen reaction can be obtained in the endothelial cells. This test has already been described in the chapter on Blood (see p. 46).

Rieder has lately called attention to the occurrence of cells undergoing division, their nuclei presenting essentially typical karyokinetic

figures, which he regards as pathognomonic of carcinoma. Cover-slip preparations are prepared from the sediment, dried in the air, fixed by immersion for an hour in a mixture of equal parts of absolute alcohol and ether, and stained with a dilute solution of hæmatoxylin.

Putrid Exudates.

Putrid exudates are observed following the perforation of a gangrenous focus or of a gastric or intestinal ulcer into one of the body-cavities. At other times they are encountered in cases of neoplasm and at times even without any apparent cause. The material obtained in such cases presents a brown or brownish-green color, and emits an odor which in itself indicates the character of the exudate. Microscopically cholesterin, hæmatoidin, and fatty-acid crystals, as well as degenerating leucocytes, are found. In cases in which aspiration of a higher intercostal space reveals the presence of serous fluid, while putrid material is obtained at a lower point, the existence of a subphrenic abscess should be suspected. In such cases a pure culture of the bacillus coli communis has been obtained. The reaction of putrid exudates is usually alkaline, but an acid reaction may be obtained in cases of perforation of a gastric ulcer; the sarcina ventriculi and saccharomyces may then be found.

Pus.

General Characteristics of Pus. If pus, which usually presents a color varying from yellowish-gray to greenish-yellow, be allowed to stand for some time, a liquid gradually appears at the top, increasing in amount, until it is finally possible to distinguish two distinct layers, the one above—the pus-serum, the other at the bottom—the pus-corpuscles. Upon the number of the latter the consistence as well as the specific gravity of the pus is dependent. This may vary between 1.020 and 1.040, with an average of 1.031 to 1.033. Fresh pus has always an alkaline reaction, which may become neutral or slightly acid upon standing, owing to the development of free fatty acids, glycerin-phosphoric acid, and lactic acid. The color of pus-serum may be a light straw, a greenish, or a brownish-yellow.

The Chemistry of Pus. The chemical composition of pus-serum and pus-corpuscles may be seen from the following tables:

ANALYSIS OF PUS-SERUM.

	I.	II.
Water	913.7	905.65
Solids	86.3	94.35
Albumins	63.23	77.21
Lecithin	1.50	0.56
Fat	0.26	0.29
Cholesterin	0.53	0.87
Alcoholic extract	1.52	0.73
Aqueous extract	11.53	6.92
Inorganic salts	7.73	7.77

ANALYSIS OF PUS-CORPUSCLES.

	I.	II.
Albumins	137.62	.....
Nuclein	342.57	673.69 685.85
Insoluble matter	205.66	.....
Lecithin Fat	143.83	75.64 75.00
Cholesterin	74.0	72.83
Cerebrin Extractives	51.99 44.33	101.84

Peptone is usually present, being derived from the pus-corpuscles. Leucin and tyrosin are likewise frequently met with in the pus of old abscesses, and fatty acids, urea, sugar, glycogen, biliary pigments, and acids (in catarrhal jaundice), acetone, uric acid, several xanthin bases, cholesterin, etc., have occasionally been observed.

MICROSCOPIC EXAMINATION OF PUS. *Leucocytes.* If a drop of pus be examined with the microscope, it will be seen to contain innumerable leucocytes, the diameter of which varies from 8 μ to 10 μ, and which in fresh pus exhibit the characteristic amœboid movements. It is curious to note that the so-called lymphycotes do not occur in pus, and even in the rare cases in which a predominance of this variety is met with in the blood, as in cases of lymphatic leukæmia, it will be observed that only the larger forms occur in the pus of abscesses which may have formed. While the leucocytes of fresh pus usually present a normal appearance, specimens may be observed in which amœboid movements can no longer be observed, even upon the application of heat, and in which rounded vacuoles, filled with a clear liquid, and fatty granulations in moderate numbers may be seen. A predominance of such dead leucocytes usually in-

dicates that the pus is old or has been formed in greatly debilitated subjects.

Owing to a resorption of water in accumulations of pus of long standing such material finally assumes a caseous aspect, and the leucocytes will be seen to have greatly diminished in size, and to have assumed an angular, shrunken appearance; it is then hardly possible to demonstrate the presence of a nucleus even after the addition of acetic acid.

It is noteworthy that in cases of hepatic abscess referable to the amœba coli it is seldom possible to demonstrate any normal leucocytes, the pus upon microscopic examination consisting essentially of granular and fatty detritus, while in liver-abscesses due to other causes the leucocytes usually present a fairly normal appearance.

Giant corpuscles. So-called giant pus-corpuscles, measuring at times from 30 μ to 40 μ in diameter, have been observed in abscesses of the gum, hypopyon, and in the contents of suppurating ovarian cysts, but do not appear to have any special significance. Upon careful examination these bodies will be seen to contain one oval nucleus, usually located excentrically within the cell, and from one to thirty or even forty pus-corpuscles.

Detritus. Fatty and albuminous detritus in variable amount may be observed in every specimen of pus, increasing with the length of time that the latter has been confined within the body. The same holds good for the presence of free nuclei, which were formerly regarded as young pus-corpuscles, but which have now been definitely recognized as originating during the disintegration of the corpuscles.

Red corpuscles. Red blood-corpuscles in variable numbers are usually seen in every specimen, their appearance depending upon the length of time that they have been confined. Pus-corpuscles may at times be seen to contain a red corpuscle.

In doubtful cases it is always well to search carefully for the presence of tissue-elements, as it is at times possible only in this manner to recognize the true character of the morbid process. As the data of importance have already been detailed in other sections of this book (viz., Sputum and Urine), it will be unnecessary to recapitulate at this place.

Pathogenic vegetable parasites. Among the pathogenic organisms encountered which are of especial interest from a clinical standpoint there may be mentioned the true pus-organisms, notably the staphy-

lococcus pyogenes aureus and the streptococcus pyogenes; furthermore, the tubercle bacillus, the bacillus of syphilis, the actinomyces hominis, the bacillus of glanders, the bacillus of anthrax, leprosy, tetanus, influenza, and Fränkel's pneumococcus, etc. The majority of these have already been described, and the reader is referred for more detailed information to special works on bacteriology. In this connection it will be sufficient to state that, so far as pleural exudates are concerned, an absence of micro-organisms is usually indicative of tuberculosis, while the presence of Fränkel's pneumococcus in exudates forming in the course of a pneumonia appears to be a favorable omen, as far as the origin of the pleurisy is concerned.

Protozoa, with the exception of the amœba coli, have only rarely been found. Künstler and Pitres observed numerous large spores with from ten to twenty crescentic corpuscles in the pus taken from the pleural cavity of a man, which closely resembled the coccidia of mice. Litten observed cercomonads in the fluid withdrawn from a pleural cavity. Trichomonads have been found in a case of empyema.

Most important in this connection is the demonstration of the presence of the amœba coli in the pus, and in cases of liver-abscess an examination with this view should never be neglected, as the prognosis to a large extent will depend upon the results obtained. As far as the occurrence of amœbæ in *pus* is concerned, the observation of Flexner, who demonstrated their presence in an abscess of the lower jaw, shows that they should not be looked for in the pus of abscesses of the liver only.

Vermes. Of these, the filaria and hydatids are very rarely observed in this country. Bothriocephalus leguloides has been found in the pleural cavity of a Chinese patient.

Crystals. As has been stated, crystals of cholesterin are frequently found in old pus and in exudates of long standing, but are rarely seen in recent exudates. They may be recognized by their characteristic form and their chemical reactions, as described in the chapter on Feces (p. 195). Triple phosphates, fatty-acid crystals, and hæmatoidin are likewise frequently seen, the presence of the latter, of course, indicating a previous admixture of blood.

Chylous and Chyloid Exudates.

Chylous and chyloid exudates have been repeatedly observed. They are most frequently met with in the abdominal cavity (104

times out of the total number of 155, which have thus far been reported), less commonly in the pleural cavity (forty-nine times), and only rarely in the pericardial sac (twice only). Quincke believed that the two forms can be etiologically distinguished from one another by means of a microscopic examination, as the cloudy appearance in the chyloid form is usually referable to the presence of endothelial or epithelioid cells undergoing fatty degeneration. Later observations, however, have shown that the differentiation of the two forms cannot be made upon this basis, as the same anatomical changes, such as carcinoma, may at times give rise to the formation of a chylous exudate, at others to that of the chyloid form, and both, moreover, may coexist. Senator claimed that the presence of more than mere traces of sugar is strongly suggestive of the chylous nature of the exudate. Possibly this observation may be of some value, but it must not be forgotten that sugar is quite commonly met with in all forms of transudates and exudates. The presence of more than 0.2 per cent. can only be of value.

Chylous exudates in their general appearance resemble milk, while the chyloid fluid is more suggestive of pus. The turbidity in both cases is usually referable to the presence of innumerable fat globules, which are especially abundant in the chylous form. In chyloid exudates the origin of the fat from cellular elements is often apparent at once, but, as has been said, it is impossible to draw definite etiologic conclusions from that difference. Some chyloid exudates contain no fat at all, and Lion has shown that the milky appearance in such cases is owing to the presence of a curious albuminous substance, belonging to the class of nucleo-albumins.

CHAPTER IX.

THE EXAMINATION OF CYSTIC CONTENTS.

CYSTS OF THE OVARIES AND THEIR APPENDAGES.

THE material obtained from cysts of the ovaries or their appendages varies greatly in character. On the one hand, it may be fluid, clear, of low specific gravity, and containing but little albumin, while, on the other, it may be dense, viscous, of colloid appearance, and of specific gravity varying between 1.018 and 1.024, owing to the presence of a large amount of albumin, viz., serum-albumin, serum-globulin, and, most important of all, metalbumin or paralbumin. The latter is almost constantly met with in ovarian cysts, and its presence is quite characteristic of fluids derived from this source.

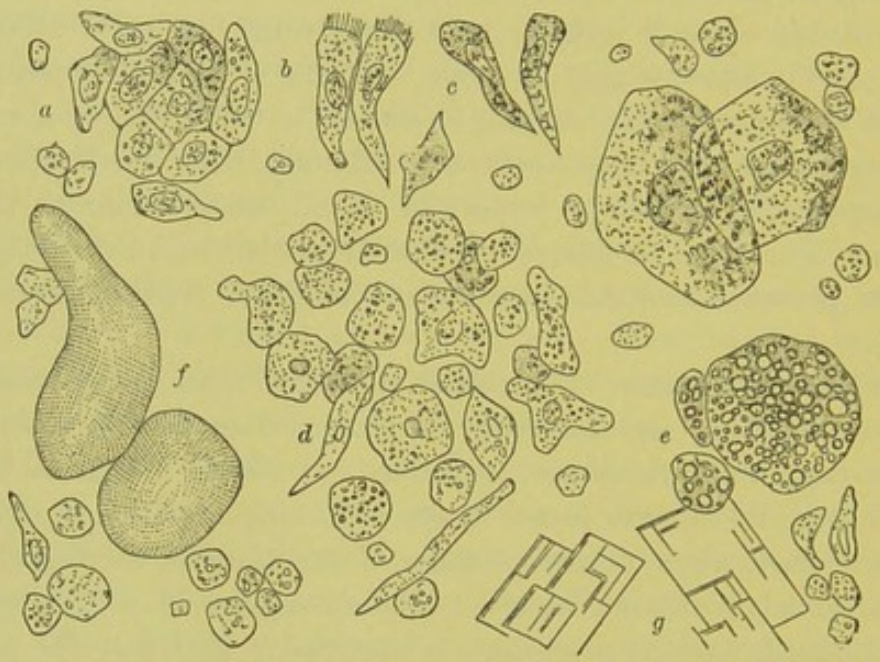
Test for metalbumin. The fluid is mixed with three times its volume of alcohol and set aside for twenty-four hours, when it is filtered and the precipitate suspended in water. This is again filtered and the filtrate tested in the following manner: 1. A few c.c. are boiled, when in the presence of metalbumin the liquid will become cloudy, without, however, the formation of a precipitate. 2. With acetic acid no precipitate is obtained. 3. Upon the application of the acetic acid and potassium ferrocyanide test the liquid becomes thick and assumes a yellowish color. 4. When boiled with Millon's reagent a few c.c. of the filtrate will yield a bluish-red color, while the addition of concentrated sulphuric acid, without boiling, gives rise to a violet color.

The color of cystic fluids may vary from a light straw to a reddish-brown, or even chocolate; the latter color may be observed when hemorrhage has taken place into the cyst.

Of morphologic elements, ovarian cysts contain red blood-corpuscles, leucocytes, and at times fatty granules in large numbers, crystals of cholesterin, hæmatoidin, and fatty acids. Most important, however, from a diagnostic standpoint is the presence of cylindrical or prismatic ciliated epithelial cells, derived from the internal lining of the cyst, in the presence of which the diagnosis may be

definitely made. (Fig. 125.) At times such cells cannot be demonstrated, owing to their having undergone fatty degeneration; moreover, if the epithelium, lining the cyst, be squamous in character, it may be difficult, if not impossible, to arrive at a satisfactory conclusion from an examination of the morphologic elements alone. *Colloid concretions*, which may vary in size from several micromillimeters to 0.1 mm., are occasionally observed, more particularly in cases of colloid cysts. They may be recognized by their irregular form, their homogeneous appearance, their slightly yellowish color, and delicate outlines.

FIG. 125.



Contents of an ovarian cyst. (Eye-piece III, obj. 8 a, REICHERT.) (V. JAKSCH.)
a. Squamous epithelial cells. *b*. Ciliated epithelial cells. *c*. Columnar epithelial cells. *d*. Various forms of epithelial cells. *e*. Fatty squamous epithelial cells. *f*. Colloid bodies. *g*. Cholesterin crystals.

In dermoid cysts, epidermal cells and occasionally hair are observed, in which case the diagnosis is no longer doubtful.

The differential diagnosis of ovarian, parovarian, and fibro-cystic (uterine) cysts cannot always be made by the characters of the fluid withdrawn by puncture, but at times it is possible. The most important points of difference are here given: 1. The fluid in ovarian cystomata is usually more or less viscid, and often contains non-nucleated granular corpuscles about the size of leucocytes, the granules not dissolving in acetic acid, nor disappearing when treated with ether. In all probability they are free nuclei and are often called Drysdale's corpuscles in our country. 2. In parovarian cysts the

fluid is thin, watery, of low specific gravity (under 1.010), and contains very few morphologic elements. Cylindrical epithelium is very rarely found in the fluid withdrawn by aspiration from either ovarian or parovarian cysts during life. 3. The fluid from fibro-cystic tumors of the uterus is thin, watery, and spontaneously coagulable, while that from ovarian and parovarian cysts never coagulates spontaneously, unless blood be present. Fibro-cystic tumors of the uterus have no epithelial lining.

HYDATID CYSTS.

Hydatid cysts are scarcely ever seen in this country, and may practically be excluded in a differential diagnosis. The fluid in question is clear, alkaline, of a specific gravity varying between 1.006 and 1.010, and contains no albumin. *Succinic acid* is usually present, and may be demonstrated by acidifying a small amount of the fluid with hydrochloric acid and evaporating to dryness. The residue is extracted with ether and the ether evaporated, when the aqueous solution of the second residue in the presence of succinic acid will yield a rust-colored gelatinous precipitate when treated with a few drops of a solution of the sesquichloride of iron. *Sodium chloride* is always present in notable amounts and may be recognized by evaporating a drop of the liquid upon a slide, when the characteristic crystals of salt will be found. Most important, of course, is the microscopic examination, which may reveal the presence of hooklets and shreds of membrane, and at times of scolices (see Sputum).

HYDRONEPHROSIS.

The diagnosis of hydronephrosis can usually be made without difficulty if a sufficient amount of fluid can be obtained, as the presence of urea and uric acid in *notable quantities*, as well as of renal epithelial cells, which latter especially should be sought for, is quite characteristic. Small amounts of uric acid may also be present in ovarian cysts.

PANCREATIC CYSTS.

These cysts may be recognized by the fact that the fluid possesses the power of digesting albumin in alkaline solutions. A small amount of the liquid is added to milk, when after precipitation

of the casein the biuret test is applied, a positive reaction indicating the presence of *trypsin*. Unfortunately, however, this test does not always yield positive results, even if the fluid in question be derived from a pancreatic cyst, as the trypsin is apparently destroyed in the course of time. The larger the size of the cyst, the less likely will it be possible to obtain the reaction described. A positive result is hence only of value, while a negative result does not exclude the existence of the disease.

CHAPTER X.

THE EXAMINATION OF THE CEREBRO-SPINAL FLUID.

According to our present knowledge, the cerebro-spinal fluid is secreted by the choroid plexuses into the lateral ventricles. Passing through the foramina of Monroe, the third ventricle, and the aqueduct of Sylvius, on the one hand, it reaches the fourth ventricle and enters the cistern-like subarachnoid spaces at the base of the brain through the foramen of Magendie and the lateral clefts of the fourth ventricle. On the other hand, a certain portion of the fluid reaches the same destination directly through the cleft in the descending horn of each lateral ventricle. The larger portion of the fluid then passes upward through the subarachnoid spaces along the convexity of the brain to the Pacchionian granulations, while the smaller portion enters the vertebral canal through the subarachnoid spaces of the spinal arachnoid membrane.

Within recent years puncture of the vertebral canal has been resorted to repeatedly, not only for therapeutic purposes, but also for diagnostic purposes, after Quincke had drawn attention to the fact that cerebro-spinal fluid can thus be obtained with comparative ease. The practical value of this new method of diagnosis is now beyond question, and it is to be hoped that ere long physicians will resort to spinal puncture in obscure cases of cerebro-spinal disease with as little hesitancy as puncture of the thoracic and abdominal cavities is now practised.

The *operative method* to be employed is the following: With the patient placed upon his left side—some observers prefer the sitting-posture—and the body bent well forward, a long aspirating-needle is introduced upon a level with the lower third of the third or fourth lumbar spinous process and a little to the side of the median line, the needle being directed slightly upward and inward. The depth to which it is necessary to puncture will, of course, vary with the age of the patient. In a child two years of age the vertebral canal may be reached at a depth of two centimetres, while in the adult it is necessary to insert the needle for a distance of from 4 to 8 cm.

As soon as the subarachnoid space is reached the cerebro-spinal fluid will flow from the needle. *Aspiration* should always be avoided.

Some writers have advised that the operation should be performed under narcosis, and without doubt this may be necessary at times, particularly when contracture of the dorsal muscles exists. In the majority of cases, however, it is probably not necessary.

Amount. As far as the writer has been able to ascertain, no observations have thus far been made regarding the amount of fluid which may be obtained by puncture in normal individuals. In all probability, however, this is small. Under pathologic conditions the amount may vary from a few drops to 100 c.c., and even more. In general terms it may be stated that the amount is directly proportionate to the degree of intra-cranial pressure. Exceptions, however, are frequent. Small amounts of cerebro-spinal fluid or none at all may thus be obtained, when owing to the formation of a thick exudate or the existence of a cerebral tumor the communication between the basilar subarachnoid spaces of the brain and those of the spinal cord has been interrupted. Whenever, then, symptoms of intra-cranial pressure exist, while no fluid or minimal amounts only can be obtained by puncture, the conclusion will usually be justifiable that we are dealing with a purulent meningitis or with a tumor of the brain, and more especially of the cerebellum. It should be remembered, however, that the same result may be reached in cases of obliteration of the aqueduct of Sylvius or when sclerotic processes involve the foramen of Magendie, which is occasionally observed in certain forms of hydrocephalus. Adhesions of the pia mater with the arachnoid and the dura mater may, by interfering with the flow of cerebro-spinal fluid, also lead to the formation of hydrocephalus, but in these cases a tumor can usually be excluded, as the changes in question always develop as sequelæ to a meningitis. A serous or tubercular meningitis, as well as acute hydrocephalus and tetanus, can, however, always be excluded when only minimal amounts of fluid are obtained by puncture. The largest amounts, on the other hand, are seen in cases of serous meningitis, tubercular meningitis, and cerebral tumors, which do not interfere with the circulation of the cerebro-spinal fluid.

Appearance. Normal cerebro-spinal fluid, as well as that obtained in cases of serous meningitis, tubercular meningitis, hydrocephalus, and tumors of the brain, is perfectly clear, and as a rule colorless, unless indeed a small bloodvessel has been

punctured, when the fluid may present a slightly reddish tinge. More or less pronounced yellow shades are, however, also at times observed. Important from the standpoint of diagnosis is the fact that in cases of hemorrhage into the ventricles pure blood is obtained, while such a result is, of course, a mechanical impossibility in cases of epidural hæmatoma. In subdural hæmatoma, on the other hand, blood may also find its way into the subarachnoid space, but the amount is always small, and cannot be compared to that seen in cases of ventricular hemorrhage. Whenever, then, as in traumatic cases with severe cerebral symptoms, the surgeon is confronted with the question whether or not to trephine, puncture of the subarachnoid space may furnish much valuable information. If in such cases no blood at all is obtained, it may be inferred that an epidural hæmatoma or a subdural hæmatoma of slight extent only exists; an operation might then be performed. If, however, pure blood be found, it would be justifiable to assume the existence of extensive injury to the brain-substance proper, or in cases in which the history of the case is obscure an intra-cerebral hemorrhage with rupture into the ventricles. In such cases the idea of an operation would, of course, only be entertained under exceptional conditions. If, further, the fluid is only tinged with blood a subdural hæmatoma probably exists, and an operation could be advised. Accidental hemorrhage, viz., hemorrhage referable to the puncture itself, can be readily recognized, as the first few drops only are then tinged with blood, or the blood appears only after the flow has been definitely established; the amount, moreover, is insignificant.

Cloudy fluid is obtained in all cases of purulent meningitis unless this be limited to a very small area. This is, of course, most important from a diagnostic standpoint. Cases of abscess of the brain or sinus thrombosis occur again and again in which the question as to the advisability of operative interference is largely dependent upon the presence or absence of a complicating purulent meningitis. In certain instances a satisfactory conclusion may, of course, be reached without puncture; but in many others this is impossible, and Lichtheim's dictum that an operation should never be undertaken in such cases unless the integrity of the meninges has been established by spinal puncture should be borne in mind.

The degree of cloudiness naturally varies in different cases, and while in some instances the character of the fluid is sero-purulent, pure, creamy pus may be found in others. Generally speaking, a

cloudy fluid indicates the existence of an acute inflammatory process or an acute exacerbation of a chronic process.

Important, furthermore, is the fact that the fluid in non-inflammatory diseases of the brain, such as tumor or abscess, rarely undergoes coagulation, while this is the rule in all inflammatory diseases. In tubercular meningitis the coagula are very delicate, and may be well compared to spider-webs, extending throughout the fluid, while in purulent meningitis the coagula are much firmer.

Specific Gravity. The specific gravity of cerebro-spinal fluid normally varies between 1.005 and 1.007, corresponding to the presence of from 10 to 15 p. m. of solids. Under pathologic conditions variations from 1.003 to 1.012 may be observed, the specific gravity, generally speaking, being higher in the inflammatory than in the non-inflammatory diseases of the brain. From a diagnostic standpoint, however, the determination of the specific gravity is of no special interest, as numerous exceptions occur to the above rule.

The *reaction* is always alkaline.

Chemical Composition. An idea of the chemical composition of the cerebro-spinal fluid may be formed from the following analysis, taken from Gautier:

Water	987.00
Albumin	1.10
Fat	0.09
Cholesterin	0.21
Alcoholic and aqueous extract, minus salts Sodium lactate	2.75
Chlorides	6.14
Earthy phosphates	0.10
Sulphates	0.20
Ammonia	.....

In addition urea is at times found, as also a substance which reduces Fehling's solution and gives rise to a brown color when boiled with caustic potash, but which neither undergoes fermentation nor forms an osazon when treated with phenylhydrazin. The substance in question is generally regarded as pyrocatechin. Its amount varies between 0.002 and 0.116 per cent. According to C. Bernard, moreover, glucose is said to be present, but it is questionable whether this is actually the case under normal conditions (see below). As far as the albuminous bodies are concerned which may be found in the cerebro-spinal fluid, serum-albumin is said to be present only under exceptional conditions, while normally a mixture

of globulin and albumoses is found. The question whether or not mucin may also be present is still undecided.

Under pathologic conditions the amount of albumin may vary considerably, and is of some diagnostic importance. According to the majority of observers the figure given in the above analysis is somewhat too high, and it is questionable whether 1 p. m. may be regarded as normal. The lowest values have been obtained in cases of chronic hydrocephalus (traces only), meningitis serosa (0.5 to 0.75 p. m.), and tumors of the brain (traces to 0.8 p. m.), while the largest amounts have been found in chronic hydrocephalus, the result of hyperæmia (1 to 7 p. m.), and tubercular meningitis (1 to 3 p. m.).

Lichtheim claims to have found glucose—by means of the phenylhydrazin test—in all cases of tumor which he examined. In cases of tubercular meningitis, on the other hand, a positive result was only exceptionally obtained. Quincke also reports that he was able to demonstrate the presence of sugar whenever the liquid obtained was sufficient in amount for the necessary tests. Unfortunately, however, he does not detail his cases.

The experience of other observers does not agree with that of Lichtheim and Quincke, and Fürbringer, who has thus far reported the largest number of spinal punctures, has found sugar in only two cases of diabetes associated with tuberculosis.

Microscopic Examination. The microscopic examination of the fluid withdrawn by spinal puncture is most important.

Under normal conditions, as well as in cases of tubercular meningitis, tumor, abscess, acute and chronic hydrocephalus, only a few leucocytes and endothelial cells from the subarachnoid spaces are usually found, enclosed in extremely delicate meshes of fibrin. In purulent meningitis, on the other hand, leucocytes are present in large numbers, and in some instances pure pus may even be obtained.

Most important from a diagnostic standpoint is the fact that pathogenic micro-organisms may be found. Lichtheim, Fürbringer, Freyhan, Dennig, and Fränkel were thus able to demonstrate the presence of tubercle bacilli in a fairly large number of cases of tubercular meningitis. Other observers, it is true, have been less fortunate, but the fact that Fürbringer found tubercle bacilli in thirty cases out of thirty-seven is certainly encouraging. In order to examine for tubercle bacilli the fluid should be allowed to stand until a slight coagulum has formed, when the fine spider-web-like threads of fibrin

are transferred to a cover-slip, spread out in as thin a layer as possible, and stained as described in the chapter on Sputum. If a centrifugal machine be available, the examination may, of course, be made at once, and the chances of finding the bacilli are undoubtedly much greater. In every case a number of specimens should be prepared before the search is abandoned. A positive result only is of value.

In cases of purulent meningitis associated with median otitis Lichtheim was repeatedly able to demonstrate the presence of streptococci, and in some instances of the diplococcus pneumoniæ. The latter organism, as also the staphylococcus pyogenes aureus and albus, has been found in cases of epidemic cerebro-spinal meningitis.

CHAPTER XI.

THE SEMEN.

DEFINITION.

THE ejaculated semen is a mixture of the secretions furnished by the testicles, the prostate gland, the seminal vesicles, and the glands of Cowper.

GENERAL CHARACTERISTICS.

Semen is white or slightly yellowish in color, semi-fluid, sticky, and of an opaque, non-homogeneous, milky appearance, which is due to the presence of white, opaque islets floating in the otherwise clear fluid; these consist almost entirely of the specific morphologic elements of the semen, the spermatozoa. Its odor, strongly resembling that of fresh glue, is very characteristic, and is owing to the presence of *spermin*. It is generally attributed to an admixture of prostatic fluid, as the semen obtained from the vasa deferentia is odorless. According to Robin, however, this odor is only produced at the moment of ejaculation, and cannot be ascribed to any single one of the secretions present. The reaction of human semen is slightly alkaline, and its specific gravity is greater than that of water, in which it readily sinks.

CHEMISTRY OF SEMEN.

Curiously, no accurate analyses of human semen or of mammalian semen have been made, and only the old analyses of Vauquelin and Köllicker can be given.

	Man.	Horse.	Ox.
Water	90	81.9	82.1
Albuminous material	6	...	15.3
Extractives		16.45	
Ethereal extract		...	2.2
Mineral material	4	1.61	2.6

The mineral matter consists largely of calcium phosphate.

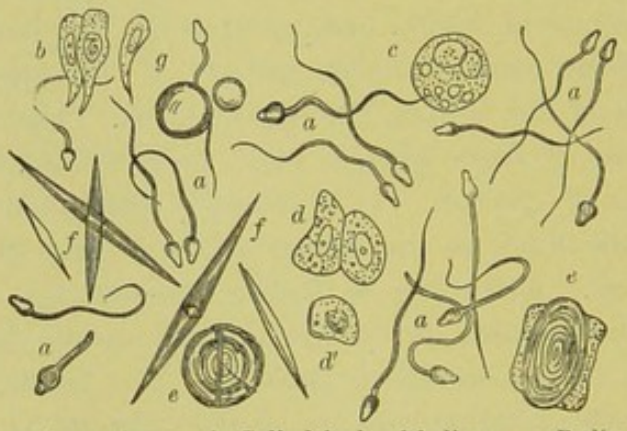
If semen be kept for any length of time, or if it be slowly evapo-

rated, crystals of spermin will separate out. These have been shown to be chemically identical with the phosphate of ethylenimin, $C_2H_4(NH)$, and hence with the so-called Charcot-Leyden crystals so frequently seen in asthmatic sputa and in the blood of leukæmic patients.

MICROSCOPIC EXAMINATION OF THE SEMEN.

Upon microscopic examination normal semen is seen to contain innumerable, actively moving, thread-like bodies, measuring from 50 μ to 60 μ in length, the *spermatozoa*. These consist of an egg-shaped head, when seen from above, 3 μ to 5 μ in length, the broader end being directed anteriorly; a middle portion, 4 μ to 6 μ in length, with which the head is united by its smaller end; and a posterior piece or tail, into which the middle piece gradually fades (Fig. 126).

FIG. 126.



Human semen. *a*. Spermatozoa. *b*. Cylindrical epithelium. *c*. Bodies enclosing lecithin granules. *d*. Squamous epithelium from the urethra. *d'*. Testicle cells. *e*. Amyloid corpuscles. *f*. Spermatic crystals. *g*. Hyaline globules. (V. JAKSCH.)

In addition to the spermatozoa a few hyaline bodies are seen, derived from the seminal vesicles, numerous small, pale granules of an albuminous nature, some testicular and urethral epithelial cells, lecithin-corpuscles, and so-called prostatic or *amyloid corpuscles*, which at first sight resemble starch-granules in appearance, owing to their concentric striations; a few leucocytes and occasionally a few red corpuscles may also be found.

PATHOLOGY OF THE SEMEN.

The study of the semen has as yet received but little attention from clinicians, and gynecologists frequently hold the wife respon-

sible for sterility where an examination of the husband's semen would —according to Kehrer, in 40 per cent.—reveal an absence of spermatozoa, constituting the condition usually spoken of as *azoospermatism*. This may be temporarily observed following venereal excesses, when the fluid finally ejaculated is almost entirely of prostatic origin; it then possesses no significance, but persistent azoospermatism must of necessity be associated with sterility.

Cases have been recorded in which, notwithstanding the presence of spermatozoa and otherwise normal sexual conditions in both husband and wife, sterility nevertheless existed, but in which it was observed that the spermatozoa lost their motile power almost immediately after ejaculation, while under normal conditions it is a well-known fact that following intercourse actively moving spermatozoa may be found in the vagina after many hours, days, or even weeks.

Whenever it is deemed advisable to make an examination of the semen, this should be done immediately following ejaculation, or as short a time as possible at least be allowed to elapse, and note be taken, not only of the presence, but also of the motility of the spermatozoa, a drop of the semen being mixed with a drop of normal (0.6 per cent.) saline solution, and at once examined with the microscope.

THE RECOGNITION OF SEMEN IN STAINS.

In medico-legal cases the physician may be called upon to decide whether or not certain stains on the linen are caused by spermatic fluid, whether or not a rape has been committed, etc. In such cases it is frequently only necessary to examine a drop of the vaginal fluid in order to arrive at a positive result at once. At other times, however, recourse must be had to the following method: A fragment of the linen or scrapings from the vulva or vagina are placed in a watch-crystal and allowed to soak for at least one hour in from 27 to 30 per cent. alcohol, when a bit of the material is teased in a solution of eosin in glycerine (1 : 200), and examined. The heads of the spermatozoa are thus stained a deep red, while the tails, which are often found broken, exhibit a pale rose-tint, and can readily be distinguished from any vegetable fibres present, which do not take up the stain at all. A positive statement can thus be made in every case, even after months or years, as the spermatozoa not only resist the action of reagents, but also the process of putrefaction, probably owing to the greater proportion of mineral matter

which enters into their composition, and which insures the preservation of their form. Instances have been recorded in which it was possible to demonstrate the presence of spermatozoa in stains after eighteen years.

The test recently described by Florence has already attracted much attention, and may be recommended in doubtful cases. It is based upon the observation that very characteristic crystals of *iodospermin* are formed when spermatic fluid is treated with a solution of iodo-potassic iodide, especially rich in iodine. The reagent is composed of 1.65 gramme of pure iodine and 2.54 grammes of potassium iodide, dissolved in 26 grammes of water. When a drop of this solution is added to a drop of spermatic fluid or an aqueous extract of a seminal stain, dark brown crystals of iodospermin separate out at once and may be readily recognized under the microscope. They occur in the form of long rhombic platelets, or fine needles, often grouped in rosettes, but also occurring singly or as twin crystals. The examination with the microscope should be made at once after the addition of the reagent, as the crystals gradually disappear on standing.

As the reaction may also be obtained in cases of azoospermatism, and with pure prostatic secretion, while a negative result is obtained with the fluid from spermatoceles, it is manifest that the test is not applicable for the determination of the presence or absence of spermatozoa *pro se*. This fact, however, would rather make the test more valuable than otherwise.

Posner states that he obtained the same crystals when the test was applied to a glycerin extract of ovaries, an observation which cannot be surprising, as the ovaries, like the testes and prostatic gland, are rich in spermin. Negative results were reached with *putrefying* semen.

The author found that upon the addition of a drop of a 0.5 per cent. alcoholic solution of dimethyl-amido-azo-benzol to a drop of spermatic fluid, the heads of the spermatozoa are stained a distinct blue, while the neck and tail remain unstained.

CHAPTER XII.

VAGINAL DISCHARGES.

GENERAL CHARACTERISTICS.

THE secretion which is normally furnished by the vaginal glands is small in amount, and just sufficient to keep the mucous membrane moist. It is a clear or somewhat milky-looking, semi-liquid material, in which numerous epithelial laminæ, which have been thrown off during the normal process of desquamation, may be found. It has been stated that the reaction of the vaginal secretion in virgins is *invariably* acid, while an alkaline reaction is the rule in the *déflorées*. During pregnancy, however, the secretion is probably always acid. In 500 cases, which Kroenig examined in this direction, an alkaline reaction was never observed.

FIG. 127.



Vaginal secretion: *a*, mucous corpuscles; *b*, vaginal epithelium; *c*, epithelium from vulva.

Microscopically numerous epithelial cells, mucous corpuscles, a few large, mononuclear leucocytes, cellular detritus, and bacteria are found. (Fig. 127.) Doederlein has described a non-pathogenic bacillus or a group of bacilli, which are characterized by the fact that they give rise to marked acid fermentation of sugar, and he regards these organisms as the only ones which are constantly present in the normal vagina. Kroenig and Menge, however, state that they

are often absent. They have found, on the other hand, that there are various bacilli and cocci present under normal conditions, which belong to the class of obligatory anaërobes and are likewise non-pathogenic. Unfortunately they have not described these organisms in detail. Near the outlet they further found bacteria which can be cultivated upon alkaline aërobic culture media, but which are usually absent in the upper portion of the vagina.

It is important to note that various diplococci may also be found under normal conditions, and care should be taken not to confound these with the gonococcus. Like the gonococcus, they are unfortunately decolorized by Gram's method. If the various characteristics of the former be borne in mind, however, mistakes can always be avoided. In married females, and in children especially, it will probably always be best to make the diagnosis of gonorrhœa only when the gonococcus has been isolated by cultivation.

The question whether or not pathogenic bacteria may occur in the normal vagina of pregnant or non-pregnant women may be answered in the affirmative, although it must be admitted that with the exception of the gonococcus they are not often found. The vaginal secretion has been shown to possess most powerful bactericidal properties, so that pathogenic organisms, even if they are artificially introduced into the vagina, are rapidly killed. Kroenig thus found that the bacillus pyocyaneus disappears from the vagina of pregnant women in from ten to thirty hours, the staphylococci in from six to thirty-six hours, and the streptococcus pyogenes within six hours. Important from a practical standpoint is the fact that the bacteria disappeared less rapidly when irrigation of the vagina with water or even antiseptics was employed.

Of animal parasites the *trichomonas vaginalis* is apparently the only one which may be encountered in the vaginal discharge. The organism is identical with the trichomonas found in the feces and in the urine. In this country it is rarely observed, while it is decidedly common among the peasant population of Central Europe. As far as is known the organism is of no pathologic significance, and may occur both under normal and pathologic conditions. From a medico-legal standpoint, however, its presence may not be unimportant, as cases are on record in which trichomonades have been confounded with spermatozoa. Such a mistake, in the writer's judgment, can only occur when the observer is entirely without microscopic training. In doubtful cases the test of Florence may be

advantageously employed (see p. 534). Or the specimen may be stained with dimethyl-amido-azo-benzol (0.5 per cent. alcoholic solution), when the heads of the spermatozoa will exhibit a blue color, while the body of the trichomonas is stained yellow.

VAGINAL BLENORRHŒA.

In physiologic conditions an increased vaginal secretion is observed during sexual excitement, especially during coitus, just preceding and at the beginning of the process of menstruation and during pregnancy, when a profuse blenorrhœa is frequently seen, which often assumes a virulent character. The secretion under such conditions readily becomes purulent. When not depending upon a gonorrhœal infection the secretion is thicker than normal, white and creamy. At times also the vaginal catarrh observed in pregnancy is complicated with mycosis, when white or yellowish-gray patches may be seen at the orifice of the vagina; the latter may, indeed, even be filled with particles which consist entirely of fungi.

MENSTRUATION.

At the beginning of menstruation, as has been pointed out above, an increase in the amount of vaginal secretion is observed, in which leucocytes, prismatic epithelial cells coming from the uterus, as well as the usual vaginal cells, may be seen upon microscopic examination. Later the secretion becomes sanguinous in character, and finally only epithelial cells, leucocytes, and granular detritus are encountered, the cells usually showing evidence of fatty degeneration. The amount of blood lost at each menstrual period amounts to about 200 grammes in perfectly healthy females.

THE LOCHIA.

The lochia during the first day following parturition are red in color, the *lochia rubra*, and emit the characteristic sanguinous odor. At this time a microscopic examination will reveal an abundance of red corpuscles, some leucocytes, and a variable number of epithelial cells, which are almost exclusively of vaginal origin. On the second and third days the number of red corpuscles diminishes while the leucocytes increase in number. Still later the diminution in the red

and the increase in the white corpuscles becomes more marked, the discharge at the same time assuming a grayish or white color, until about the tenth day the red corpuscles have almost entirely disappeared, while the leucocytes and epithelial cells are quite abundant. Finally, the secretion becomes thicker, mucoid, and milky-white in color—the *lochia alba*, which condition may persist for from three to four weeks in nursing-women, and still longer in those who do not nurse, until at last the normal secretion is again observed. Numerous bacteria are encountered in the lochia, and it is curious to note that among these pus-organisms are quite constantly present, without giving rise to any symptoms. When a portion of the placenta or membranes has been retained the lochia soon give off a fetid odor, and assume a dirty brownish color; the retention of blood-clots alone may also produce this result. In such cases the lochia swarm with bacteria of all kinds.

VULVITIS AND VAGINITIS.

In cases of vulvitis and vaginitis a marked increase is observed in the number of cellular elements, both leucocytes and epithelial cells, the character of the latter depending, of course, essentially upon the portion of the genital tract affected. Red corpuscles are also met with at times, their number generally bearing a direct relation to the intensity of the inflammatory process. In some instances epithelial casts of the entire vagina have been observed, constituting the condition which has been termed *vaginitis exfoliativa*. The disease, however, is very rare.

The discharge of large amounts of pure pus through the vagina points to perforation of an abscess of the genital organs or of the neighboring structures into the uterus or the vagina, but is of rare occurrence. Much more common is the discharge of fecal matter or of urine through this channel, indicating the existence of a vagino-rectal or vagino-vesical fistula.

MEMBRANOUS DYSMENORRHŒA.

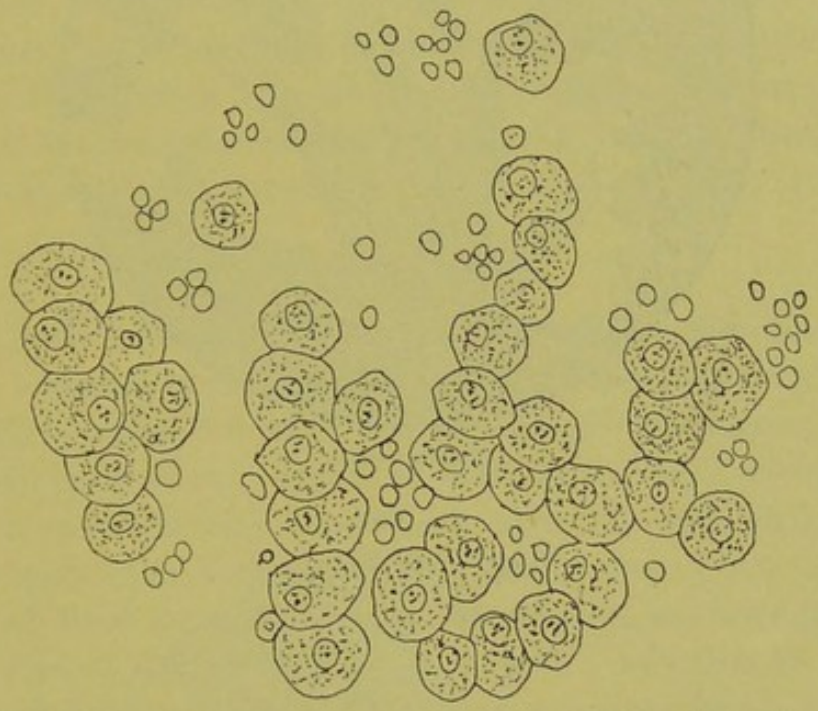
While ordinarily, during menstruation, shreds of desquamated uterine lining are frequently encountered, it is rare to meet with large pieces or complete casts of the uterus, the elimination of which is usually associated with the symptoms of a severe dysmenorrhœa,

constituting the condition generally spoken of as *membranous dysmenorrhœa.*

CANCER.

While the diagnosis of a malignant growth of the uterus has probably never been based upon a microscopic examination of the vaginal discharge, it may be mentioned that such, however, is possible, as fragments of an epithelioma of the cervix, for example, may frequently be detected upon microscopic examination. (Fig. 128.)

FIG. 128.



Vaginal secretion from a case of epithelioma of the cervix uteri.

GONORRHŒA.

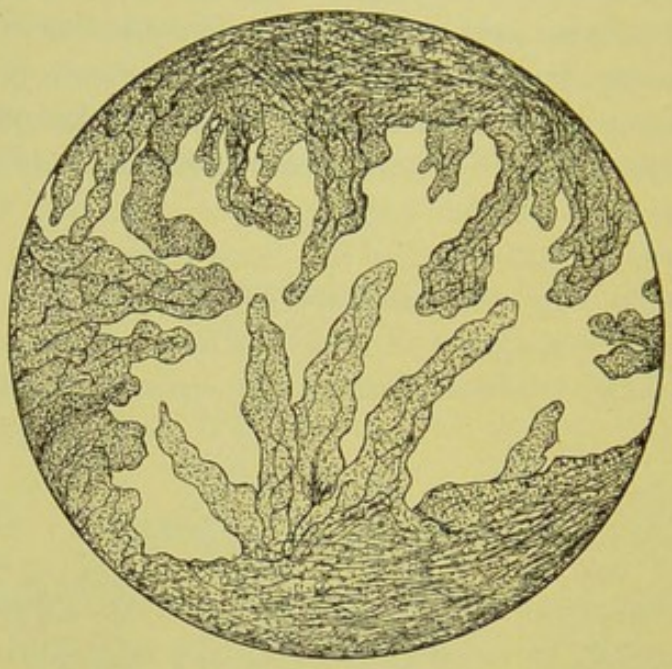
Very important is the examintion of both vaginal and urethral discharges in suspected cases of gonorrhœa for the presence of gonococci, as it is practically impossible to diagnose this condition positively in any other manner. Care should be taken, however, not to confound the diplococci, which may be normally present in the urethra and vagina, with the gonococcus (see chapter on Urine).

ABORTION.

In cases of abortion it is often possible to discover *chorion villi* in the blood-clots which have been expelled, presenting their charac-

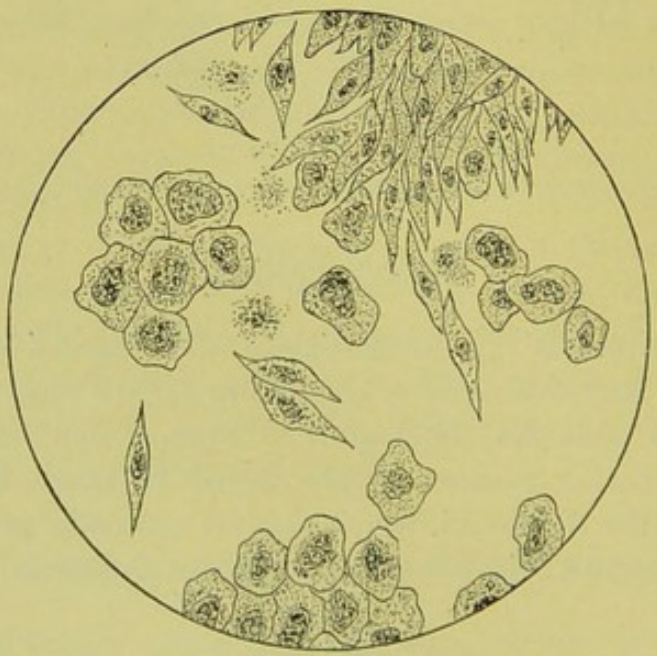
teristic capillary networks (Fig. 129), and often manifesting signs of advanced fatty degeneration. Important also from a diagnostic point of view is the presence of *decidual cells* (Fig. 130), which are

FIG. 129.



Chorion villi.

FIG. 130.



Decidual cells.

characterized by their large size, their round, polygonal or spindle-like form, and their characteristic nuclei and nucleoli.

CHAPTER XIII.

THE SECRETION OF THE MAMMARY GLANDS.

THE SECRETION OF MILK IN THE NEWLY BORN.

A SECRETION from the mammary glands in the male is only observed in the newly born, with the exception of the very rare cases where adult males were known to suckle infants. The fluid in question, which may also be obtained from the female infant, is termed "Hexenmilch" (witches' milk) by the Germans. Qualitatively it has the same composition as milk, but may manifest considerable quantitative variations.

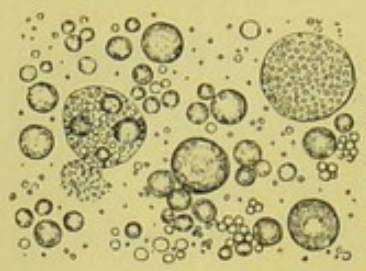
COLOSTRUM.

Aside from those curious instances in which a secretion of milk has been observed in non-pregnant adult women, mammary activity is essentially connected with the physiologic phenomena of pregnancy and parturition. Often as early as the third month a small drop of a serous-looking fluid can be obtained from the nipple by pressure upon the breasts. Immediately after birth a variable amount of fluid is secreted, which is watery, semi-opaque, mucilaginous, and of a yellowish color. To this secretion as well as to that observed during pregnancy the term colostrum has been applied. It is distinguished from true milk by its physical characteristics and by the presence of a greater proportion of sugar and salts. The fluid, moreover, is coagulated by boiling. An idea may be formed of its chemical composition from the appended tables:

	4 weeks before birth.		17 days before birth.	9 days before birth.	24 hours after birth	2 days after birth.
Water . . .	945.2	852.0	851.7	858.8	843.0	867.9
Solids . . .	54.8	148.0	148.3	141.2	157.0	132.1
Casein . . .	.....	.....	.....	.....	.....	21.8
Albumin . . .	28.8	69.0	74.8	80.7		
Fat	7.3	41.3	30.2	23.5	.....	48.6
Lactose . . .	17.3	39.5	43.7	36.4	.....	61.0
Salts	4.4	4.4	4.5	5.4	5.1	

Upon microscopic examination minute fat-droplets, a few leucocytes, some epithelial cells, and so-called *colostrum-corpuscles* are

FIG. 131.



Colostrum of a woman in sixth month of pregnancy. (Eye-piece III., obj. 8 *a*, REICHERT.) (v. JAKSCH.)

found. The latter are highly refractive bodies of irregular size, whose interior is filled with fatty granules. (Fig. 131.)

THE SECRETION OF MILK PROPER IN THE ADULT FEMALE.

The secretion of milk proper usually begins about the third day following parturition, and may continue for a variable length of time. On the one hand, the amount of milk secreted may be so small as to be insufficient for the wants of the child, so that lactation may have to cease after several days. On the other hand, women are not infrequently seen who nurse children for two years or even longer. Usually, however, infants are nursed until six or seven teeth have appeared, which period varies with the individual child, averaging about the eleventh month.

HUMAN MILK.

Human milk is of a bluish color, in this respect differing from the milk of cows. Its reaction is alkaline. The specific gravity may vary between 1.026 and 1.035, one between 1.028 and 1.034 being the most common. The amount of milk secreted in twenty-four hours varies from 500 to 1500 c.c. Microscopically it is a fairly homogeneous emulsion of fat, being practically destitute of cellular elements. From the following table an idea may be formed of its chemical composition :

	Biehl.	Gerber.	Christenn.	Pfeiffer.	Pfeiffer.	Mendes de Leon.
Water . . .	876.0	891.0	872.4	892.0	890.6	877.9
Solids . . .	124.0	109.0	127.6	108.0	109.4	
Albumin . . .	22.10	17.90	19.00	16.13	17.24	25.30
Fat	38.10	33.00	43.20	32.28	29.15	38.90
Lactose . . .	60.90	53.90	59.80	57.94	59.92	55.40
Salts	2.90	4.20	2.60	1.65	2.09	2.50

Upon comparing this table with the following analysis of cow's milk, it will be seen that the latter usually contains more albumin and less sugar than human milk. Human milk, moreover, is relatively deficient in mineral matter and especially in CaO and P_2O_5:

Water	874.2	
Solids	125.8	
Casein	28.8	34.5
Albumin	5.3	
Fat	36.6	
Lactose	48.1	
Salts	7.1	

The albumins found in milk-plasma are casein, lacto-globulin, and lactalbumin. It is claimed by numerous observers that the casein of human milk differs from that obtained from cow's milk. The casein-coagula in human milk are not so large and dense as those observed in cow's milk. Human casein, moreover, is not so readily precipitated by acids and salts; it does not always coagulate upon the addition of rennet ferment, and while it can be precipitated by the gastric juice it is readily dissolved by an excess. Although accurate analyses of human casein are not accessible, it is probable that the two forms are not identical (Hammarsten).

The question whether or not normal human milk contains micro-organisms may now be answered in the affirmative. There can be no doubt, however, that the milk as it is secreted by the healthy gland is sterile, but upon passing along the lacteal ducts in the nipple it is always contaminated by the staphylococcus epidermidis albus (Welch). This micro-organism must be regarded as a constant inhabitant of the skin, and is the only one of the cutaneous bacteria which regularly penetrates into the deeper layers of the epidermis and into the glandular appendages of the skin. It is thus at once apparent why this organism is so constantly met with,

and practically the only one that is found in normal human milk. Exceptionally only the staphylococcus pyogenes aureus is found.

THE MILK IN DISEASE.

The chemistry of the milk in pathologic conditions has received but little attention. It appears, however, that the milk of women while ill usually contains less fat, and that the proportion of lactose is diminished. In cases of jaundice the presence of bile-pigment and of biliary acids has not as yet been satisfactorily demonstrated. In cases of mammary tumors bloody secretion has been observed in rare cases, the nipple itself being intact.

FIG. 132.



Quevenne's lactodensimeter.

Microscopically an admixture of leucocytes is observed in various diseases of the breast, and especially in cases of abscess. Of pathogenic micro-organisms streptococci may be found in cases of puerperal fever; more commonly, however, they are absent. The typhoid bacillus has been occasionally seen in cases of typhoid fever, and pneumococci have been obtained from the milk of pregnant women affected with lobar pneumonia. The important question whether or not tubercle bacilli are eliminated through the milk in cases of phthisis cannot be definitely answered. In cows such an occurrence is certainly quite common, even when there is no demonstrable tuberculosis of the udder, while they are constantly present when this is diseased. As far as the writer has been able to ascertain they have never been found in human milk.

A blue and red color has at times been observed in the milk of cows, owing to the presence of the bacillus cyanogenus and the micrococcus prodigiosus, respectively.

A chemical examination of the mother's milk is often of the greatest importance, and should always be made whenever it is apparent that the nutrition of the baby is below normal. Most valuable dietetic suggestions may thus be obtained.

In other cases, as when the mother is unwilling or unable to nurse her child beyond a certain period, a knowledge of the composition of her milk will enable the physician to give specific instructions regarding the proper modification of cow's milk. If a wet-nurse is to be employed, her milk should likewise be examined.

Most important is the determination of the specific gravity and of the amount of fat. The former may vary between 1.029 and 1.033. The amount of fat should not be less than 3 per cent.

Determination of the Specific Gravity.

The specific gravity is best determined with the lactodensimeter of Quevenne. (Fig. 132.) As the instrument is graduated for a temperature of 60° F., it is necessary to correct the specific gravity whenever the temperature rises above or falls below this point. In the following tables the corrected specific gravity may be found corresponding to temperatures ranging from 46° to 75° F.:

CORRECTIONS FOR TEMPERATURE.

Specific gravity.	Degrees of thermometer (Fahrenheit).									
	46	47	48	49	50	51	52	53	54	55
1020	19.0	19.1	19.1	19.2	19.2	19.3	19.4	19.4	19.5	19.6
1021	20.0	20.0	20.1	20.2	20.2	20.3	20.3	20.4	20.5	20.6
1022	21.0	21.0	21.1	21.2	21.2	21.3	21.3	21.4	21.5	21.6
1023	22.0	22.0	22.1	22.2	22.2	22.3	22.3	22.4	22.5	22.6
1024	22.9	23.0	23.1	23.2	23.2	23.3	23.3	23.4	23.5	23.6
1025	23.9	24.0	24.0	24.1	24.1	24.2	24.3	24.4	24.5	24.6
1026	24.9	24.9	25.0	25.1	25.1	25.2	25.2	25.3	25.4	25.5
1027	25.9	25.9	26.0	26.1	26.1	26.2	26.2	26.3	26.4	26.5
1028	26.8	26.8	26.9	27.0	27.0	27.1	27.2	27.3	27.4	27.5
1029	27.8	27.8	27.9	28.0	28.0	28.1	28.2	28.3	28.4	28.5
1030	28.7	28.7	28.8	28.9	29.0	29.1	29.1	29.2	29.4	29.4
1031	29.6	29.6	29.7	29.8	29.9	30.0	30.1	30.2	30.3	30.4
1032	30.5	30.5	30.6	30.7	30.9	31.0	31.1	31.2	31.3	31.4
1033	31.4	31.4	31.5	31.6	31.8	31.9	32.0	32.1	32.3	32.4
1034	32.3	32.3	32.4	32.5	32.7	32.9	33.0	33.1	33.2	33.3
1035	33.1	33.2	33.4	33.5	33.6	33.8	33.9	34.0	34.2	34.3

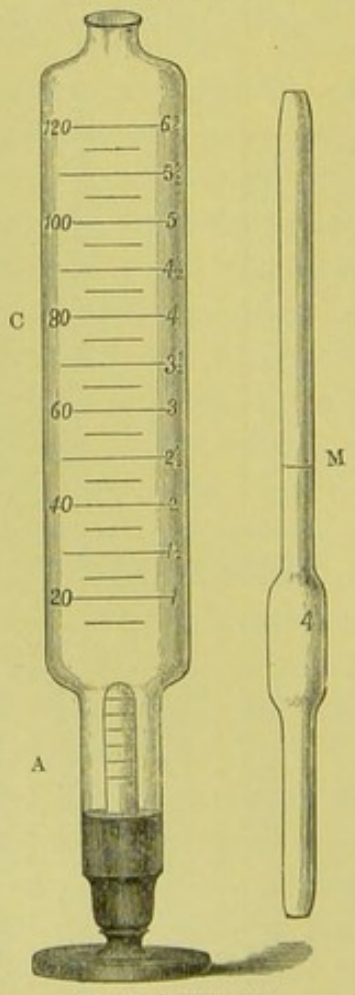
Specific gravity.	Degrees of thermometer (Fahrenheit).									
	56	57	58	59	60	61	62	63	64	65
1020	19.7	19.8	19.9	19.9	20.0	20.1	20.2	20.2	20.3	20.4
1021	20.7	20.8	20.9	20.9	21.0	21.1	21.2	21.3	21.4	21.5
1022	21.7	21.8	21.9	21.9	22.0	22.1	22.2	22.3	22.4	22.5
1023	22.7	22.8	22.8	22.9	23.0	23.1	23.2	23.3	23.4	23.5
1024	23.6	23.7	23.8	23.9	24.0	24.1	24.2	24.3	24.4	24.5
1025	24.6	24.7	24.8	24.9	25.0	25.1	25.2	25.3	25.4	25.5
1026	25.6	35.7	25.8	25.9	26.0	26.1	26.2	26.3	26.5	26.6
1027	26.6	26.7	26.8	26.9	27.0	27.1	27.3	27.4	27.5	27.6
1028	27.6	27.7	27.8	27.9	28.0	28.1	28.3	28.4	28.5	28.6
1029	28.6	28.7	28.8	28.9	29.0	29.1	29.3	29.4	29.5	29.6
1030	29.6	29.7	29.8	29.9	30.0	30.1	30.3	30.4	30.5	30.7
1031	30.5	30.6	30.8	30.9	31.0	31.2	31.3	31.4	31.5	31 7
1032	31.5	31.6	31.7	31.9	32.0	32.2	32.3	32.5	32.6	32.7
1033	32.5	32.6	32.7	32.9	33.0	33.2	33.3	33.5	33.6	33.8
1034	33.5	33.6	33.7	33.9	34.0	34.2	34.3	34.5	34.6	34.8
1035	34.5	34.6	34.7	34.9	35.0	35.2	35.3	35.5	35.6	35.8

Specific gravity.	Degrees of thermometer (Fahrenheit).									
	66	67	68	69	70	71	72	73	74	75
1020	20.5	20.6	20.7	20.0	21.0	21.1	21.2	21.3	21.5	21.6
1021	21.6	21.7	21.8	22.0	22.1	22.2	22.3	22.4	22.5	22.6
1022	22.6	22.7	22.8	23.0	23.1	23.2	23.3	23.4	23.5	23.7
1023	23.6	23.7	23.8	24.0	24.1	24.2	24.3	24.4	24.6	24.7
1024	24.6	24.7	24.9	25.0	25.1	25.2	25.3	25.5	25.6	25.7
1025	25.6	25.7	25.9	26.0	26.1	26.2	26.4	26.5	26.6	26.8
1026	26.7	26.8	27.0	27.1	27.2	27.3	27.4	27.5	27.7	27.8
1027	27.7	27.8	28.0	28.1	28.2	28.3	28.4	28.6	28.7	28.9
1028	28.7	28.8	29.0	29.1	29.2	29.4	29.5	29.7	29.8	29.9
1029	29.8	29.9	30.1	30.2	30.3	30.4	30.5	30.7	30.9	31.0
1030	30.8	30.9	31.1	31.2	31.3	31.5	31.6	31.8	31.9	32.1
1031	31.8	32.0	32.2	32.2	32.4	32.5	32 6	32.8	33.0	33.1
1032	32.9	33.0	33.2	33.3	33.4	33.6	33.7	33.9	34.0	34.2
1033	33.9	34.0	34.2	34.3	34.5	34.6	34.7	34.9	35.1	35.8
1034	34.9	35.0	35.2	35.3	35.5	35.6	35.8	36.0	36.1	36.3
1035	35.9	36.1	36.2	36.4	36.5	36.7	36.8	37.0	37.2	37.3

The Estimation of Fat.

The estimation of the fat is most conveniently made by means of the lactoscope of Feser, shown in Fig. 133. Milk is drawn into

FIG. 133.



Feser's lactoscope.

the pipette up to the mark M, when it is emptied into the cylinder C. The pipette is then rinsed with water and the washings added to the milk. While shaking, water is added, until the black lines upon the milk-colored glass plug A can just be discerned. The figure upon the right of the scale which is reached by the mixture will at once indicate the percentage-amount of fat, while the number upon the left indicates the amount of water in c.c. that has been added.

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