Compliments of the Editors.

J. A. Scott
1321 So. 18th St.
Phila.

Oct. 1st 05

NOTES

ON

THE LECTURES OF PROF. JOHN GUITÉRAS

ON

GENERAL AND SPECIAL PATHOLOGY,

Delivered before the Second and Third Year Students
of the University of Pennsylvania,

AND ON

THE LECTURES OF DR. JOSEPH McFARLAND

ON

BACTERIOLOGY,

Delivered before the Third Year Class.

ARRANGED BY

DR. WILLIAM S. CARTER AND DR. DAVID RIESMAN,

Quiz Masters in Pathology.

AVIL PRINTING COMPANY,
3941-43-45 Market Street,
PHILADELPHIA.

PREFACE.

IN response to a frequently expressed desire on the part of the students, we have undertaken the publication of this volume of notes. During its preparation we have been stimulated by the interest and encouragement of Professor Guitéras, to whom we beg to acknowledge our grateful indebtedness.

We are under obligations to Dr. Alfred Stengel for the cuts of many of the illustrations.

By the kind permission of Dr. Joseph McFarland we have been able to add an epitome of his lectures on Bacteriology.

We hope that the notes will assist the student in mastering the important subject of Pathology.

CHAPTER I.

Pathology is that branch of the science of medicine which concerns itself with the study of the manifestations of energy and the changes in structure which take place in a diseased living being. Broadly speaking, it is the science of disease.

The term "*disease*" includes all those disturbances of the normal manifestations of life which impair, more or less, the adaptability of the individual to surrounding media.

By "*a disease*" we understand a group of such modifications occurring with sufficient regularity of association to constitute a distinct species.

Disease adds no new element to the body; it merely modifies previously existing functions and structures. We deal, therefore, in pathology with two factors: the changes in the function, *i. e.*, the manifestations of energy, and the changes in the structure, of diseased organs or tissues.

The first recognizable change is one affecting the structure. But we cannot conceive of such a change occurring without some antecedent force or cause to bring it about. This fundamental cause is believed to be certain obscure functional derangements which lead to modifications of structure, and these, in turn, to secondary changes of function. The last become recognizable to us as the *symptoms* of the disease.

DIVISIONS OF PATHOLOGY.

Analogous to the division of **Biology** into **Morphology, Physiology,** and **Embryology, Pathology** is divided into **Morbid Anatomy,** or the study of the changes of structure in disease, **Morbid Physiology,** the study of the changes of function in disease, and **Etiology,** the study of the causation of disease. Of these three branches morbid anatomy is the most

advanced; etiology is also highly developed, chiefly through the impetus which bacteriology has given to it; morbid physiology, probably the most important branch, is still very obscure.

Pathology may be further divided into

GENERAL AND SPECIAL PATHOLOGY.

In general pathology we study disease from a general point of view; we study those changes of function and structure that can occur in any organ, *e.g.*, inflammation. In special pathology we study these changes as they occur in special organs, *e. g.*, pneumonia.

GENERAL PATHOLOGY.

Morbid processes are of two kinds: (*a*) **Elementary** or **Simple**—those in which the changes in the tissues are of one kind only, or those occurring in individual cells, *e.g.*, fatty degeneration. They are the elements of which disease is made up.

(*b*) **Compound**—those composed of several elementary morbid processes; *e.g.*, inflammation.

Morbid processes may be **integrating** or **progressive,** those in which there is a building up of tissue, or **disintegrading** or **retrograde,** those in which tissues are destroyed. The former are exemplified by hypertrophy and hyperemia, the latter by atrophy and degenerations.

SIMPLE MORBID PROCESSES.

HYPERTROPHY.

Hypertrophy is an increase in the size of a tissue or organ, taking place independently of the general growth of the organism and without any marked alteration in the outline of the organ.

Normal Example.—Enlargement of the uterus during pregnancy.

Hypertrophy may be (1) *general,* affecting several parts of the body, or (2) *local,* limited to a single organ or part. Local hypertrophy is classified into (*a*) *true* or *functional* hypertrophy, and (*b*) *false* or *pseudo-hypertrophy.*

True hypertrophy is a uniform enlargement of an organ affecting all the tissues, and is accompanied by an exaltation of function. It is caused by an increased functional demand upon the part, either directly, as in the uterus in pregnancy, or indirectly, when the demand on the organ is the result of the imperfect action of another, usually of a companion organ, as in hypertrophy of a kidney after the removal of its fellow, or the enlargement of one lung when the other is diseased. In false hypertrophy the tissue most apt to be increased is that least concerned in the function of the organ, *i. e.*, connective tissue. Hypertrophic cirrhosis of the liver, and pseudo-hypertrophic muscular paralysis are examples.

Morbid Anatomy.—In true hypertrophy the outline of the organ is generally preserved; in false hypertrophy it is apt to undergo some change, owing to the presence of an excess of connective tissue.

Hypertrophy is divided into (1) *simple*, or that in which there is an increase in the size of the individual cells, and (2) *numerical*, that in which there is an increase in the number of cells. The latter is the more common form, although both very frequently occur together. Simple hypertrophy is not easily demonstrated: we see it best in the pregnant uterus and in the hypertrophied heart.

The term *hyperplasia* is used as a synonym of numerical hypertrophy; it implies a multiplication of cells with a tendency to form new tissue. It does not necessarily lead to hypertrophy; indeed, it may cause atrophy, as in atrophic cirrhosis of the liver.

The subject of numerical hypertrophy brings up the question as to the manner in which cell-proliferation takes place. It occurs in one of two ways—(1) by direct cell-division, or *amitosis*, or (2) by indirect cell-division, *mitosis*, *karyomitosis*, or *karyokinesis*. The latter is the more frequent and more important mode, and depends upon complicated changes in the filamentary substance of the nucleus. This substance is known as *mitome*, or, on account of the readiness with which it takes up the nuclear stains, hematoxylin, safranin, gentian-violet, etc., as *chromatin*. The inter-filamentary substance, staining poorly, is termed *achromatin*.

The threads of the mitome are arranged in the form of **U**-shaped loops, the closed ends of which are all directed toward the same pole of the nucleus.

From these primary loops delicate secondary filaments are given off, which by their interlacing produce a dense, compact network.

The essential changes preparatory to cell division take place in the loops. The process is usually divided into three stages:

1. Concentration—the thickening of the primary and disappearance of the secondary filaments.

2. Splitting of the filaments in their longitudinal axis.

3. Rearrangement of the filaments—(*a*) Monaster, or mother-star, (*b*) Diaster, or daughter-star.

When these changes are completed the cell protoplasm and the nucleus become constricted; division then takes place, leaving two independent cells, each with its nucleus. Special methods of preparation of tissues are necessary to show the appearances just described. The most important point is to "fix" the tissues as quickly as possible. For this purpose the pieces should be very fresh, should not exceed one-half c. cm. in size, and should immediately be immersed in a good fixing fluid, the best being Flemming's solution: 1 per-cent sol. chromic acid, 15 parts; 2 per-cent sol. osmic acid, 4 parts; glacial acetic acid, 1 part. The tissue is left in this six to forty-eight hours; it is then washed in running water three to six hours, and finally hardened in alcohol and imbedded.

The sections are stained for from one to twenty-four hours in a one per-cent watery solution of safranin; they are then briefly washed in water and differentiated in absolute alcohol containing a few drops of a one per-cent solution of hydrochloric acid in alcohol. When clouds of color cease to be given off the section is removed to absolute alcohol, thence to oil, and mounted.

Under the microscope the nuclei undergoing karyokinetic changes are stained a dark reddish-brown, while the quiescent nuclei are light in color. The most striking appearance is the daughter-star

Clinical Causes. 1. *Increased functional activity.*

2. *Congenital tendency, e. g.*, giant growth of certain parts.

3. *Removal of pressure.* The growth of certain structures is kept within bounds by the pressure of adjacent organs. We commonly find increased thickness of the skull in cases where parts of the brain are absent.

4. *Direct stimulation*, taking the form of intermittent pressure; *e. g.*, corns. Constant pressure leads to atrophy.

5. *Disturbances of nutrition.* (*a*) Direct disturbances (trophic) of innervation, as thickening of the skin in some nerve lesions. (*b*) Interference with the function of certain obscure organs, viz., the thyroid gland, the thymus, the pituitary body, and probably the suprarenal capsules.

There is a disease known as *Acromegaly*, which is characterized by an enlargement of the extremities, chiefly the hands, and of the face. Both the bony and the soft parts are involved. In a number of cases the disease was associated with pathologic changes in the pituitary body.

ATROPHY.

Atrophy is a diminution in the bulk of one or more of the component parts of an organ. Since the more important tissue-elements are usually affected, there is also a diminution of functional activity. Normal examples are the atrophy of the thymus gland in early life; of the umbilical blood-vessels after birth; and of the female reproductive organs at the menopause. There may be smallness of size not due to atrophy. For example, an organ may be diminutive from an arrest of development, a condition termed *hypoplasia.* It is seen in chlorosis, in which we frequently find that the sexual organs and the heart and great vessels are abnormally small. Total absence of an organ or a part of an organ is called *aplasia or agenesis;* it gives rise to monstrosities.

Morbid Physiology.—Atrophy is brought about either by an insufficiency in the food supply of the cells, or by an inability on the part of the cells to use the nutritive material brought to them. It is (*a*) *simple*, due to a diminution in the size of the cells, without marked change in their protoplasm, or (*b*) *degenerative*, due to a breaking down of the protoplasm of the cells.

Morbid Anatomy.—(*a*) *Macroscopy.* An atrophic organ is smaller; its outline is usually retained, although the surface may be

irregular; the consistency is, as a rule, greater than normal, on account of a relative or absolute increase of the connective tissue; its color is darker, from a relative excess of pigment; frequently, too, new pigment is deposited. (*b*) *Microscopy.* The cells are diminished in size or degenerated; the connective tissue is increased.

Brown Atrophy occurs in organs the seat of chronic congestion, especially in the heart and liver.

Clinical Causes.—1. *Senile changes.*—These are to a certain extent physiologic; are pathologic when occurring early. They affect especially the testicle, heart and lungs (senile emphysema).

2. *Defective nutrition.*

(*a*) General, as in starvation.

(*b*) Local deficiency of blood-supply, as from obstruction of an artery.

3. *Constant pressure*, as atrophy of bones from pressure of an aneurysm.

4. *Disuse*, as atrophy of muscles in ankylosis of a joint.

5. *Disturbances of innervation.* Neuropathic atrophy. This is due to a loss of the trophic influence and is most strikingly exemplified by the atrophy of the muscles in acute anterior poliomyelitis, or infantile palsy, a disease affecting the ganglion cells of the anterior horns of the spinal cord. It is a degenerative atrophy.

INFILTRATIONS AND DEGENERATIONS.

Both imply retrograde changes in the cells, infiltration being the lowest one in the series of disintegrating processes. It consists in the deposit in the cell of an abnormal substance or of a normal constituent in excess. The nucleus and cell-protoplasm are pushed to one side and generally preserve their integrity. Degeneration is the conversion of the cell-protoplasm into an abnormal substance. It is a more serious process since it destroys the cell.

The infiltrations are: *Fatty, calcareous, pigmentary, serous, and glycogenic.*

FATTY INFILTRATION.

This consists in the storage of excessive quantities of fat within the cell, the protoplasm remaining relatively intact.

Normal examples are the adipose tissue and the liver. Pathologically, it occurs in the subcutaneous tissue, where, if general,

it is termed obesity or polysarcia; in the liver, in the heart, around atrophic organs, etc. In obesity certain parts, as the eyelids, the alæ nasi, the lobules of the ears, the lips, and the prepuce escape. Histologically, the fatty deposit affects both the cells and the intercellular substance, the red corpuscles and the ganglion cells of the nervous system being alone exempt.

Morbid Physiology.—There exists in fatty infiltration a disturbance of the fat-building and fat-storing functions. The deposit of fat may be due to an excess of food ingested or to an impairment in the consumption of the fat normally brought to cell. Defective oxidation is at the bottom of the process.

All food-stuffs, fats, albuminoids, and carbohydrates may give origin to the deposit of fat, particularly the last-named.

The albuminous food may be converted into fat within the body; thus, the cow which consumes but little fat produces a large quantity of it out of the vegetable proteids. Certain post-mortem changes also illustrate the derivation of fat from albuminous substances; *adipocere*, a fatty material, may be formed out of the muscles after death.

Animals fed on carbohydrates deposit fat. Bees produce wax out of the plant-sugar upon which they feed. How this conversion is brought about within the body is not known.

Morbid Anatomy.—(*a*) *Macroscopy.* The size of the organ is increased, but the outline is preserved; the consistency is usually diminished, yet it may not be greatly altered; the color is yellowish, either uniformly or in streaks, the latter being the case especially in the heart. The surface of section shows minute fat droplets, and the knife used is oil-stained.

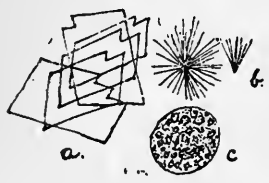
(*b*) *Microscopy.* Primarily the fat is deposited in small granules, which have a tendency to run together to form large rounded droplets, possessing a light center and a dark contour, or vice versa, depending on the manner of focusing. The protoplasm and nucleus are pushed to one side. The latter retains its structure and can be seen distinctly unless covered by the fat-droplet. In fatty degeneration the tendency of the fat-granules to run together is exceptional.

Fatty infiltration may be selective, affecting particular parts of an organ. In the heart, for instance, it is found in the connective tissue between the muscle fibers, and beneath the pericardium. In

the liver it is especially marked toward the periphery of the acini, where the portal vein deposits the fat coming from the digestive tract.

Chemically, the fat of fatty infiltration is the same as that found in the body normally, namely, a mixture of the neutral fats, stearin, palmatin, and olein.

In the horse olein predominates, the fat therefore is soft and yellow; in cattle the harder and whiter stearin is chiefly found.



(*a*) Cholesterin, (*b*) Fat-crystals, (*c*) Compound granule-cell.

After death, and in certain pathologic states, such as gangrene and other degenerations, during life, the fat may take on a crystalline form, the crystals being needle-shaped, the so-called margaric-acid crystals, or in large rhombic plates, each with a corner cut out, constituting the cholesterin-plates.

Clinical Causes.—1. *Heredity.* This is the important factor in general obesity.

2. *Disturbed digestion.* This may cause chemical changes favoring the deposit of fat; generally, however, it is associated with an excessive appetite.

3. *Lack of exercise.* Not only does deficient physical exercise conduce to fatty infiltration, but also lessened mental activity, as is seen in certain forms of insanity. In fattening animals it is customary to restrict their exercise to the lowest limit by confinement.

4. *Anemia,* probably by lessening oxidation-processes. We may have an extensive deposit of fat in chlorosis. The fattening of animals for slaughter may be hastened by one or two bleedings.

5. *Alcohol.* The ingestion of alcohol, especially in the form of malt-liquors, favors the deposit of fat either by increasing the consumption of food or by diminishing oxidation.

6. *Local disturbances of circulation* interfering with the proper nutrition of a part.

CALCAREOUS INFILTRATION OR CALCIFICATION.

Calcification is the deposition in the tissues of earthy salts, principally the carbonates and phosphates ot calcium and magnesium.

Physiologic example. The deposit of salts in bone. The salts of pathologic calcification do not differ from those deposited in health.

The term ossification should never be used as synonymous with calcification. Calcification is only a step in the process of ossification.

Pathologic Seats. 1. The tissues that normally tend to undergo calcification, as cartilage.

2. The connective tissues in general, particularly those ot the blood-vessels.

3. Tumors.

4. Foreign bodies, as dead parasites (*Trichina Spiralis*).

5. Old inflammatory foci.

6. Thrombi and emboli, especially in veins (*Phleboliths*).

7. Ganglion cells of the nervous system and epithelial cells.

8. Certain cavities, as that of the gall-bladder, of the urinary bladder, and of the intestines. The deposits here take the form of concretions or stones, the composition of which varies. They are as a rule not made up of earthy salts.

True calcification affects tissues the blood supply of which is poor. Cartilage, for example, possesses no capillaries, and its cells are separated very widely from one another.

Morbid Physiology.—(*a*) There may be an excess of earthy salts in the blood, a condition present in osteomalacia. The salts are removed from the bones and deposited in other tissues. (*Metastatic calcification.*)

(*b*) In other cases the calcification can only be explained by ascribing it to defective nutrition.

Morbid Anatomy.—We meet calcareous infiltration:

1. *In plates*—especially in tissues arranged in layers, as in the dura mater, the serous membranes of thorax and abdomen, the intima of blood-vessels.

2. *In granules*, which may be microscopic in size or larger. The organ preserves its outline, the surface of section is gritty.

3. *In spicules and needles*, as in the brain, extending in various directions, especially near the surface of the organ.

Microscopy. Both the cells and the intercellular substance are affected. In connective tissue, the intercellular substance, in epithelium, the cells are first affected. The cell-body becomes granular; the nucleus is concealed by the granules and remains unstained. If the process is intense, the cells appear black and their outline is obscured.

There is in some pathologic processes an attempt at ossification, but the new bone is imperfect.

It differs from normal bone in several ways.

1. The cells are not arranged in whirls around a central vessel.

2. There is no formation of regular plates around canals.

3. The intercellular substance is stained by hematoxylin, while that of normal bone is not.

Reactions and Tests. The mineral acids dissolve the granules with effervescence and the liberation of CO_2. The granules are insoluble in ether and in alcohol, and are thereby distinguished from fat-granules.

Clinical Causes.—1. *Osteomalacia* and other diseases breaking down bony tissue.

2. *Old age.* Here the circulatory system is especially selected by the infiltration.

3. *Defective circulation.*

4. *Poisons*, especially corrosive sublimate. The manner in which poisons produce calcification is not well understood. They may cause anemia of the tissues. In $HgCl_2$ poisoning, the deposit occurs especially in the renal epithelium. Bismuth and aloin act similarly.

5. *In cavities*, from a *chemical change* in the fluids whereby the salts are precipitated from solution.

In gout, sodium urate and also the carbonate and phosphate are deposited, this deposit occurring almost exclusively in the connective tissues, especially that of joints and tendons (*Tophi*).

The deposit occurs in the form of fine granules in the cells and the intercellular substance. As the disease progresses large masses or minute needles may be produced, the latter having the peculiarity that they run parallel with the fibers of the tendons. The urate salts are soluble in mineral acids, with the production of crystals of uric acid.

PIGMENTARY INFILTRATION.

This consists in the deposit of abnormal quantities of pigment in the tissues.

Normal seats. The red blood-corpuscles, the skin, the choroid coat of the eye, the hair, etc.

Morbid Physiology.—The pigment may be introduced from without, *external*, or may be formed within the body, *internal*

pigmentation. The latter is again divided into (*a*) *hematogenous* and (*b*) *metabolic* pigments. Hematogenous pigments are those derived from the coloring matter of the blood; they are either hemoglobin or derivatives of it. The metabolic pigment is elaborated out of the albuminates of the cells themselves; or it may be brought to the pigmented parts by wandering connective tissue cells.

The pigment of the rete mucosum is of metabolic origin.

Hematogenous Pigmentation.—The hematogenous pigments are *hemoglobin, hemosiderin, hematoidin, biliary pigment,* and *ferrous sulphid.* The pigmentation occurs in one of two ways:

(*a*) The pigment may stain the tissues in a soluble form, in other words, it may be hemoglobin. The first tissue to be stained is the blood—*hemoglobinemia.* In severe degrees of this condition, the hemoglobin also colors the urine—*hemoglobinuria.* Hemoglobinemia is met with in some of the infectious diseases, as pyemia, and in malaria; after the injection of certain poisons; sometimes after the transfusion of serum from one animal to another.

(*b*) The pigment may be deposited in an insoluble form, being a decomposition-product of hemoglobin. The insoluble pigments are *hemosiderin*—a dark, granular pigment, containing iron—and *hematoidin,* a brownish pigment, occurring in rhombic crystals, not containing iron. The form which the insoluble pigment takes depends to some extent upon the activity of the tissues the seat of pigmentation. Where active cell-processes are going on, hemosiderin is produced; where this is not the case, hematoidin will be formed. In old hemorrhagic foci in the brain, we find hemosiderin at the periphery, hematoidin in the center.

Melanosis is a general tendency to the formation of abnormal blood-pigments, which appear as minute granules in the blood itself or in organs. It occurs chiefly in malaria, where the pigment may be so abundant, particularly in the pernicious varieties of the fever, as to cause capillary emboli. These are met with especially in the brain. The pigment of melanosis may be devoid of iron; it then resembles melanin; sometimes it contains iron. The malarial pigment is generally free from iron.

NOTE.—The student should observe that the term melanosis has nothing to do with the metabolic pigment melanin; it signifies the deposition of altered blood-pigment. The word originated at a time when the differentiation of the various pigments had as yet not been attempted.

Morbid Anatomy.—We find the insoluble pigments in bruises—here chiefly as hemosiderin—and in hemorrhages in the interior of organs. In the latter instance the pigment is apt to remain for a long time, assuming often a bluish or slate color, as in the intestines after an attack of dysentery.

Tests for blood-pigment. To a watery solution of the blood-stain add tincture of guaiac; a white or whitish-red precipitate is produced which turns blue on the addition of an ethereal solution of hydrogen dioxid. The blue precipitate may be dissolved out with alcohol. (*Almén's Test.*) This test is very characteristic.

The spectroscopic test, which is absolutely positive. The spectrum of hemoglobin (*i. e.* oxy-hemoglobin), consists of two dark bands, one at the junction of the yellow and green, the other in the middle of the green. Non-oxidized hemoglobin presents a single band, which may be considered to be the result of the union of the two oxy-hemoglobin bands. It is, however, smaller than the combined width of these two bands. Methemoglobin gives rise to three dark bands, the two characteristic of oxy-hemoglobin, with an additional one in the orange.

Bile-pigmentation: Jaundice, or *Icterus.* Since bile is elaborated exclusively by the liver, the origin of jaundice must always be hepatogenous. It may, however, arise in one of two ways: (*a*) from simple obstruction of the bile-ducts; (*b*) from excessive formation of bile-pigment, this generally occurring when there is an exaggerated destruction of blood-coloring matter. It is the latter form to which some clinicians give the name of hematogenous jaundice.

Tests. Bile-pigment is insoluble in water and in alcohol; it is soluble in chloroform, and gives a pretty play of color with nitrous acid or nitric acid containing nitrous acid fumes. (*Gmelin-Heintz' Test.*)

Ferrous sulphid, FeS. This results from the action of hydrogen sulphid on the iron contained in the hemoglobin. It is seen post-mortem in the abdominal walls and peritoneum, as a diffuse bluish discoloration.

Metabolic Pigmentation.—The pigment—called melanin—is elaborated out of the protoplasm of the cells, without the intervention of blood-pigment. It occurs normally in the skin, the choroid, in hair, etc. Its composition is variable—sometimes it contains iron, at others it does not. Sulphur is generally present.

Pathologic occurrences. (*a*) *Addison's disease.* The chief characteristic of this is the bronzing of the skin, due to an excessive deposit of melanin. The majority of cases are associated with disease of the suprarenal capsules.

(*b*) *Tumors*—as melanotic sarcoma, or melanoma.

(*c*) In *degenerations of muscles*, as in the heart, particularly in atrophy.

Tests. Melanin is as a rule soluble in boiling acids, and in boiling KOH; also in boiling alcohol. Sometimes it is insoluble.

External Pigments.—1. *Bacterial pigments*—as in blue pus, the color of which is due to the bacillus pyocyaneus.

2. *Silver*—which may be deposited during the medicinal administration of silver salts. The pigment discolors the skin, producing the condition termed *Argyria.*

3. *Coal dust*, especially in the lungs—*Anthracosis.* When the pigmentary deposit is excessive, it leads to chronic fibroid changes.

4. *Iron-dust. Siderosis.*

5. *Stone-dust. Calcicosis.*

6. *Tattoo-pigment.* This is found also in the lymphatic glands nearest to the tattooed area.

7. *Lead.* The blue line on the gums.

SEROUS INFILTRATION. DROPSY.

This consists in the infiltration of the tissues with diluted lymph.

Pathologic seats. (1) Serous cavities. (2) Loose areolar connective tissue. (3) Lungs. (4) Epithelium—here it is probably of a different character, resembling more a degeneration.

Morbid Physiology. Serous infiltration may be brought about in various ways. (1) Through obstruction of the lymphatics and veins. Being the result of mechanical influences, the dropsy under these conditions appears first in the dependent parts, as in the lower limb, and in the lower portions of the pleural and peritoneal cavities. (2) Through a change in the composition of the blood, as in anemia. Weakness of the vessel-walls may contribute to the production of the infiltration. (3) Through changes in metabolism. The healthy state of the organism depends upon the normal character of the interchange constantly going on between the tissues and the blood. This interchange is not merely the result of a mechanical transudation; it is an active process. If disturbed at

any point, disease develops, at one time serous infiltration, at another, as we shall see later, inflammation. (4) Through changes in the walls of the blood-vessels: (*a*) over-distension (*b*) disease of the vessel-walls.

Character of the Fluid. It has the same composition as the lymph, but contains more water and less corpuscular elements. From inflammatory fluid, which it resembles, it is distinguished by being less inspissated. Its specific gravity does not exceed 1016, and its proportion of albumin is less than three per-cent. Inflammatory fluid is denser and contains more albumin.

Morbid Anatomy.—(*a*) *Macroscopy.* The part, as a limb, is swollen, pale, somewhat translucent in appearance, pits on pressure, and has a lower temperature than the same part in health. In the case of the lung, we find that the organ is enlarged and on section oozes a frothy serum.

Different terms are employed, according to the seat of the effusion:

1. *Anasarca.* When the general subcutaneous connective tissue is infiltrated.

2. *Edema* is applied to the infiltration of the subcutaneous tissues and the internal organs, as edema of the lungs. Edema of the brain is in reality edema of the membranes, the pia-arachnoid.

3. *Hydropericardium, hydrothorax, and ascites* refer to serous effusion into the pericardial, pleural, and abdominal cavities respectively.

(*b*) *Microscopy.* The fluid infiltrates the intercellular substance and separates the cells widely from each other; the fibrils of the intercellular substance are swollen and also widely separated. These features are seen best in fresh tissues.

In *epithelium* the process is really a degeneration; it occurs principally in catarrhal and other inflammations of mucous membranes; it is also observed in the muscle of the heart. In the case of mucous membranes the cells are large and filled with fluid; they lose their shape and appear dropsical. Clear vacuoles, free from the granules found in the protoplasm, are present. In the heart the serous degeneration gives rise to the semblance of cavities within the muscular fibers.

Clinical Causes.—1. *Valvular Heart Disease.* The dropsy begins in the feet.

2. *Diseases of the liver*, especially cirrhosis, which causes obstruction of the portal circulation, and this in turn ascites.

3. *Diseases of the kidney.* Here several factors are active in the production of the serous infiltration—(*a*) changes in metabolism, (*b*) changes in the composition of the blood, and (*c*) changes in the walls of the blood-vessels. The edema begins, as a rule, in the loose areolar tissue of the eyelids. It may be noticed quite early in the finger-tips, from the swinging of the hands in walking.

4. *Cachectic states*, as in tuberculosis and cancer. The edema in cachexia depends upon changes in the composition of the blood and upon a feeble state of the heart.

5. *Nervous disturbances*, as in hysteria and in certain organic diseases of the nervous system. In the former, the edema is brought about by changes in metabolism, the result of trophic disturbances.

GLYCOGENIC INFILTRATION.

This is the deposit of glycogen in the tissues.

It is normal in the liver.

Under pathologic conditions we find it (*a*) in pus, (*b*) in several organs in diabetes, chiefly in the kidney, and (*c*) in certain tumors. The process lies on the border-line between infiltrations and degenerations, for there is a tendency to the disintegration of the affected cells.

The deposit appears as minute droplets in the cells, especially about the nucleus. The droplets resemble somewhat those of fat.

Test. Glycogen strikes a dark reddish-brown color with iodin, which should be distinguished from the yellowish-brown color which that reagent imparts to normal tissues. The test is applied as follows:

The section is for a moment immersed in a solution of

Tincture of iodin	1 part.
Absolute alcohol	4 parts.

It is then washed in water and mounted in glycerin.

DEGENERATIONS.

The degenerations are *amyloid, hyaline, mucoid, colloid, parenchymatous* (*cloudy swelling*), *and fatty.*

AMYLOID DEGENERATION.

This is a progressive degenerative process, affecting especially the connective tissues, and giving rise to the formation of a substance characterized by the amyloid reaction.

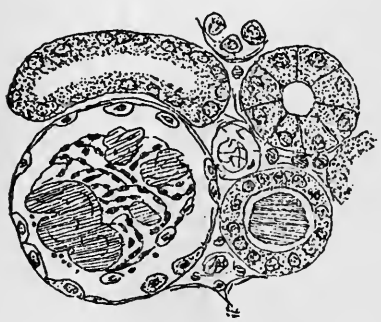
It is not found in health, although it occurs at times in organs belonging to apparently healthy individuals—it is there indicative of local disease.

Seats. Liver, kidney, spleen, walls of the intestines and heart, nervous system and prostate gland. The first three of these are affected with equal frequency, and more often than the other organs.

Morbid Physiology.—Amyloid substance is the result of a reaction occurring between something derived from the blood and the juices of the tissues. It does not exist preformed in the blood, therefore its deposit is not an infiltration. The ultimate cause of its formation is perhaps in many cases, but not in all, the loss of potassium salts.

The amyloid material is an *albuminoid.* It contains less potassium and phosphoric acid and more sodium and chlorin than normal tissue. Alkalies and acids do not dissolve it, and it is very resistent to peptic digestion and to putrefactive processes.

Morbid Anatomy.—(*a*) *Macroscopy.* The affected organ is larger than normal, the increase in size being at times remarkable, the outline is uniform, the borders, if the organ have any, are rounded, the substance of the organ is denser, *i. e.*, less friable, the elasticity is decreased—the organ may be doughy and may pit on pressure. The surface of section is paler than normal, and is somewhat translucent at the edges. The appearance is well described by the term "waxy" or "bacony." As a rule the organ is affected uniformly. Not rarely, however, the process is circumscribed to minute areas; indeed, it may not be apparent to the naked eye at all, unless the characteristic test is applied.



Amyloid degeneration in kidney.

It is particularly in the spleen and kidney that the degeneration shows a tendency to limitation. In the former it selects the lymphoid bodies and adjacent blood-vessels, the condition produced

having received the name of "sago-spleen," from the resemblance of these bodies when affected by amyloid disease to boiled sago-grains. In the kidney the degeneration may be confined to the blood-vessels of the glomeruli. Both spleen and kidney may be uniformly affected.

(*b*) *Microscopy.* The microscopic appearance is that of a grayish-white, somewhat translucent substance, cloudy in color and in shape, and apparently made up of flakes. The nuclei are absent. The process begins in the connective tissue of the walls of the blood-vessels, and affects both the cells and the intercellular substance. From the blood-vessels the process may spread to the surrounding connective tissue, and thence to the parenchyma. It is highly probable that the parenchymatous tissues undergo primarily fatty degeneration, and become subsequently invaded by the amyloid material.

Reactions. 1. Iodin produces a dark reddish-brown color. It serves both a naked-eye and as a microscopic test. For the former a fresh section should be made, the surface washed with water, and Lugol's solution poured on. The reddish-brown color of the affected areas contrasts strongly with the yellowish or greenish-brown tint which the iodin gives to the healthy portions.

For the microscopic application of the test, the following solution is employed:

5 per-cent watery solution potassium iodid.
Iodin to saturation.

A few drops of this solution are added to a watch-glassful of water. The section is immersed in the mixture, which should be of a sherry-wine color, for one to two minutes; it is then washed in water and cleared in glycerin.

2. Gentian-violet produces a light red color with the amyloid substance, while the unaffected tissues become blue. The test is only used for microscopic differentiation. It is applied as follows:

(1.) Place the section for one to two minutes in a five per-cent watery solution of gentian-violet.

(2.) Wash in water acidulated with acetic acid—two or three drops to a considerable quantity of water.

(3.) Examine in this solution or in water.

The gentian-violet reaction is also given by levulose, while cholesterin and glycogen respond to the iodin-test.

The *amyloid reaction* consists in the development of a blue color when iodin and sulphuric acid are applied to amyloid substance. It is not always obtained, nor is it important. The failure to get it in all cases suggests the possibility that the amyloid substance is not always of the same composition, but that there is a series of related degenerations leading up to amyloid.

The starch reaction is most frequently given by the amyloid bodies.

Clinical Causes.—*Chronic suppuration*, especially that dependent upon tuberculous or syphilitic bone-disease.

Amyloid Bodies.—These are small masses of concentrically arranged amyloid material, which are found in the *prostate gland* and in the *nervous system.* The change is here not progressive. The bodies involve the epithelium rather than the connective tissue—at least in the prostate glands, where the epithelial lining of the follicles is affected. They may occur in healthy prostate glands, but are most common in the prostates of old persons in whom the organ is hypertrophied, and its follicles are in a state of catarrhal inflammation. In the prostrate gland the bodies are visible to the naked eye, and frequently contain pigment ("grains of snuff"). In the nervous system they are microscopic in size, and are found beneath the ependyma of the cavities. Though met with in healthy brains and cords, they are most abundant in sclerotic conditions and in epilepsy.

They give the iodin-reaction.

HYALINE DEGENERATION.

This consists in the formation of a substance similar in appearance and composition to amyloid material, but not presenting the reactions peculiar to the latter. It attacks almost exclusively the connective tissue, particularly of the walls of the blood-vessels, and shows no tendency to spread to surrounding tissues.

The organs in the vessels of which it is most common, are the brain, the lymph-glands, the kidney, the heart, and the ovary.

Morbid Physiology.—Very little is known of the morbid physiology of hyaline degeneration. Its formation is supposed to be analogous to that of amyloid substance, *i. e.*, the result of a reaction between an element exuded from the blood-vessels and the juices of the tissues. The conglutination of the blood-plaques in the clotting of blood within the blood-vessels is a form of hyaline degeneration.

It is possible that the falling of blood-plaques against the walls of the vessels may constitute the starting point of hyaline degeneration just outside of the endothelium.

Hyaline degeneration around a blood-vessel.

Morbid Anatomy. — The substance appears as minute, irregular, glassy masses just outside of the endothelium of the small vessels and capillaries, giving to them a beaded appearance. In the larger blood-vessels it affects the walls more uniformly—the intima and the connective tissue of media. This is particularly the case in the ovaries of old women. Exceptionally, the process extends to the neighboring connective tissue and to the parenchyma. Probably the parenchyma is first removed through other degenerations, and then replaced by hyaline material. We find these extensive areas of hyaline substance in chronic fibroid inflammations, especially in the heart, where the areas may be visible to the naked eye.

Clinical Causes.—1. *Acute infectious diseases.* In these the process affects especially the capillaries.

2. *Old age*: in the walls of the blood-vessels.

3. *Chronic inflammations*, as in the heart and in the blood-vessels in sclerosis.

4. *Tumors:* cylindromata.

MUCOID OR MYXOMATOUS DEGENERATION.

This consists in the formation of a colorless, viscid substance, containing mucin.

Normal examples. 1. In epithelium. The columnar epithelial cells of mucous membranes form mucin (*goblet-cells*).

2. In connective tissues, as in the jelly of Wharton of the umbilical cord, and in the vitreous humor of the eye.

Pathologic seats. 1. Mucous membranes.

2. Epithelial and connective tissue tumors.

3. In certain processes of softening.

Morbid Physiology.—Nothing definite is known of the way in which the mucous material is produced.

Morbid Anatomy.—(*a*) *In epithelium*—the mucous discharge of catarrhal inflammation. This is a viscid, ropy, transparent, colorless substance containing mucin.

Microscopically, we find that the epithelial cells are larger than normal, and that they present a granular periphery and a shining center. The mucin-granules may be discharged, the cell remaining attached, or the degenerated cells themselves may be thrown off in large numbers. We find in addition, evidences of karyokinetic processes in the epithelial cells, and here and there also newly formed cells not perfectly developed. The appearances we find in mucous membranes are also met with in cavities lined by epithelium, *i. e.*, in cysts.

(*b*) In connective tissue the intercellular substance is especially involved, the fibrils being swollen, transparent, and obscured in outline. The material produced is stringy, gelatinous, and colorless. The connective tissue cells are generally normal and readily take the stains, but on account of pressure assume modified forms, being frequently stellate or spindle-shaped. They may eventually undergo fatty or mucoid change. Mucoid degeneration of connective tissue is common in bone, cartilage, fat, and in many connective tissue tumors. In epithelial tissue, as we have seen, the degeneration affects principally the cells, in connective tissue, the intercellular substance.

Reactions. 1. Mucin is insoluble in water, but swells in it.

2. It is precipitated in stringy, ropy masses by alcohol and by acetic acid. Under the microscope these reagents give rise to a cloudy or granular appearance. The affected epithelial cells become turbid. This reaction distinguishes the mucoid substance from dropsy of the cells and from pseudomucin.

3. It is not precipitated by boiling or by tannin.

Clinical Causes.—1. *Catarrhal inflammations of mucous membranes.*

2. *Large cysts lined by epithelium*, as those of the ovary.

3. *Many so-called colloid cancers,* in which the epithelial cells are the seat of mucoid, and not a colloid, change.

4. *Myxomatous connective tissue tumors.*

5. *Certain processes of softening of bone and cartilage.*

COLLOID DEGENERATION.

This is the conversion of the protoplasm of epithelial cells into a gelatinous material resembling mucin, but not giving its reactions.

Normal seat. The epithelium of the thyroid gland.

Pathologic seat. It occurs only in epithelial structures and affects exclusively the cells.

Morbid Physiology.—Of its mode of formation nothing is known.

Morbid Anatomy.—(*a*) *Macroscopy.* The affected organ is enlarged, the amber-colored, gelatinous, *colloid* substance being distributed in "nests" or follicles, whereby a peculiar appearance, resembling somewhat that of a honey-comb, is produced.

(*b*) *Microscopy.* The colloid material occurs in the form of droplets in the protoplasm of the cells. These droplets display, as a rule, no tendency to run together, but grow in size at the expense of the cells, which may become entirely colloid. When this point is reached, the cells drop into the cavity of the follicle. Frequently a concentric arrangement is visible in the colloid substance. It seems that nearly an entire row of epithelial cells becomes colloid, is cast off, and forms a ring in the center of the follicle; a second row of cells has a like fate, and so on until several concentric layers are produced. There is no sharp line of separation between the rings, only a slight difference in color and a few pigment-granules serving to demarcate them.

Reactions and Stains. Colloid material does *not* swell in water and is *not* precipitated by alcohol, acetic acid, or chromic acid.

It is stained best by a fluid composed of acid-fuchsin and picric acid. This imparts to it a reddish-orange color, which is a mixture of the colors of the two stains. The other tissues present the yellow tint of the picric acid.

Clinical Causes.—1. *Thyroid hyperplasias* and *epithelial tumors* of the *thyroid gland.*

2. *True colloid cancers,* as those of the pylorus.

3. *Renal cysts.*
4. *Renal tube-casts.*

The renal epithelium has a pronounced tendency to undergo colloid change. It ranks next to the thyroid in frequency as a seat of the degeneration.

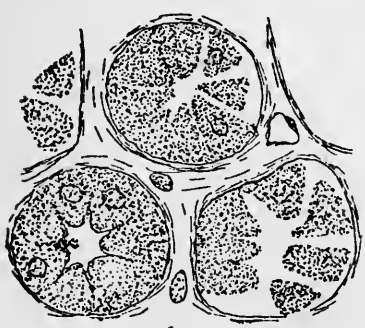
PARENCHYMATOUS OR ALBUMINOUS DEGENERATION, OR CLOUDY SWELLING.

This is a change whereby the soluble albuminous substances of the cells are precipitated in an insoluble form, as minute granules.

Seats. Archiblastic tissues.

Morbid Physiology.—Cloudy swelling is the first step toward degeneration. The granules are readily soluble, hence the change bringing about their precipitation is not a profound one. The process, indeed, may lie within the limits of normal physiology, for under certain conditions of stimulation, still physiologic, the epithelial cells, particularly those of the liver and kidney, become cloudy, from the presence of an excess of proteid-granules. These subsequently disappear with the re-establishment of the nutritive equilibrium. Under other circumstances the process is pathologic, and is the precursor of further degenerative changes.

Morbid Anatomy.—(*a*) *Macroscopy.* If the change is slight no alteration is noticeable. In well-marked cases the organ is enlarged and its tissue softer, although from being swollen within a tense, non-yielding capsule, it may convey a sensation of increased consistency. The organ contains less blood, and on section is paler than normal; its structure is obscured, the normal translucency is lost, and the organ looks as if it had been cooked.



Cloudy swelling of the kidney.

(*b*) *Microscopy.* The cells are larger and more rounded; they have lost their sharp outline, and are cloudy from the presence of innumerable fine granules. The nuclei are not well stained; in advanced cases they may not be apparent. The protoplasm may be broken down into a granular detritus; or there may be fatty degeneration.

Some cells have a greater tendency to break down than others, *e. g.*, the renal epithelium. The granular débris resulting from the degeneration of the renal cells combines with an albuminous substance to form tube-casts.

Reactions. 1. The granules are dissolved by acetic acid. Fat-granules which often are similar in appearance are not dissolved, but become more distinct under the action of acetic acid.

2. The granules are insoluble in alcohol, in ether, and in chloroform—fat-granules are dissolved by these reagents.

3. Being albuminous, the granules give the proteid-reactions.

Cloudy swelling, like all other degenerations, is best studied in fresh tissue.

Clinical Causes.—1. *Fevers.* Heat alone suffices to produce cloudy swelling.

2. *Acute infectious diseases.* The cloudy swelling may be due to the fever or to the action of a toxin. Some of the infections have a predilection for certain organs; as, for instance, diphtheria and yellow fever, which produce cloudy swelling especially in the kidney. They do this even in the absence of fever, particularly diphtheria.

3. *Poisons.* Non-bacterial.

(*a*) *Alcohol.* This, even in small quantities, produces cloudy swelling, probably on account of a stimulation of the cells to take up an excess of albuminous material. Large doses cause a more permanent degeneration.

(*b*) *Phosphorus, arsenic, mercuric chlorid.* The last may lead very rapidly to cloudy swelling.

(*c*) *Chloroform and ether.* Here the cloudy swelling may be due to an attempt at elimination of the poison.

FATTY DEGENERATION.

This is a disintegrating process whereby the proteids of the tissues are converted into fat.

Normal example. The formation of milk. Really both processes, fatty infiltration and fatty degeneration, take part in the production of milk.

Pathologic seats. It may occur in all tissues, more especially, however, in the liver, kidney, walls of blood-vessels, and muscular

substance of the heart. In these localities it constitutes almost a distinct disease.

It is also found in all morbid processes where destroyed cells are to be eliminated.

Morbid Physiology.—Deficient supply of oxygen is the basis of the process. The diminution in oxygen interferes with the combustion of the fats and of the proteids; the latter, not being oxidized into urea, water, CO_2, etc., show a tendency to be converted into fat.

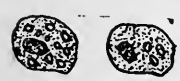
The most frequent causes of deficient oxidation are:

1. Diminished blood supply—the most common of all causes.

2. Fever, which impairs the oxygen carrying-power of the hemoglobin.

3. Poisons. Their mode of action is obscure, but they probably diminish oxidation.

Morbid Anatomy.—(*a*) *Macroscopy.* The organ may in the early stages be slightly augmented in size; later it is small and atrophied. It is paler in color and somewhat yellowish, either uniformly so or, as in the heart, in streaks. Its specific gravity is lighter; the consistency is diminished. On the surface of section fat-drops are seen, and the section-knife may be oil-stained.



(*a*) Fatty degeneration.

(*b*) Fatty infiltration.

(*b*) *Microscopy.* The cells are more spherical and contain fat-granules, some very minute, others larger and shiny; rarely small droplets are present The granules may completely fill the cells. The nucleus at first is only concealed, but later it also becomes degenerated. Eventually the cell breaks down into a fatty detritus.

In the early stages the granules are not readily distinguished from those of cloudy swelling, but as a rule they are larger and more refracting. In some situations the fat-granules show a tendency to fuse and form distinct droplets, as in fatty infiltration. This occurs particularly in the liver, in acute cases of fatty degeneration, and in the nervous system.

In fatty degeneration of muscles the fat-granules appear in rows running parallel with the long axis of the fibers, but without any special connection with the nucleus.

Compound granule-cell. This is a large cell made up of fat-granules. It is either an epithelial cell that has undergone fatty

degeneration, or a wandering connective tissue cell that has taken up much fatty detritus. The latter variety is very common in the nervous system.

After death the fat is apt to assume the crystalline forms previously described, viz., needles of margaric acid and plates of cholesterin. The latter are also formed during life. The fats are the glycerites of oleic, palmitic, and stearic acid.

Reactions. 1. The fat-granules are insoluble in acetic acid and in the alkalies.

2. They are soluble in ether, in chloroform, and, slowly, in alcohol.

3. They are stained black by osmic acid. A ready method giving fairly good results is to cut the sections with a freezing-microtome, and immerse them in a one-half per-cent solution of osmic acid for one-half to one minute; then wash and examine in water. As tissues preserved in alcohol frequently fail to show fatty degeneration, it is best to harden them in a mixture composed of *three parts* of Müller's fluid and *one part* of a one per-cent solution of osmic acid. The specimen is left in this, in the dark, for two weeks, and is then washed in running water for twenty-four hours, to remove the excess of osmic acid. It is subsequently hardened in alcohol, imbedded in celloidin, and cut into sections.

Alcohol does not dissolve the fat acted on by osmic acid, but both xylol and chloroform do. In mounting the section, pure balsam—not xylol-balsam—should be used.

Clinical Causes.—1. *Old age.* The degeneration may be found in all organs, but affects especially the blood-vessels.

2. *Anemia.* (*a*) Acute anemia, as that due to hemorrhage. The fatty degeneration may be very rapid, particularly in the heart and in the posterior layer of the retina. The degeneration in the latter case results in blindness. (*b*) Chronic anemia—both the essential forms, leukemia, chlorosis, progressive pernicious anemia, and the symptomatic—as those from cancer and tuberculosis. The fatty degeneration caused by these may be general.

3. *Local anemia.* In an hypertrophied heart fatty degeneration is very common on account of an insufficient blood supply.

4. *Fevers.* These cause defective oxidation.

5. *Poisons.* (*a*) *Toxins*, as in yellow fever, in which the liver is frequently affected. (*b*) *Non-bacterial poisons*, as carbon monoxid, phosphorus, chloroform, iodoform, etc.

CHAPTER II.

NECROSIS.

Necrosis is the change that cells undergo when they die in the midst of living tissue. Two forms are described:

(*a*) *Necrosis proper, true, or direct necrosis.* This is the death of a large number of cells, the dead mass being separated by a distinct line from the living tissues.

(*b*) *Necrobiosis, or indirect necrosis.* This is the gradual death of cells in irregular areas. There is no line of separation between the dead and the living tissues.

The degenerations previously considered are forms of necrobiosis. In this chapter we shall only deal with true necrosis.

Causes of Necrosis.—1. *Destructive agencies*, including micro-organisms.

2. *Disturbances of circulation.*

3. *Disturbances of innervation.*

About all necrotic tissues there exists an area of reaction, known as the *line of demarcation.* It is the seat of active inflammatory processes, and has for its object either the removal of the dead part or the building up of new tissue. The former end is achieved by liquefaction and softening processes; the latter by the process of organization.

The changes taking place about a necrotic focus are largely under the control of the nervous system. But even before the nervous functions come into play, there is an immediate and direct reaction, due to the influence of the dead cells upon the living. It manifests itself in a rapid accumulation of round cells about the destroyed areas.

The force or cause which brings about this peculiar phenomenon is not clearly understood—it has been named *positive chemotaxis.* We may define this as the attractive force which dead tissues exert upon living cells.

Fate of the necrotic tissue. 1. *It may be absorbed*, either in the form of a fluid, or in the form of a granular débris. In the latter case there is also a certain amount of fluid to aid in the absorptive process. Absorption occurs principally in the interior of organs.

2. *It may be retained.* The dead part may become surrounded by a connective tissue capsule—*encapsulation.* The mass may then become calcified or the dead tissue may be converted into a fluid, in which case it constitutes a *cyst* (*softening-cyst*).

3. *It may be thrown off.*

(*a*) In the form of a large mass. Here the liquefaction takes place along the line of demarcation until the part is loosened and falls off. This is common in the necrosis of bone, the separated mass being called a *sequestrum.*

Sphacelus is the corresponding term for soft parts.

(*b*) In the form of small particles (molecular) or a fluid. Example—pus.

The dead parts may be replaced—(*a*) By the same tissue as that destroyed—*regeneration.*

This is not frequent; it is in inverse ratio to the extent of the necrosis and the specialization of the tissue.

(*b*) By connective tissue—*cicatrization.* This is by far the more common process. The connective tissue is the product of the line of demarcation.

The individual cells in the various forms of necrosis to be considered, are the seat of the elementary processes of degeneration, especially fatty degeneration.

The following are the forms of necrosis: *Coagulation, liquefaction,* and *cheesy necrosis,* and *gangrene.*

COAGULATION NECROSIS.

This is a form of necrosis resulting in the production of fibrin.

Example. The coagulation of the blood, which will be considered under *Thrombosis.* The process also takes place in the tissues.

Morbid Physiology. The formation of fibrin in the blood depends upon a reaction between components of the blood-plasma and of the cells; its formation in the tissues is an analogous process. As a result of the breaking down of the tissues the

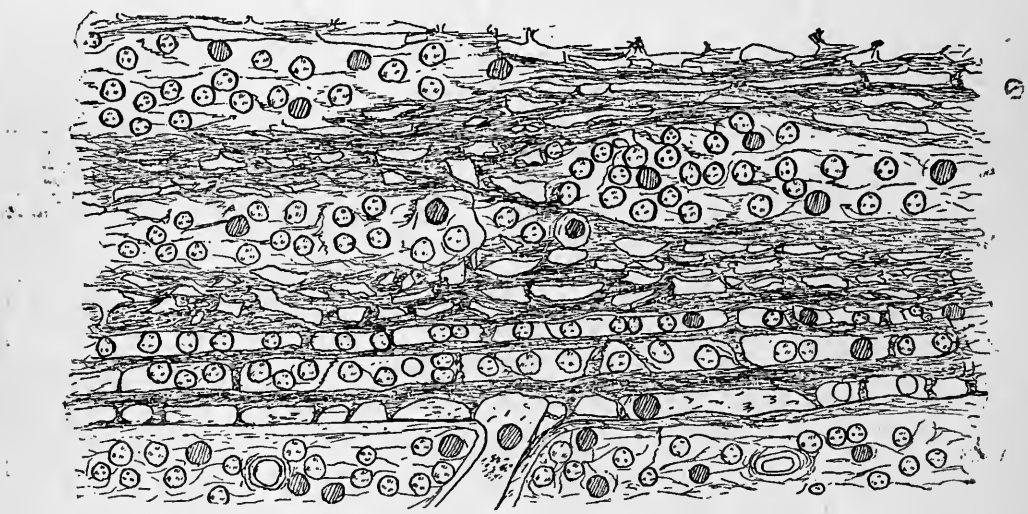
fibrinoplastin and *ferment* are liberated, while the tissue-juices contribute *fibrinogen.* The resulting fibrin is identical with that found in blood.

Causes. 1. Chemical substances, as the mineral acids, mercuric chlorid, etc. These most frequently cause coagulation necrosis on mucous membranes.

2. The toxins of micro-organisms, especially that of the bacillus of diphtheria. It is not the organism itself that kills the tissues and leads to the liberation of fibrin-factors, but the poison which it elaborates.

3. The sudden and total withdrawal of the blood-supply.

Morbid Anatomy.—(*a*) *Macroscopy.* The process appears in three distinct localities: in the blood, where the product takes



Diphtheritic membrane from mucous surface.

form of the containing vessel, on mucous membranes, and in the interior of organs. The first will be discussed under *Thrombosis.*

On *mucous surfaces* coagulation necrosis gives rise to the production of a *false membrane.* This is whitish-gray or buff-colored membrane, varying in consistence, and ranging in thickness from the merest filament to a thick layer. From exposure and the deposit of foreign matter the color may become dark or almost black.

The membrane may extend deeply into the tissues and be firmly adherent, or it may be superficial and removed with ease. This depends largely upon the anatomic structure of the parts affected. Frequently the membrane is stratified.

In organs the process affects the area of distribution of the artery to the stoppage of which it is due, and gives rise to the *anemic infarct.* This is a conical or pyramidal mass, of a pale, grayish, yellowish, or reddish color; it projects beyond the surrounding tissues, is denser, contains less blood and less fluid, and has a very sharp outline. As a rule no blood is present at all; occasionally there may be a little, giving rise to the reddish tint.

(*b*) *Microscopy.* The fibrin appears under different forms—as a *homogeneous mass*, as *fine granules*, as *fibrillar fibrin* (as in the blood), as a *fine network*, or as a *coarse mesh-work* of "lumpy" or "knobbed" appearance, or as *flakes.* The fibrin formation involves all the tissues, the intercellular substance, the cells, and the nuclei. The latter are affected very early in the process and fail to take the stain even before the fibrin has made its appearance; this is the first characteristic feature. No other necrosis attacks the nuclei so rapidly; in the anemic infarct it is a question of hours only.

The stratification of membranes is due either to an alternation of different forms of fibrin or to the presence of round cells between the layers.

These round cells which separate the membrane into layers are either leukocytes that have been spared by the necrosis or are wandering cells—leukocytes or connective tissue cells—that have migrated into the membrane. Most frequently the layers of fibrin are the same.

When the membrane falls off, it leaves a deep ulcer, except in those cases in which it was superficial and confined to the upper layers of the epithelium. We may then see no loss of tissue with the naked eye, although a certain amount must have been destroyed. In the pharynx, tonsils, and soft palate, the necrosis extends deeply. In the larynx, on the contrary, it is superficial and causes no loss of substance apparent to the naked eye. This fact gave rise to the former belief that diphtheria of the pharynx and croup of the larynx were two distinct diseases. We now know that they are the same.

Coagulation necrosis is an acute process. The dead part is separated by a process of softening, which is brought about by an accumulation of leukocytes. These evidently, judging from their presence within the membrane, make several unsuccessful attempts before they succeed in removing the membrane.

Liquefaction necrosis and suppuration may take place.

Stain. Weigert's stain gives a perfect reaction with fibrin. The following solutions are employed:

No. 1, Alcohol (95 per-cent.) . . . . . 6 parts.
Anilin oil . . . . . 1 "
5 per-cent. watery solution gentian-violet . 43 "

No. 2, 5 per-cent. solution of potassium iodid.
Iodin to saturation.

No. 3, Xylol . . . . . 1 part.
Anilin oil . . . . . 2 parts.

The application is as follows: Transfer the section from 80 per-cent. alcohol into solution No. 1, and keep in this 1 to 2 minutes; wash in water. Place the section upon a glass-slide and dry it with absorbent paper, then drop on a little of the iodin solution (No. 2). Allow this to act for ¼–½ minute, remove the iodin, and dry the section with absorbent paper. Differentiate by dropping solution No. 3 upon the section from a pipette; dry, and again drop on solution No. 3, repeating the process until clouds of color are no longer given off. The section is then cleared in pure xylol and mounted in balsam. The fibrin and any micro-organism present are colored blue.

Clinical Causes.—1. *Diphtheria.*

2. *Dysentery.*

In coagulation necrosis brought about by micro-organisms, we commonly find several varieties of bacteria present.

3. *Irritant poisons*—mineral acids, corrosive sublimate, etc.

4. *Embolism of arteries*, especially of kidney and spleen.

LIQUEFACTION NECROSIS.

In this form the juices of the tissues, instead of producing coagulation, cause liquefaction of the cells and the intercellular substance. The first visible evidence is generally a swelling of the cells: they become dropsical, lose their outline; the nuclei rapidly cease to take the stain, and the cells break down into a fluid. Frequently the fluid is the result of the liquefaction of the intercellular substance, the cells floating in the liquid.

Clinical Causes.—1. *Burns.*

2. *Embolism of certain organs*, especially of the brain (acute softening of the brain).

3. *Suppuration.*—Pus is the result of the liquefaction necrosis of the intercellular substance of the tissues, the cells floating in the fluid.

4. *It is the terminal stage of other forms of necrosis.*

CHEESY OR CASEOUS NECROSIS.

This is a process very similar to coagulation necrosis; like it it is characterized by a coagulation of the cell-body and the intercellular substance, but without the formation of fibrin. From fibrin-formation it differs also in being a slow progressive process, while the other is rapid. The substance produced is also drier and denser than fibrin. Yet it is possible that coagulation necrosis is an early stage of cheesy necrosis.

There are two forms of cheesy necrosis, the *dry* and the *moist*. In the dry the difference from fibrin is well marked. The moist form is a terminal stage of caseous necrosis, being merely the result of fatty degeneration and liquefaction necrosis.

Morbid Anatomy.—(*a*) *Macroscopy.* The affected area (in dry cheesy necrosis) is structureless, grayish-white, and denser than normal; it is of the consistency of cheese, and fades gradually into the surrounding tissues. The central portions are lighter and more fatty; toward the periphery the appearance is more that of coagulation necrosis.

(*b*) *Microscopy.* As the process is a progressive one, we find the cells in different stages of involvement. In the center of the area there is a grayish, cloudy field, granular in appearance, somewhat pigmented, and without nuclei. As we approach the circumference, we find nuclei in various stages of degeneration—some are stained only half, others only at their edges. A peculiar characteristic is a marked tendency to the accumulation of nuclei at the periphery of the necrotic area ("raked field appearance").

The presence of this aggregation of nuclei is not easily explained. Perhaps the irritant, before causing necrosis, acts as a stimulus to the tissues and brings about a multiplication of cells.

Occasionally the necrotic process is confined to a single cell, and then gives rise to the appearance described as giant-cells. The protoplasm of these cells has a peculiar opacity. Their formation represents a very early stage of cheesy necrosis.

Clinical Cause.—The necrosis may occur anywhere; in the majority of instances it is brought about by the *tubercle bacillus*. It is most common in the lungs, in tuberculosis.

GANGRENE.

This is the putrefactive fermentation of dead tissues still attached to the living body. There are two forms, the *dry* and the *moist*.

(*a*) **Dry Gangrene.**—This is brought about through the withdrawal of the blood supply and the evaporation of the water contained in the affected part.

Morbid Physiology.—The evaporation is facilitated by the removal of the skin. The absence of the blood supply—the essential cause—is produced by an arrest of the arterial circulation, either through embolism or through disease of the vessel-walls. The latter pre-eminently favors the occurrence of dry gangrene, because in diseased conditions of the vessels the collateral circulation is not readily established.

Morbid Anatomy.—The part is dark, friable, horny, "mummified," smaller than normal, and separated from the healthy tissue by a line of demarcation.

Clinical Causes.—1. *Drying of the umbilical cord* (normal).

2. *Senile gangrene.* We have here a thickening of the arterial coats, with coagulation of blood within the vessels. Gangrene results when the obstruction is diffuse.

3. *Raynaud's disease.* The cause here is probably a disturbance of the nervous system producing spasm of the arteries.

4. *Frost-bite.* This also causes contraction of the blood-vessels.

5. *Ergotism.*

(*b*) **Moist Gangrene.**—This is as a rule brought about by the obstruction of the venous outflow; the affected part is full of water. The circulation having ceased, decomposition sets in. The latter is due to the action of saprophytic micro-organisms, which are responsible for development of the chemical changes pertaining to the process.

Morbid Anatomy.—(*a*) *Macroscopy.* The part is swollen, soft, and juicy; the color is dark, passing through a series of shades, from dark-green or bluish to black, due to changes in the blood-pigment. The tissues crepitate on account of the presence of gas. The skin is raised in blisters, which are filled with a clear or a turbid, greenish fluid. There is also a characteristic odor.

(*b*) *Microscopy.* The nuclei disappear rapidly, and the cells break down, some into a granular débris, others, from liquefaction necrosis, into a fluid. Blood-pigment is deposited, either as hemosiderin or as hematoidin. Fat-crystals may also be formed. The muscle-fibers lose their striation, and the nerve-fibers become beaded, the myelin presenting a drop-like appearance. Bones and tendons are most resistant. Chemically, moist gangrene is a process of oxidation, the end products being H_2O, CO_2, H_2S, and NH_3. But before these final products are reached, aromatic compounds and ptomains, several of them active poisons, are generated. These may be absorbed and give rise to some of the symptoms attending gangrene. Ptomains may be formed wherever decomposition is taking place.

The most important feature of gangrene is the *line of demarcation*, for upon it depends the separation of the dead part and the subsequent repair. This line appears at the border of the gangrenous area as a red, inflammatory zone. Toward the dead part we early find the evidences of separation in the form of a line of liquefaction. At this line a groove is formed, which gradually deepens until the dead part is thrown off. No matter how large the gangrenous portion may be, if the patient lives sufficiently long, it will be thrown off, unless, as is the custom in practice, the part is removed by surgical means.

The process which effects the separation is called *ulceration.* Ulceration is an inflammatory process occurring on surfaces and accompanied by softening. Ulcers, under all circumstances, have one of two tendencies, either to *soften* and *break down* or to *heal.*

Clinical Causes.—1. *Inflammatory processes* that are very active and in which the blood-vessels do not recover themselves.

2. *Micro-organismal infection, e. g.*, hospital gangrene. This is an infectious and highly contagious disease, the cause of which is probably virulent forms of the ordinary pyogenic micro-organisms.

3. *Traumatism*, especially when affecting the large venous trunks, and giving rise to coagulation of the blood within them. A tight ligature around a limb by pressing directly upon the veins, may also lead to gangrene.

4. *Diabetes.* This probably induces a condition of the system favoring the action of micro-organisms.

5. *Neuropathic causes*, as *e. g.*, in certain bedsores. Bedsores may be due simply to pressure maintained for a long time, but there is a class of such lesions that occur acutely, and are dependent upon disease of the ganglion-cells of the anterior horns of the spinal cord (the trophic centers).

CHAPTER III.

ELEMENTARY PATHOLOGIC PROCESSES AFFECTING THE CIRCULATION.

LOCAL HYPEREMIA—LOCAL ANEMIA.

The amount of blood in a part is normally subject to frequent changes. These changes become pathologic when they have an abnormal cause or when they are excessive.

HYPEREMIA OR LOCAL CONGESTION.

This is an excess of blood in a part.

There are two forms: *A. Active. B. Passive.*

A. **Active Hyperemia.**—The part the seat of active hyperemia is swollen and red; its temperature is elevated; there may be a sensation of heat or even of pain.

Hyperemia and its attendant phenomena frequently disappear after death, first, because the arteries contract and drive the blood into the veins, and secondly, because the blood gravitates to the dependent portions of the body. The arterial contraction may be so pronounced as to render the part pale.

This disappearance of hyperemia is frequent in the intestinal mucous membrane, and we may find pallor in cases in which we would expect hyperemia. The presence of blood in the large vessels of an organ is no evidence of ante-mortem hyperemia. To establish the latter there must be a filling of the capillaries, producing a uniform redness. We may find the signs of active hyperemia preserved in the wall of the intestines in cholera; also at times in the gray matter of the brain.

Active hyperemia may be (*a*) *Idiopathic.* (*b*) *Collateral.*

Idiopathic hyperemia is caused by an impairment of the resisting power of the arteries leading to the affected part. The loss of resistance may be caused:

1. *By agencies acting directly on the muscular coat* of the arteries causing paralysis. These agencies may be

(α) *Mechanical*, as a blow, which causes a momentary contraction of the arteries, then dilatation and hyperemia.

(β) *Heat.* This, too, produces a primary contraction, then a dilatation.

(γ) *Drugs*, as atropin.

(δ) *Diseases of the coats of the arteries*, especially chronic inflammation with fatty degeneration.

All these causes may be aided by a general increase in blood-pressure.

2. *By disturbances of the nervous system.* These are of two kinds, those that paralyze the vaso-constrictor nerves—*neuro-paralytic hyperemia;* and those that stimulate the vaso-dilator nerves—*neurotonic hyperemia.*

The nervous forms of hyperemia occur frequently in connection with nervous diseases; they are very commonly reflex in origin.

(*b*) *Collateral hyperemia.* This is brought about by obstruction in the arterial circulation of a neighboring organ, *e. g.*, obstruction of the right renal artery causes an excess of blood to go to the left kidney.

Active hyperemia may lead (1) to hypertophy, (2) to cloudy swelling, by over-stimulation of the nutritive functions of the cells, and (3) to inflammation.

B. **Passive Hyperemia, Stasis, or Venous Congestion.**—This is caused by obstruction of the venous circulation preventing the outflow of blood from an organ or part.

On account of the free venous anastomosis, passive congestion is not readily produced. Besides the local causes there must always be some general conditions favoring the congestion. These general conditions are

1. *Valvular heart-disease.*
2. *The action of the muscles.*
3. *Disturbances of the pulmonary circulation*, and
4. *Gravity.*

The local causes are (1) *Pressure upon the veins.* Pressure more easily compresses the veins than the arteries, the latter having more resisting walls.

2. *Disease of the vessel-walls.*

3. *Thrombosis.*

Morbid Anatomy.— The affected part is swollen and of a bluish color, and its temperature is lower than normal. The bluish color is apt to disappear post-mortem after a section of the organ has been made, on account of the oxidation of the hemoglobin. Passive congestion may lead to (*a*) cloudy swelling, (*b*) to atrophy, (*c*) to degenerations, and (*d*) to necrosis, *e. g.*, to moist gangrene.

Brown atrophy is a variety of atrophy due to long-continued congestion and associated with excessive pigmentation. Prolonged congestion leads to the formation of new connective tissue and thus gives rise to *cyanotic induration* of the affected organ.

Post-mortem hypostasis, or cadaveric lividity.—This is a gravitation of the blood to the dependent parts of the body after death. It must be distinguished from bruise marks, the result of injuries during life. The following are the differential characters:

1. The cadaveric lividity occurs only in the dependent portions of the body.

2. The blood is fluid and can be pushed from one point to another, while in the bruise the blood is extravasated and cannot be pushed aside.

3. When the part is cut the blood runs out in case of cadaveric lividity, but not in that of a bruise.

LOCAL ANEMIA OR ISCHEMIA.

This is due to a diminution in the caliber of the blood-vessels leading to the affected part.

Causes.—1. *Pressure on the arteries*, as by a tumor or by a swelling of the surrounding tissues.

2. *Changes in the walls of the blood-vessels*, as (*a*) chronic inflammation, (*b*) tumors.

3. *Obstruction within the blood-vessels*, (*a*) by a thrombus or (*b*) by an embolus.

4. *Nervous disturbances*, producing a contraction of the muscular coat of the arteries. The causes generally act reflexly through

the nervous system, as, *e.g.*, anemia of the brain from disturbance in the intestines. Gastric and uterine diseases frequently cause anemia reflexly. Hysteria, especially the grave forms of the disease associated with anesthesia (hemianesthesia), gives rise to ischemia, which may be coextensive with the loss of sensation.

Collateral Anemia. This is quite rare and is brought about by congestion of a neighboring or related organ. Dilatation of the vessels of the abdomen induces anemia of the brain.

The development and character of the local anemia depend upon the facility with which a collateral circulation can be established. If the latter is ample, the anemia is not marked. In organs possessing so-called *terminal* or *end-arteries* the collateral flow is established with difficulty. There is no true collateral circulation in these cases, no communication by large branches, but only through the medium of capillary vessels. Obstruction of such arteries leads to anemia of the part supplied.

Morbid Anatomy.—The anemic organ is pale, its temperature is lowered, and its size diminished. Later, when necrotic changes develop, the part may become swollen and larger. In cases where the stoppage of the vessel is complete, as by a thrombus or an embolus, an infarct is produced, which may be anemic or hemorrhagic.

THROMBOSIS.

Thrombosis is the coagulation of the blood in the circulatory stream. Consisting in the formation of fibrin, it is an example of coagulation-necrosis.

Seats. Chambers of the heart, veins, arteries and capillaries.

Morbid Physiology.—The process of coagulation within the vessels is the same as that occurring in shed blood. In order to understand it, it is necessary to consider those conditions which prevent coagulation in the physiologic state. It is generally accepted that the fluidity of the blood depends upon the maintenance of a normal, vital relation between the blood and the endothelial lining of the vessels. Any disturbance of this relation leads to thrombosis.

The disturbance may be:

(*a*) In the vessel-walls.

(*b*) In the blood.

(*a*) *Changes in the vessel-walls.* These are principally those that bring about a roughness and desquamation of the endothelium of the intima, as occurs in acute and chronic inflammation of the vessels, and in injuries.

(*b*) *Changes in the blood.* These may affect (α) the chemical composition, (β) the rate of flow.

(α) *Changes in chemical composition.* Chemical changes predisposing to thrombosis may be produced (1) by the injection of blood-serum from one species of animal into the blood-vessels of another species. The serum probably acts upon the leukocytes of the injected animal in such a way as to liberate fibrin-ferment. The blood of certain species of animals has a greater tendency than that of others to produce coagulation. (2) By the injection of certain substances that destroy the corpuscles. (3) By extensive burns.

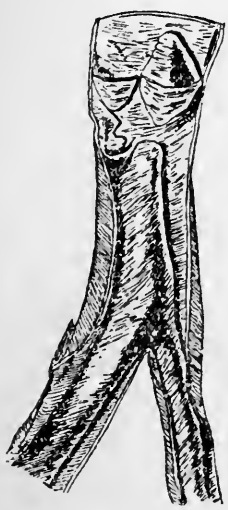
(β) *Change in the rate of flow.* This is probably the most frequent cause of the thrombi seen post-mortem, which are formed during the closing hours of life, in the agonic period.

When the blood stream flows with its normal velocity, the red corpuscles occupy the center, or the axial current, while the white corpuscles and blood-plaques are at the periphery. This difference in position is due to physical causes; the heavier elements, the red corpuscles, seek the center of the stream; the lighter, the white corpuscles and plaques, the periphery. When the current is slowed, the corpuscles at the periphery of the stream show a tendency to fall against the vessel-wall. The plaques are the first to be deposited, and by a process of agglutination, a form of hyaline degeneration, which occurs when the flow is not of the normal rapidity, adhere together. This agglutination constitutes the first step in the production of the thrombus. The resulting mass projects as a coral-like formation from the inner wall of the vessel. To this mass leukocytes readily adhere; changes take place in the latter by which certain substances are liberated: fibrin is formed and deposited on the coral-like projection. In this way a *white thrombus* is formed; at times many red corpuscles are caught in the clot, and the latter then has a red or marbled color.

It is easily comprehended that whenever the current is slowed, chemical changes will rapidly be induced in the blood, and will contribute to the formation of the thrombus. As soon as there is any departure from the normal composition of the blood, the vessel-walls

cease to be properly nourished, and anatomic changes take place in the endothelial lining, which further favor coagulation. Thus it is evident that all the causes of thrombosis are intimately correlated, and that, given any single one, the others must of necessity follow.

Morbid Anatomy.—Thrombi are made up of layers of different color, and present radiating trabeculae of fibrin that may be visible to the naked eye. The color of the clot depends upon the presence or absence of red corpuscles, which in turn is probably dependent upon the rapidity of the current at the time of clotting. The longer the clot remains in the living body, the whiter, firmer, dryer, and more adherent to the vessel-wall it becomes.



Obstructing thrombus in the femoral and saphenous veins; also a thrombus on one of the valves. (*Ziegler.*)

The coagula formed after death in the heart and large blood-vessels are soft, jelly-like, not adherent, dark-red in color, and are known as "currant-jelly" clots. During the agonic period clots are deposited which are light in color, from the whipping-out of the red cells, are soft, jelly-like, edematous, and almost diffluent. These are the "chicken-fat" clots; frequently they are combined with currant-jelly clots. The thrombi formed during life are dryer, denser and more adherent, and on microscopic examination are found to contain more fibrin and more leukocytes.

Thrombi are classified in various ways:

1. According to shape:

(*a*) *Occluding.*

(*b*) *Parietal*—one formed only on one side of the vessel-wall, or produced by the washing away of a part of an occluding thrombus.

(*c*) *Valvular.* A form of parietal thrombus taking the shape of a valve of a vein or a heart-valve.

(*d*) *Channeled or tunneled.* A clot may be deposited in an annular form or an occluding thrombus may become hollowed out.

2. According to period of formation:

(*a*) *Primary.* One formed at the original seat of lesion.

(*b*) *Secondary.* That deposited on the primary thrombus and extending to the nearest branch.

3. According to etiology:

(*a*) *Infecting.*

(*b*) *Non-infecting* or *mechanical.* The infecting thrombus is produced by micro-organisms, which act upon the leukocytes and cause the liberation of fibrin-ferment. The first results of the thrombus are mechanical, but the presence of the bacteria speedily leads to inflammatory changes, which frequently terminate in suppuration at the site of the thrombus, and also induce a general infection of the system, with or without the formation of multiple abscesses.

Thrombi have a tendency to undergo certain changes:

(*a*) *Organization, i. e.,* the growth of new connective tissue into the thrombus from the walls of the containing blood-vessel, the fibrin of the clot acting as a frame-work for the developing tissue.

(*b*) *Liquefaction.* This affects chiefly the interior of the thrombus and leads to the formation of a reddish, puriform fluid. In heart-clots the process may give rise to large cavities filled with fluid. The softening is, in some instances, caused by micro-organisms; in others, of obscure nature, micro-organisms are absent.

Clinical Causes.—1. *Cachectic* and *marasmic conditions,* in which we have a slowing of the current and an alteration in the character of the blood (*marasmic clots*).

2. *Chronic diseases of the heart,* associated with changes in the endocardium or the valves.

3. *Acute endocarditis.*

4. *Atheroma.*

5. *Injury to the walls of the blood-vessel,* as in ligation.

6. *Obstruction* or *dilatation of the veins.*

7. *Micro-organisms.*

EMBOLISM.

Embolism is the stoppage of a blood-vessel by a fragment of fibrin or other material carried in the circulation. The obstructing particle is termed an *embolus.*

Emboli in the majority of instances follow the course of the circulation: in the arteries, toward the periphery, in the veins, toward the heart. Exceptionally there is a reverse flow in the large veins by which emboli may be carried into the latter from the heart. As a

rule emboli consist of fibrin derived from a thrombus, but fragments of tissue, of tumors, particles of fat or of pigment, and micro-organisms, may be carried in the blood-stream and constitute emboli.

Owing to their anatomic position certain vessels are more frequently the seat of embolism than others. Thus the left carotid artery is more prone to receive emboli than the right; the left iliac than the right; the right pulmonary than the left.

The superior and inferior mesenteric arteries are practically exempt from embolism. In the brain emboli follow as a rule the channel of the left middle cerebral artery.

Occasionally a large vessel is obstructed by an embolus, but more commonly we meet with many small emboli which give rise to *miliary embolism*, a condition not rarely seen in ulcerative endocarditis. The symptomatology of miliary embolism is very variable and obscure. By some it is held that chorea is a possible consequence of miliary emboli of the brain.

Emboli are (*a*) *simple*, or *mechanical* or (*b*) *specific*. The former produce merely obstruction—if in a terminal artery, the result will be an anemic or a hemorrhagic infarct.* The latter contain micro-organisms, which set up, at the point of lodgment of the emboli, the same changes as in the original seat whence they were derived, most frequently small abscesses (*metastatic abscesses*).

HEMORRHAGE.

This is an out-pouring of blood from the blood-vessels.

Hemorrhages are divided as follows:

I. According to source:

1. *Arterial.*
2. *Venous.*
3. *Capillary.*

II. According to the mode in which the blood leaves the vessels:

1. *Hemorrhage by laceration* or *per rhexin.*
2. *Hemorrhage by diapedesis*—a gradual extrusion of the blood through the vessel-walls (capillaries and veins) without previous rupture.

---

* Anemic infarction has been discussed under coagulation necrosis; hemorrhagic infarction will be described under hemorrhage.

III. Hemorrhage may be

1. *From free surfaces.*

2. *Into tissues—interstitial.*

Hemorrhage from free surfaces may be

(*a*) *External*, as epistaxis, hematemesis, hemoptysis, menorrhagia, metrorrhagia, hematuria.

(*b*) *Internal*, as hematometra, hemothorax, hematocele, hemopericardium.

2. Interstitial hemorrhage.

(*a*) The hemorrhage may form a *cavity* for itself (hematoma).

(*b*) It may *infiltrate* the tissues (hemorrhagic infiltration or extravasation). Various terms are employed to designate hemorrhagic infiltration.

(α) *Ecchymosis* is applied to localized hemorrhages beneath surfaces.

(β) *Petechiae*—are small punctiform hemorrhages beneath the skin.

(γ) *Suffusion* or *sugillation*—is an extensive hemorrhage beneath the surface.

(δ) *Hemorrhagic infarct*—a well-circumscribed, wedge-shaped area of hemorrhage, the result of embolism or thrombosis.

According to causation hemorrhages are divided into

1. *Traumatic*—due to direct injury received from without.

2. *Essential*, *idiopathic*, or *autogenous*—those the causes of which reside within the body.

The causes of essential hemorrhage are:

(*a*) *Excess of blood-pressure*, (α) as in whooping-cough (hemorrhage into conjunctiva, hemoptysis); (β) in mitral stenosis (hemoptysis, epistaxis, hematemesis); (γ) in cirrhosis of the liver (from esophageal veins, from stomach, from intestines).

(*b*) *Diseases of the vessel-walls.* (α) Atheroma; (β) inflammation; (γ) infectious diseases. The last cause alterations in the vessel-wall and, probably, also in the blood itself. Examples: hemorrhagic or black small-pox; yellow fever.

(*c*) *Changes in the blood*—as in the so-called hemorrhagic diseases, hemophilia, purpura, and scurvy. The nature of the changes leading to the bleeding in these cases is not clearly understood. Very probably there is also a disturbance in the walls of the blood-vessels. Purpura and scurvy, particularly the latter, may be due to micro-organismal infection.

(*d*) *Neurotic disturbances*, as (α) in hysteria, in which hemorrhage may occur in strange localities—sometimes from the hands and feet, simulating the crucifixion; (β) in acute insults to the nerve-centers of the brain, as in apoplexy, which at times leads to hemorrhage from the lungs and stomach.

(*e*) *Embolism or thrombosis of an artery*—causing hemorrhagic infarction.

Terminations of Hemorrhage. If death does not result, the bleeding is stopped by thrombosis. The clot then acts as a foreign body and is gradually removed by organization. It is not itself converted into fibrous tissue, but merely serves as the skeleton or framework for the newly forming connective tissue. The vessel is eventually changed into an impervious fibrous cord.

Fate of the effused blood. In interstitial hemorrhage the blood is usually removed by absorption, but the blood pigment, in the form of crystals or granules, remains for a long time. Connective tissue replaces any portions of the organ or part that were destroyed by the hemorrhage.

In the case of a hematoma the blood may remain in the cavity for a long period. At times it becomes surrounded by a connective tissue capsule, the blood-pigment is absorbed, and a clear cyst is produced. The fluid of the cyst or the original hematoma may be absorbed, and the gap filled up by the process of organization.

The effusion of the blood in the serous cavities produces scarcely any inflammatory reaction; the blood is as a rule rapidly absorbed. Hence it is unnecessary to tap a serous sac for the evacuation of blood.

HEMORRHAGIC INFARCTION.

A hemorrhagic infarct is a wedge-shaped infiltration of blood, brought about by the obstruction of the artery leading to the affected area. The cause of the obstruction is usually an embolus or a thrombus. A rapid degeneration takes place in the walls of the blood-vessels of the region supplied by the occluded artery, and renders possible the occurrence of hemorrhage from these vessels.

To explain the extravasation into an area from which the natural blood supply is cut off, the following theories have been advanced:

1. The stoppage of the current in the artery produces a condition of negative pressure, by reason of which blood flows back from the veins.

2. The blood flows into the area from the neighboring capillaries.

3. The sudden lodgement of an embolus provokes a reflex contraction of all the arteries and veins beyond the seat of obstruction and even above it, *i. e.*, to the proximal side of it, whereby an excess of blood is forced into the capillaries, and they rupture.

The majority of infarcts are best explained by the last theory.

Morbid Anatomy.—(*a*) *Macroscopy.* The infarct is pyramidal in shape, the base of the pyramid being directed to the periphery of the organ; it is raised above the surrounding surface, and is firmer and darker in color.

(*b*) *Microscopy.* We see the breaking down of the red blood-corpuscles; pigment is present, and fibrin.

Terminations. The infarcted area is converted into a cyst or is removed and replaced by a scar.

The hemorrhagic infarct is produced by mechanical obstruction. If an infecting embolus lodges in a vessel it usually sets up inflammatory changes. At times we find some extravasation of blood, especially at the periphery; while at the center, at a point corresponding to the seat of the infecting embolus, the changes peculiar to the infectious agent are developed—generally an abscess.

Hemorrhagic infarcts are most common in the lung, kidney, spleen, and brain.

CHAPTER IV.

COMPOSITE MORBID PROCESSES.

In the preceding part of the subject, the cell was looked upon as an entity, and was not considered in its relation to other cells. In composite morbid processes we deal with the pathology of the *tissues* rather than with that of the *cells*. Hemorrhage and gangrene are, in reality, not simple morbid processes, but they are most conveniently studied with that group.

The composite morbid processes are three in number—inflammation, regeneration, and tumor formation. In all of them we have hyperplasia of tissues.

Inflammation is an *eliminative* process; regeneration, since it produces new tissue, is *formative*; tumor-formation, leading to the development of useless tissue, is termed *pseudo-formative*.

INFLAMMATION.

Inflammation is the reaction of the parablastic tissues to the action of irritants, when this reaction is attended by an overfilling of the blood-vessels with blood, a change in their walls, an extrusion from them of a modified plasma and of leukocytes, and a proliferation of the connective tissue-cells. These changes have for their object the removal or isolation of the source of irritation.

The changes in the archiblastic tissue are secondary, as far as the actual changes in inflammation are concerned. Frequently the parenchyma is primarily affected, but it should then be looked upon as the cause of the inflammation, constituting the source of irritation which excites the inflammatory changes in the parablast.

Sources of Irritation.

(*a*) *Those arising within the body*, viz.: *Portions of tissue* or *abnormal metabolic products* that have become unfit for the normal functional activity, and require removal.

(*b*) *Micro-organisms.*

Although these two groups are quite distinct in character, they are separated with difficulty as causes of inflammation; we find them nearly always associated together. The reasons for this are plain: tissues unfit for further use act as irritants and inaugurate the inflammatory process, but at the same time they offer a favorable soil for micro-organisms; both then seem to act together. On the other hand, if micro-organisms enter the tissues, one of their first effects is to cause the death of cells, and then both sources of irritation are again combined.

Micro-organisms, whatever their exact relation, play a very important part in the inflammatory process. Inflammation as it was described by the ancients, with its four cardinal symptoms, referred to the abscess, which is always micro-organismal in origin.

The sources of irritation arising within the body are due to two causes which may be termed (*a*) *external* and (*b*) *internal.*

(*a*) *External*—traumatism. This primarily causes a destruction of cells; the latter then set up the inflammation.

(*b*) *Internal.* 1. *Disturbances of circulation*—as the stoppage of a vessel by an embolus, leading to hemorrhagic or anemic infarction.

2. *Disturbances of innervation, i. e.,* interference with the trophic function of the nerves. This we see in the bed-sores of myelitis—the dead tissues, for their removal, require the inflammatory process.

3. *Disturbances of metabolism.* These are not clearly understood. In certain diseases abnormal products are elaborated which act on the tissues and start up the inflammatory process.

In Bright's disease we may have inflammation of the serous membranes; gout leads to chronic inflammatory changes in the kidney—the gouty kidney; cirrhosis of the liver is sometimes associated with obscure inflammations in other organs.

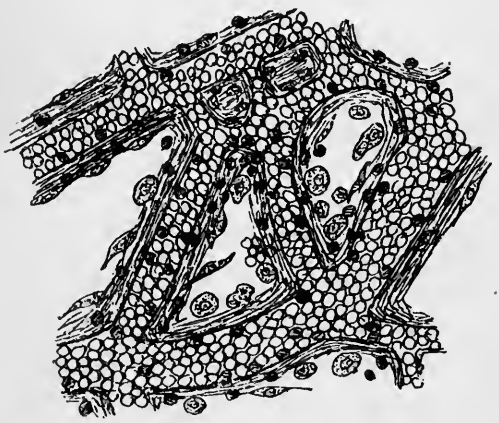
Morbid Anatomy.—(*a*) *Microscopy.* The changes in inflammation are generally described under three separate heads:

1. Vascular changes.
2. Changes in the parablastic tissues.
3. Changes in the archiblastic tissues.

1. **Vascular Changes.** The first change that is apparent is a *contraction* of the blood-vessels. This is merely accidental, being due to a reflex action excited by the irritant; it is no part of the

inflammatory process, and may disappear without being followed by inflammation. The next change is a *dilatation* of the blood-vessels, with an *increased activity of the circulation at the periphery.* This dilatation is both active, or idiopathic, and collateral—idiopathic, because of the increased activity of the circulation in that region; collateral, because there is in the center a tendency to stasis. In the central area the dilatation is passive, and is due to a simple yielding of the vessels. Eventually there is complete *stasis in the center.* The filling of the blood-vessels causes them to become wider, and some that were invisible before appear now as fine red lines.

The slowing of the current produces the same phenomenon as in thrombosis, namely, a tendency of the white corpuscles to fall against the vessel-wall. This tendency is termed the *peripheral drift* of the leukocytes. As soon as the circulation is completely arrested, the leukocytes begin their ameboid movements, and *wander out* through the wall, and also into the center of the vessels. Normally, the blood-vessel walls constitute a barrier to the passing out of cells, but when the blood supply is arrested they become more yielding, and the leukocytes pass out through the softened cement-substance between the endothelial cells. This wandering-out occurs especially from the smaller veins and capillaries and gives rise to a dense accumulation of cells about these vessels. As early as ten hours after the application of the irritant we may find the capillaries embedded in compact cylinders of round cells.



There is also an *exudation* through the vessels of a modified *plasma*, which is richer in albumin and higher in specific gravity than the plasma of dropsy. This fluid may remain in the liquid state, when we speak of inflammatory edema, or it may coagulate and form "lymph." Whether the one or the other occurs depends on the character of the inflamed tissues and on the cause of the inflammation. In diphtheria we have coagulation.

There is also, in some inflammations, particularly those of an intense degree, a *diapedesis of red corpuscles.*

Historical.—The outwandering of the leukocytes was first observed by Waller, in 1823; subsequently by Dutrochet and by Addison. None of them, however, recognized the importance of the phenomenon, and it was left for Cohnheim to point out, in 1867, its true significance. He may, therefore, be justly considered the actual discoverer.

Another important and essential part of the vascular changes consists in a *softening of the walls of the blood-vessels,* especially of the cement-substance holding the endothelial cells together.

(*b*) *Naked-eye phenomena and symptoms.* These are redness, swelling, pain, and heat, and may nearly all be accounted for by the histologic changes described.

(1) *Redness.* This is due to the overfilling of the blood-vessels. The outer area is lighter, the central darker in color.

(2) *Swelling.* This is the result of (α) the excess of blood in the vessels, (β) the passing out of plasma and corpuscles, and (γ) the multiplication of cells.

(3) *Pain.* This is due to pressure exerted by the swollen tissues upon the terminal nerves, or by an action of irritant products upon the nerve-endings.

(4) *Heat.* It is difficult to determine whether this is due to increased heat-production or increased heat-elimination. In the central area of stasis there can be no augmented production, but at the periphery the active chemical changes may lead to an increased production of heat.

Morbid Physiology.—The phenomena which characterize inflammation can only occur when the *blood-current is slowed.* But this alone is not sufficient, for a similar condition of slowing obtains in some hyperemias, yet in them the blood is retained within the vessels. There must be some *alteration in the vessel-wall* to allow the emigration of leukocytes and the exudation of plasma. Between the blood and the tissues there exists normally a reciprocal, *metabolic* current, over which the endothelial cells of the blood-vessels have considerable control, *i. e.*, the lymph bathing the tissues does not pass out through the capillary walls by mere filtration, but owing to a selective action of the endothelial cells. The entrance of waste products into the blood stream is likewise not a simple physical process. The function of the endothelial cells is to a certain extent comparable to that of the cells of secreting glands. Any disturbance in the metabolic current between blood-vessels and tissues brings about changes that may pass on to inflammation.

The disturbance may give rise to the passing out from the vessel of substances that should be retained; or substances are retained that should be extruded; or, as seems most probable, something is formed in the tissues which, in its passage into the vessel, causes serious changes in the vessel-wall. As the normal circulation depends upon the physical and chemical relations between the blood and the vessel-wall, such a change rapidly leads to a slowing and, finally, to a stagnation of the blood-current. This induces further alterations in the endothelial cells, which may undergo various elementary morbid changes.

While the wandering-out of the leukocytes is in part accounted for by their power of ameboid movement, there is another factor: the presence of certain substances termed *chemotactic*, which stimulate the emigration of these cells.

Chemotaxis is the property possessed by certain bodies of attracting or of repelling the leukocytes. It is, therefore, of two kinds: (*a*) *Positive chemotaxis*—that which attracts the leukocytes; (*b*) *Negative chemotaxis*—that which repels them.

The experiments to determine the chemotactic nature of different substances are performed somewhat as follows: Small capillary glass tubes are filled with the material to be tested and introduced, with all antiseptic precautions, into the loose cellular tissue, or into the anterior chamber of the eye. They are allowed to heal in and are subsequently broken. If the substance used is positively chemotactic, the ends of the glass tube will become packed with leukocytes, while if the material is negatively chemotactic, the tube will remain empty.

The positive chemotactic substances as a rule are component parts of cells; the products of cell-activity, or waste-products of metabolism, as urea, are negatively chemotactic. The positive chemotactic substance is a nitrogenous compound (certain non-nitrogenous substance used experimentally manifest positive chemotaxis); it may be nuclein arising from cell-nuclei, or a complex proteid substance derived from the cell-protoplasm. The most active chemotactic substances resemble vegetable casein. In inflammation these bodies are set free and exert a positive chemotactic action.

Among positive chemotactic substances may be named gluten casein, legumin, bone gelatin, isinglass, alkali albuminates from muscles, liver, and lung, and hemi-albumoses. Since bacteria are

vegetable cells with large nuclei, they contain a very positive chemotactic substance.

Negatively chemotactic are ammonia and some of its salts, as the butyrate and valerianate, trimethylamin, urea, ammonium urate, peptones, tyrosin, etc.

While nearly all bacteria possess positive chemotactic properties, some present this quality in a much more marked degree than others. Thus the group of pyogenic bacteria and the bacillus of tuberculosis are strongly chemotactic.

The positive chemotactic substance may be extracted from bacteria. It has been obtained from the bacillus pyocyaneus by treating the culture with a dilute alkaline solution, precipitating it from the latter with weak acids, and again dissolving it in alkalies.

In order that chemotaxis may become operative and cause an outwandering of leukocytes, the other changes described must be present, viz., a slowing of the blood-current and an alteration in the vessel-wall.

Changes in the Fixed Connective Tissues.—These are of two kinds, (*a*) degenerative and (*b*) proliferative.

The *degenerative* changes are the different forms of degeneration and necrosis already described under the simple pathologic processes, chiefly coagulation necrosis, liquefaction necrosis, and fatty degeneration.

The *regenerative* changes consist in a multiplication of the fixed connective tissue cells, and have for their object the repair of the parts destroyed. They are a part of inflammation only within certain limits; beyond these they belong to regeneration.

The proliferation of the connective tissue cells is a marked feature of inflammation, and manifests itself very early in the process by karyokinetic changes. The nucleus of the connective tissue cells is large, vesicular, and stains feebly, the periphery staining best.

The leukocytes have generally multiple nuclei, or the nucleus may be single, but indented and irregular. They stain intensely. The greater the number of new connective tissue cells, the more likely is regeneration to take place; if the multinuclear cells are in excess, suppuration will probably be the termination.

The accumulation of cells in an inflammatory area is so great and takes place with such rapidity, being quite marked in ten hours, that the explanation of their origin from only two sources,

the emigration of leukocytes and the proliferation of fixed connective tissue cells, seems scarcely sufficient. The number of leukocytes must obviously be limited on account of the stasis in the blood-vessels, and the number of connective tissue cells can also not be very great on account of the comparatively few cells from which they spring.

These two processes thus seeming inadequate, the theory has been advanced, and on very good grounds, that we have in the connective tissue certain "slumbering-cells" (*Schlummerzellen*), germinal particles of cells, which cannot be demonstrated with the ordinary nuclear stains, but which under the influence of the irritation present in the inflammatory process, develop into cells. We recognize in bacteria a condition quite analogous to this: the germinal particles or spores of bacteria do not stain under ordinary circumstances, and generally escape detection; but under favorable conditions they are capable of developing into perfect bacteria.

Some of the cells in the inflamed area, principally the leukocytes, have a tendency to degenerate—they undergo fatty degeneration, or take part in the coagulation necrosis or liquefaction necrosis. It is possible that they may contribute to the nutrition of the fixed connective tissue cells, which are associated with regeneration.

Changes in the Intercellular Substance. This may undergo any of the degenerations, but as a rule it presents the following three changes:

1. *Liquefaction necrosis.* In this it melts away and contributes to the formation of pus.

2. *Coagulation necrosis.* It may suffer coagulation necrosis alone, or with the cells of the connective tissue, or with the fluid plasma.

These two are the destructive changes; the cells may, of course, participate in them.

3. *It may undergo a reparative change,* and contribute the basis of the regenerative process, forming the network in which the cells find support.

Inflammation lays the foundation for the regenerative process in a double manner: (1) *by furnishing certain cells*; (2) *by supplying a skeleton-work* for these cells, which holds them together.

Is the cellular accumulation absolutely characteristic of inflammation? No, for we find normally such collections of round

cells, "lymphoid tissue," especially in the mucous membrane of the digestive tract. They are either distinct lymphoid follicles, limited by a wall, or have no special structure and are without wall. The latter are with great difficulty distinguished from the inflammatory accumulation. The diagnosis is based on the fact that the lymphoid whirls are isolated and surrounded by normal tissue, while the inflammatory areas are irregular, and fade gradually into the surrounding tissue. It is, however, possible that the lymphoid whirls are the result of an attempt to eliminate an irritant, perhaps bacteria.

Inflammation in tissues devoid of blood-vessels, as the cornea and cartilage, presents all the phenomena that have been described. The chemotactic influence acts, in the case of the cornea, on the leukocytes in the blood-vessels at the periphery, and causes them to wander in along the lymphatic channels. The proliferation of the fixed connective tissue cells is also observable.

Naked Eye Appearances of Inflammation.—Inflammatory exudate, or inflammatory infiltration, is the name given to all the materials thrown out in inflammation—both the cells and the fluid. Different names are employed to designate the nature of the fluid element—serous, sero-fibrinous, fibrinous or croupous, and hemorrhagic. Inflammatory edema indicates the presence of a large amount of fluid infiltrating the tissues.

Various names are given to the cellular element: cellular infiltration, cellular exudate, round cell infiltration, small cell infiltration, granulation tissue.

SUPPURATION.

Suppuration is a liquefaction necrosis of the inflammatory exudate. It may occur in the following localities:

1. On free surfaces—
   - (*a*) *On serous membranes*, when it takes the name of the membrane affected, *e. g.*, pyothorax, pyopericardium.
   - (*b*) *On mucous surfaces*, when it is termed purulent catarrh.
   - (*c*) *On free surfaces, with loss of tissue*—ulceration.
2. Within tissues—
   - (*a*) *As a circumscribed collection of pus*—abscess.
   - (*b*) *As a diffuse infiltration*—purulent edema, purulent infiltration, or phlegmon.

Suppuration may spread from the original seat to neighboring tissues along the lymphatic channels, this being most apt to occur when the primary process is not sharply circumscribed. When the process is circumscribed, we find the pus separated from the healthy tissues by a line of demarcation, termed *pyogenic membrane.*

In this pyogenic membrane one of two processes is going on —either a liquefaction necrosis, when the suppuration is spreading, and the line is truly pyogenic, or regeneration, when we find the uninuclear cells originating from the connective tissue in excess, and the line is healing or granulating.

These two processes are well represented in ulcers and in abscesses. From a pathologic standpoint, ulcers are divisible into (*a*) those that are spreading, in which the pyogenic membrane is liquefying, and (*b*) those that are healing, in which the line is forming granulations. Some of the clinical varieties of ulcers are the serpiginous, diphtheritic, gangrenous, fungous, indolent, and varicose.

The wall of an abscess is analogous to the floor of an ulcer— if the abscess is spreading, the membrane is pyogenic; when the abscess is healing, it is regenerating. Frequently both processes are going on at the same time, which is in accord with the clinical history of abscess. An acute abscess does not stand still, but spreads until it reaches the surface and discharges. This tendency of an abscess to reach the surface, technically termed *pointing*, depends upon changes in the circulation. An abscess is in the way of its own circulation. The blood comes from below, hence the deeper layers are better supplied with nutrition and are able to organize. In the upper layers the abscess presses upon the smaller blood-vessels, and the tissues break down from want of food supply.

Looking at pointing from this standpoint, we can understand the peculiar direction which abscesses sometimes take. Abscesses near the intestines or the bronchi, especially if acute, do not tend to rupture into these tubes, but through the surface, because the intestine and the bronchi have their own blood-supply. At times the circulation is interfered with, and the abscess breaks into the intestine or the bronchus. After the abscess is opened, the pyogenic membrane becomes a healing or granulating membrane. The broken-down material is comparable to the sphacelus in gangrene.

Abscesses are divided into (*a*) *primary*, those produced at the site of the original infection; and (*b*) *secondary*, or metastatic, those

brought about by the carrying of the infecting agent from the primary seat to distant parts. The latter are generally multiple, occurring in the lung, kidney, liver, spleen, and elsewhere, and result from the lodgement of specific emboli in these organs.

Clinically, abscesses are divided into (*a*) hot and (*b*) cold. (*a*) A *hot or acute abscess* is one in which active inflammatory processes are going on, with liquefaction and the formation of true pus. (*b*) *Cold abscesses* are such as present no marked evidences of inflammation, are not as a rule the result of suppuration, and do not, except in rare instances, contain true pus. They are most frequently the product of cheesy necrosis brought about by the tubercle bacillus. Under certain conditions, however, the tubercle bacillus is capable of producing suppuration.

Etiology of Suppuration.—Clinically, suppuration is always the result of micro-organismal infection. Experimentally, it may be produced by proteids extracted from bacteria, by calomel, turpentine, sabine oil, etc.

The micro-organisms which most frequently cause suppuration are:

1. *Staphylococcus pyogenes aureus, staph. pyog. citreus, staph. pyog. albus.* These are widely disseminated, occurring in the air, sometimes in water, on the surface of the body, and in cavities communicating with the exterior. The distinguishing names are given by reason of the color of the cultures on artificial media. Staphylococci generally produce circumscribed suppuration, *i. e.*, abscess.

2. *Streptococcus pyogenes.* This is found in the same places as the staphylococcus, but in less abundance. It occurs in long and in short chains, the former being more virulent. The suppuration produced by it is diffuse—a phlegmon. It is probable that the streptococcus of erysipelas is identical with the streptococcus pyogenes, for it has been shown that when the former is rubbed into the tissues of a rabbit's ear, it causes erysipelas, but when introduced elsewhere, it produces diffuse suppuration. The difference depends largely upon the animal, to a much less extent upon the micro-organism.

The staphylococcus and the streptococcus are the most common causes of suppuration, and are the bacteria that are commonly referred to as pyogenic micro-organisms. Both are readily destroyed

by heat, carbolic acid, and other germicides, yet when undisturbed, they retain their virulence for a very long time, from six months to a year or more.

3. *Bacillus pyocyaneus.* This produces a localized suppuration, in which the pus is of a blue color. In culture media the bacillus gives rise to a bluish-green fluorescence.

4. *Pneumococcus.* This is normally found in the mouth; at times it produces a localized suppuration, especially in the middle ear and in the meninges.

5. *Diplococcus of Friedländer.* This occurs in the same localities as the pneumococcus, and resembles it closely in its pyogenic properties.

6. *Bacillus coli communis.* This is a constant inhabitant of the intestines. It has been found at times as the cause of purulent peritonitis, secondary to appendicitis and to intestinal obstruction, and is frequently associated with suppuration in the bile-passages. The suppuration produced by it is as a rule diffuse and malignant.

Besides the organisms named there are other bacteria that at times cause suppuration, *e. g.*, the bacillus tuberculosis, the bacillus of typhoid fever, the gonococcus, and others.

General results of suppuration:

(*a*) *Pyemia* (literally, "pus in the blood"). This is a condition in which the micro-organisms are carried from the original seat and set up abscesses wherever they lodge. As a rule there is no pus in the blood, but a few cells may occasionally enter the circulation.

(*b*) *Septicemia.* This is a condition produced by the absorption of the poisons, or *toxins*, generated by the bacteria or produced by the breaking down of tissues. Neither micro-organisms nor cells are carried in the blood. The toxins act chiefly upon the nervous centers.

In addition to this form of septicemia, which is best termed *bacterial septicemia*, there is another form of poisoning, one not connected with suppuration, which is known as *septic intoxication* (auto-intoxication). It is not bacterial in origin, but is due to the development within the body, of poisons from faulty metabolism, especially from perverted digestion.

Phagocytosis.—It has been asserted, most earnestly by Metchnikoff, that the leukocytes in inflammation act as *phagocytes*, *i. e.*, that they swallow and digest other cells. At first this theory seemed to have a very general application, but further researches have

lessened its importance. Leukocytes do unquestionably at times act as phagocytes in inflamed areas: if the micro-organisms are few in number, and their chemotactic and liquefying influence is slight, they may be swallowed by the leukocytes. When the bacteria are abundant and strongly chemotactic, the leukocytes suffer by the contact with them and die. The theory which has replaced that of phagocytosis is, that *the destruction of bacteria is brought about by the juices of the body.* It has been found that when micro-organisms are exposed to the action of the blood-serum, in the absence of all phagocytes, they perish just as completely and rapidly as when these cells are present.

It has also been observed that, besides destroying the bacteria, the body-juices (the serum) counteract, by means of *antitoxins*, the poisons elaborated by the micro-organisms. The antitoxins chemically antidote the toxins. Thus there are two influences involved in the recovery from and in the immunity to infectious diseases: (*a*) *the bactericidal* and (*b*) *the antitoxic.* Antitoxins have been found in diphtheria, tetanus, pneumonia, typhoid fever, and cholera. The substances which destroy the bacteria and neutralize their poisons probably arise from obscure metabolic changes in certain cells of the body, the resulting products being held in solution in the blood and lymph.

Changes in the Archiblastic Tissues.—The archiblastic tissues may be primarily or secondarily affected. The changes are usually of a degenerative character, and are not characteristic, but are such as can occur under other circumstances, not associated with inflammation. The changes may, however, be proliferative; in that case we may properly speak of a true inflammation of the archiblast. We find this proliferation in catarrhal inflammation of mucous membranes, in catarrhal pneumonia, and in catarrhal nephritis. In these the epithelial cells multiply rapidly by karyokinesis; many are thrown off and contribute to the formation of the inflammatory exudate. In the kidney and lung the exudate may be retained in the natural spaces, constituting casts in the former, and causing consolidation in the latter organ. The inflammation is not confined to the archiblast, but the blood-vessels of the parablast beneath show all the phenomena of inflammation; there is an outwandering of cells and an exudation of plasma, which pass to the surface and contribute to the discharge.

Varieties of catarrhal inflammation. 1. *Mucous catarrh.* In this we have chiefly a stimulation of the normal function of the cells—there is an excessive secretion of mucus; leukocytes are few.

2. *Purulent catarrh.* This is characterized by the great abundance of leukocytes wandered out from the blood-vessels. Muco-purulent cataarh is intermediate between the mucous and the purulent forms—it is the variety present in bronchitis.

3. *Desquamative catarrh.* This occurs especially in the air-vesicles and small bronchioles of the lung and in the tubules of the kidney. There is little fluid, but a marked proliferation and desquamation of the epithelial cells which are held in the spaces in which they are deposited.

Depending upon the extent of surface affected, we speak of (*a*) *diffuse* catarrh, which spreads over an extensive area, and (*b*) *circumscribed or follicular*, which is confined to small follicles or glands in the mucous membrane. The latter is generally desquamative.

CHRONIC INFLAMMATION.

This is brought about through (*a*) the continuous or (*b*) the frequently repeated action of the irritant. In chronic inflammation elimination is slow, and time is given for the building up of connective tissue, in other words, regeneration plays an important part. Some forms of chronic inflammation are readily accounted for, as, *e. g.*, that of the skin produced by the dribbling of urine, or the various forms of pneumokoniosis. Micro-organisms, as the tubercle bacillus, for instance, may be the cause of chronic inflammation. There is, however, in the action of these causes, something peculiar or specific, some phenomena which are not characteristic of inflammation, nevertheless they set up a chronic inflammation. The tubercle bacillus kills cells, and as these are removed with difficulty, time is given for the gradual production of connective tissue.

There is yet another form of chronic inflammation, one in which there is a tendency to the permanent overgrowth of connective tissue, beginning in the blood-vessels—*arterio-capillary fibrosis*—and extending to the connective tissue, of nearly all the organs of the body. The blood-vessels are thickened, and the organs hardened from the excessive formation of connective tissue. This tissue contracts and produces *cirrhosis* of the different organs, especially of the liver, kidney, and spleen.

The cause of this generalized form of chronic inflammation is not well understood, but it is thought to be the circulation of some irritant in the blood, as alcohol, arsenic or, experimentally at least, salts of chromic acid. In some cases in which the irritant is not demonstrable, it is surmised that it is generated in the body as the result of faulty metabolism, or that certain excrementitious products which are not eliminated constitute the irrritant.

Sources of the Connective Tissue.—1. Multiplication of the previously existing connective tissue—this is the most important source.

2. Obliteration of the blood-vessels and their conversion into fibrous cords.

3. Degeneration of the parenchyma, giving rise to a relative increase of the connective tissue.

4. Organization of the leukocytes—this is problematic.

Another important feature of chronic inflammation is the *hyperplasia of the parenchyma*, which goes on hand in hand with the degenerative changes, but is much less prominent.

We find karyokinetic processes in some of the cells. In cirrhosis of the liver, for example, the liver cells undergo atrophy and are removed, but the cells of the bile-ducts multiply, and new ducts are formed. A similar condition is met with in the kidney, in which the cells of the uriniferous tubules proliferate and give rise to certain forms of cysts.

REGENERATION.

The process of regeneration is best studied in the healing ulcer. As soon as an ulcer begins to heal, the cells, which are the basis of regeneration, are held together by a coagulable material, called lymph, and are enabled to form their intercellular substance, which eventually takes the place of the coagulable skeleton-work.

Changes in the Cells. The cells gradually assume the permanent form of the connective tissue, which they replace—fibrous tissue, bone, fat, cartilage, or mucoid tissue. Generally a form of fibrous tissue is elaborated; the cells first become oval, then elongated, and fibrillæ grow out from their ends. They also form an intercellular substance, which becomes fibrillated. In this manner the granulation tissue, at first cellular, is converted into a

tissue in which the intercellular substance forms an important part. This new fibrous tissue has a tendency to contract and form cicatricial or scar-tissue.

Formation of Blood-vessels. This is the most important element in regeneration. The formation always occurs from pre-existing blood-vessels. Quite early in the inflammatory process, as soon as the tendency to regeneration manifests itself, the endothelial cells of capillaries present karyokinetic changes. One of the new cells grows into the interior of the vessel, the other protrudes outward; the latter multiplies, and the resulting cells repeat the process until a chain is formed, which unites with a similar chain from the same or a neighboring capillary. The cells then become hollowed out, and a channel is opened—the capillary is then complete. The loops of capillaries project into the newly formed tissue and nourish it, and enable it to form connective tissue. A loop with its surrounding cells is known as a *granulation.*

The healing of wounds, the organization of a thrombus, and the growing together of two serous surfaces, are all comparable to the healing of an ulcer. In connection with wounds, we speak (*a*) of healing by granulation, and (*b*) of healing by first intention. In the former there is always some pus, but the tendency to liquefaction is overcome and connective tissue formation takes place. If wounds are thoroughly cleansed and the edges carefully brought together, healing quickly takes place, by the same histologic processes as in the healing by granulation. There is a multiplication of connective tissue cells and a throwing out of a cement substance holding them together. But as the gap to be filled is small, very little granulation tissue is produced; indeed, the approximation may be so complete that none is visible microscopically. Nevertheless, it must exist, for a few cells must have been divided by the wound, and can only be replaced by karyokinetic changes. Small gaps may be filled by the same tissues as those destroyed; large losses of substance heal by cicatrization.

The study of regeneration is facilitated by the study of the formation of connective tissue in foreign bodies. A piece of sterile lung, sponge, or elder-pith is introduced into the tissues, preferably the peritoneal cavity, of several animals; the wound is closed, and the bodies are removed on different days. The presence of the foreign body sets up an inflammatory reaction; the blood-vessels become dilated, and leukocytes and plasma pass out and enter the

foreign body. In twenty-four hours after its introduction we find the spaces in the body filled with leukocytes and with a fluid which tends to coagulate into fibrin just as far as the leukocytes extend in the body. On the second day evidences of regeneration appear in a multiplication of the connective tissue cells of the peritoneum. The new cells penetrate into the meshes of the body, especially at its periphery, the leukocytes and fibrin occupying the center. The connective tissue cells have a tendency to arrange themselves along the walls of the spaces in the foreign body. The leukocytes degenerate and disappear, perhaps supplying nutriment to the connective tissue cells. The fibrin acts as a skeleton work, but in time also disappears. Blood-vessels are formed from capillaries in the peritoneum; the new cells become elongated, and are converted into fibrous tissue.

The foreign body itself is as a rule gradually removed by solution, the rapidity of the process varying with the nature of the body. Absorption is more rapid in case of lung than when sponge or pith is used.

If the foreign body is resistant *giant-cells* appear. These are the result of a multiplication of the nuclei of the connective tissue cells without corresponding division of the cell-protoplasm. It seems that the irritant is capable of causing the nuclei to multiply, but either the resistance of the body or the chemical conditions present prevent the individualization of the cells.

Ordinarily, in regeneration, the embryonal tissue is converted into fibrous tissue, but any of the connective tissues, bone, cartilage, fat, etc., may be formed from it.

The cells have received names corresponding to the tissue which they are engaged in forming, *e.g.*, fibroblasts, osteoblasts, and chondroblasts.

It is possible for one kind of connective tissue to be formed from another, as bone from cartilage, without the intervention of embryonal connective tissue, a process that has been termed *metaplasia.*

CHAPTER V.

SPECIFIC INFLAMMATIONS, OR INFECTIOUS GRANULATION TUMORS.

These are peculiar forms of chronic inflammation, the exact position of which among pathologic processes was for a long time doubtful. They are classed among the inflammations because they give rise to tissues that are unfit for further use and have to be removed, and because the parablast is concerned in the removal. There is in all of them a leukocytic infiltration for the purpose of elimination, and likewise a tendency to regeneration, which, however, as a rule, falls short of complete success; sometimes a cure is achieved.

The characteristic features of the specific inflammations are (*a*) a tendency to degeneration, (*b*) the absence, more or less complete, of blood-vessels, and (*c*) the tendency to form tumor-like masses.

Various names have been given to these tumors: infectious granulation tumors or granulomata, because some consist of granulation tissue and resemble tumors in outline; leukocytomata, because they are characterized by a leukocytic infiltration and form tumor-like nodules; and specific inflammations, for the reasons given. The last is the preferable designation. The most important specific inflammations are tuberculosis, syphilis, leprosy, glanders, and actinomycosis.

TUBERCULOSIS.

Tuberculosis comprises the morbid changes produced by the presence of the tubercle bacillus in the body.

Historical. In the history of tuberculosis, the names of three men overshadow all others. These names are *Laennec*, *Villemin*, and *Koch*. To Laennec (1837) we owe the discovery of the physical signs of pulmonary tuberculosis; to Villemin (1865), the demonstration, by experiments upon lower animals, that tuberculosis is an infectious disease; and to Koch (1882), the immortal discovery of the cause, the *bacillus tuberculosis*.

The disease affects man and the lower animals, especially horned cattle; somewhat less frequently, the monkey, guinea-pig, rabbit, dog, horse, sheep, and cat. Nearly all animals are susceptible to inoculation, some, as the guinea-pig, rabbit, and field-mouse, succumbing readily; others, as the horse, dog, and cat, offering considerable resistance.

Seats of the disease. The following organs, named in the order of frequency, are affected by the disease.

1. The respiratory and intestinal tract. In the former the disease attacks the lung substance proper, the bronchioles, and the larynx; in the latter, the lower portion of the ileum, the mouth, throat, and rectum. 2. Lymphatic glands. 3. Serous membranes—peritoneum, pleura, meninges. Tuberculosis of the peritoneum is more often primary than that of the pleura, which is generally secondary. 4. Bones. 5. Spleen. 6. Kidney. 7. Suprarenal capsules. 8. Brain. 9. Middle ear. 10. Uterus and its appendages. 11. Testicle. 12. Bladder. 13. Skin.

In the adult the lung is the most common seat of the disease; in children, the lymphatic glands, serous membranes, and bones.

The following organs and tissues are rarely affected: Salivary glands, thyroid gland, ovary, muscles, cartilage, and heart.

Cause.—The *Bacillus tuberculosis* of Koch. The bacillus is the only cause of tuberculosis, and is always derived from a person or animal suffering from the disease.

Tuberculosis is, therefore, contagious, and there is absolutely no ground for the contrary view maintained by some physicians. If we are sure of anything it is that in every case in which the origin of the disease has been traced, it has been found to be another person or animal.

The Bacillus. The bacillus is rod-shaped, slightly bent upon itself, 3 μ long, 0.2 μ in width, non-motile, and when stained frequently presents a beaded appearance. The beading has been supposed to be due to the presence of spores, but this has never been proved. More probably it is caused by the contraction and breaking up of the stainable portion, permitting us to see the empty spaces formed between the fragments and the outer membrane. It is believed that bacilli undergoing degeneration are those chiefly acted upon by the stain in this manner. The presence of the bacillus is readily demonstrated in the secretions and discharges, and in the tissues of the affected organs.

Special processes are required to stain the bacillus, all depending upon two peculiarities possessed by it: (1) It takes the stain with difficulty; (2) after being stained it holds the stain tenaciously.

In order to facilitate the staining certain substances are used as mordants. Carbolic acid, anilin oil, and the alkalies are thus employed. Strong mineral acids and alcohol serve as differentiating agents, both being generally used. The stain may be applied to fluids and to tissues. For the rapid demonstration of bacilli in the latter, it is advisable to rub up a portion of the tissue in a mortar into a fine pulp and to treat it as sputum.

For all practical purposes the best stain is that known as *Ziehl's solution.* It has the great advantage that it keeps indefinitely, while those made with gentian-violet and other dyes deteriorate with age.

Ziehl's Solution:

Fuchsin	1
Alcohol	10
5 per cent watery sol. carbolic acid	90

As a decolorizing agent and counterstain we employ *Gabbet's solution.*

Methyl blue	1-2
Sulphuric acid	25
Water	75

The bacilli appear as dark-red, almost black, rods on a blue field.

Cultivation. This is more difficult than in the case of most other pathogenic microbes, and at first was only achieved on blood-serum. The serum is obtained from an animal, as a horse, and after decantation is placed into tubes and sterilized by heating for one hour on six successive days to 50° C.; on the sixth day the temperature is raised to 60° C. It is then placed into an incubator for twenty-four hours, and is finally heated to 68° C. By this process the serum becomes stiff, but the albumin is not coagulated.

The bacillus also grows on agar or bouillon to which about six per-cent. of glycerin has been added.

To secure the growth of the bacillus it is necessary (1) to keep the tube constantly at 37° C.; (2) to avoid drying by too much ventilation; (3) to eliminate the presence of other micro-organisms.

To obtain a pure culture. (*a*) A guinea-pig is inoculated with tuberculous material, and is killed in the third or fourth week of the disease, at a time when the morbid tissues are not yet breaking down. Under antiseptic precautions a lymphatic gland is removed, cut with a sterile knife, and the surface rubbed upon glycerin agar.

(*b*) A pure culture may also be obtained directly from sputum in the following way: The patient disinfects his mouth and spits into sterile Petri dishes. A grayish-yellow nodule is taken up with sterile forceps, and carefully washed in several dishes of sterile water, and finally rubbed upon glycerin agar or introduced into glycerin bouillon. The repeated washing removes the contaminating micro-organisms.

Growth of the bacillus. The growth becomes visible in from seven to fourteen days, appearing first in the form of isolated, minute, grayish-white scales. As a rule the growth does not proceed any further, and it is necessary to inoculate a second tube. Here the growth is more active, producing a grayish membrane rising somewhat above the surface.

Under a low power (80 diameters) the bacilli are seen to arrange themselves in peculiar S-shaped curves.

The tubercle bacillus does not lose its virulence except after having been grown for many generations.

Morbid Anatomy.—The characteristic lesion of tuberculosis is a small nodule called the *gray nodule* or *miliary tubercle.* This is a small semi-translucent nodule, slightly elevated above the surrounding tissue, and somewhat harder, and varying in size from $\frac{1}{20}$ to 2 mm.

Miliary tubercles as a rule are present in large numbers, and are distributed, especially in parenchymatous organs, with some regularity, being about equidistant. On serous membrane they follow the course of the lymphatic vessels.

Their outline is not sharp; they merge into the surrounding tissue, cannot be peeled out, and are frequently surrounded by an inflammatory zone, which is always visible with the microscope. Quite often the grayish masses are opaque in the centre; at times they present a yellowish tint. This indicates a cheesy change and is in direct proportion to the size of the nodule.

Besides appearing as the miliary tubercle the disease occurs also in the form of the *tuberculous infiltration*, which is produced either

(*a*) by a coalescence of numerous tubercles or (*b*) by a peculiarity in the cellular infiltration, which does not arrange itself in nodules, but infiltrates large areas, the size depending on the anatomic relations of the parts. In the lung an entire lobe may be affected. The larger the diseased mass, the greater the cheesy degeneration.

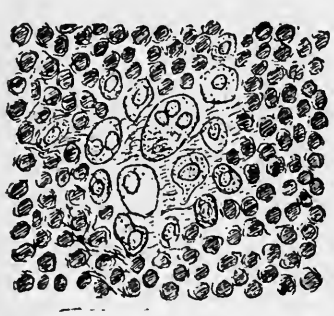
The tuberculous infiltration is formed in chronic processes, while miliary tubercles indicate acuteness. An exception is acute tuberculous pneumonia, which is an acute, rapid, general tuberculous infiltration with a tendency to caseation.

When the tuberculous infiltration is extensive the structure of the affected parts is lost, and is replaced by cheesy material, pale, yellowish or dirty-gray in color, dryer and harder than the surrounding tissue. This is known as the *yellow tubercle.*

The changes in tuberculous areas depend somewhat upon the animal affected, and also upon the organ involved. In general the lesions show a tendency to *degenerate.* They break down by liquefaction necrosis, with the formation of ulcers—*tuberculous ulcers*—or cavities.

These cavities (*vomicæ*) are most common in the lung, and are apt to become infected with the micro-organisms of suppuration, which assist in the destructive process. Cavities not communicating with the external air are seen in connection with bone disease, and are termed *cold abscesses* (psoas, vertebral, hip-joint abscess). The contents of these abscesses is as a rule not purulent, but may be from mixed infection, or, rarely, from a pyogenic activity unfolded by the tubercle bacillus itself.

At times there is in tuberculous lesions a tendency to *regeneration*, the result being the encapsulation of the lesion or the complete healing with removal of the diseased structures and their replacement by a scar.



Tubercle.

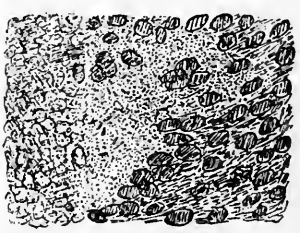
(*b*) *Microscopy.* The essential feature of the tuberculous process is a group of connective tissue cells lying closely together. These cells possess a vesicular nucleus and a comparatively large amount of protoplasm, and are known as *epithelioidal cells.* Frequently the nuclei stain imperfectly. The characteristic picture of the tubercle is completed by the appearance, in the center, of a *giant cell*, and at the periphery, around the

epithelioidal cells, of a group of *round cells* of leukocytic origin, the so-called *lymphoid cells*.

It is not necessary that these three kinds of cells should always be present together, but when associated they constitute the typical tubercle. The giant cell may be absent and the round cells may form an unimportant part of the picture, but the epithelioidal cells are an invariable feature, since they are the first evidence of the presence of the bacillus.

The epithelioidal cells show no tendency to form connective tissue, but remain *indolent*, their protoplasm becoming granular and even fatty. The formation of the giant cell is an evidence of degeneration. It seems as if the irritant gave rise to a multiplication of nuclei, but that something prevented the division of the protoplasm. The appearance of the giant cell in the tubercle is the same as in other conditions—it is a large, irregular protoplasmic mass, 8–200 μ in diameter, with a large number of nuclei. These are vesicular, like those of the epithelioidal cells, and are arranged either around the periphery or toward one pole of the cell.

The degeneration begins in the giant cell, and is a form of *coagulation necrosis*, but not a fibrin formation; in appearance it resembles amyloid. The degenerated portion does not stain. Frequently the central cells, the giant cell and epithelioidal cells fuse and together undergo degeneration. In this way a large degenerated mass is produced, with giant cells and epithelioidal cells at the periphery, the whole being surrounded by a leukocytic infiltration. The structureless center with the wreath-like accumulation of nuclei at the periphery has been aptly compared to a "raked field" (Professor Guitéras). Considerable debris and pigment are present in the degenerated area, particularly toward the periphery—in the lung this pigment is in part coal-dust, in part it is of obscure origin.



Cheesy Tubercle.

The structures that have undergone coagulation necrosis very soon become the seat of fatty degeneration. By the union of these two degenerative processes—coagulation necrosis and fatty degeneration—the picture of *cheesy necrosis* is produced.

Fate of the fibrillar intercellular substance. This participates in the degenerative changes, but at times is preserved for a somewhat longer period than usual, in which case it holds the cells in a fine fibrillar reticulum. This constitutes the *reticulated tubercle*.

In some tubercles the round cells so predominate as to conceal even the epithelioidal cells. Such tubercles resemble lymphatic glands and are known as *lymphoid tubercles.* They are not rare in the mucosa of the intestines.

Position of the bacillus. In the early stages the bacilli are found between the epithelioidal cells, rarely within them. Later they occur in largest numbers in the giant-cell, occupying a position just within or among the nuclei; rarely one is seen in the degenerated portion. Eventually, the bacilli are found in the epithelioidal cells, and among and within the leukocytes.

Although some of the epithelioidal cells are derived from the endothelial cells of blood-vessels, they show no tendency to form new blood-vessels, a fact that in a large measure accounts for the degeneration in the tubercle. At times there is a more or less successful effort at regeneration.

Sources of the cells in the miliary tubercle. (*a*) The leukocytes come from the blood-vessels. (*b*) The epithelioidal cells are derived (1) from pre-existing connective tissue cells; (2) from endothelial cells; (3) from epithelial cells. (*c*) The giant-cell originates from epithelioidal cells.

Localities in which giant-cells are found. Besides in the tubercle, giant-cells occur (1) where bone is being absorbed (physiologic); (2) in the placental site of the uterus; (3) about foreign bodies; (4) in the air-vesicles in pneumonia; (5) in syphilitic gumma; (6) in syphilitic endarteritis; (7) in granulating wounds healing slowly; (8) in giant-cell sarcoma, and (9) in actinomycosis.

Pathogenesis of Tuberculosis.—Tuberculosis is at first a local disease, and may remain so indefinitely. In the center of the affected structures we find an area of cheesy or liquefaction necrosis, and surrounding it a grayish zone of cellular infiltration, through which miliary tubercles are scattered. It is through the gradual extension of these miliary tubercles that the neighboring and adjacent tissues are invaded. This mode of spreading is spoken of as *extension by continuity or contiguity.* But the disease is still a local process. Local tuberculosis is also termed *primary tuberculosis.*

Secondary tuberculosis is produced (*a*) *by extension along the lymphatic channels.* This is well shown in tuberculosis of the mucous membrane of the intestines, in which we find miliary tubercles along the lymphatic vessels of the peritoneum, or we may find the

mesenteric glands tuberculous, with or without involvement of the lymphatic vessels. (*b*) *By extension along the normal* (*open*) *channels*, with the material carried along these channels, viz.: along the respiratory and intestinal tracts. (*c*) *By extension along the blood-vessels*, with the blood. The resulting tuberculosis is apt to be general and very acute.

The relation between the secondary and primary tuberculosis is as a rule readily traced; but in tuberculosis of the lymph glands we may not find any disease of the rootlets. In such cases we are forced to assume that either (1) the bacilli enter through the surface, as *e. g.*, the mucous membrane of the intestines, and cause disease in the lymphatic glands, without producing any recognizable lesion at the point of entrance; or (2) that there is a *latent tuberculosis*, *i. e.*, the bacilli enter the fetus in utero and develop at a variable period after birth. Both explanations are acceptable; they probably account for different cases.

Modes of Infection.—(*a*) *By inhalation*, which is the most common mode of infection in the human subject. The tubercle bacilli are contained in the air. This has been clearly proved in the experiments of Cornet, who found by exposing pans in the wards of hospitals, collecting the dust that was deposited, and introducing it into guinea-pigs, that the animals inoculated with dust from wards containing tuberculous patients died of tuberculosis. The presence of bacilli in dust results from the drying and pulverization of the sputum. Sputum in the moist condition does not contaminate the air.

(*b*) *By the food*, especially by the milk of tuberculous cows the udders of which are affected, and by the meat of tuberculous animals. Infection from milk is more common in children than in adults. Thorough cooking of the food destroys the bacilli, but the methods of smoking and curing meat as generally applied are insufficient for the destruction of the micro-organisms.

(*c*) *By direct inoculation.* This is an infrequent mode of infection. It gives rise to a local tuberculosis, which may after a time become generalized. Examples are the anatomical wart, and the tuberculosis of the penis, that in a few instances has followed the rite of circumcision.

(*d*) *By hereditary transmission.* The transmission of the tubercle bacillus to the offspring is possible, as instances of

tuberculosis of the fetus have been recorded, but the occurrence is rare. In such cases the bacilli usually pass through the placenta from the mother to the fetus; their transmission by means of the semen is possible, but must be exceedingly infrequent.

As the majority of cases of tuberculosis occur after the first year of life, it is highly probable that infection is most frequently post-natal. Nevertheless, we must recognize an hereditary tendency or predisposition to the disease. Certain families are more susceptible than others just as guinea-pigs succumb more readily than other animals. This predisposition is assumed to depend on a faulty condition of the body-juices. The so-called "signs" which formerly were supposed to indicate a predisposition to phthisis, and which collectively were termed "scrofulous diathesis," in reality indicate the existence of the actual disease: scrofulosis in the majority of instances is tuberculosis.

Many of the early manifestations of tuberculosis in children are curable; indeed, complete healing may occur at any period of life.

Tuberculosis in *children* affects most commonly the lymphatic glands, the bones, and the meninges; in *adults*, the lungs, the other manifestations being secondary to the pulmonary infection.

Local and general effects of the tubercle bacillus.

(*a*) *Local action.* (1) The bacillus exerts a marked chemotactic action, the chemotactic substance being an integral part of it and not a product of its life activity. This fact has been demonstrated by Prudden who obtained the same round cell infiltration by the injection of *dead* tubercle bacilli as is produced by living bacilli.

(2) The bacillus has a tendency to cause special forms of degeneration—caseous and liquefaction necrosis. In many instances the liquefaction necrosis is due to mixed infection, especially the entrance of pyogenic micro-organisms. But the tubercle bacillus alone is also capable of inducing suppuration, as is seen in some cold abscesses.

(*b*) *General effects.* These may consist (1) in a local or general outburst of miliary tubercles, the dissemination taking place through the blood-current, or (2) in a cachexia. This is to some extent due to the circulation of toxic compounds elaborated by the tubercle bacilli. Mixed infection is, however, an important factor in the production of the cachexia, and in the majority of cases a

septicemia develops from toxins originated by pyogenic micro-organisms. Advanced stages of cachexia are often associated with an amyloid change in many organs.

The frequent injection of tuberculin is also capable of bringing about a cachectic state.

Tuberculosis in the Lower Animals.

(*a*) *In cattle.* Two forms of the disease occur; (1) that of the serous membranes, and (2) that of the parenchymatous organs.

(1) The tuberculosis of *serous membranes*, the so-called "pearl-disease," assumes the form of pendulous or sessile conglomerate masses, occurring in the pleura or peritoneum. The histologic features are, in the main, the same as those of tuberculosis in man, but there is a larger amount of fibrous tissue, which accounts for the ability of the masses to hold together, and there is also, together with cheesy necrosis, a marked tendency to calcification.

(2) *In parenchymatous* tuberculosis we find the same tendency to cheesy degeneration and cavity formation as in the human being, but it is generally associated with calcification.

Not rarely in cows the udder is tuberculous, in that case the milk necessarily contains tubercle bacilli, although they are not easily demonstrated. Whether the milk of tuberculous cows, the udders of which are not affected, contains the bacilli, has not been positively proved. Milk is a frequent source of infection (though by no means as frequent as the inhaled dust), and tuberculosis is more common in localities where milk is largely used as a food.

Certain breeds of cattle, especially the deep milkers, as, *e. g.*, the channel breeds, are eminently prone to tuberculosis.

(*b*) *In horses*, the pleural and peritoneal cavities are especially involved, the process giving rise to pendulous masses resembling lympho-sarcomata. Calcification is not as marked as in bovine tuberculosis. Infection is most common through the intestinal tract.

(*c*) *In sheep* tuberculosis is rare, but can be produced experimentally.

(*d*) *In dogs and cats* it is not frequent, although more common than in sheep.

(*e*) *In the hog* the disease affects first the digestive tract, later the respiratory organs. There is in this animal a strong tendency to connective tissue formation.

(*f*) *In fowls* tuberculosis of the digestive tract, particularly of the liver, is not rare.

(*g*) *In rabbits and guinea-pigs.* Both are very susceptible to the disease. In the lung the lesions in both animals are the same: multiple small cavities; in the abdomen there is a striking difference. In the rabbit, tuberculosis of the liver and spleen is miliary; in the guinea-pig, the process is more extensive, involving larger areas and giving to the liver and spleen a *marbled* appearance, from the presence of the yellowish tuberculous areas in the reddish tissue of these organs.

Course of tuberculosis produced experimentally in the guinea-pig. Under antiseptic precautions an incision is made in the skin and the tuberculous material introduced into a pocket in the subcutaneous tissue. The wound heals rapidly. Toward the end of the second week the nearest lymphatic glands enlarge, the wound becomes indurated, and soon reopens and discharges a flaky, purulent material; gray tubercles become visible at the point of inoculation. In the third or fourth week general symptoms appear, fever, emaciation, rapid respiration. Death takes place in from four to eight weeks.

In order to study the phenomena of local tuberculosis, step by step, the anterior chamber of the eye of a rabbit is inoculated. On the fifth day there will be found an accumulation of epithelioidal cells; the tubercles on the iris become visible to the naked eye by the twelfth or fourteenth day. The process rapidly becomes general.

SYPHILIS.

Syphilis is a contagious disease, due to a specific micro-organism, which up to the present has not been isolated. Lustgarten has discovered a bacillus in the lesions of syphilis, but its inoculation into animals in pure culture has failed to produce the disease.

Syphilis presents three characteristic lesions: The hard chancre, the mucous patch, and the gumma.

(*a*) *The hard chancre or initial sclerosis.* Though characteristic clinically, this cannot be differentiated from other inflammatory processes microscopically. It appears at the point of inoculation, usually the corona of the penis, two or three weeks after infection, as a papule the size of a split pea; it has a tendency to ulcerate, the surface being covered with a layer of fibrin and discharging a serous fluid, which contains but few cellular elements. The lesion also becomes indurated from a peculiar coagulation necrosis of the

intercellular substance of the deeper parts. In addition, there is a cellular infiltration of the walls of the blood-vessels, affecting chiefly the intima. This does not differ from the same process in other inflammations, but is rather characteristic of all syphilitic lesions. The hyperplasia contributes to the hardness of the chancre.

Microscopically, we find round cells and epithelioidal cells and sometimes giant-cells.

The disease soon extends along the lymphatic vessels to the nearest lymphatic glands. The latter become enlarged, and constitute the *indolent buboes* of syphilis.

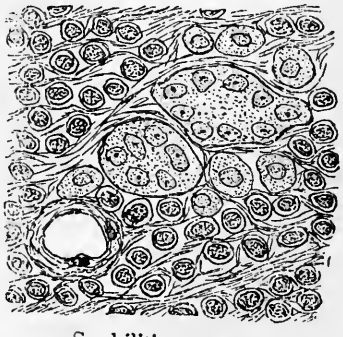
The secondary lesions are the skin manifestations, the mucous patch, and the gumma. The skin eruptions are, as a rule, inflammatory, and do not differ pathologically from similar affections due to other causes.

The mucous patch and the gumma are the truly characteristic lesions of syphilis.

The mucous patch or condyloma latum. This is a flat swelling, slightly elevated above the surrounding level, with an ulcerated surface, developing chiefly at the junction of skin and mucous membrane, as on the lip, anus, corona, and external genitals of the female.

Microscopy. We have a marked round cell infiltration of the upper layers of the corium, causing an enlargement and elongation of the papillæ. But this is not characteristic, since it occurs under other conditions. The peculiar features are the imbibition of the epithelial cells of the rete mucosum with fluid and their separation by this fluid. The upper layers of cells are thrown off in the discharge.

The gummy tumor, or gumma. This, clinically a so-called ~~testing~~ tertiary lesion, is a rounded tumor with an indefinite outline varying in size from the size of a pea to that of a small apple. It is raised slightly above the surface and has a variable consistence, being at times harder, at times softer, than the surrounding tissue; quite often the tumor becomes soft in the later stages. On section we find in the center a grayish or yellowish mass, "gummy" in appearance, whence the name. The gummy material occurs especially in the gummata of the bones and the skin, and



Syphilitic gumma.

is due to a mucoid degeneration of the connective tissue. Solid gummy tumors are found chiefly in the viscera; they are very rich in cells—epithelioid cells and round cells, and occasionally giant cells, particularly at the periphery. The last are not so abundant as in tuberculosis. In the center of these visceral gummata there are areas of fatty degeneration.

There is in syphilis a marked tendency to the formation of connective tissue. Not only does this tissue form a capsule around the gumma, but new bands of fibrous tissue pass into the tumor, forming trabeculæ which separate islands of fatty material. In addition, bands of connective tissue extend in a radiating manner into the surrounding tissue. Upon this depends the peculiar stellate character of the scar remaining after the absorption of the gumma.

Gummata situated on surfaces tend to break down by a process of suppuration, the resulting ulcer healing very slowly. In viscera absorption is most common, the scar being stellate.

In connection with the gummy tumor as well as in other syphilitic processes we find a hyperplasia of the intima of blood-vessels, which is to a certain extent characteristic of the disease. It gives rise to thickening of the arteries, and also leads to a formation of new blood-vessels, a feature so strikingly deficient in tuberculosis. But even in syphilis the new sprouts tend to degenerate, and the lesions, as the gumma, are insufficiently nourished.

Seats of gummata. Gummata are found in the subcutaneous tissue; in bones—especially the skull, tibia, and sternum; in viscera, as the liver, testicle, spleen, brain, and, rarely, in lung and kidney.

Hereditary Syphilis.—The following statements may be made concerning the transmissibility of syphilis:

1. Syphilis is readily transmitted from the parents to the fetus.

2. The poison may pass through the placenta in either direction, *i. e.*, from mother to child, or vice versa. Syphilitic lesions may occur in the placenta, *e. g.*, condyloma of decidua. These are not the result of direct infection, but are the local manifestations of a general disease.

3. Most frequently the fetus is infected by the mother.

4. The more recent the syphilitic manifestations in the mother before conception, the more apt is transmission to take place.

5. A syphilitic father may beget a healthy or syphilitic child, the latter without infecting the mother.

6. The syphilitic fetus may or may not inoculate the mother; as a rule, it, the fetus, produces a profound impression upon the mother, since the latter shows a distinct immunity to syphilis. An actual infection of the mother does not take place, but the toxins of the disease enter her blood and stimulate the formation of the antitoxins. This seems to be proved by the failure of the mother to become inoculated from the sores in the infant's mouth (Colles' Law).

7. The disease may be transmitted by the mother infected during pregnancy.

Abortion is common in pregnant women suffering from syphilis. It is generally the result of syphilitic endometritis.

Syphilitic children present frequently no outwardly manifestations of the disease at birth, although on post-mortem examination, we find lesions in the skeleton. Distinct phenomena appear at the second or third month, and are either chronic fibroid processes in the lung, pancreas, and spleen, or gummata in the bones, liver spleen, and lung.

GLANDERS.

This is a contagious disease occurring ordinarily in horses and asses, but transmissible to man and most other mammalia. The guinea-pig and the field-mouse are particularly susceptible to experimental inoculation.

The *cause* of the disease is the *bacillus of glanders*, or *bacillus mallei*, discovered by Löffler. It is about the same length as the tubercle bacillus, but broader and straighter; it is facultative anaerobic, motile, and occurs in groups forming angles, and usually lies between the cells. It does not stain by Gram's method, but is stainable with the ordinary anilin dyes. The best solution is carbol-methyl-blue.

Methyl-blue, ... 1.5
Alcohol, ... 10
5 per-cent. watery sol. carbolic acid, ... 90

This is allowed to act on the section for 10–30 minutes. For differentiation a weak solution of hydrochloric acid is employed.

Hydrochloric acid, ... 10 drops.
Water, ... 500 c.c.

The section is then washed in water, placed on a slide, dried, and mounted in Canada balsam.

The bacillus grows readily on all alkaline media, but characteristically only on the potato. If the potato is kept at 37° C., we find in two or three days the development of amber-colored drops looking like beads of honey. The colonies gradually enlarge and grow darker.

Morbid Anatomy.—There are two forms of glanders (*a*) that affecting the respiratory mucous membrane—*glanders* proper, and (*b*) that of the skin, subcutaneous tissue, and lymphatic glands. The latter is more chronic and is termed *farcy.*

In the horse the disease appears most frequently in the nasal mucous membrane, and presents itself either in the form of distinct tumors or as a diffuse infiltration. The tumors vary in size from those just visible to the size of a cherry; they are slightly raised above the surface, are pearl-gray in color, and surrounded by an inflammatory zone. They either occur as isolated nodules or, as is more common, are aggregated in groups. The central portions are at first translucent, but rapidly become opaque and yellow.

The nodules have a marked tendency to undergo fatty and puriform changes in the center, being eventually transformed into ulcers of varying size and depth. The ulceration frequently extends to the cartilages and produces a "honey-comb" appearance.

In chronic cases there may be a tendency to healing with the formation of a puckered cicatrix.

Nodules similar to those just described may occur in the lung; they are here usually surrounded by areas of *broncho-pneumonia.* Abscesses are very apt to form both in the pneumonic patches and in the nodules. Apart from these manifestations the lung as well as other organs may be the seat of *miliary or "embolic" glanders.* We may also have, in the lungs, a general infiltration affecting a large area, and resembling a lobar pneumonia. It is, however, not a true pneumonia, but a specific infiltration similar to caseous tuberculous pneumonia. The affected portions are more gelatinous and translucent in appearance than those of caseous pneumonia, they have a greater tendency to break down, and are very frequently the seat of hemorrhagic infiltration.

The lymphatic glands become involved very early in glanders. The characteristic features of glanders, to be noted in performing autopsies, are (1) ulceration of the air-passages, (2) a tendency to a rapid breaking down and suppuration of the nodular masses.

Microscopy. Histologically, we find in glanders round cells and epithelioidal cells, and, as evidences of acute inflammation, the accumulation of multinuclear leukocytes.

Farcy presents subcutaneous nodules of varying size, associated with a diffuse inflammation of the subcutaneous tissue and the intermuscular septa, particularly of the lower extremities. The lesions are distinct nodules as well as inflamed lymphatic vessels and lymphatic glands. Suppuration is the rule, and leads to the formation of deep, ragged-edged ulcers, which heal very slowly.

Chronic glanders occurs either as isolated tumors along the lymphatic channels or on the mucous membranes, or as chronic, slowly-spreading ulcers. The latter may heal, the scars being usually stellate.

The *duration* of glanders is from eight to twelve days to several years.

Glanders in man. In man, glanders is an acute febrile disease of typhoid type, the local lesions being those of the respiratory mucous membrane and of the subcutaneous tissue, together with a diffuse pustular eruption. Lobular pneumonia is generally present, the consolidated areas being as a rule the seat of hemorrhagic infiltration.

In *chronic glanders*, we have the formation of nodules at different periods, or torpid ulcers on the skin and mucous membranes. The points of accidental inoculation in man are the conjunctiva, the nose, and the skin.

LEPROSY.

Leprosy is a chronic infectious disease due to the *bacillus leprœ.*

It affects especially the skin and the peripheral nerves, and leads to great deformity, to ulceration, and to disturbances of sensation.

Some obscure forms of nervous disease, associated with alterations in the peripheral nervous system (anesthesias, etc.), are said to be due to leprosy.

There are a number of foci of leprosy in the United States, the most important being those of the Pacific coast, Louisiana (near New Orleans), Florida, and South Carolina (near Charleston). The disease shows a tendency to increase, especially in Europe.

ACTINOMYCOSIS.

This is a contagious disease, affecting especially the mouth of horned cattle and pigs. It is caused by a micro-organism, the *actinomyces*, the position of which has not been definitely settled, though it is generally described as a *cladothorix* form of bacterium.

The micro-organisms are club-shaped, and are grouped in the form of rosettes, the club-ends being at the periphery, while the center is made up of a mass of fine filaments. The latter are the active living elements, while the club-ends are dead, the clubbing being an evidence of degeneration. The spores are found in the center, among the filaments; they are spherical in shape, resembling micrococci. The rosettes vary in size, from 40 to 50 μ to 1 or 2 mm.; the larger ones are visible to the naked eye, being either grayish like fragments of mucus, or yellow. The yellow granules are particularly striking; they float in the pus, and are generally the first objects to attract attention.

Morbid Anatomy.—(*a*) *Macroscopy.* In cattle, the disease is usually circumscribed to the lower, at times also to the upper jaw, and gives rise to the formation of nodular tumors. The growth begins in the submucous tissue, and extends to the periosteum and even to the bone. Suppuration occurs in the form of innumerable small abscesses, the rupture of which leads to a peculiar honey-comb appearance. Frequently there is a successful attempt at connective tissue formation, resulting in the development of large tumors about the jaws (*lumpy jaw*), commonly with a degenerated center.

Actinomyces.

(*b*) *Microscopy.* The rosettes are found in the midst of granulation tissue made up of epithelioidal cells and sometimes giant-cells. Suppuration is the rule; exceptionally, abundant connective tissue is formed.

The *seats of the disease in cattle* are the jaws, tongue, and submaxillary glands. Although generally circumscribed to these places, it may extend to the respiratory and alimentary tracts.

In man the disease presents the same characters as in cattle.

Pathogenesis.—The micro-organism is introduced with the food, especially with grains, such as barley and wheat. These

grains penetrate the mucous membrane and carry the fungus with them. They have been found in the mucous membrane of the mouth and in the tonsils.

Cultivation. The actinomyces can be grown on the ordinary media, glycerin-agar being especially adapted.

Staining. The most striking appearance is produced by picro-carmin, which stains the actinomyces yellow and the granulation tissue red. Gram's method also yields good results; it is advisable to use a preliminary carmin stain.

CHAPTER VI.

TUMORS.

Tumors are hyperplasias which, though presenting no new cells, *i. e.*, none the counterpart of which cannot be found in the body at some time of its development, yet have certain peculiarities which separate them from other hyperplasias. These peculiarities are:

1. They change the configuration of the part in which they develop.
2. Their tissue differs from that of the surrounding parts.
3. The tumor-growth is persistent and progressive.
4. Tumors have a special blood-supply.
5. The hyperplasia has no apparent cause or object.
6. The tissue is generally embryonal in character, either in part or throughout.
7. Tumors are malignant—they give rise to metastasis, and recur after removal.
8. They tend to degenerate.

Tumors are said to be *heterotopic* growths because they are found in places where the tissue of which they are composed should not exist; *heterochronic*, because the tissue occurs at a time when it should not be found in the body; tumors may also be produced by the *excessive growth* of a tissue in places where it is usually present in small quantity.

Pathogenesis of Tumors.—The true causes of tumors are not known, but several theories have been advanced to explain their development.

1. The theory of *tumor diathesis* (Billroth), which assumes the existence of peculiar predisposition, inherited or acquired, to the development of tumors. This theory has very little value.

2. The *mechanical theory* (Virchow). According to this certain tumors are due to injuries. In a sense this is true, but the same injuries do not cause tumors in all individuals; moreover, many of the so-called tumors following injuries, are really inflammatory hyperplasias.

3. The *embryonal or evolutional theory* (Cohnheim). This ascribes the origin of tumors to errors of development during embryonal life; some portions of tissues are misplaced, and afterwards taking on active growth, become tumors. This theory accounts satisfactorily for a certain class of new growths, particularly the so-called mixed tumors and the dermoid cysts.

4. The *nervous theory.* It is assumed that tumors may be due to disturbances in the trophic functions of the nervous system. This is probably true in some cases.

5. The *parasitic theory.* The development and course of many tumors could be best explained on this theory, but unfortunately the parasites have not yet been found.

Classification of Tumors. — 1. *Parablastomata* — Parablastic, or connective tissue tumors.

2. *Archiblastomata*—Archiblastic tumors.

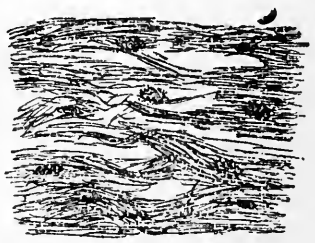
3. *Teratomata*—Complicated tumors, the result of errors of development.

PARABLASTOMATA.

FIBROMA.

This is a non-malignant tumor of slow growth, consisting of fibrous tissue. There are two varieties, the *hard* and the *soft* fibroma.

(*a*) *Hard fibroma.* This is a firm, nodular, well circumscribed tumor, surrounded by a capsule and presenting on the surface of section a white, glistening appearance and striae indicating the direction of the fibers. It may be single or, as is usual in the skin, multiple.

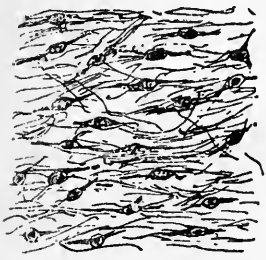


Hard Fibroma.

Microscopy. It consists of fibrous tissue poor in cells, being chiefly made up of a dense fibrillar intercellular substance. Blood-vessels are few in number, unless the tumor has undergone telangiectatic change. The fibrous bundles may be disposed regularly, in layers, or irregularly.

Seats. These are the skin, fasciæ, tendons, periosteum, uterus, along nerves, rectum, and mammary gland.

(*b*) *Soft fibroma.* This is a soft tumor with a moist surface of section; it is usually not as clearly circumscribed as the hard; it may be single or multiple, polypoid or sessile.



Soft Fibroma.

Microscopy. We find a large number of cells; the fibrillar intercellular substance does not run in distinct bundles, but forms a loose network resembling areolar tissue, differing, however, in its greater richness in cells.

Seats. These are the subcutaneous and submucous connective tissues, periosteum, intermuscular septa, retro-peritoneal connective tissue, and along the course of nerves. The fibroma of nerves is known as *false neuroma.*

Fibroma molluscum is a soft fibroma developing in the course of the fine nerve fibers of the skin and subcutaneous tissue. It is multiple.

Papillomatous fibroma (*wart*). In this there is a great overgrowth of the connective tissue in the shape of papillary excrescences. They are covered by epithelium, which is also hypertrophied, but this is a secondary feature. If the same process occurs in glands, an *adeno-fibroma* is produced.

There is no sharp line of separation between these fibromata and certain epithelial growths, although in some cases, as in the examples cited above, the fibrous tissue is clearly primarily hyperplastic.

Combinations. Fibroma combines with myoma, lipoma, myxoma, and sarcoma.

Degenerations. These are calcareous infiltration, fatty infiltration, mucoid degeneration, and telangiectatic or cavernous change.

There are several conditions that have been described as fibromatous, which in reality are inflammatory processes—(*a*) *Extensive thickening of the serous membranes.* We may look upon these as inflammatory. (*b*) *Elephantiasis.* This is characterized in part by a great overgrowth of the fibrous tissue, especially of the lower extremities, the cause of which is a chronic irritative obstruction of the lymphatic vessels. There is also dilatation of these vessels. Analogous changes are met with in the scrotum and labium, which here must be considered as true tumors, since no cause has been discovered. (*c*) *Keloid tumor.* This is also an inflammatory hyperplasia—an overgrowth of a scar; it is most common in the colored race.

MYXOMA.

This is a parablastic tumor after the type of the jelly of Wharton or the vitrous humor of the eye.

(*a*) *Macroscopy.* It is a rounded, lobular tumor, frequently encapsulated, consisting of a jelly-like substance traversed by fibrous partitions. The consistency varies with the extent of the mucoid change in the intercellular substance; at times the tumor is quite hard, at others it is soft and contains mucoid cysts. The tumor may be congenital.

(*b*) *Microscopy.* We find large numbers of *stellate* connective tissue cells, at considerable distances from each other, the interspaces being filled with a mucoid intercellular substance. The mucoid material gives the reactions of mucin.

Seats. The loose subcutaneous tissue, especially of the back, about the umbilicus, the cheeks, the labia, the scrotum, and the axilla; also in the membranes of the brain and cord, along nerves, in the mammary gland, and in the uterus.

In the mammary gland the myxoma occurs both combined with other tumors and as a pure myxoma. The latter is peculiar in that it affects both glands and gives rise to an enormous, uniform, symmetrical enlargement of the breasts, a condition formerly termed hypertrophy. In the uterus myxoma develops in the villi of the chorion, and is known as the *hydatidiform mole.* It has a tendency to involve the uterine wall, and to recur after removal.

Combinations. Myxoma combines with lipoma, fibroma, and chondroma.

Degenerations. There may be complete myxomatous degeneration, with cystic formation; cavernous and telangiectatic changes also occur.

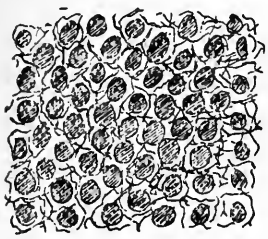
Myxomas are, as a rule, *benign*, the hydatidiform mole being an exception.

GLIOMA.

This is a tumor consisting principally of neurogliar tissue.

Macroscopy. The tumor is of moderate size, not encapsulated, and is at times not easily distinguished from the surrounding tissues, being quite similar to the gray matter of the brain. As a rule it produces in the brain a slight projection on the surface; is usually reddish in color, and presents minute hemorrhages; it is generally

also a little harder than brain-substance, and its tissue appears somewhat gelatinous. The tumors are single, of slow growth, non-metastatic, but scarcely benign on account of their seat.

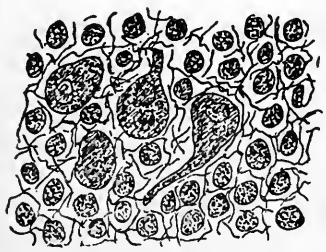


Glioma.

Microscopy. We find a dense aggregation of neuroglia cells (Deiter's cells), which have a large nucleus and a small amount of protoplasm, and fine filaments extending in all directions. These filaments form an intricate network, which is best seen in teased preparations. The blood-vessels are often telangiectatic; sometimes hemorrhages are present.

Seats. These are the brain, spinal cord, retina, suprarenal capsules, nerves and kidney.

Combinations. The glioma combines with fibroma, myxoma, neuroma, and sarcoma. The combination with neuroma occurs in the nerve centers and consists in the presence of ganglion cells in the neurogliar tissue—*ganglionar neuroglioma.* They are rare. *Glio-sarcoma* most commonly grows from the granular layer of the retina, and is malignant on account of the presence of sarcomatous tissue. It is rare in the brain.



Ganglionar Neuroglioma.

Degenerations. These are calcareous, myxomatous, and fatty; hemorrhages are common, and may lead to softening and to cystic formation; cysts may also arise independently of hemorrhages.

LIPOMA.

This consists of fatty tissue.

Macroscopy. Lipomata are rounded, lobulated, encapsulated tumors, that can be peeled out; they are usually single, sessile or pendulous, and vary in size, being sometimes very large. Their consistency varies also, and depends on the amount of connective tissue and the extent of mucoid change. They are benign; in some cases a hereditary predisposition is traceable.

Microscopy. The tumor consists of lobules of fat, which are larger than in normal fat, and are enclosed in more prominent connective tissue trabeculæ.

Seats. The subcutaneous connective tissue, especially on the dorsum of the body—neck, shoulders, gluteal region; also in the

submucous and subserous tissue of the gastro-intestinal tract, where they are usually multiple.

Combinations. Lipoma combines with fibroma and with myxoma.

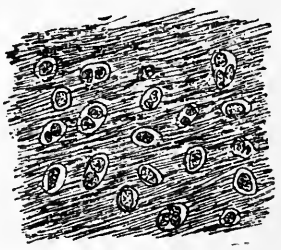
Degenerations. These are calcareous and myxomatous; the latter may lead to the formation of cysts; inflammation occurs as the result of injuries in the large lipomata, the blood supply of which is often defective—the tumors may ulcerate and break down.

Lipoma in the lower animals. It is quite common, especially in horses, in which it grows from the subserous tissue of the peritoneum, and at times causes strangulation of the bowels. The lipoma in the lower animals presents the fat which is characteristic of the species—chiefly olein in the horse, stearin in cattle.

CHONDROMA.

This is a tumor after the type of cartilage.

Macroscopy. They are well circumscribed nodular tumors, of considerable size; usually hard, but sometimes soft from mucoid change. They are frequently multiple, especially when growing from the hands and feet; elsewhere they are generally single. In young persons they are not rarely congenital.



Chondroma.

Microscopy. There are two varieties, the *hyaline* and the *fibrous* chondroma. The former arises from the skeleton, the latter is found in the internal organs. Histologically, the structure of chondroma differs from normal cartilage in the presence of cells irregular in shape and in grouping, and of bands of fibrous tissue. The cells are often spindle-shaped and stellate and some are devoid of a capsule; but normal cells are also present.

Chondromas are benign, although cases of metastasis to the lung have occurred.

Seats. Chondromas are found in the skeleton, springing from the bone or the cartilage; in the lungs, growing from the bronchial cartilages; in the parotid gland and in the testicle. In the last two organs they are "mixed tumors." Chondroma springing from bone may develop from the periosteum or the medulla of the bone. The multiple tumors of the hands and feet as a rule arise from the medulla.

Degenerations. These are mucoid, which may lead to cyst formation; fatty and calcareous. Calcification may be simple or a true ossification.

Combinations. Chondromas combine with osteoma, fibroma, myxoma, and sarcoma. The chondro-sarcoma is malignant. The mixed chondroma (usually a chondro-sarcoma) of the parotid gland and of the testicle, is as a rule congenital; its formation is explicable on Cohnheim's theory.

In the lower animals, chondroma is found on the sternum and ribs, especially in the horse. The mammary gland of the dog is at times the seat of a mixed chondroma.

OSTEOMA.

This is a tumor after the type of bone.

Many inflammatory bony formations assume the form of tumors—they have received the general name of *hyperostoses.* When dendritic they are called *osteophytes*; when dense, *exostoses.* They are common about joints.

True osteomata are often congenital, and are then symmetrical in their distribution; at times an hereditary tendency exists—all these features show that they are true tumors. They are smooth, of considerable size, harder, more regular and slower in growth than chondromata, and well-encapsulated.

Histologically, three varieties are distinguishable: (*a*) the *hard* or *osteoma durum;* (*b*) the *spongy* or *cancellated,* or *osteoma spongiosum,* and (*c*) the *medullary, i. e.,* one possessing medullary cavities, *osteoma medullare.* In osteoma the arrangement of the Haversian canals is similar to but not as regular as in normal bone. Osteoma is benign. It may be multiple when growing on the extremities.

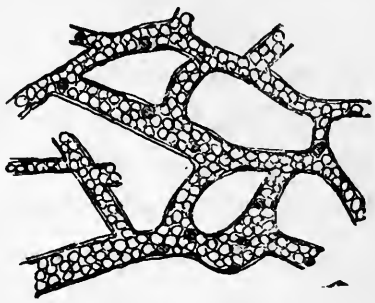
Seats. The skeleton, especially the bones, also the cartilages; the pleura and the dura—in these the tumors assume the form of plates, particularly in the falx cerebri; in viscera, as in the brain and lung.

In the *lower animals* the inflammatory bony outgrowths are common, *e. g.,* the *spavin* of horses. True osteoma occurs in the jaws of cattle, and in the horse, growing from the bones of the skull into the cranial cavity and into the nasal chambers.

ANGIOMA (HEMANGIOMA.)

This is a tumor consisting mainly of blood-vesssels. It is also known as *erectile* tumor.

There are two varieties—the telangiectatic and the cavernous. (*a*) The *telangiectatic* angioma consists of dilated loops of capillaries and small veins. The walls have all the characters of those of normal vessels, but the connective tissue may be thickened. They are benign and usually congenital.



Telangiectatic Angioma.

Seats. They occur on the skin, where they constitute the mother's marks, naevi, etc.; in internal organs, as the brain; in bones; they are rare in mucous membranes.

(*b*) The *cavernous* angioma consists of blood-spaces formed by trabeculæ of connective tissue, and lined by endothelium. Its type is the cavernous tissue of the penis. They are small, well circumscribed tumors, dark in color, not raised above the surface, with a distinct capsule, and are either single or multiple.

Seats. It is most frequent in the liver of old people, but occurs also in the spleen, kidney, orbit, and bones. That of the liver may be injected from any system of vessels of the organ.

Most visceral angiomata are cavernous.

Degenerations. Angiomata are not subject to any peculiar degeneration, but hemorrhages may occur into the tumors from rupture of vessels.

Combinations. They may be combined with fibroma or lipoma, but under such circumstances it is a difficult matter to decide whether the tumor was originally a fibroma or lipoma that has undergone telangiectatic change, or whether it was an angioma, in the walls of which an excess of fibrous or adipose tissue has developed. Sarcoma is also frequently combined with angioma.

LYMPHANGIOMA.

This is a tumor consisting of dilated lymphatic vessels.

There are two varieties—the *telangiectatic* and the *cavernous*; these are not sharply differentiated, and generally occur together. They are most frequently found as *congenital* tumors, about the tongue (*macroglossia*) and the lips and cheeks (*macrochilia*), and at

first sight appear as hypertrophies. Macroglossia is common in *cretinism*. A similar tumor is also found about the neck (*hygroma*).

These forms of lymphangioma are readily accounted for on the theory of Cohnheim.

Lymphangiomatous formations are also produced by obstruction of the lymphatic channels—these can scarcely be called tumors, but are frequently parasitic diseases, as, *e. g.*, elephantiasis, which is due to the *Filaria sanguinis hominis*. In elephantiasis we have, in addition to the dilatation of the lymphatic vessels, a hyperplasia of the skin and subcutaneous tissue. At times the lymphangiomatous formation is circumscribed, particularly to the *scrotum* or *labium*—as it is difficult in these cases to discover a cause, the condition is classed as a true tumor.

SARCOMA.

Sarcomas are tumors composed of embryonal tissue. They may be defined as connective tissue tumors in which the cells so predominate in number or size, that the intercellular substance becomes a subordinate element. In ordinary connective tissue the intercellular substance constitutes the prominent feature, the one upon which the differentiation of the various kinds depends; in sarcoma it fails to assume any of the types of adult connective tissue, and the differentiation is based on the character of the cells. There is at times, in sarcoma, a tendency to a better development of the intercellular substance, but the latter never becomes prominent.

The Characteristics of Sarcoma.—1. *Origin and mode of growth.* Sarcomas arise either from healthy connective tissue (which is most common), or from connective tissue showing a tendency to hyperplasia. Growth occurs in one of two ways: (*a*) by proliferation of the sarcoma cells, or (*b*) by metaplasia, *i. e.*, by the conversion of the surrounding tissues into sarcoma.

2. *Rapidity of growth.* The growth of sarcoma is rapid, especially in the small-celled forms, and, as in all rapidly growing neoplasms, the tumor is apt to be circumscribed, although usually not encapsulated. Carcinoma on the other hand always infiltrates.

3. *Blood supply.* This is abundant. We find normal blood-vessels as well as, and this is characteristic, blood-vessels without parietes, the sarcoma cells forming the walls. The endothelial

lining is always present. In many sarcomas the growth occurs along the walls of well-formed blood-vessels.

4. *Consistency and color.* These vary with the richness in cells, the amount of pigment, and the abundance of blood-vessels. As a rule sarcomas resemble brain matter. The small-celled forms are soft; in some the intercellular substance is ossified—such tumors are hard. It is a general rule that the softer tumors the more malignant, but there are two striking exceptions: the periosteal sarcoma is very hard, yet highly malignant, while the myxo-sarcoma is quite soft, yet comparatively benign.

5. *Degenerations.* These are (*a*) fatty and cheesy change, (*b*) calcification, (*c*) ossification, (*d*) inflammation which may lead to superficial ulceration (that of carcinoma is deep); the granulation tissue at times forming fungous masses; (*e*) cystic change—cysts may be due to softening, or to retention of secretion from pressure on gland ducts, this giving rise to the *adeno-sarcoma* and, when the dilated ducts are large, to the *cyst-adeno-sarcoma*; or they may be due to extravasation; (*f*) telangiectasis, which often leads to thrombosis; (*g*) hemorrhages into the tumor.

6. *Seats.* These are, in the order of frequency, the skin and subcutaneous tissue, inter-muscular septa, subserous connective tissue, eye, and periosteum of long bones. Less frequently, we find sarcomas in the interior of bone, in lymphatic glands, nerve sheaths, adventitia of blood-vessels, and membranes of brain and cord. They are rare in mucous membranes, especially of the uterus and bronchial tubes; in the kidney, liver, and brain substance. In the skin, liver, heart, and lung, they are often secondary.

7. *Age.* Sarcomas are most common between the ages of twenty and forty; they may be congenital.

8. *Malignancy.* They are malignant in two ways, (*a*) by recurrence, and (*b*) by giving metastasis. Metastasis is most frequent in the skin, liver, lung, and heart. The pigmented forms are most malignant; next to these those composed of small round cells. Those growing rapidly are more malignant than those of slow growth. Peripheral sarcomas possess greater malignancy than those that are deep-seated; this is particularly true of sarcoma of bone, and depends on the proximity of the tumor to the blood-vessels. Metastasis takes place through the blood-vessels. Occasionally there is a general deposit of sarcoma nodules all over the body—*miliary sarcosis, or sarcomatosis.*

9. *Etiology.* Traumatism seems to play an important rôle in the pathogenesis of sarcomas, and the mechanical theory finds in them its greatest support. The sarcoma may develop immediately after an injury or from an old scar.

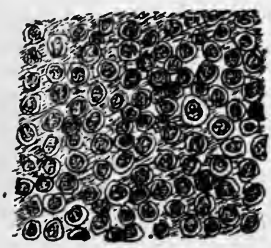
VARIETIES OF SARCOMA.

ROUND CELL SARCOMA.

There are three forms of round cell sarcoma: (*a*) small round cell; (*b*) large round cell, and (*c*) lympho-sarcoma.

(*a*) **Small Round Cell Sarcoma.**—This is a rather soft, rapidly growing tumor which at times attains a larger size than any other form of sarcoma. On section it is somewhat translucent and pinkish-white, and on pressure several hours after removal exudes a milky fluid. In color it resembles brain substance or the flesh of fish. When large, the center may be cheesy; hemorrhagic infiltration also occurs.

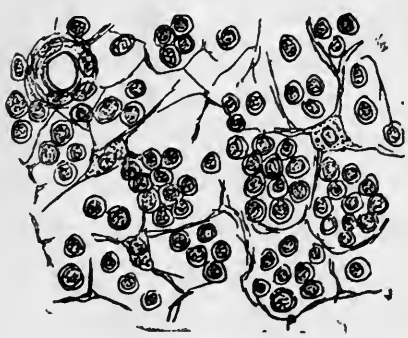
Microscopy. The tumor consists almost entirely of small round cells with a large pale nucleus. There is only a very slight amount of intercellular substance, usually homogeneous, at times fibrillar, around each cell.



Small Round Cell Sarcoma.

Stroma. A characteristic feature of cancer is the stroma which surrounds groups of epithelial cells. In sarcoma we do *not* find the connective tissue arranged in the form of chambers; if it exists at all, it follows the course of the blood-vessels.

Seats. The skeleton, intermuscular septa, subcutaneous connective tissue, skin, testicle, and ovary. In the last two it may be congenital.



Lympho-sarcoma.

(*b*) **Lympho-sarcoma.** — The characteristic feature of this is the intercellular substance which resembles that found in lymphatic glands and consists of a delicate reticulum of branching cells. The meshes contain a few round cells which are smaller and stain more intensely than the cells of the small round cell sarcoma.

The distinction from lymphatic gland is not always easy; it is to be based on the mode of growth. The tumors are very

malignant; they spring from lymphatic glands, and easily break through into the surrounding tissue; they also give metastasis and recur.

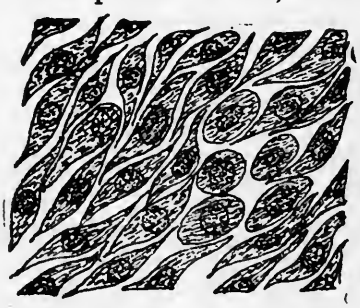
(*c*) **Large Round Cell Sarcoma.**—This grows in the same localities and has the same appearance as the small round cell form, but is somewhat firmer.

Microscopy. As a rule we find large irregular cells with a large amount of protoplasm and with nuclei of the same size as or larger than in the small round cells. Besides these there are other cells, small round and spindle cells and cells with several nuclei (polymorphous cells). The intercellular substance is small in amount.

SPINDLE CELL SARCOMA.

This is smaller and firmer than the round cell sarcoma; the surface of section is fasciculated—like muscle—whence the name sarcoma (σάρξ, flesh): its color, however, is not that of muscle, but pinkish and translucent. There is no milky fluid. The tumor is not very malignant; the tendency to metastasis is small, but recurrence is common. It is the latter property that caused surgeons to term it "recurrent fibroid."

Microscopy. We find large numbers of spindle cells, which may be small or large in size; they have an oval, vesicular nucleus, and run in bundles, which gives rise to the fasciculated appearance. The amount of intercellular substance is slight; at times the presence of delicate fibrillar projecting from the ends of the cells contribute to the intercellular substance.



Large Spindle Cell Sarcoma.

Sarcomas always possess some intercellular substance, a feature which distinguishes them from carcinoma in which the cells are packed together without any such substance.[1]

Many spindle cell sarcomas are really polymorphous in character.

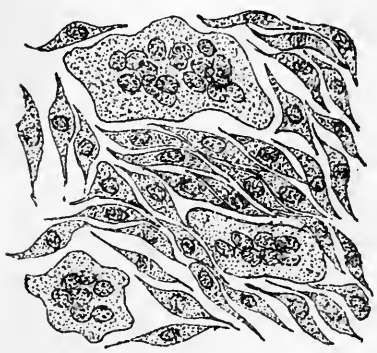
Seats. The skin, periosteum, bones, breast, intermuscular connective tissue, and testicle. It is the most common sarcoma.

---

[1] It is important to remember that *intercellular substance* and *connective tissue* are not synonymous terms. Intercellular substance refers to the material between the cells, and is possessed by all tissues, including connective tissue.

GIANT CELL SARCOMA.

This is a sarcoma containing giant cells. The latter are large cells, with numerous pale vesicular nuclei generally grouped toward one pole of the cell. The protoplasm appears to have undergone a hyaline degeneration. As a rule the giant cells lie free in spaces, being separated from each other by intercellular substance, or by true connective tissue. The intercellular substance is a prominent feature in the giant cell sarcoma.



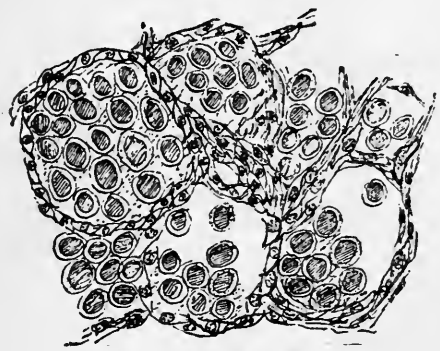
Giant Cell Sarcoma.

The tumor does not generally consist solely of giant cells; spindle cells and round cells are usually also present. It is comparatively benign.

Seats. Bones, especially the jaws and about the knee-joint. The giant cell sarcoma of the jaw is commonly described as *malignant epulis*. Epulis is a tumor growing from the jaw; it is frequently fibromatous.

ALVEOLAR SARCOMA.

This tumor strongly resembles cancer from the fact that the sarcoma cells, usually of the round cell variety, are held in a stroma. This stroma is as a rule made up of spindle cells, while in carcinoma we find it composed of fully-formed fibrous tissue. At times the stroma is truly fibrous; then the distinction from carcinoma becomes difficult, and has to be based on the character of the cells, which are of the connective tissue type in the one, of the epithelial in the other.



Alveolar Sarcoma.

The mode of development of alveolar sarcoma is obscure. Either previously existing bands of fibrous tissue fail to become sarcomatous, and remain, or the sarcomatous growth takes place along the adventitia of blood-vessels. Some forms cannot be accounted for on these theories.

Seats. Moles of the skin, bone, serous membranes, especially that of the brain.

ENDOTHELIOMA.

This is a sarcoma growing from the endothelial lining of lymphatic spaces and blood-vessels. It forms diffuse, extensive masses on the surface of serous membranes.

Microscopically, we find long branching cylinders of cells, the appearance being to a certain extent like that of alveolar sarcoma.

Seats. Serous membranes—pleura, peritoneum, dura.

MELANO-SARCOMA.

This is a sarcoma containing melanin. The pigment granules are in the cells and intercellular substance; the cell-nucleus is usually free from melanin; nor are all the cells of the tumor pigmented. Any of the types of sarcoma may become melanotic, but it is generally the spindle-cell form.

Seats. They are found where pigment is normal—in the skin, the choroid coat of the eye, and the meninges.

It is very malignant, especially when growing in the eye. Metastasis in that case is to the digestive tract, particularly the liver. Melano-sarcoma of the skin gives metastasis to the skin and the internal organs—the digestive tract, heart, and lungs. The secondary deposits are generally, but not always, melanotic.

CHLOROMA.

This is a pigmented, round cell sarcoma growing from the periosteum of the skull. Its greenish color is due to a peculiar fatty degeneration. It is rather benign.

PSAMMOMA.

This is found in the ependyma of the brain, and is a sarcoma, really a fibro-sarcoma, in which the intercellular substance is infiltrated with lime. It is not very malignant.

Other forms of sarcoma are the *myxo-sarcoma*, the *lipo-sarcoma*, or *sarcoma lipomatodes*, both of which occur in the subcutaneous connective tissue, the *glio-sarcoma*, the *chondro-sarcoma*, and the *osteo-sarcoma*. In the last two we have the sarcoma combined with cartilaginous and bony tissue, respectively. They grow from bone and from cartilage, although not all tumors of cartilage or of bone are chondro-sarcoma or osteo-sarcoma; they are also found in the parotid gland and testicle. The glio-sarcoma occurs in the retina, rarely in the brain.

CYLINDROMA.

This may be (*a*) a form of myxo-sarcoma, in which the myxomatous tissue is arranged in bundles or cylinders. (*b*) In some of the cylindromata the walls of the blood-vessels have undergone a hyaline degeneration, and are greatly thickened, particularly in certain places. Subsequently the hyaline material becomes covered by a mantle of sarcoma cells. (*c*) The tumor may be produced by a myxomatous degeneration of an endothelioma.

Cylindroma.

SARCOMA IN THE LOWER ANIMALS.

It is most common in the horse and dog, infrequent in cattle, very rare in cats. Gray horses are especially affected with sarcoma, the tumor being generally melanotic, growing from the pigmented tissues about the external genitalia and the anus. Two forms are met with: the hard, which is quite benign, and the soft, which is very malignant, and gives rise to general metastasis. Other sarcomas, when they occur, are the same as in man.

ARCHIBLASTOMATA.

MYOMA.

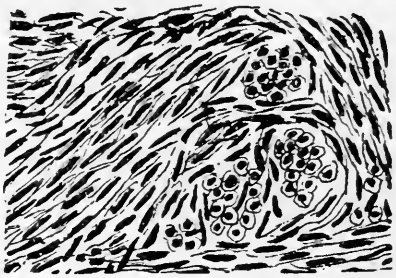
There are two forms, the rhabdomyoma, or striated muscle tumor, and the liomyoma, or non-striated muscle tumor.

(*a*) **Rhabdomyoma.**—This is rare, and is most often congenital, originating in the *segmental organs* of the fetus; hence, we find it in after-life in the kidney, testicle, and, more rarely, in the ovary. Its occurrence in these localities is only explicable on Cohnheim's theory. It is usually combined with sarcoma, which endows it with the tendency to metastasis that it sometimes presents.

A pure rhabdomyoma is found as a small tumor in the heart; there is in this form no evidence of congenital origin.

Microscopically, we find ordinary striated muscle fibers as well as striped spindle cells, the embryonal forerunners of the striped fibers.

(*b*) **Liomyoma.**—This is quite common, forming smaller or larger, well-circumscribed tumors, which on section show bundles of fibers running in different directions. Very often the tumor is combined with fibroma, *myo-fibroma.*



Liomyoma.

Microscopy. Liomyoma is composed of long spindle cells with *rod-shaped* nuclei. It might be confounded with spindle cell sarcoma, but the rod-shaped nucleus is characteristic.

Seats. The most frequent seat is the uterus (uterine fibroid). The tumor may be submucous, subperitoneal, or in the muscular wall itself—intramural. It is also found in the esophagus, the wall of intestines, and the prostate.

Degenerations. Calcification; myxomatous degeneration; fatty degeneration; softening with cyst formation; cavernous change.

NEUROMA.

A tumor containing nerve tissue.

The neuroma proper should be distinguished from the false neuroma, which may be a *fibroma*, a *myxoma*, or a *glioma*. False neuroma growing along the nerves is often multiple.

The true neuroma is of two kinds—the ganglionar and the fibrillar.

(*a*) *Ganglionar neuroma.* This is rare; it consists of ganglion cells; fibers are also present.

(*b*) *Fibrillar neuroma* grows along the course of nerves or in stumps, although in the latter locality it is often a false neuroma. The true fibrillar neuroma may be *myelinic*, or *medullated*, or *amyelinic*, or non-medullated.

The multiple neuroma of the skin at times has a peculiar distribution—somewhat in the form of an intertwining network—it is then termed *plexiform neuroma.*

EPITHELIAL TUMORS.

The best designation for this class of tumors would be *epitheliomata*, but as this word is habitually applied to certain forms of carcinoma, it cannot be used as a generic term.

Although classed as epithelial growths, all the tumors contain connective tissue, for we can have no new growth consisting solely

of epithelium. It is important in this connection to understand the relation of epithelium to connective tissue. Normally, the epithelium is on the surface, and beneath it is the connective tissue with the blood and lymphatic vessels. In certain places we find projections of these tissues, in others depressions. The former are termed *papillæ*, the latter *glands*. Epithelial tumors are simply exaggerations of these normal variations.

In the *simple epithelial tumors* the histologic relation of epithelium to connective tissue is maintained, but the plan of structure is altered—the growths are *atypical organoidally*. These tumors are benign.

There is another group, *histologically atypical*, in which the epithelium breaks through the connective tissue and forms separate nests directly in it; these are the *cancers*.

SIMPLE EPITHELIAL TUMORS.

PAPILLOMA.

It is frequently impossible, owing to a co-incident hyperplasia of the connective tissue, to separate epithelial from fibrous papillomata. Many papillomata are inflammatory, and are best classified as *hypertrophies*, being due to irritation.

Examples are: (*a*) **Callositas.** This is a hyperplasia of the epiderm and the papillæ. If it becomes excessive and projects both outward and inward, causing atrophy of the connective tissue papillæ, it constitutes (*b*) **Clavus,** or **Corn.**

Cornu cutaneum, or **Corn,** is an enormous hypertrophy of the epiderm and the papillæ that partakes of the character of a true tumor. A small blood-vessel generally penetrates into the horn. Horns are most frequent on the face and extremities; they may become spiral.

On mucous membranes we have also examples of papillary growths that are hypertrophies rather than tumors. They are common in chronic inflammation of the gastro-intestinal tract and the uterus, and are often dendritic in shape.

True papillomatous tumors of mucous membranes may grow from squamous epithelium (*hard papilloma*), or from columnar epithelium (*soft papilloma*). The consistency depends also on the amount of connective tissue present.

Papillomata may become cystic from myxomatous degeneration of the connective tissue; cysts may also arise from pressure on gland ducts.

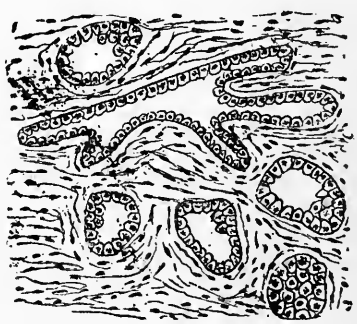
Seats. Larynx; nose; intestines, especially toward rectum; bladder. The papilloma of the uterus is usually an hypertrophy, and not a true tumor.

Elephantiasis.—This is characterized by a hyperplasia of the skin and the subcutaneous connective tissue, and by dilatation of the lymphatic and blood-vessels. It is the result of repeated attacks of acute inflammation, erysipelatous in appearance, due as a rule to irritation of the lymphatic circulation (*filaria sanguinis hominis*). As evidence of the inflammatory nature of the affection, we find foci of round cell infiltration.

In the circumscribed forms, those limited to the scrotum or labium, the cause, as already stated, is not evident, and it is proper to class them as tumors, leaving undecided the question whether they are fibromas, lymphangiomas, or simple epithelial tumors.

ADENOMA.

A normal gland may be compared to a properly constructed house. In such a house we have chambers (acini) and corridors (ducts) arranged after a definite plan, and composed of the masonry (connective tissue) and the plaster lining (epithelium). The plaster everywhere covers the walls. In an adenoma the relation of the plaster to the masonry (of the epithelium to the connective tissue) is normal, but the *architecture* of the house is faulty. Instead of a proper proportion of chambers and halls, we have an excessive and purposeless multiplication of chambers (acini) without adequate halls, or a multiplication of halls (ducts) without corresponding chambers. An adenoma, therefore, is a gland-like tumor, histologically normal, but *organoidally*, or architecturally, *atypical.*



Adenoma.

Continuing the comparison, and applying it to the cancers, we may say that in them the plaster no longer covers the walls everywhere regularly, but that it breaks *into* the masonry and forms collections within the body of the walls. In other words, there is in cancers a histologic disturbance—they are *histologically atypical.*

Varieties of adenoma. These are, histologically, (*a*) tubular, (*b*) racemose; clinically, (*a*) circumscribed, (*b*) diffuse.

(*a*) *Circumscribed adenoma.* This is a firm, well-circumscribed or encapsulated tumor, found in large glands—ovary, mamma, kidney, and liver; it is benign, although that of the ovary may become malignant.

(*b*) *Diffuse adenoma.* This develops on mucous membranes, forming flat swellings without definite outline. It is apt to become malignant. It is most frequent at the pylorus and in the body of the uterus.

Pure adenomata are found in the breast and kidney, but are rare; combinations are common. The latter are:

(*a*) *Cyst-adenoma.* The cells continue to pour out their secretion, the pouches becoming thereby distended until they constitute cysts. This is the commonest form of adenoma, and is most frequent in the ovary (ovarian cyst).

(*b*) *Papillomatous adenoma*, or *adenoma papilliferum.* In this we have a proliferation of the epithelium and connective tissue of the walls of the sacs into the interior of the acini in the form of arborescent growths. Seats. Ovary; mamma.

(*c*) *Adeno-carcinoma.* The epithelium breaks through the basement membrane and develops in the connective tissue.

CARCINOMA.

This is an epithelial tumor *histologically atypical.*

The epithelial cells break through the basement membrane, and lie "naked" in the recesses of the connective tissue.

The breaking through occurs usually in the form of solid plugs or cylinders, not in the form of glands. There is no intercellular substance between the cells (cf. sarcoma).

The *connective tissue* which surround the cells is termed the *stroma;* it is necessarily hyperplastic, and as evidences of its proliferation shows multiplication of cells (karyokinetic figures) and round cells in considerable numbers. Variations in the amount of connective tissue cause differences in the consistency of carcinomas. The stroma may be embryonal in character or dense; or it may be the seat of degenerations.

The *epithelial cells* frequently tend to reproduce the arrangement of the parent epithelium; thus, in cancers of the mucous

membranes, we find that there is an outer layer of cylindrical cells arranged in the form of a gland, the interior of the nest being filled with cells of a modified shape.

Forms of cells. The cells have a tendency to resemble those from which they grow. (*a*) *In skin cancers* the cells are cuboidal like those of the rete mucosum; they may undergo horny change and become flattened out; they also tend to be arranged in whorls. (*b*) *In cancer of mucous membranes*, as the intestine, the epithelial cells are cylindrical and present a tendency to mucoid change. (*c*) *In cancers of glands* we find cells of glandular type; the degenerations are those of the parent epithelium—a fatty degeneration in cancer of the mammary gland; sebaceous in that of the sebaceous glands. While, however, the cells in a certain degree resemble the epithelium from which they grow, they nevertheless show a marked irregularity in shape, due to mutual pressure. This gives rise to the *polymorphous* cells of cancer.

The cells are large, irregular, have a pale, vesicular nucleus, and a large amount of protoplasm, the latter frequently presenting evidences of degeneration.

Naked Eye Appearances.—(*a*) *Primary cancers.* These are rather hard; they grow upon surfaces or in glands, forming in the latter large, deep-seated masses, pale, yellowish or reddish-white in color, not encapsulated, and extending by infiltration. On surfaces, particularly on mucous membranes, they are often papillomatous in character. Surface cancers are apt to ulcerate. Primary cancers as a rule are single.

(*b*) *Secondary cancers.* These are sharply circumscribed, but not encapsulated; they occur as multiple growths in the interior of organs, in the form of rounded, whitish masses.

Degenerations.—These may affect the epithelium or the connective tissue. The epithelium undergoes the forms of degeneration peculiar to the parent cells: *Fatty*, in cases of cancer of the mamma; *horny*, in that of the skin; *mucoid*, in that of mucous membranes; *sebaceous*, in that growing from the sebaceous glands. In these degenerations the cells maintain their individuality; in other forms large masses of cells are affected, either with *fatty* or *cheesy* change. *Atrophy* and *absorption* of the cells may be brought about by pressure of the stroma. *Inflammation*, the result of bacterial infection, leads to the formation of ulcers with thick, undermined borders upon which papillomatous growths are frequently

developed. *Calcification* may occur, but is rare; *hemorrhage* is more frequent *from* the tumor than *into* it. *Cysts* are common in carcinoma and result (*a*) from softening, (*b*) from retention of secretion, and (*c*) from proliferation of the epithelium. The last variety is produced by a hyperplasia of the epithelium of glands, which hyperplasia give rise, in the first place, to cysts and then, by penetration through the basement membrane into the connective tissue, to cancer—*adeno-carcinoma.*

In the other varieties the cyst formation is a passive process. Cysts are common in cancers of the ovary and the mammary gland.

Combinations. Carcinoma combines (*a*) with adenoma—adeno-carcinoma; (*b*) in the parotid gland and testicle, with chondroma and myxoma, forming a variety of "mixed tumors."

Seats. The seats of primary cancer, in the order of frequency, are: (1) vaginal portion of the uterus, (2) skin of face, (3) mamma of female, (4) pylorus, (5) rectum, (6) esophagus, (7) ovary, (8) testicle, (9) external genitals, (10) prostate and bladder, (11) pancreas, (12) kidney, (13) small intestines, (14) thyroid gland, (15) biliary passages, (16) liver, (17) bronchial tubes.

Metastasis. Cancer extends (*a*) by *gradual infiltration* of the surrounding parts; (*b*) by spreading along the *lymphatic vessels*, and (*c*) by dissemination through the *blood-vessels*, especially those of the portal circulation.

The seat of the secondary growths is at times peculiar, thus in general metastasis of cancer of the mammary gland, the bones are frequently involved.

Seats of secondary cancer. (1) Lymphatic glands, (2) liver, (3) lung, (4) peritoneum and pleura, (5) spleen, (6) kidney, (7) brain, (8) skeleton.

Course. The course of carcinoma is usually chronic, the duration being a year or more. Pregnancy hastens the growth of mammary and uterine cancer; at times there is also a rapid spread along the blood-vessels, particularly in the abdominal cavity from cancer of the stomach or ovary. This is termed *acute carcinosis*, and is rapidly fatal.

Effects. These are (*a*) *those resulting from pressure*, either upon gland ducts or upon other structures; (*b*) *the cancerous cachexia.* The latter may be due (1) to hemorrhage, (2) to micro-organismal infection with consequent suppuration and septicemia, (3) to the production of a special cancer poison.

Age. Cancers of the skin and of the intestines occur after forty; uterine cancer at about thirty; those of the kidney and the sexual organs early in life or even congenitally.

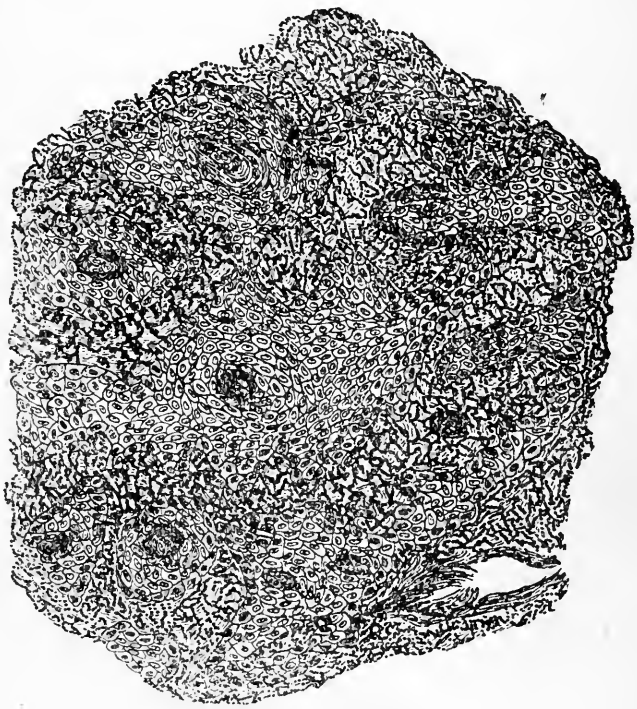
VARIETIES OF CARCINOMA.

Cancers are classified according to the character of the epithelial cells into (*a*) *squamous*, (*b*) *cylindrical*, and (*c*) *glandular*.

SQUAMOUS CANCER.

This is often termed epithelioma. It consists of flat or cuboidal cells, like those of the deeper layers of the skin.

Seats. The skin, the muco-cutaneous junctions, and the mucous membranes covered with flat epithelium. Named individually, the seats are, the lips, nose, eyelids, vagina, rectum, mouth, pharynx, glans penis, esophagus, cardia, bladder, and larynx.



Squamous Epithelioma.

Macroscopy. The tumor begins in the form of a warty growth which infiltrates the surrounding structures and produces flat swellings that have a tendency, especially on mucous membranes, to papillomatous formation. Ulceration is common. The surface of section is whitish, and on pressure yields, from separate points, an inspissated fluid consisting of epithelial cells and the juices of the tumor tissue.

Microscopy. The epithelial cells are arranged in solid branching plugs or masses, surrounded by the connective tissue stroma. The majority of cells, particularly those near the periphery of the nests, are cuboidal, like those of the deeper layers of the skin, but toward the center the cells are apt to be flat and to take on a peculiar concentric arrrangment producing whorls, termed *pearly*

bodies. The cells tend to undergo a horny change; many also contain granules of eleidin and keratohyalin.*

CYLINDRICAL CANCER.

This is a cancer containing cylindrical epithelium. It is generally termed cylindrical epithelioma.

Seats. Mucous membranes covered by cylindrical epithelium, particularly the intestinal tract, from the cardia to the lower third of the rectum, and the uterus; kidney, mammary gland.

Macroscopy. It appears either as soft, whitish nodes, or as flat swellings, with a tendency to the formation of papillomatous growths. It is softer than the squamous cancer.

Microscopy. Toward the periphery of the nests we find columnar cells, which are often converted into goblet cells by mucoid change. In the center of the nests the cells are altered by pressure.

Cylindrical cancer is frequently combined with adenoma.

GRANDULAR CANCER—CARCINOMA SIMPLEX.

This is made up of polyhedral cells.

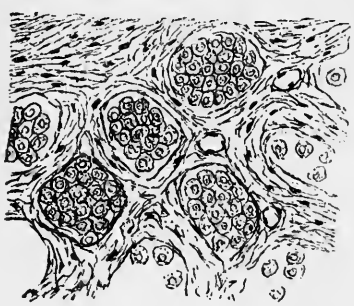
Seats. Mamma, liver, salivary glands, pancreas, ovary, and testicle.

Macroscopy. The tumor appears generally in the form of a node that is harder than the surrounding structures, although it is not usually a hard cancer. It may also occur as a diffuse infiltration, particularly in the liver.

Microscopy. The cells are polyhedral.

CLINICAL VARIETIES.

Cancers are classified clinically, according to their naked-eye appearance and consistency, into (*a*) hard, (*b*) soft and (*c*) colloid. Any of the types described above may assume any one of the clinical forms.



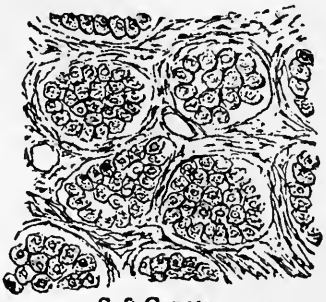
Hard Cancer.

(*a*) **Hard, or Scirrhous Cancer.**—The hardness depends on the amount of connective tissue; the nests are small, the cells few. Here and there the alveoli are empty, from atrophy and degeneration of the cells.

Seats. The mamma, where it is usually a glandular cancer; the pylorus, where it may be glandular or cylindrical.

* Many of the so-called parasites are simply granules of these substances.

(*b*) **Soft, Encephaloid, or Medullary Cancer.**—This is a large, soft, juicy, whitish tumor, which, microscopically, shows very little connective tissue, but presents large nests containing many cells. Many cylindrical cancers are encephaloid.



Soft Cancer.

Seats. Mucous membranes, testicle, and ovary.

(*c*) **Colloid Cancer, Carcinoma gelatinosum.**—This is a carcinoma in which the epithelium has undergone a mucoid or a colloid change, most frequently the former. The tumor has an alveolar structure visible to the naked eye, the alveoli being filled with a gelatinous material producing a honeycomb appearance.

Seats. Pylorus—here the degeneration is usually mucoid; thyroid gland, and breast.

Among rare forms of carcinoma we have the following:

(*a*) **Carcinoma myxomatodes.**—One in which the *stroma* has undergone myxomatous degeneration.

(*b*) **Carcinomatous Cylindroma.**—One in which portions of the stroma have undergone a hyaline change, the degenerated areas running in the form of cylinders through the tumor.

(*c*) **Giant-cell Carcinoma.**—In this the alveoli are rather small, and may contain one or two giant epithelial cells. The latter are termed *physalids*. There is considerable similarity between a giant-cell carcinoma and an alveolar large round cell sarcoma containing giant-cells. The differentiation depends on the general characters of sarcomas and carcinomas, and particularly on the fact that sarcoma cells may constitute the walls of blood-vessels—a thing epithelial cells never do. The stroma is as a rule abundant in giant-cell carcinoma.

(*d*) **Melano-carcinoma.**—One containing pigment—melanin.

Cholesteatoma.—This is a benign epithelial tumor occurring in the central nervous system. It is distinct from carcinoma, and is best classified with the teratomata. Its existence in the brain is explained in concordance with Cohnheim's theory. It contains peculiar shining whorls, largely composed of cholesterin plates; sebaceous glands, hair, and other dermal structures may be present.

CARCINOMA IN THE LOWER ANIMALS.

Cancer is rare in the lower animals, especially in herbivora; it is more common in dogs and cats, occurring, in the first-named, in the breast, thyroid gland, prostrate body, and skin. In horses, when cancer develops, it is found in the skin about the penis or in the intestines.

DIFFERENCES BETWEEN SARCOMA AND CARCINOMA.

1. NAKED EYE APPEARANCE.

SARCOMA.	CARCINOMA.
Fleshy, smooth, rounded or bossellated.	Nodular, with irregular outline, or an unhealthy ulcer, with papillary excrescences at borders; base of ulcer indurated.

2. SURFACE OF SECTION.

Milky color, smooth, pearly, often with a reddish tint.	More granular and opaque; less apt to be reddish.

3. JUICE.

Absent as a rule.	Present.

4. ADIPOSE TISSUE.

Absent.	May be present.

5. CAPSULE.

May be present; if not, is pretty well circumscribed.	Very rare.

6. RELATION TO SURROUNDING STRUCTURES.

Usually not infiltrating locally; may be seen with microscope.	Always infiltrating.

7. CONSISTENCY.

Softer, with exceptions.	Harder, with exceptions.

8. RELATION TO SKIN.

Not adherent; if so, due to inflammation.	Adherent.

9. PAIN.

Absent.	Present.

10. LYMPHATIC GLANDS.

Not involved.	Involved.

11. METASTASIS.

As a rule, along blood-vessels.	Along lymphatics; at times, along blood-vessels.

12. RAPIDITY OF GROWTH.

Varies, but may be more rapid than carcinoma.	Growth rapid compared with other tumors, except some sarcomata.

13. AGE.

Sarcoma.	Carcinoma.
Middle life; not rare after ten years.	After middle life.

14. SITES.

Connective tissue, e. g., corium, fasciae, intermuscular septa, bone, periosteum; brain, ovary. Rare in liver, lung, uterus.	Epithelial surfaces and glands—lips in male, vaginal portion of uterus in female; breast, stomach, intestine.

15. CELLS.

Embryonal connective tissue cells, with slight intercellular substance.	Epithelial cells, packed without intercellular substance between partitions of connective tissue.

16. STROMA.

Slight intercellular substance between the cells, homogeneous or faintly fibrillar.	Fully-formed fibrous tissue forming distinct alveoli.

17. BLOOD-VESSELS.

Embryonal, without distinct walls, simply channels with endothelial lining.	Well-developed vessels in the stroma.

ETIOLOGY OF CARCINOMA.

During the last few years strong efforts have been made to discover the cause of cancer, but while these investigations have not been crowned with success, they have taught us two important facts: First, that cancer can be communicated from one individual to another; secondly, that it can be inoculated from one animal into another. The majority of experimenters have looked upon protozoa as the cause of cancer, since they have found in the tumors certain bodies resembling *gregarines* and *coccidia*. If these bodies are really present, they are merely accidental and not causal; in most instances, however, the bodies are not protozoa at all, but materials elaborated by the cancer cells.

It should be stated that coccidia are at times found associated with hyperplasias of epithelial cells—thus in the biliary passages of the rabbit, coccidia are occasionally seen to produce papillary growths, with the cells arranged in layers. Similar bodies may be found in cancer; also in *Darier's disease*, an affection of the sebaceous glands and hair follicles, characterized by a hyperplasia of the epithelial structures. In *molluscum contagiosum*, in which there is likewise a hyperplasia of the hair follicles and sebaceous glands, the bodies are also present.

In cancer the cyst-like bodies (coccidia) are found within the cells, pushing the protoplasm and nucleus to one side and growing until the entire cell is filled. Around the cyst is a capsule (whether formed by the parasite or by the protoplasm of the cell is not

known). The coccidium divides into four sacs, each containing spores of future coccidia.

Certain spindle-shaped bodies, with and without capsule, are also met with outside of the cells, but the greater part of the life-history of the protozoa is intracellular.

While cyst-like bodies are quite common in cancer, spore-formations are rare, and when found, are an accidental and secondary infection.

In the majority of instances the cyst-like bodies have been demonstrated, by staining peculiarities and by chemical tests, to be substances elaborated by the cells—sometimes this substance is mucin, when in cancers the cells of which undergo this change; in squamous epithelioma, the material is eleidin and keratohyalin.

We are then forced to conclude that protozoa cannot be looked upon as the cause of cancer.

CYSTS.

There are two classes of cysts, those that are tumors and those that are not. The following are *non-tumorous* cysts: (*a*) *Extravasation cyst.* This results from hemorrhage into the tissues, with subsequent absorption of the blood-pigment and encapsulation of the fluid.

(*b*) *Softening cyst.* This is due to circulatory disturbances, liquefaction necrosis, and encapsulation of the fluid.

(*c*) *Parasitic cyst.* Of this the echinococcus, or hydatid cyst is an example.

Cysts that are tumors. (*a*) **Retention or Occlusion Cysts.**—These are produced by the obstruction of gland ducts; the secretion accumulates and distends the ducts. The cysts are lined by the epithelium of the gland.

Varieties: 1. *Follicular cysts.* These are small, cystic tumors, occurring chiefly in the skin, where they are due to occlusion of sebaceous glands (*Comedo, atheroma*).

2. *Mucoid cysts.* These are commonly multiple, and originate from obstruction of the mucous glands of mucous membranes. They are found in the cervix uteri, mouth, lips, cheeks, antrum of Highmore (*dropsy of the antrum*), rectum, and larynx.

3. *Retention cysts of large glands.* These are found in connection with the salivary glands (*ranula*), in the liver, and kidney. But not all cysts of the liver and kidney are retention cysts.

4. *Retention cysts of embryonal structures.* These are congenital. They may occur in glands existing in later life, but the formation of the cyst was congenital. Examples are the parovarian cyst, a single congenital cyst of the parovarium; certain cysts of the testicle and ovary; hygroma of the neck, which may be either a congenital cyst or a lymphangioma; cysts of the urachus and the suspensory ligament of the liver.

(*b*) **Teratoid, Teratomatous, or Dermoid Cysts.**—These are of embryonal origin, but are not retention cysts. They are the results of errors in development, of misplacements of tissues which proliferate later in life and produce the structures that normally spring from them. Epithelium gives rise to epidermis, hair, teeth, etc. Teratoid tumors are usually cystic in character, a large portion of the contents being an atheromatous material like that found in sebaceous tumors. It consists of fatty matter, fat crystals, cholesterin plates, fatty epithelial cells, hair, skin, sweat glands, sebaceous glands, teeth, etc.

When very complicated, teratoid growths properly come under the head of monstrosities.

(*c*) **Proliferation Cysts.**—These are really forms of adenoma (*cyst-adenoma*), which are produced by a proliferation of the epithelial cells of gland-acini, all the cells remaining attached to the basement membrane; in consequence hollow spaces filled with the secretion of the cells are formed. Generally they are multiple new cysts being developed from the walls of larger cysts by a proliferation of the epithelium.

Seats.—Ovary, most frequently, here constituting the ordinary *multilocular cyst;* mammary gland, testicle, kidney, and liver. The majority of renal cysts are due to obstruction, but there are instances of proliferation cysts.

Proliferation cysts show a marked tendency to the development of papillary growths into the interior of the spaces which may become entirely filled by sponge-like masses (*cyst-adenoma papilliferum*). Those of the mammary gland and ovary are especially apt to become papilleferous, a tendency that should excite suspicion, since these tumors are apt to become carcinomatous, solid epithelial masses being formed instead of hollow spaces.

These cysts are lined by columnar epithelium, although they grow in organs, as mamma and ovary, which contain no such epithelium. This peculiarity is best explained in Cohnheim's theory.

CHAPTER VII.

SPECIAL PATHOLOGY.

THE BLOOD.

The blood is a fluid tissue which is the seat of active biologic changes, yet it is not directly under the control of the nervous system. The great mass of changes which it presents do not take place in it, but in the blood-forming and blood-destroying organs, which are under the influence of the central nervous system.

The red corpuscles are formed in the spleen, bone-marrow, and lymphatic glands; destruction of these corpuscles takes place, not in the blood itself, but in organs—the spleen and liver. The white corpuscles are formed chiefly in the lymphatic glands, also in the spleen.

Usually, the blood contains 4,000,000 to 5,000,000 red cells, and 5000 to 10,000 white cells, per cubic millimeter, and hemoglobin to the amount of 14 per cent.

I. Changes in the Total Quantity of the Blood.—(*a*) *Plethora*—an increase in quantity. (*b*) *Oligemia*—a decrease in the quantity. Both conditions are transient; they result from excessive and deficient ingestion of food, respectively. In the case of oligemia, other changes soon follow, usually a condition of hydremia develops.

II. Changes in the Red Corpuscles.—(*a*) Change in *number*.

(α) *Polycythemia*—An increase in the number of red corpuscles, a transitory condition usually due to the rapid removal of the watery constituents of the blood, as occurs in cholera.

(β) *Oligocythemia*—A decrease in the number of red corpuscles. This is a more frequent change, and is seen in all forms of anemia (using the term *anemia* in the general sense to denote an impoverishment of the blood).

Oligocythemia is said to be *symptomatic*, when the cause is apparent, and *idiopathic*, or *essential*, when no cause is discoverable.

Symptomatic oligocythemia is produced by (1) cachexia, (2) starvation, (3) wasting discharges, as in syphilis and tuberculosis, (4) poisons, as lead and arsenic, (5) infectious diseases, as malaria and syphilis, and (6) by hemorrhages. Essential oligocythemia is due to changes in the blood-forming and blood-destroying organs. Its causes are (1) leukemia, or leukocythemia, (2) chlorosis, and (3) progressive pernicious anemia. The last may at times be symptomatic.

(*b*) *Changes in size.* The normal red corpuscle is 5-7μ in diameter. In pathologic states we meet with (α) *macrocytes* or *megalocytes*, large corpuscles measuring 10-11μ, and (β) *microcytes*, small corpuscles, 2-4μ in diameter. Both forms indicate retrograde changes in the blood.

(*c*) *Changes in form.* In anemia the red corpuscles are changed in outline, becoming irregular and misshapen. Such corpuscles are called *poikilocytes*; they are usually large and indicate destructive changes in the red cells.

(*d*) In profound anemias the blood contains *nucleated red corpuscles.* Their presence in the blood is ascribed to a rapid formation of red cells, and their discharge into the blood-stream before they are sufficiently mature. They occur normally in the blood of the fetus.

III. **Changes in the Hemoglobin.**—Normally, 14 parts of hemoglobin are found in 100 parts of blood. The clinical standard is entirely arbitrary.

(*a*) *Diminution—Oligochromemia.* This change depends upon one of two factors, (α) a dimunition in the number of red cells, each cell containing a normal, or even a greater amount of hemoglobin; (β) a decrease of the amount of hemoglobin in each individual cell.

(*b*) *Solution in the plasma—Hemoglobinemia.* The causes of this are mineral poisons, such as potassium chlorate; infectious diseases; transfusion of foreign serum. If the hemoglobin passes out with the urine, the condition is called *hemiglobinuria.*

(*c*) *Changes in chemical composition.* This is evidenced by a change in color, although not every change in color is indicative of a chemical alteration.

The blood is (α) *dark* in asphyxia; (β) *chocolate color* in potassium chlorate poisoning; (γ) *cherry-red* in carbon monoxid poisoning; (δ) *dark or inky-black* in sewer-gas poisoning.

IV. **Changes in the Leukocytes.**—The average ratio of white to red cells is 1 : 700; it may vary normally from 1 : 1000 to 1 : 500.

An increase in the number of leukocytes is termed *leukocytosis*. Leukocytosis is physiologic (*a*) during digestion, and (*b*) in pregnancy. The pathologic conditions giving rise to it are (*a*) hemorrhage, (*b*) certain inflammations, (*c*) certain infectious diseases, (*d*) chronic diseases associated with anemia, the increase being absolute or relative (from diminution of the red corpuscles), (*e*) leukemia —in this disease there is an absolute increase exceeding that seen in any other condition, with a change in the proportion of the different forms.

Forms of leukocytes. Leukocytes are divided according to their size and the character of the nucleus into (*a*) *small lymphocytes*, small cells with a large darkly-staining nucleus; (*b*) *large* uninuclear cells with a feebly-staining nucleus; (*c*) *transitional forms* —cells with an irregular, often sigmoid, nucleus, and (*d*) *multinuclear leukocytes*. The last are the most numerous in normal blood, constituting about 75 per-cent. of all white cells.

The majority of leukocytes normally contain in their *protoplasm* fine granules, which are *neutrophile*, *i. e.*, when subjected, simultaneously, to an acid and a basic dye, they take a color midway between the two stains. The stains generally employed are eosin (acid) and methyl-blue (basic). Some of the cells contain granules of a larger size than the neutrophile cells—these granules take acid stains, and are termed *eosinophile*. Eosinophile cells have relatively small, though absolutely large, nuclei, which stain but feebly with the nuclear dyes. In the normal blood of adults, the eosinophile cells constitute from 1–2 per cent. of all leukocytes; in the blood of children they are more numerous. While a proportion of 5 per-cent in an adult would point to serious disease of the blood-making organs, it would not do so in children.

There is another form of leukocytes, rarely if ever present in normal blood, which contains large granules taking the basic stains, hence termed *basophile*. It is uninuclear, and corresponds to the *mastzelle*, *granule cell*, or *wandering cell*, found in the connective tissue.

In physiologic leukocytosis the increase usually affects the neutrophile, multinuclear cells and sometimes the lymphocytes. In pathologic conditions, when the blood-making organs are

diseased, the increase involves particularly the eosinophile cells. This is true especially of leukemia. It was maintained at one time that it was possible to determine, by the forms of leukocytes, which organs were affected in leukemia, but this cannot be done.

In some cases of leukyocytosis, due to disturbances of the blood-making organs, the basophile cells are present in large numbers—this is an indication of grave lesions of these organs.

V. **Changes in the Plasma.**—(*a*) *Changes in the amount of water.* (α) *An increase—hydremia.* This occurs in anemia, where it is relative; in dropsy. (β) *A decrease—anhydremia.* This is a transient condition, generally due to excessive watery discharges from the bowels, as in cholera.

(*b*) *Changes in quantity of fibrin factors.* (α) *An increase—hyperinosis.* This exists when there is a tendency to thrombosis; it is transient and not important. Sometimes it is rapidly produced by changes in the cellular elements of the blood. (β) *A decrease—hypinosis.*

(*c*) *Particulate substances in the blood.* A large variety may be found; sometimes they give rise to embolism. (1) Fibrin. (2) Pieces of heart valves. (3) Portions of tumors. (4) Particles of an atheromatous wall of a blood-vessel. (5) Gases. (6) Fat globules, in fractures of the long bones. (7) Pigment particles—usually hemosiderin, though frequently incorrectly termed melanin; bile-pigment. (8) Charcot-Leyden crystals. These are octohedral crystals composed of phosphoric acid and a peculiar organic base; they are never found in circulating blood, only in dead blood, especially in leukemia. They are also met with in asthmatic sputum. There appears to be a connection between these crystals and eosinophile cells; both are found in the sputum of asthma as well as in leukemic blood. (9) Fat in the form of an emulsion, not in large droplets. An excess of fat in the blood (*lipemia*) occurs normally after the ingestion of large amounts of fat; pathologically, we find it in diabetes. (10) Micro-organisms. In the majority of infectious diseases the micro-organisms do not develop in the blood; there are, however, a few pathogenic bacteria that are essentially hemic, viz., the bacillus of anthrax and the spirillum of relapsing fever. The latter is found only in the blood and in the pulp of the spleen; the former is found in the blood and in the tissues, at the site of the local lesions. Besides these staphylococci may at times be demonstrated in the blood; also the influenza bacillus (this is doubted by

some writers). Protozoa are also met with, as *e. g.*, the plasmodium malariae. Protozoa are more frequent, however, in the lower animals. Finally, we have the embryos of the filaria sanguinis hominis.

(*d*) *Changes in chemical composition.* (1) *Increase in the amount of albumin—hyperalbuminosis.* This occurs in overfeeding, and as a result of a loss of salts and water, as in cholera. (2) *Decrease in the amount of albumin—hypalbuminosis.* Normally, we find from 70 to 80 parts of albumin per 1000 of blood; in disease the proportion may sink to 50 per 1000. Hypalbuminosis occurs in albuminuria, inanition, and anemia. (3) The presence of urates, especially of sodium urate—*uratemia.* This condition prevails during an attack of gout. We may at times have also an excess of uric acid in the blood. (4) An excess of urea—associated with *uremia.* The normal amount of urea in the blood is .16 parts per 1000; in uremia it is from .4 to .6 per 1000. (5) An excess of sugar—*glycemia.* In diabetes the amount may be doubled. (6) The presence of acetone—*acetonemia*—in diabetes. (7) The presence of *toxins* and *antitoxins.*

Toxins are poisonous compounds elaborated by bacteria. Each bacterium produces its own specific toxin, regardless of the organ wherein it develops. Toxins, like drugs, have selective affinities for certain cells. The disturbances which they cause may be functional or structural, the latter being of a degenerative character. Toxins are eliminated by the excretory organs, especially by the kidney, and it is during their elimination that they determine the degenerative changes: first cloudy swelling, later fatty degeneration.

Certain infectious diseases, it is well known, have a tendency to be limited, although the micro-organisms causing them are still present in the body. This limitation seems to be brought about by the presence within the blood of certain substances known as *antitoxins.*

The toxins produced by the micro-organisms, which are, as has been said, specific, are carried in the circulation and exert a peculiar stimulating influence upon the body cells, on account of which the latter elaborate a specific antitoxin, which counteracts the toxin. An animal charged with a large amount of antitoxin is immune to the corresponding disease. That the immunity is due to a substance circulating in the blood is proved by the fact that when the blood-serum of this animal is introduced into another animal, the latter becomes also immune. The immunity of the

first animal is termed *active*, since the antitoxin was produced by its own cells; that of the second is called *passive*, and is much less lasting.

The living blood has a destructive action on micro-organisms, but this germicidal action is to be distinguished from the influence of antitoxins in the production of immunity. The latter is a specific property acquired by the blood in consequence of the introduction of certain toxic substances.

A state of immunity may be produced against poisons that are not bacterial in origin. Ehrlich experimented with *ricin*, an albuminous substance found in the castor-oil plant, and with *abrin*, the active principle of abrus, or jequirity seed. Both are irritant poisons, but when animals are fed with small doses, they are made immune against toxic quantities of these substances. This immunity is not a toleration, such as we see after the prolonged use of arsenic or morphin, for it comes on suddenly, and at a definite time —in about fifteen days. Ehrlich also proved that the blood of the immune animal contained an antitoxin, and that the latter was a *direct chemical antidote* to the toxin. He did this by mixing a little of the blood-serum of the immune animal with the poison in a test tube, and finding that the mixture was harmless when introduced into unprotected animals.

In producing immunity against diphtheria, the toxin is first separated from the bacteria by filtration, and then is gradually introduced, in ascending doses, into horses until these no longer react to large amounts. The animals are then immune, and their blood-serum can be employed to confer immunity upon other animals.

In diphtheria, and also in tetanus, the laboratory experiments upon animals have yielded perfectly satisfactory results; in the case of the human subject the success has not been so positive.

We find in the normal metabolism of the body instances comparable to the reaction of the cells in infectious diseases: the liver, for example, counteracts the poisons produced during digestion. It is also known that the gastric cells, which normally elaborate an acid juice, secrete an alkaline fluid when acids are given; while the salivary glands, the secretion of which is naturally alkaline, under the influence of acids secrete an excess of alkaline fluid.

In regard to the mode of action, and the source of the antitoxins, the theory of Ehrlich—*that the body cells elaborate a chemical*

antidote—seems to be the best (Professor Guitéras). There are however, some weak points in this theory, for it is not always possible to demonstrate a chemical antidotal action. It has, therefore, been asserted by some authorities, that the action of the antitoxins is not a chemical one, but that they, the antitoxins, *protect* the body cells, *i. e.*, render them immune against the toxin, instead of *neutralizing* the latter. This theory, evidently, is not an explanation at all.

As to the origin of the antitoxins, it is claimed that they may be produced by the bacteria themselves. Strong arguments can be brought forward in favor of this view, but it seems doubtful whether we shall ever be able to settle the question conclusively. Whatever view we may take, we must accord to the body cells an important function, be it that they produce the antitoxin, or that they supply a favorable nutriment for its production.

Not all the cells of the body are equally concerned in the formation of the antitoxin, but especially those that are directly acted upon by the toxins, usually those nearest the point of inoculation. This statement is based on the fact that immunity can be induced against certain diseases only in certain directions. Pasteur discovered a vaccine against splenic fever. When this vaccine is inoculated beneath the skin, the animal is immune to anthrax introduced in the same way, but the immunity is much weaker or absent when the poison is introduced through another channel, as the intestine or lung.

These facts seem to show that the cells first acted upon by the toxin react with the formation of an antitoxin—perhaps it is the cells of the lymphatic glands.

The subject of antitoxins and immunity seems destined to revolutionize medicine. It is quite possible that the agents which are held of great account in the treatment of infectious diseases, derive their value from their power to stimulate the production of antitoxins. From this point of view our drugs and remedial measures should be examined.

Diseases of the blood. (*a*) *Simple anemia*, (*b*) *pernicious anemia.*

The second may be considered an aggravated form of the simple anemia. We find in both the same changes, in kind, in the blood, but they are more marked in the pernicious anemia. In addition, the latter is associated with disturbances in the blood-making and blood-destroying organs—the spleen, lymphatic glands,

liver, and bone-marrow. The last becomes red and "splenified;" the liver is the seat of an excessive pigmentary deposit. The marrow changes may indicate a rapid formation of red corpuscles, but also an active destruction; the pigmentation of the liver certainly points to destruction of the red cells.

Blood-changes in simple and in progressive pernicious anemia. (1) Oligocythemia. (2) Proportionate oligochromemia. (3) Hydremia. (4) Diminution of the specific gravity. (5) Diminution of the alkalinity. (6) Microcytosis. (7) Macrocytosis. (8) Poikilocytosis, especially marked in the pernicious form of anemia. (9) Presence of nucleated red corpuscles. (10) Relative or slight absolute leukocytosis. (11) Fatty degeneration of the parenchyma of organs, especially of the heart, kidney, and liver, of the blood-vessels, the nerve-structures and retina.

Many cases of progressive pernicious anemia are not essential, but symptomatic, as, *e. g.*, those due (1) to intestinal parasites, as the *anchylostomum duodenale* (constant abstraction of blood); the *bothriocephalus latus;* (2) to cancer; (3) to grave disturbances of digestion, the primary cause of which, in a certain group of cases, is atrophy of the mucous membrane of the stomach.

(*c*) *Chlorosis.* The characteristic features of this essential anemia are as follows: (1) Disproportionate oligochromemia. (2) Oligocythemia, of less degree than in ordinary anemia. (3) Diminished specific gravity. (4) Hydremia. (5) Increased alkalinity. (6) Only slight changes in the form of the red corpuscles. In a few cases there is (7) hypoplasia of the sexual organs in females, and (8) hypoplasia of the heart and large blood-vessels. The last cannot be considered, as has been done by some, as the cause of chlorosis, but it is likely that cases presenting that condition are more liable to terminate fatally. Death in chlorosis is usually due to profound nervous disturbances—hysteria and hystero-epilepsy.

(*d*) *Leukemia.* The features of this anemia are: (1) Oligocythemia. (2) Proportionate oligochromemia. (3) Extraordinary leukocytosis, affecting especially the multinuclear eosinophiles, and causing, in some cases, the appearance of a new variety—the basophiles. (4) The changes in the blood-making organs are marked—there is hyperplasia of the lymphadenoid tissue of the lymph-glands, the spleen, and the bone-marrow, either of each alone or of all. The lymphoid tissue may become hyperplastic throughout the body. (5) The shed blood contains Charcot-Leyden crystals.

(*e*) *Melanemia.* In this the hemoglobin becomes precipitated as fine granules in the blood-plasma, the red cells, or the leukocytes. The granules have been termed melanin—an unfortunate name, since melanin is really a metabolic pigment. Melanemia occurs in malaria.

(*f*) *Hemoglobinemia.* This is a condition in which the hemoglobin is in solution in the plasma. Its causes are mineral poisons, certain infectious diseases, and the transfusion of blood from another species of animal.

CHAPTER VIII.

DISEASES OF THE LYMPHATIC GLANDS, THYMUS GLAND, BONE-MARROW, AND SPLEEN.

Anatomy.—A lymphatic gland consists of a large number of nodes of lymphadenoid tissue within a fibrous capsule, that sends numerous trabeculæ into the gland. The nodes, which are spherical in the cortical and pyramidal in the medullary portion of the gland, are made up of a reticulum of stellate cells, the meshes of which are filled with lymphocytes. To the stellate cells endothelial cells are attached; endothelial cells also cover the trabeculæ. In some places the lymphoid tissue is packed densely against the trabeculæ; in others there are spaces known as the lymphatic sinuses, between the lymphoid tissue and the trabeculæ.

Functions.—1. Lymphatic glands form leukocytes; probably all leukocytes are formed in lymphoid tissue.

2. They may form red corpuscles or certain leukocytes which change into these.

3. They act as filters, arresting especially micro-organisms introduced from without.

Inflammation. *Lymphadenitis.*—The gland is enlarged, red, juicy, and surrounded by an inflammatory edema. The redness is most marked in the cortex; minute hemorrhages may be present. On microscopic examination we find large numbers of

round cells; the lymph sinuses are packed with lymphocytes, and epithelioidal cells derived from the endothelium. In addition, we find cells from the original focus, *i. e.*, the lymphatic radicles; also, micro-organisms.

Cause. The inflammation is always secondary to a similar process in the radicles of the gland.

Terminations. (*a*) *Resolution*, the most frequent termination. The gland, at first red, becomes pale from pressure on the blood-vessels; later, when resolution is in progress, it again turns red or "splenified," from secondary congestion after the removal of the inflammatory exudate.

(*b*) *Suppuration.* This manifests itself very early to the eye as minute yellow spots. Under the microscope we find a large accumulation of multinuclear cells, with a tendency to breaking down. Parts or the whole of the gland may suppurate; the process may even extend to the capsule and to the surrounding tissues, as, *e. g.*, in chancroidal buboes. The abscess discharges and leaves a fistulous tract, healing by granulation.

(*c*) *Fibroid change.* This depends upon a hyperplasia of the connective tissue of the trabeculae, with fibrous change.

(*d*) *Cheesy necrosis.* This is most frequently due to tuberculosis. The gland may be affected as a whole or in part; it loses its translucency and elasticity, and becomes white and cheesy. Microscopically, the process is characterized by a marked proliferation of the endothelial cells of the lymphatic spaces—a desquamative catarrh, we might say, of the lining of these spaces, comparable to caseous pneumonia. Miliary tubercles may be present; at times they constitute the sole lesion of tuberculosis. Tubercle bacilli are generally found only in small numbers, if at all, but the tuberculous nature of the inflammation can be proved by inoculation into animals and by the reaction which the patients give after the injection of tuberculin.

The glands may become calcified, or they may break down and discharge through long sinuses; or fibroid changes may take place.

Chronic inflammation of the lymphatic glands has been called *scrofula;* in the majority of instances scrofulous glands are tuberculous.

It is generally possible to demonstrate disease of the radicles of the lymphatic glands; at times no peripheral lesion is found.

Causes of inflammation of lymphatic glands. 1. *Septic infection.* The changes are the same as those in the radicles of the glands, usually suppurative. Example: the chancroidal bubo, which is probably due to virulent forms of pyogenic organisms.

2. *Glanders.* The glands are involved more often in the lower animals than in man. Suppuration is common; there is nothing specific save the bacillus of glanders.

3. *Anthrax.* The glands are the seat of a permanent congestion, and are "splenified." Large numbers of anthrax bacilli are present.

4. *Typhoid fever.* Characteristic of this disease is the hyperplasia of the lymphoid tissue, particularly of the intestines, mesenteric glands, spleen, etc. The bacillus is present. In the glands there is at first a transient congestion, soon succeeded by a marked anemia due to the proliferation and dense packing of the cells. The anemia leads to softening, which, however, is not a true suppuration. The softening gives rise to ulceration in the intestines. In the glands necrosis is rare; it may occur and cause rupture into the peritoneal cavity, peritonitis following, or into a vein, with the production of embolism.

5. *Syphilis.* This affects all the glands of the body. There is a chronic hyperplasia, with a tendency to fibroid change; the blood-vessels and trabeculæ are thickened. Gummy tumors may also occur. At times syphilitic glands present nothing differing from the hyperplasia due to other causes.

6. *Tuberculosis.*

7. *Leukemia.* In lymphatic leukemia the glands are greatly enlarged.

8. *Pseudo-leukemia, or malignant lymphadenoma.* The appearance is the same as in leukemia, but it is said that the lymph spaces of leukemic glands can be more readily injected than those of pseudo-leukemic glands. It is really proper to speak of two kinds of malignant lymphadenoma—a leukemic and a non-leukemic. The non-leukemic lymphadenoma partakes of the character of a tumor; the leukemic seems to be of an infectious nature. But there is as yet no pathologic evidence for either of these views; the statements rest upon clinical observations.

9. *Leprosy.* The bacillus is present.

10. *Plague.* This gives rise to acute suppurating buboes.

The glandular enlargements, if chronic, are often called lymphomas; and we speak of hard and soft lymphoma, according to the amount of connective tissue present.

Tumors. Lympho-sarcoma; endothelioma; other sarcomas may be primary (rare) or secondary; secondary carcinoma.

THE THYMUS GLAND.

In structure and function the thymus resembles a lymphatic gland. It is divided into lobules by trabeculæ, which are lined by endothelial cells; between the trabeculæ we find lymphoid tissue. As an evidence of its epithelial origin, we have the presence of concentric bodies of flat cells (*corpuscles of Hassall*).

Weight. At birth the thymus weighs 13 grams; at the end of the first year, 19 grams; at the end of the second, 26 grams. It remains stationary until fourteen, then begins to atrophy, disappearing entirely by the twentieth year.

Fatty degeneration. This is physiologic.

Calcareous infiltration may occur.

Circulatory disturbances. Parenchymatous hemorrhage is met with in asphyxia in the young; in purpura.

Inflammation. This is generally suppurative, being either of hemic origin or resulting from extension.

Tumors. Lymphadenoma, *i. e.*, hyperplasia of the lymphoid tissue, is met with in leukemia and pseudo-leukemia in children.

The enlargements of the thymus may give rise to asphyctic symptoms from pressure on the trachea.

Tuberculosis and *syphilis* may attack the thymus gland.

THE SPLEEN.

The spleen is surrounded by a fibro-elastic capsule, from which trabeculæ extend into the organ, dividing it into spaces in which we find the peculiar elements of the spleen, the Malpighian bodies, and the splenic pulp. The Malpighian bodies are lymphoid nodules surrounding the walls of the arteries. They are numerous, generally rounded, in places elongated; their structure is identical with that of lymphatic glands. In the pulp the blood-vessels cease to have distinct walls, and break up, the endothelial cells lying loosely together without any definite arrangement. The pulp, therefore, is composed of the endothelial cells of the flayed-out blood-vessels.

Functions. (*a*) The formation of red corpuscles, as evidence of which we have the existence in the spleen of nucleated red cells and the presence of red corpuscles in the protoplasm of some of the splenic cells. (*b*) The destruction of red corpuscles is rendered probable from the presence of pigment granules in the cells. (*c*) The neutralization of toxins. (*d*) The destruction of micro-organisms has been considered one of the functions of the spleen. It is highly probable that the spleen has no such action.

Size and weight. The spleen is 14 cm. long, 9 cm. wide, and 3 cm. thick, and weighs 200 grams, the ratio to the body weight being 1:400 (.25 per cent.).

MORBID PROCESSES.

1. **Fatty Degeneration.**—This occurs in the spleen, but possesses no clinical importance.

2. **Amyloid Degeneration.**—Two forms of this degeneration are described: the *circumscribed* (*sago-spleen*) and the *diffuse.* The former affects the Malpighian bodies, which appear as semi-opaque, grayish nodules on the dark background of the spleen. In the diffuse we have a uniform degeneration of the organ.

Amyloid disease is generally connected with cachectic conditions depending upon chronic suppuration.

3. **Pigmentation.**—This is quite common, and is most marked in malaria, in which the spleen is of a slate color. The pigment is in the pulp and the trabeculæ.

4. **Atrophy.**—This may be produced by symptomatic anemias and by starvation.

5. **Circulatory Disturbances.**—(*a*) *Hemorrhagic or anemic infarction*, the result of embolism, both infarcts occurring with about equal frequency. By their healing, deep scars are produced. If the emboli are specific, the effect will be abscess formation, either a single large, or many small abscesses.

(*b*) *Passive congestion* gives rise to *cyanotic induration* of the spleen, in which we find thickening of the capsule and prominence of the trabeculæ, the organ being firmer and also darker. The cause is generally cirrhosis of the liver or valvular heart disease.

6. **Composite Morbid Processes.**—It is impossible, on account of the absence of the blood-vessel walls, to distinguish between active hyperemia and true inflammation, or between either of these and the acute enlargements in infectious fevers.

I. In infectious diseases the enlargement may be very great; it is sometimes spoken of as *acute splenic tumor.*

Among the most common causes are *malaria* and *typhoid fever.* The spleen is enlarged and darker; the capsule is thinned from stretching, although in malaria, from frequently repeated swellings, the capsule may become thickened; the organ feels harder, but when cut open is really much softer, and, on section, has a peculiar granular appearance from the protrusion of the pulp. The projecting granules can easily be scraped off with the knife; a considerable amount of blood oozes from the surface of section. Under the microscope we find a hyperplasia of all the elements, the lymphoid structure and the splenic tissue proper. There is an increase in the number of lymphocytes, free nuclei, and cells containing red corpuscles, and of the pigment.

In certain infectious diseases, as in scarlet fever and in some cases of typhoid fever, the hyperplasia affects particularly the lymphoid bodies which stand out prominently on section, resembling miliary tubercles. They may be distinguished from the latter by the fact that they are cut through when the section is made, are often irregular in shape, and do not contain the bacillus.

In the acute splenic tumor we may find the micro-organisms of the particular infectious disease, often when they cannot be found elsewhere. This is especially true of anthrax, malaria, and typhoid fever. The micro-organisms may be obtained by tapping the spleen.

II. **Suppuration** of the spleen is the result either of the extension of the suppurative process from neighboring organs or of septic embolism.

III. **Chronic Indurative Splenitis.**—This is most frequently of malarial origin, being the result of repeated acute attacks of the disease. It is termed "ague-cake." There is, histologically, a marked hyperplasia of all the elements of the spleen, with a tendency to the formation of fibrous tissue, particularly in the trabeculæ. The color is very dark, from the presence of an excess of pigment. In some instances the hyperplasia affects especially the tissues of the capsule and trabeculæ; the spleen is then hard, irregular on the surface, and adherent to surrounding structures. The organ may return to normal. The condition of fibroid spleen is comparable to cirrhosis of the liver, and is a later stage of the uniform enlargement. The size, therefore, though still greater than normal, is less than it was primarily.

In the *leukemic spleen* the enlargement may be of the same nature as in malaria, *i. e.*, a hyperplasia of all the elements. At times, however, the lymphoid follicles are especially affected, and, becoming prominent, give to the spleen a *marbled* appearance.

In the uniform leukemic enlargement the spleen has a cherry-wood color; the differentiation from malaria is difficult—it depends upon the presence, in the case of the latter, of pigment and the parasite.

Hodgkin's disease (*splenic anemia*) may be associated with splenic enlargements, like those of leukemia. It is at present difficult to say whether the changes in leukemia and Hodgkin's disease are primary or secondary.

Tuberculosis.—This is not rare in the spleen, and is usually secondary; although occasionally the spleen is the only part affected. There are two forms—(*a*) miliary tuberculosis, and (*b*) caseous tuberculosis. Both, as a rule, are the result of hemic infection, rarely of extension.

Syphilis.—Gummy tumors are rare, as they are in all viscera at the present time. They are multiple, translucent, yellow, encapsulated nodules, and have radiating from them bands of fibrous tissue. The spleen itself is fibroid, and the capsule thickened.

Tumors.—1. *Leukemic* and *pseudo-leukemic enlargements* are sometimes classed as tumors—*lymphadenoma.* 2. *Sarcoma,* generally secondary melanotic sarcoma. 3. *Cancer* is always secondary; the so-called primary cancers are endotheliomata. 4. *Endothelioma.* 5. *Cavernous Angioma.* 6. *Lymphatic cysts.*

Malformations.—The organ may be absent without the health being impaired. When removed from animals and man, other lymphoid tissues, as the bone marrow, become hyperplastic and splenified. Supernumerary spleens are frequent; they may hypertrophy.

THE MEDULLA OF BONE.

The medulla of bone is comparable to a lymphatic gland. It consists of a connective tissue reticulum holding in its meshes lymphoid cells, large cells with large nuclei, and giant cells. Some of the large cells contain red corpuscles; they are especially abundant in acute anemias. Free red corpuscles, with and without nuclei, are also present.

In early life the marrow is red; in the long bones of the adult it is fatty and useless as a blood-forming organ, but in certain

forms of anemia, especially in acute and in pernicious anemia, there is a tendency for it to return to the red or embryonal condition.

Suppuration. In general septic infection the medulla of bone may be involved; suppuration may also begin in the marrow and extend outward.

Changes in the marrow in anemia. In pernicious anemia the marrow often becomes soft and splenified. In leukemia (*myelogenic form*) we may have a uniform hyperplasia, as in the case of pernicious anemia, or a proliferation of the lymphoid elements alone; in the latter case the marrow has a marbled appearance.

CHAPTER IX.

DISEASES OF THE CIRCULATORY ORGANS.

THE PERICARDIUM.

The pericardium is a shining, transparent, serous membrane, forming a closed sac, which normally contains from 30 to 100 c. c. of clear fluid.

Infiltrations and Degenerations.—1. *Fatty infiltration.* This occurs in advancing life, in general obesity, and in certain anemias. It affects chiefly the visceral layer, but may extend into the substance of the heart, into the connective tissue between the muscle fibers. The pressure of the fat causes the muscle fibers to atrophy and to degenerate.

2. *Calcification.* Plates of lime are deposited in fibrous patches, the result of previous inflammation. These patches may undergo fatty degeneration before becoming calcified.

3. *Serous or dropsical infiltration* occurs in conditions of general dropsy. The sac may contain an enormous quantity of fluid, which embarrasses the heart by pressure.

4. *Myxomatous degeneration.* This generally involves the visceral layer, giving to it a swollen, jelly-like appearance.

Circulatory Disturbances.—1. *Hyperemia.* This occurs in inflammations; if intense, it may lead to small hemorrhages.

2. *Hemorrhage.* The causes of hemorrhage are—(*a*) inflammation, (*b*) the purpuric diseases, (*c*) infectious diseases, especially septicemia, (*d*) asphyxia, (*e*) certain forms of poisoning, as by phosphorus. In all of these conditions blood is generally present in the membrane, and also tinges the fluid.

Large quantities of blood may be poured into the sac (*hemopericardium*) in cases of rupture of an aortic aneurysm, and rupture or wound of the heart itself. Death is usually instantaneous; if not, the blood speedily coagulates.

Inflammations.—Four varieties are described: (*a*) serous, (*b*) fibrinous, (*c*) sero fibrinous, and (*d*) purulent.

(*a*) In *serous* pericarditis the sac is filled with a large amount of clear fluid containing only a few flocculi of fibrin, which are easily overlooked. Some fibrin may usually be found on the pericardium, in the grooves between the vessels.

(*b*) In *fibrinous* pericarditis the quantity of fluid is small, but there is a great deal of fibrin; adhesions between the pericardial layers are apt to form. The constant friction between the two surfaces of the membrane causes the fibrin to assume peculiar forms; it may be disposed in ridges or lumps, or in the shape of small, villous-like projections (*cor villosum*). The fibrin is quite firm, and gives to the hand the sensation of the cat's tongue.

The membrane itself is opaque, and dotted over with minute hemorrhages; the fluid is turbid, blood-stained, and contains small flocculi.

The *sero-fibrinous* pericarditis is a combination of the two forms just described.

Microscopy. In the microscopic section we note the deposit of fibrin, a breaking-down as well as a proliferation of the endothelial cells, the presence of leukocytes within the fibrin, and a round-cell infiltration with multiplication of the connective tissue cells in the deeper layers. New blood-vessels are also seen; it is their rupture that is responsible for the small hemorrhages observed in the membrane. The elastic tissue generally marks the point of separation of the new tissue from the normal part of the pericardium.

Terminations. 1. Absorption. 2. The formation of fibrous patches, especially in the visceral layer (*milk spots*). 3. Partial or complete adhesion of the two layers. 4. Calcification.

Milk spots are localized patches of thickening, variable in size, whitish in color, and most frequent in the epicardium. They are

either the result of a simple fatty degeneration or of a previous inflammation, the remains of a localized pericarditis.

Effects of pericarditis on the heart. 1. Mechanical effects, from the pressure of the fluid. 2. Extension of the inflammation to the connective tissue of the heart itself, producing an interstitial myocarditis. 3. The pressure of adhesions and the obstruction offered by them to the heart's action lead primarily to hypertrophy of the heart; later, from interference with the nutrition of the organ, to atrophy.

In *purulent pericarditis* the pericardium is covered with a creamy layer of pus and fibrin. The cavity contains a thick exudate consisting also of pus and fibrin. The micro-organisms reach the heart either through the circulation or by extension from neighboring organs.

Etiology.—Rheumatism, Bright's disease, and infectious fevers are the most frequent causes of pericarditis. Of the last, septicemia and pyemia produce a purulent inflammation; pneumonia usually the sero-fibrinous, occasionally the purulent pericarditis.

Tuberculosis is the result of hemic infection, and is then miliary, or of direct extension from adjacent structures, when it is either miliary or in the form of a diffuse cheesy mass. The tubercles are always best seen toward the base near the root of the large blood-vessels.

Tumors are rare, and practically never primary. The most frequent is the secondary sarcoma, as a rule melanotic. Other tumors are the result of extension of new growths from neighboring organs.

THE HEART.

The weight of the heart at different periods of life is as follows:

At birth	=	21 grams.	16–20 years	=	218–234 grams.
1 year	=	37 "	20–30 "	=	260–294 "
2–5 years	=	50–70 "	30–50 "	=	297–308 "
6–10 "	=	77–115 "	50–65 "	=	318–332 "
11–15 "	=	130–205 "			

After 65, the weight diminishes to 300 grams.

Proportion to body weight	1:175
Length of left ventricle	8–9 cm.
Thickness of left ventricle	7–10 mm.
Thickness of right ventricle	2.5–4 mm.

The heart consists of striated muscle fibers, measuring 70 μ in length and 10 to 15 μ in width, and characterized by an absence of sarcolemma and by the fact that they branch and anastomose. A few non-striped cells exist in the endocardium and valves.

The heart is lined by a serous membrane, the endocardium, consisting of a surface endothelium supported by fibrous and elastic connective tissue. Like the cornea, the endocardium is devoid of blood-vessels; this is also true of the semilunar valves. In the auriculo-ventricular valves vessels extend to within a short distance of the free edge. The lymphatic vessels likewise do not reach to the border of the valves.

The heart is nourished through the coronary arteries, which are filled during *systole*. It is during the heart's contraction that the capillaries are dilated, and therefore best prepared to receive the blood supply.

Hypertrophy.—This is a common condition, and is generally a consequence of an increase in the work of the heart. From an anatomic standpoint, five kinds of hypertrophy may be distinguished. (*Figure a* represents the normal heart.)

1. *Concentric hypertrophy.* (*Fig. 1.*) This is exceedingly rare, and is characterized by a diminution in the cavity of the heart and an increase in the thickness of the wall.

2. *Simple, or pure hypertrophy.* (*Fig.* 2.) In this the cavity is of normal size, but the muscular wall is thickened. It is a transitory stage, rarely seen at autopsy.

3. *Hypertrophic dilatation.* (*Fig.* 3.) This is the commonest form of hypertrophy—the wall is increased in thickness and the cavity is enlarged.

4. *Dilated hypertrophy.* (*Fig 4.*) This is a further stage, and is characterized by dilatation of the chamber, with a muscular wall which is thinner than that of hypertrophic dilatation, being about the thickness of the normal muscle.

5. *True dilatation.* (*Fig. 5.*) The cavity is enlarged, and the wall is thinner than normal. Since the muscular wall has to surround a very large cavity, there is even here some hypertrophy.

From the functional standpoint we may divide hypertrophies into the *sufficient* and the *insufficient.* The first four varieties may be sufficient, the last three insufficient. The first two are always sufficient; the fifth is always insufficient. The possible insufficiency of the third and fourth is due to degenerative changes in the cardiac muscle.

The hypertrophy, although it affects to a certain extent all cavities, is not uniform, but usually involves one cavity more than the others—as a rule, the left ventricle. The auricles may be hypertrophied, generally in association with ventricular hypertrophy.

When the *left ventricle* is hypertrophied the heart preserves its shape, but is lengthened downward in the direction of the apex. When the hypertrophy is in the right ventricle the heart becomes globular in outline. Dilatation also imparts to the heart a globular shape.

Histologically, the hypertrophy affects all the structures of the heart. In the muscle the hypertrophy is chiefly *numerical,* but there is also a slight degree of simple hypertrophy.

Etiology.—1. *Mechanical interference from without,* as pressure from an adherent pericardium or from tumors. The hypertrophy is not marked, and is soon succeeded by atrophy.

2. *Mechanical defects in the valvular apparatus.* The hypertrophy involves different chambers according to the seat and nature of the valvular lesion.

The greatest hypertrophy is seen in obstruction and insufficiency of the aortic valve. The heart may weigh 1000 grams or more. The left ventricle is especially affected.

3. *Disturbances of the general circulation,* increasing the resistance against which the heart has to pump. (*a*) Arterio-sclerosis; (*b*) aneurysm.

4. *Disturbances of the pulmonary circulation.* (*a*) Congenital defects; (*b*) diseases of the lung, as emphysema, fibroid phthisis; (*c*) disturbances in the pulmonary circulation from disease of the left side of the heart. In all of these the right ventricle is especially hypertrophied.

5. *Idiopathic causes,* as nervous palpitation (exophthalmic goiter); exercise. The latter cause, *i. e.,* exercise, might also be classified under disturbances of the general circulation.

Causes of dilatation. Although in hypertrophy the coronary arteries share to a certain extent in the enlargement, becoming

longer and wider, the increase in size is insufficient to supply the heart with blood. At the same time, the coronary veins empty themselves with difficulty into the right auricle, and the blood is dammed back in the heart. There is generally also a sclerotic process in the coronary arteries diminishing their caliber. All these causes favor degeneration of the heart muscle and consequent dilatation. Hypertrophy, we may therefore say, always carries the danger of dilatation with it.

Atrophy.—The heart becomes smaller, darker, and firmer; the pericardial vessels are prominent and tortuous, the endocardium and pericardium thickened.

Causes. (1) Continued pressure, as from pericardial adhesions. (2) Senility. (3) Starvation. (4) Constriction of the auriculo-ventricular orifice, causing a relative atrophy of the corresponding ventricle. (5) Passive congestion. (6) Sclerotic endocarditis, with extension of the sclerotic process to the heart. This acts analogously to pericardial adhesions. (7) Congenital hypoplasia, as in some cases of chlorosis.

Brown atrophy is the result of long-continued passive congestion. Pigment granules are deposited about the poles of the muscle nuclei; the connective tissue is hyperplastic.

Infiltrations.—1. *Fatty.* This takes place between the muscle fibers and occurs in obesity and in pernicious anemia. It may lead to fatty degeneration by pressure on the fibers.

2. *Pigmentary infiltration*—in cyanotic atrophy; after hemorrhages. The pigment is deposited about the poles of the nuclei.

3. *Calcification* is most common in the valves; it may occur at the auriculo-ventricular rings, and between as well as in the muscular fibers.

Degenerations.—1. *Amyloid degeneration* affects the connective tissue of the blood-vessels.

2. *Fatty degeneration* is the most important degeneration. It begins as cloudy swelling, especially when due to acute conditions, as fevers or acute anemias. The muscle is softer, friable, slightly opaque, brownish or yellowish-brown in color. The process is best marked just beneath the endocardium of the left ventricle, where it presents itself as pale yellowish striæ. At times the fatty degeneration is uniform. In some cases it produces no change in color.

Microscopy. The muscle fiber becomes filled with fine granules which are albuminous at first and obscure the striation. They are

soluble in acetic acid. Later they become fatty, arranging themselves in longitudinal rows, parallel with the axis of the fiber. Finally, the whole fiber passes into fat.

Causes. (1) Poisons—chloroform, phosphorus, arsenic. (2) Toxins of acute infectious diseases. (3) General anemia. (4) Disturbances of the cardiac circulation, usually from excessive hypertrophy. In great enlargement the heart never completely empties itself, hence, the capillaries are never perfectly filled; the veins also are not fully emptied; and in addition we have the sclerosis of the coronary arteries.

3. *Waxy degeneration.* This is a form of hyaline degeneration at times met with in infectious diseases, particularly in typhoid and typhus fever. The muscle fibers first suffer cloudy swelling, then, instead of passing to fatty change, become opaque and waxy. In other instances, in these fevers, we have the ordinary fatty degeneration.

4. *Hyaline degeneration* is seen in the connective tissue of the arteries in old age; it may attack the capillaries in acute infectious diseases.

Circulatory Disturbances.—1. *Hyperemia and anemia.*

2. *Embolism and thrombosis.* Thrombosis is more common than embolism, being favored by atheromatous changes in the coronary arteries. Emboli lodge most frequently in the anterior coronary artery. Both processes lead to infarction, either hemorrhagic or anemic, generally the latter. The infarct softens (*myomalacia cordis*, or *cardiomalacia*) and, if extensive, the heart may *rupture.* If rupture does not occur, the infarct is replaced by a *scar;* the latter may yield and give rise to an *aneurysm.*

Inflammation—Myocarditis.—Parenchymatous degeneration (cloudy swelling) which occurs in acute infectious diseases, is sometimes termed *parenchymatous myocarditis*, but should only be so considered when accompanied by the vascular changes pertaining to true inflammation.

Suppurative myocarditis is secondary to suppuration elsewhere in the body. We may have a single large abscess or many small abscesses. *Causes.* (1) Extension from neighboring structures, as the pericardium or the endocardium. (2) Septic embolism.

The possible results are the same as in cardiomalacia from infarction.

Interstitial myocarditis. (1) This may be *localized*, the result of a regenerative process following abscess, infarct, or wound of the heart. (2) It may be diffuse, being a part of a general sclerotic process affecting the entire vascular system. (3) It may be due to extension of chronic inflammation from the endocardium or pericardium.

As a result of the chronic inflammation the muscle fibers are pressed upon and atrophy—we may then have rupture of the heart or the formation of an aneurysm.

THE ENDOCARDIUM.

Endocarditis is of three varieties: (*a*) verrucose, or warty; (*b*) ulcerative, and (*c*) sclerotic. The first two are acute, the third often begins acutely, but pursues a chronic course.

(*a*) *Warty endocarditis* affects especially the left side of the heart, attacking the mitral and aortic valves with nearly equal frequency. The valve, particularly at the "line of contact," loses its luster and becomes somewhat thickened and granular in appearance, or it may be the seat of a number of warty projections. From the line of contact the process may extend along the valve to the endocardium of the heart or, in the case of the aortic valve, to the intima of the aorta.

The process begins with a rapid formation of fibrin, which in the first place results from a coagulation necrosis of the endothelial cells and the fluid exudate from the valve. There is also a proliferation of the endothelial and connective tissue cells leading to a round cell infiltration of the base of the projections. Secondarily, there is a deposit of fibrin from the blood upon the roughened surface. This deposit is somewhat laminated and can readily be removed.

Terminations. (*a*) Resolution. (*b*) Organization of the cellular exudate and scar-formation.

Etiology. It is probable that bacteria are always the cause of warty endocarditis, although none are found as a rule, very likely because the cases are examined long after the process has started. The disease can be produced by the injection of certain microorganisms which are the same as those causing ulcerative endocarditis. A comparison may be drawn between warty endocarditis and croup, on the one hand, and ulcerative endocarditis and

pharyngeal diphtheria, on the other. In warty endocarditis, as in croup, the process is superficial; while in ulcerative endocarditis and in pharyngeal diphtheria, it is deep.

The disease occurs at all ages, and most frequently in males, involving, in the order of frequency, the mitral, aortic, and pulmonary valves. The most common causes are rheumatism, chorea, and infectious diseases, as pneumonia and diphtheria.

(*b*) *Ulcerative, destructive, diphtheritic, or malignant endocarditis.* (The name mycotic was applied at a time when the warty form was considered not to be of bacterial origin.)

Macroscopy. The naked-eye appearance varies from a simple opacity and slight roughness to the most extensive destructive process. We find excavated ulcers, with ragged edges; perforation of the valves; acute aneurysms of the valves or the heart wall; abscesses; involvement of the heart itself.

Four varieties are distinguishable: (1) *Endocarditis polyposa.* In this the deposit of fibrin is abundant and forms polypoid masses. (2) *E. villosa*—a name given when the projections are small. (3) *E. ulcerosa*—when ulcers are present. (4) *E. pustulosa* is applied when there are small abscesses. The process begins at the line of contact of the valves and extends to the base, and thence in the direction of the circulation, as, *e. g.*, from the anterior mitral leaflet to the aortic valve, and from this to the intima of the aorta.

Embolism is common, particularly in the skin, where it leads to hemorrhages.

Microscopy. We have the formation of a granulation tissue which has a tendency to undergo coagulation and liquefaction necrosis. The large accumulation of round cells in a valve deficient in blood-vessels and having but little connective tissue, can only be accounted for by a cell-formation from dormant cells (*Schlummerzellen*), the stimulus to which is given by the micro-organisms. Dense masses of bacteria are present in the affected area. Besides the evidences of necrosis we find minute hemorrhages in the valves from the rupture of newly-formed blood-vessels.

Etiology. The causes are as a rule the ordinary pyogenic micro-organisms, especially staphylococcus pyogenes aureus and streptococcus pyogenes; the pneumococcus and the gonococcus have also been found.

How do the micro-organisms reach the heart? In some cases the disease is secondary to a pyogenic process elsewhere in the

body, but usually it is a primary affection, engrafted, in the majority of cases, upon a valve the seat of chronic endocarditis. The micro-organisms are probably brought in the general circulation and not by the branches of the coronary arteries. The latter sometimes happens, however, the embolus lodging at the base of the valve, where the process then begins.

The line of contact is especially subject to lesions, and as a rule the bacteria are first deposited there from the blood passing over the valve.

(*c*) *Sclerotic endocarditis.* This may be (*a*) *a local regenerative process*, either the formation of a scar, following wound, abscess, or infarct of the heart, or the final step in the other forms of endocarditis. More commonly it is (*b*) *a primary chronic inflammation*, progressive in character, with an attempt to form new connective tissue. It occurs as a part of a general sclerosis affecting the arterial system and certain organs, as the liver and kidney, and is not confined to the valves but may involve the endocardium of any part of the left ventricle.

Macroscopy. The appearance varies from a slight thickening and bulging at the line of contact or on the body of the valve, to enormous thickening, contraction, and puckering of the valve, with constriction of the ring in which it is inserted.

These changes bring about the ordinary valvular heart disease, the lesions being such as either cause *obstruction* or *insufficiency* of the valves.

The papillary muscles and chordæ tendineæ may also be greatly thickened.

Microscopy. The structural changes depend upon the formation of granulation tissue in the fibrous layer of the endocardium. The newly-formed blood-vessels as well as any pre-existing ones are the seat of proliferation (in the intima) and become obstructed. As a result of the malnutrition the new tissue undergoes fatty degeneration, the affected area becoming yellowish-white. This degeneration is termed *atheroma.* When calcification occurs in the fatty area an *atheromatous plate* is produced. The degenerated tissue may also break down into an emulsion, which may be discharged into the blood, an *atheromatous ulcer* remaining.

Sclerotic endocarditis affects especially the left side of the heart, and to a certain extent seems to be physiologic in old age.

Rupture of the heart occurs most commonly in the center or toward the apex of the left ventricle. The causes are infarcts, abscesses, interstitial myocarditis, aneurysm, and traumatism.

Tumors. The primary tumors are fibroma, lipoma, and rhabdomyoma. Among secondary tumors, which are more frequent, we have sarcoma, especially melanotic, and carcinoma.

Malformations. The most frequent are defects in the septa, usually a patulous condition of the foramen ovale; at times also imperfection in the interventricular septum. Fenestration of the valves is not rare and is apparently an attempt at the formation of chordæ tendineæ in the semilunar valves. We may have constriction of the large vessels, especially the pulmonary artery.

Valvular lesions of the right heart are often met with at birth. They are not to be considered malformations, but as the results of endocarditis during intrauterine life, during which the right heart has the most work to perform.

Tuberculosis is rare in the heart. It may be miliary, affecting the endocardium of the right side especially, or it may be a caseous tuberculosis, the result of extension from neighboring organs through the pericardium.

Syphilis. Gummata are met with but are rare.

THE BLOOD-VESSELS.

An artery has three coats—the intima, the media, and the adventitia. The *intima* consists of an internal layer of long *endothelial cells* arranged longitudinally; outside of this is a delicate fibrous connective tissue containing stellate cells—the *subendothelial layer.* The outermost part of the intima is made up of elastic tissue, appearing in transverse section as a distinct corrugated membrane, the *internal elastic membrane.* In the larger vessels this is fenestrated. The *media* consists chiefly of unstriped muscular tissue. The *adventitia* is made up of areolar and fibro-elastic tissue, and is the most resistant of the three coats.

Functions. 1. Arteries are channels for the blood, but by reason of their contractile property, which is under the influence of the nervous system, they control to a large extent the amount of blood passing through them. The demand of the organ receiving the supply has much to do with the variations in caliber.

2. The endothelial cells have specialized properties; they are not merely filtering-cells, but have what might be termed a selective action.

The Pulse.—In a pulse-tracing taken with the sphygmograph, three main waves are recognizable. The first, *the inertia*, or *percussion wave*, ordinarily the highest, is due to the ascent of the lever, which, by the sudden impulse given to it, is carried beyond the point which it would reach if it were merely lifted by the gradual dilatation of the artery. After the lever has fallen, it is again lifted by the true expansion of the artery, produced by the influx of the blood—this gives rise to the second, or *tidal wave*. The third wave is due to the closure of the aortic valve, and is known as the *recoil*, or *aortic wave*. The remaining portion of the tracing is termed the *wavy remainder*, and is made up of a number of small, *secondary* waves.

When the artery is yielding, in other words, when tension is low, as in fevers, all waves are well marked; when the artery is tense—high tension—the first wave may be absent, the apex being flat. In aortic insufficiency, the recoil, or aortic wave is absent.

Diseases of the Arteries. Hypertrophy occurs (*a*) in the establishment of collateral circulation; (*b*) in conditions of excessive blood-pressure.

Atrophy.—Atrophy of arteries is seen (*a*) in atrophic organs, (*b*) in the stumps remaining after amputation, (*c*) in conditions of wasting, as, *e. g.*, in tuberculosis. But while the general emaciation in tuberculosis may account in part for the atrophy, it is probable that there is often an under-development of the large vessels in persons susceptible to the disease.

Infiltration.—*Calcification* occurs in the intima and media as a frequent part of the atheromatous process, being preceded by fatty degeneration. It presents itself as minute granules in the fibrillar layer of the intima and in the connective tissue and, at times, in the muscle cells of the media.

Degenerations.—1. *Amyloid degeneration* is most common in the smaller arteries, affecting first the connective tissue of the media. In the larger vessels it occurs in the intima and media. It is most frequent in the glomeruli of the kidney.

2. *Fatty degeneration.* This is very common and involves the fibrillar layer and endothelium of the intima; in the media the

muscle cells are affected. To the naked eye it presents itself as opaque whitish patches.

Causes. (*a*) Poisons—as phosphorus; chloroform. (*b*) Acute infectious diseases. (*c*) Sclerotic arteritis, in this giving rise to the process termed atheroma. (*d*) Poisons the result of faulty metabolism.

3. *Hyaline degeneration.* This is a frequent process, being an early stage of arterio-sclerosis. It affects the connective tissue, first of the intima, then of the media, causing in the latter atrophy and disappearance of the muscle cells. In the capillaries it appears as minute, glassy, shining beads or globules just outside of the endothelium; in the larger vessels it produces a homogeneous appearance. As a local process it is common in the ovary. Hyaline material stains well with eosin.

Causes. (*a*) It is a part of the atheromatous process, preceding fatty degeneration. (*b*) It may be produced acutely by infectious diseases.

Inflammations.—1. *Acute purulent arteritis.* This corresponds to the pustulous form of ulcerative endocarditis. Its causes are (*a*) extension from without, which gives rise to periarteritis, (*b*) septic embolism or thrombosis, leading to an endarteritis, (*c*) in the aorta, extension of the suppurative process from ulceration of the endocardium.

2. *Acute productive arteritis, thrombo-arteritis,* or *obliterating endarteritis.* This is analogous to verrucose endocarditis. It begins in the intima, but may extend to the other coats, and is characterized by the formation of new connective tissue. As a rule it is started by a thrombus, into which, as a framework, the newly-formed tissue and blood-vessels project, the process usually terminating in complete obliteration of the artery. This at least is true of the smaller arteries. In the larger vessels there is generally not complete occlusion, but only a patch on one side or an annular constriction. New vessels permeate the thrombus in about twelve days after its formation.

The best example of thrombo-arteritis is that following ligation of arteries.

Obliterating endarteritis is seen in the healing of arteries in wounds, after ligation, after occlusion of arteries by non-specific emboli, and in organs the seat of great hyperplasia of the connective tissue, as in cirrhosis of the liver or the kidney.

3. *Sclerotic endarteritis*, or *arterio-sclerosis*. This is comparable to sclerotic endocarditis, and gives rise to a gradual thickening of the intima, either diffuse or circumscribed. The diffuse form is to a certain extent physiologic in advanced life. The localized form causes circumscribed swellings of the intima which are at first translucent, later firmer and opaque, and yellowish-white in color, and become visible to the naked eye as plates. Still later the patches become infiltrated with lime, or they may break down and discharge into the artery leaving ulcers.

In the stage of translucency we have *hyaline degeneration* of the intima; the opacity and the yellowish-white color are due to *fatty degeneration* (cholesterin plates may be deposited); the hardening is due to *calcification;* the breaking-down to *liquefaction necrosis.* The ulcer may become the seat of thrombosis—a thrombo-arteritis follows, with eventual cicatrization of the ulcer.

As a rule we find all the processes going on in the arteries at the same time.

It is customary to term arterio-sclerosis atheroma; this is not correct since atheroma defines only one stage of the process, viz., the fatty degeneration, and leaves out of consideration the inflammatory element.

Microscopy. The process begins in the fibrillar layer of the intima, close to the media, and gives rise to a very marked swelling of the inner coat, usually on one side of the artery. Hyaline degeneration sets in and causes a disappearance of the nuclei, the affected region becoming homogeneous. As the process advances minute granules appear in the area—some are fatty in nature, others albuminous. They are the result of a degeneration, either of the hyaline material or of the cells spared by the hyaline change. The hyaline material now breaks up into lamellae. As the disease progresses there is a tendency for the accumulation of fatty detritus in certain large areas, often with the deposit of cholesterin plates. These areas appear as yellowish spots visible to the naked eye. They finally break down and are discharged into the lumen of the vessel, leaving the so-called *atheromatous ulcers.*

In addition to these degenerative changes the process of arterio-sclerosis presents as a very important feature, evidences of *proliferation of the connective tissue.* We find an accumulation of round cells about the degenerated area; new blood-vessels, coming from the vasa vasorum, are seen to push into the round cell infiltration

in the intima. The media and adventitia are also the seat of cell proliferation, with the production of dense fibrous tissue. The vasa vasorum of the adventitia are involved in the sclerotic process—the diminution in the blood-supply thereby produced, accounts in part for the degeneration of the wall of the blood-vessel.

As a rule the cell proliferation in the intima does not succeed in forming new connective tissue, although this may occur in syphilitic sclerosis.

Sclerosis is common in advanced life. It is more frequent in certain sections of the country than in others; it is, for instance, more marked along the coast of North and South Carolina than elsewhere; perhaps this is connected with an excessive use of fish as food (Professor Guitéras). The negro race is especially liable to sclerosis.

Pathogenesis. The process begins in one of two entirely different ways.

(*a*) It is *a primary process of degeneration* of the arteries, such as we find in other organs, being the result of the action of poisons, as alcohol and the infectious diseases. It may, for example, follow measles or scarlet fever, especially when either occurs in advanced life. The poison produces a hyaline degeneration of the vessel; this is then followed by the other degenerative changes. As the degenerated material requires removal, an inflammatory process is developed.

(*b*) The process may originate from *minute tears* in the vessels *the consequence of a loss of elasticity.* It has been found, especially by Thoma, that arteries lose their elasticity before they show sclerosis. If we examine the arteries from a body in which there is sclerosis of the aortic arch, we may find neither macroscopic nor microscopic changes in the other arteries, although it was, *a priori*, to be supposed that they should present an earlier stage of the process. We can demonstrate, however, a *functional* change—the arteries stretch more readily than normal vessels.

The loss of elasticity is as yet not explained, but as a result of it we very likely have minute tears in the intima, or in the connective tissue of the media, due to sudden changes in pressure. In these tears the inflammatory process is started. It extends to the vasa vasorum, leads to defective blood-supply of the arterial wall, and, secondarily, to degeneration.

The loss of elasticity is in the early stages compensated for by an *hypertrophy of the muscular coat,* which, together with the

hyperplasia of the connective tissue, leads to an increase in the resistance to the circulation. The last manifests itself, clinically, as high arterial tension, and gives a characteristic pulse-tracing.

Seats. The process is most marked in arteries subject to sudden changes in pressure, in those not well protected, and in those with but few branches. Most frequently affected are the arch of the aorta, the thoracic and abdominal aorta, the splenic, iliac, femoral, and coronary arteries, and the vertebral inside of the cranium. The pulmonary and mesenteric arteries are very rarely the seat of sclerosis.

Causes. Among the clinical causes are named senility, alcohol, probably syphilis, rheumatism, gout, and heredity.

Effects. The effects of sclerosis are narrowing or occlusion of the artery, rupture, aneurysm.

Syphilitic Arteritis.—This may occur diffusely, affecting all the arteries of an organ, or locally, in the true syphilitic lesions, the gumma and chancre. It is characterized by a *great proliferation of cells, without any marked tendency to degeneration.* The *intima* and *adventitia* are especially affected; the media remains passive, and degenerates in the later stages. In the intima and adventitia the process may go on to the formation of fibrous tissue. This form of sclerosis is not absolutely characteristic of syphilis, but if we find all the vessels of an organ so affected, we may infer, but not positively predicate, syphilis. The process is most common in the brain. The vessels appear like fibrous cords.

The ordinary sclerosis with atheroma can, of course, also occur in a syphilitic subject.

Tuberculous Arteritis.—This involves especially the adventitia, being the result of extension from neighboring structures. We find tubercles in the adventitia, usually on one side only, with giant cells and cheesy degeneration; the intima and media at the same level present a round cell infiltration. The effects of tuberculosis are miliary aneurysms or, more commonly, erosion and rupture of the arteries.

Periarteritis Nodosa.—This is rare and not well understood. It gives rise to the appearance of nodules on the adventitia, which are either inflammatory masses or minute aneurysms filled with clots. The mesenteric and muscular arteries are the seats of the process.

ANEURYSM.

An aneurysm is a circumscribed dilatation of a blood-vessel. There are three varieties of aneurysms: (1) the ectatic, (2) the saccular, and (3) the dissecting.

(1) *Ectatic aneurysm.* This is simply a dilatation of the vessel, the wall consisting of all the arterial coats. Three forms are described: (*a*) the *fusiform;* (*b*) the *cylindrical,,* and (*c*) the *cirsoid.* In the last the dilatation goes around the vessel in a spiral manner.

(2) *Saccular aneurysm.* This is a localized dilation of the vessel wall and consists of a sac communicating with the vessel by a narrow neck.

Varieties. (*a*) *True*—one consisting of all the coats of the vessel. (*b*) *False*—one in which one or more of the coats are absent, the wall being usually made up of the adventitia, or part of it, and newly-formed connective tissue.

True saccular aneurysm may be single or miliary, the latter being common in the vessels at the base of the brain.

Varieties of false aneurysm. (α) *Simple.* This is the most frequent form and consists of a sac made up of adventitia or of newly-formed tissue, or of both.

(β) *Varicose aneurysm.* This is an aneurysm communicating with a vein.

(γ) *Aneurysmal varix.* This is produced by the opening of an artery into a varicose vein. The latter pulsates.

(δ) *Arterio-venous aneurysm.* In this we have a simultaneous injury of an artery and a vein, the blood from both being poured into the surrounding tissues.

(3) *Dissecting aneurysm.* This is produced by a rupture of the inner coats of an artery, the blood finding its way between the intima and adventitia. After separating the tunics for some distance, the blood breaks either through the inner coat into the vessel, or outside into the surrounding tissues. Dissecting aneurysm is most common in the aorta, beginning at the junction of the ascending and transverse portions of the arch; it generally dissects backward and ruptures into the pericardium.

Causes of Aneurysms.—(1) Arterio-sclerosis with atheroma is the commonest cause. (2) Inflammatory processes affecting the arteries from the outside, as tuberculosis. (3) Changes within the vessels, as embolism. This is sometimes the cause of

splenic aneurysm, although it is probable that the walls of the artery are primarily diseased. The embolus may be a parasite, as in aneurysm of the mesenteric arteries of the horse. (4) Traumatism—this usually causes a false aneurysm.

Changes produced by aneurysms. Prominent are the pressure symptoms. Pressure in the early stages causes hyperplasia, later atrophy, of the surrounding structures. This is seen best in bones, as the sternum, ribs, or vertebræ.

Healing of an aneurysm is not common. Thrombosis is frequent in the sac, but the space to be filled is so large that occlusion is not successful as long as the sac communicates with the artery, owing to the constant current of the blood. After ligation, healing may take place, the clot becoming organized by a process of thrombo-arteritis.

Seats. (*a*) Of large aneurysms: arch of the aorta, popliteal and femoral artery, abdominal aorta, carotid and subclavian artery. (*b*) Of miliary aneurysms: the vessels at the base of the brain, the pulmonary arteries.

The Veins.—The veins present changes analogous to those found in arteries, but being more elastic and yielding, and less subject to sudden distention, they are less liable to sclerosis.

Phlebitis. Suppurative Thrombo-phlebitis.—Acute inflammation of the veins is generally suppurative, and is the result of extension of suppuration from neighboring organs. The perivascular lymph spaces are first involved, the process extending from them to the veins. A thrombus forms within the vein; as it softens, emboli are carried in the circulation and produce pyemia.

Phebectasia, Varix, or Varicose Veins.—This varies from slight to very marked degrees of dilatation. The vessels become elongated and tortuous, and small veins become prominent; the walls are thickened, and there is also a hyperplasia of the surrounding connective tissue.

Causes. 1. Mechanical disturbances in the venous circulation, as pressure from without (tumors), inflammation of the walls, thrombosis.

2. Failure of the cardiac circulation, the result of the degenerative processes of advanced life. This may not be sufficient until aided by a slight local disturbance in the veins.

3. Want of muscular exercise, favoring especially varicose veins of the lower extremities.

4. Gravity—this is a factor in varix of the lower parts of the body.

5. Some congenital defect in the walls of the veins, a condition that may be transmitted in families.

6. Race. The white race is more often affected with varicose veins than the colored.

Seats. Varix is most common below the bifurcation of the two common iliacs, and may involve, particularly when due to intra-pelvic pressure, the veins of the broad ligament, labia, bladder, and prostate, the spermatic veins, the hemorrhoidal veins, and the veins of the lower limbs.

Hemorrhoids, or piles, are produced by general disturbances in the circulation, by pressure of pelvic tumors, by cirrhosis of the liver, and by constipation, and in structure differ somewhat from ordinary varicose veins. In the latter we have dilated parts with intervening healthy tissue; in hemorrhoids the dilatations are so close together as to resemble cavernous angioma. Septic infection about hemorrhoidal veins is common; tuberculous abscesses may form and lead to fistulæ.

Complications of varix. (1) Rupture and bleeding, especially in the case of hemorrhoids. (2) Inflammation about the veins, either chronic with thickening, or acute. The thickening may give rise, in the lower extremities, to *varicose elephantiasis.* In association with this, and also without it, we may have *varicose ulcers.* (3) Thrombosis is common—it may lead to thrombo-phlebitis. The clot may become infiltrated with lime and constitute a *phlebolith,* or *veinstone.*

Tumors. Both arteries and veins may become involved from the outside; sarcoma is especially apt to grow along the blood-vessel.

If the tumor spreads from other tissues, it is much more apt to affect the veins than the arteries. This is seen very plainly in the portal vessels, where in certain cases the tumors can be observed to project into the lumen of the veins. Whenever there is metastasis to the lung from cancer of the stomach or liver, we find such projections in the portal vessels.

Phleboliths, or veinstones, are calcareous nodules formed in the interior of veins, and represent calcified thrombi.

THE LYMPHATIC VESSELS.

Lymphangitis and **Perilymphangitis** are the result either of extension or of embolism, and, pathologically, do not differ from inflammation of other vessels.

Lymphectasia.—This is common in the lower extremities, especially in elephantiasis. It is also seen in the mesentery, where it gives rise to an appearance resembling miliary tuberculosis. The mesentery is dotted over with whitish nodules, which when cut exude a little fluid. Similar nodules are found in the lung and pleura, and are here the result of pressure upon the lymphatics by tumors or by an hypertrophied heart. The effects of the compression may manifest themselves also in the liver, where the condition bears such a close resemblance to miliary tuberculosis that only the microscope can at times decide.

Metastasis of cancer is common along the lymphatic vessels. *Endothelioma* is most frequent in serous cavities. The serous cavities are to be looked upon as huge lymphatic spaces.

CHAPTER X.

DISEASES OF THE NERVOUS SYSTEM.

The weight of the brain is in man about 1350 grams, in woman, 1220 grams. The brain is covered by three membranes, the dura, the arachnoid, and the pia. The *dura* consists of an outer periosteal and an inner serous layer. In children it is adherent to the calvarium and has to be removed with it; in adults it is normally unattached. The *arachnoid* is a delicate membrane which has no relation to the dura, but is connected with the pia by means of fibrous bands. It does not dip down into the sulci, but passes over them. The *pia* closely invests the entire surface of the brain and contains the blood-vessels nourishing the cortex. It dips down into the fissures, carrying the vessels with it. The relation of these vessels is indicated in the diagram, viz., from above downward, vein, artery, vein. Between the arachnoid and the pia is the subarachnoid space containing cerebro-spinal fluid.

The blood-vessels of the brain are divisible into two groups, the cortical and the central or basilar. The former supply the cortex; they are terminal vessels and are often the seats of embolic processes. The central arteries nourish the ganglia and other structures at the base of the brain. Being small and coming off directly from the large vessels of the circle of Willis, they are subject to great pressure, and in consequence are often the seat of atheroma and miliary aneurysms, as well as of rupture.

ANATOMY AND PHYSIOLOGY OF THE BRAIN.

But few words can be devoted to this subject in this place. It should be recognized, however, that a study of diseases of the brain as well as the localization of lesions is impossible without a thorough knowledge of the anatomy and physiology of the organ.

The brain consists of the cerebrum, cerebellum, pons, and medulla oblongata, the last being, physiologically, a part of the spinal cord. The cerebrum, which chiefly concerns us, is made up of two symmetrical halves, each consisting, in a general way, of a cerebral mantle and basal ganglia. In the center of the brain we have a series of communicating cavities, the *ventricles*. The cerebral mantle is thrown into a number of folds or convolutions of which the most important are the following: the ascending frontal and ascending parietal, which constitute the main motor area; the posterior extremity of the third left frontal convolution which together with the lowest portion of the ascending frontal represents the center for voluntary speech; the occipital convolutions, particularly the cuneus, in which the center for psychic vision is situated; the superior temporo-sphenoidal convolution, the center for hearing; the uncinate gyrus, the center for olfaction.

At the base of the brain, projecting into the ventricles we have two important ganglia, the corpus striatum and the optic thalamus, the former being composed of two parts, the caudate nucleus and the lenticular nucleus.

Projecting upward from the pons, and connecting the cerebrum with the remainder of the nervous system, is the crus cerebri, or cerebral peduncle. This enters the base of the brain and passes upward between the basal ganglia as the internal capsule. The internal capsule consists of an anterior and a posterior limb which join at an angle, termed the *knee*. The anterior limb is bounded on the outer side by the lenticular nucleus, on the inner, by the

caudate nucleus. The posterior limb lies between the optic thalamus on the inner, and the lenticular nucleus on the outer side. The lenticular nucleus is situated on a lower level than the other nuclei, and is, in a sense, covered over by the internal capsule, so that a horizontal section of the brain would first uncover the caudate nucleus and optic thalamus, and on removing a portion of these, the internal capsule would be exposed. If the latter be folded toward the mesial surface like a flap, the lenticular nucleus comes into view.

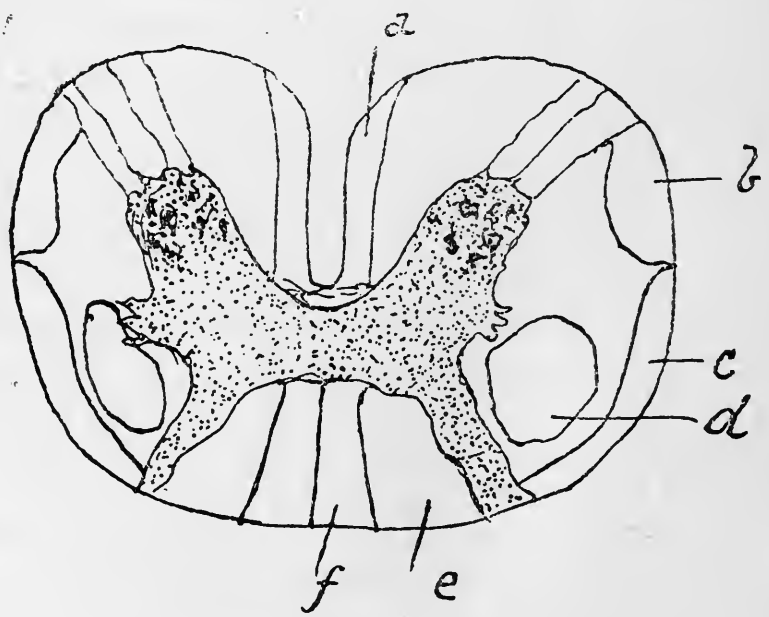
In the knee and the anterior two-thirds of the posterior limb of the internal capsule we find the motor fibers carrying impulses to the muscles of the opposite side of the body. The posterior third of the posterior limb gives passage to sensory fibers.

The crus cerebri, the continuation of the internal capsule, consists of two chief parts, an upper, or *tegmentum*, carrying sensory fibers, and a lower, or *crusta*, composed mainly of the motor tracts.

The upward expansion of the internal capsule is known as the corona radiata—it spreads out like a fan and goes to almost every part of the cortex.

ANATOMY AND PHYSIOLOGY OF THE SPINAL CORD.

The spinal cord has a covering corresponding to that of the brain, but the dura does not form the periosteum of the vertebræ.



In the white matter of the cord the following physiologically distinct tracts can be made out:

1. Anterior or direct pyramidal tract (*a*).
2. Lateral or crossed pyramidal tract (*d*).
3. Postero-lateral tract, or column of Burdach (*e*).
4. Postero-median tract, or column of Goll (*f*).
5. Direct cerebellar tract (*c*).
6. Antero-lateral or Gowers' tract (*b*).

The lateral limiting tract is a narrow band of fibers bordering on the gray matter, between the anterior and posterior horns.

The anterior and crossed pyramidal tracts are descending, or motor; the tracts of the posterior column and the direct cerebellar tract are ascending, or sensory tracts. The antero-lateral tract is not well understood, but is supposed to be ascending in character.

DISEASES OF THE MEMBRANES.

Bone.—The skull should always be examined for tuberculous or syphilitic bone disease. The distinction between the two is difficult, but tuberculous lesions are generally funnel-shaped, with the widest part toward the periphery, and occur more frequently in the calvarium; syphilis is more common at the base. At times the microscope alone will serve to determine the nature of the lesion.

Dura.—1. *External ossifying pachymeningitis* generally involves the bone as well as the outer layer of the dura, and is usually connected with tuberculous, syphilitic, or other inflammatory disease of the cranium. Osteophytes and exostoses are produced.

2. *Purulent pachymeningitis* is due to pyogenic organisms which as a rule reach the dura by extension from neighboring parts, as the middle ear, or through wounds in the skull.

3. *Thrombosis* is most common in the large sinuses, and is generally the result of extension of a suppurative process either from the bone (middle ear disease) or from the interior of the brain. The clots may soften and lead to pyemia.

The lesions of the internal layer of the dura are the following:

1. *Tumors*. Tumors are more frequent in the dura than in other parts of the brain, sarcoma being the most common form.

2. *Syphilis*—gummata.

3. *Tuberculosis*—tubercles.

4. *Internal ossifying pachymeningitis*. This is an inflammation affecting especially the falx cerebri, the newly-formed tissue being

Brain.

Bone

Tumors, Syphilis, Tuberculosis } **Dura** — **Ext. Ossifying Pachymeningitis** — { **Purulent Pachymeningitis, Thrombosis**

Int. Ossifying Pachymeningitis

Internal Hemorrhagic Pachymeningitis

Inter-Meningeal Hemorrhage

Hematoma
Hygroma

No Exudative Process on Arachnoid

Arachnoid

Edema | **Vacuum Dropsy** | **Acute Arachnitis or Leptomeningitis** | **Chronic Arachnitis or Leptomeningitis (Superficial)**

Acute Arachnitis or Leptomeningitis

1. *Cortical* | 1. *Serous*
2. *Basilar* | 2. *Purulent*

Chronic Arachnitis or Leptomeningitis (Superficial)

1. *Fibrous*
2. *Ossifying*
3. *Pacchionian*

and
(Deep)
or

Pia

V — Vein
A — Artery
V — Vein

Encephalo-Meningitis, or Progressive Paralytic Dementia

Cord.

Vertebra

Periostitis
Extra-Meningeal Abscess

External Pachymeningitis

Dura

Internal Pachymeningitis

Spinal Meningitis—Leptomeningitis

Arachnoid and Pia

{ **Meningo-Myelitis** }

Cord

converted into bone by metaplasia. When evidences of inflammation are absent, the bony plates might be considered to be osteomas.

5. *Internal hemorrhagic*, or *fibrinous pachymeningitis.* This is a chronic inflammation, with subacute exacerbations, in which patches of delicate connective tissue form on the inner surface of the dura. New blood-vessels project into the tissue; their rupture gives rise to hemorrhages, the blood being held in the meshes of the new connective tissue. The condition is circumscribed, often symmetrical, affecting especially the parietal and occipital regions.

6. *Intermeningeal hemorrhage.* This is due to rupture of veins passing from the pia to the sinuses. Its causes are either direct injury from the outside or indirect trauma, as concussion. It is usually diffuse and may extend down to the base.

7. *Hematoma* is a blood tumor resulting either from hemorrhagic pachymeningitis or intermeningeal hemorrhage.

8. *Hygroma* is the clear cyst left after the absorption of the pigment from a hematoma.

The Arachnoid.—This differs from other serous membranes in having no exudative processes upon its surface, except in the rare cases of penetrating wounds.

Edema of the membranes. The fluid is in the subarachnoid space, especially in the region of the occipital lobes. The causes are (*a*) valvular heart disease, (*b*) Bright's disease, (*c*) inflammations within the cranial cavity, (*d*) pressure of tumors. A certain amount of edema occurs frequently during the agonic period.

Vacuum dropsy is a localized serous effusion due to atrophy or aplasia of a part of the brain.

Inflammations. From the pathologic standpoint it is not possible to separate the arachnoid and pia, and we consider inflammation of the two together under the head of *leptomeningitis.*

(*a*) *Acute leptomeningitis* is either sero-fibrinous or purulent. Sero-fibrinous inflammation has to be distinguished from edema—opacity and the presence of flakes of lymph indicate the former, although a certain degree of opacity develops in long-standing edema.

In the purulent we have a distinct accumulation of pus, especially along the blood-vessels.

Acute leptomeningitis is generally due to the ordinary forms of pyogenic micro-organisms, which reach the meninges either through

the blood or by extension; or to the pneumococcus, the bacillus coli communis, or to other micro-organisms.

The *causes* are epidemic cerebro-spinal meningitis, pneumonia (pneumococcus), malignant endocarditis, pyemia, typhoid fever, tuberculosis, and other infectious diseases. Middle ear disease or brain abscess may cause leptomeningitis by extension.

According to distribution we have *cortical* and *basilar* meningitis, though these are not distinctly separable. Epidemic cerebro-spinal and tuberculous meningitis affect principally the base. In the former the brain substance is also involved. There is also a syphilitic basilar meningitis.

Chronic leptomeningitis is of two varieties, the superficial, which affects the membranes alone, and *deep*, which involves also the brain—hence, the term, encephalo-meningitis, or peri-encephalitis.

(*a*) *Superficial leptomeningitis* (α) *Fibrous.* In this we have a marked thickening of the pia-arachnoid, the result either of frequently repeated congestions and slight inflammation (especially in alcoholic subjects), or of certain forms of insanity. The membranes are opaque. (β) *Pacchionian*—This is either due to areas of localized inflammation, or consists in the formation of fibrous tumors. (γ) *Ossifying*—This occurs in the late stages of fibrous leptomeningitis, as the result of metaplasia.

(*b*) *Deep leptomeningitis.* This is a chronic inflammation involving the pia-arachnoid, and the gray and white matter of the brain, and is the anatomic basis of general paralysis of the insane. The disease usually has an acute beginning. Histologically, the process begins as an inflammation of the vascular apparatus and the neuroglia, as evidence of which, in the acute cases coming under observation, we find a marked round cell infiltration of the perivascular spaces, the ganglion cells being healthy. The latter degenerate secondarily.

DISEASES OF THE NERVE SUBSTANCE.

Atrophy.—This is not promiscuously distributed, but is circumscribed to definite parts, especially to the cells of the anterior horns of the spinal cord and the corresponding nuclei in the medulla. In the cord it gives rise to chronic anterior poliomyelitis, in the medulla to bulbar palsy.

Microscopy. The ganglion cells lose their processes, become plumper, smaller, and pigmented. At times the cells are larger than

normal, from a peculiar hyaline degeneration, and are vacuolated. The nerve fibers also degenerate; the neuroglia is hyperplastic.

The atrophy is progressive in character, extending gradually to neighboring groups. Atrophy also follows amputations in early life.

Softening.—There is no sharp boundary line between softening and inflammation.

Causes of softening. 1. Hemorrhagic or anemic infarction.

2. Gradual compression, as from tumors, disease, or displacement of the vertebræ.

3. Traumatism, as a sudden crushing.

4. Toxic agents, as the toxins of hydrophobia, tetanus, and other infectious diseases; diabetes; progressive pernicious anemia, and certain poisons introduced from without.

The varieties of softening are the red, yellow, and white, the color depending upon the amount of blood present. In white softening we have merely a fatty emulsion without blood.

Microscopy. In softening, the archiblast suffers more than the parablast. The *ganglion cells* swell, become vacuolated, and lose their prolongations; the nucleus ceases to stain, and the cells finally break down into a fatty detritus. The nerve-fibers undergo similar changes—the myelin breaks up into drops and appears beaded, and eventually is converted into fat granules. The axis cylinder is somewhat more resistant, but finally it degenerates also—it swells, becomes varicose, and breaks up into fatty granules which tend to run together.

There is also an exudation of fluid which converts the fatty detritus into an emulsion. The *neuroglia* to a certain extent degenerates also; but it may remain and hold the emulsion in its meshes.

Accompanying the fatty degeneration we have distinct evidences of an inflammatory process, namely, the liquid exudate and a leukocytic infiltration. The wandering cells take up the fatty detritus, and become compound granule cells.

Terminations. (*a*) Cicatrization—the neuroglia becomes hyperplastic; (*b*) cyst formation—the fatty debris is removed, a clear fluid being left. Such softening cysts are common in the brain. (*c*) Resolution.

Secondary Degenerations.—These are circumscribed to certain tracts of fibers functionally allied, and hence, are called

systemic degenerations. They are due to lesions of the trophic centers. Two kinds of secondary degenerations are described—the ascending and the descending.

Ascending degeneration affects the posterior columns, especially the column of Goll, the direct cerebellar tract, and the ascending antero-lateral tract. The trophic centers for the posterior column are in the ganglia on the posterior root; those for the direct cerebellar tract, in the vesicular column of Clarke. *Descending degeneration* occurs in the anterior and the crossed pyramidal tracts, the trophic centers for which are situated in the motor area of the brain.

Macroscopy. The affected areas are grayish in color and firmer than the healthy tissue.

Microscopy. The changes are similar to those noted in softening, but there is much less fluid; we have a slow, fatty degeneration, which is dry, because any fluid present is absorbed, and time is given for neurogliar hyperplasia.

The degenerative changes begin within two weeks after separation of the fibers from their trophic centers; they continue for two or three months; then the neuroglia become hyperplastic. It is during the last stage that the cases generally come under observation. These secondary degenerations affect the entire tract at the same time, and not that part nearest the trophic center first.

Stained sections present two distinctly different appearances, according to the nature of the stain employed. When a nuclear dye like carmin is used, the affected area will be darkly stained, because it contains an abundance of neuroglia cells. With a myelin stain, such as Weigert's hematoxylin method, the diseased parts appear pale, since they are deficient in myelin sheaths. By the use of either of these stains the affected areas can be distinguished with the naked eye.

Primary Degenerations.—These like the secondary degenerations are also systemic, but are not due to lesions of the trophic centers. Two theories are held in regard to their etiology. According to the one the changes are primarily parablastic, *i. e.*, inflammatory; the neuroglia undergoes an excessive hyperplasia. The second assumes a primary degeneration of the archiblast, with a secondary hyperplasia of the neuroglia. Neither theory covers all cases; in some there is evidently a primary inflammation, affecting the blood-vessels and neuroglia, in others a primary

degeneration of the ganglion cells, perhaps from poisons, followed by neurogliar hyperplasia or true inflammation.

In a general way we may say that those lesions which are circumscribed to definite groups of cells functionally associated, are primarily *archiblastic*, as, *e. g.*, amyotrophic lateral sclerosis and bulbar palsy; while those which are distributed in irregular areas are primarily *vascular*, as, *e. g.*, meningo-encephalitis and multiple sclerosis.

Some authorities are inclined to connect primary degenerations with tumors (those explained on Cohnheim's theory). There is a congenital tendency to degeneration of the ganglion cells, at times quite early in life, and this is followed by hyperplasia of the neuroglia. Others claim that there is a congenital impulse to neurogliar hyperplasia, the degeneration of the nervous structure being secondary to this.

Posterior sclerosis, Locomotor ataxia, or Tabes dorsalis. In this disease the primary degeneration is limited to the posterior columns, and has the character of an ascending degeneration. Its distribution varies—in the lumbar region the whole of the posterior column, especially the part nearest the posterior horn, is affected. A small rim in contact with the gray commissure usually escapes. In the higher parts of the cord the lesion is more median; in the dorsal region there is generally a layer of healthy tissue between the affected postero-external and postero-median columns. In the cervical part of the cord only the column of Goll is affected. Advanced cases show involvement of the entire posterior column. In the sclerosed portions amyloid bodies are often found.

In addition to the cord lesion we have changes in the nerve tracts of the brain, as the optic tract and oculo-motor nerve, and trophic alterations in the joints (arthropathies).

Pathogenesis. There is a primary hyperplasia of the connective tissue and neuroglia, which begins in the ganglia on the posterior root and in the pia about the roots and the posterior columns.

Amyotrophic lateral sclerosis has the character of a descending degeneration. We have degeneration of the ganglion cells of the anterior horns and of the motor tracts of the cord. It is most marked in the cervical region.

Pathogenesis. Amyotrophic lateral sclerosis is probably a primary degeneration of the ganglion cells.

Bulbar palsy. This is a primary degeneration of the motor ganglion cells in the medulla, affecting the nuclei of origin of the facial, hypoglossal, spinal accessory, and vagus nerves.

Lateral sclerosis, or Spastic paraplegia. The primary nature of this is questioned. The pyramidal tracts (especially the lateral) are said to be involved, but the lesions found at autopsy vary.

Disseminated, multiple, or insular sclerosis. This is a process usually affecting both cord and brain, and characterized by the formation of gray patches which vary in size from those barely visible to others 3 and 4 cm. in diameter. The patches are generally distributed along the central cavities of the cerebro-spinal axis —in the brain, we find them in the wall of the lateral ventricles, in the caudate nucleus and optic thalamus; in the cord, near the central canal.

The degeneration is of slow development; the axis cylinder may remain intact long after the myelin has disappeared; eventually it also degenerates, and is replaced, like the other structures, by neuroglia. The microscopic appearance is the same as in the systemic degenerations, *i. e.*, we have an excess of neuroglia. Amyloid bodies are rare.

The patches may become cystic from degeneration of the neuroglia.

In all the degenerations two stages are recognizable—(*a*) the degeneration of the nerve substance, (*b*) the replacement by neuroglia. Both go on simultaneously, but in certain areas we find one more prominent than the other.

Congenital Degenerations.—*Syringo-myelia.* In this disease cavities of varying length surround the central canal of the cord, particularly in the posterior region of the upper part of the cord. It occurs early in life, and is the result either of a congenital insular sclerosis with cystic change or of a true gliomatous formation, with softening of the tumor.

Porencephalon. This is a condition in which through some disturbance, intra-uterine or early in life, a part of the brain degenerates, and is replaced by fluid (*vacuum dropsy*). It is comparable to syringo-myelia.

Circulatory Disturbances.—*Congestion.* The presence of blood in the dependent parts of the nervous system is not a sign

of active congestion. The existence of the latter can only be predicated when we find the capillaries of the nerve structures filled with blood. Post-mortem congestion is generally limited to the membranes. The color of the gray matter when congested is peculiar: it is much darker than normal. The white matter has a punctated appearance, and may be the seat of minute hemorrhages.

Edema is most marked in the subarachnoid space; the nerve substance is soft and moist. In porencephalon we have a large accumulation of fluid in a depression of the brain—vacuum dropsy.

Hydrocephalus is a collection of fluid in the ventricles of the brain; the corresponding condition in the cord is known as *hydromyelia*, or *hydrorhachis*. Hydrocephalus is generally due to a chronic inflammation of the ependyma, either simple or tuberculous. The ependyma is cloudy and granular, and to the finger conveys the sensation of a cat's tongue. There may be distinct tubercles.

Hemorrhages are of two kinds, (*a*) extensive, and (*b*) punctated, or capillary.

(*a*) *Extensive hemorrhage.* This is the ordinary lesion of apoplexy and hemiplegia, and occurs from the branches of the middle cerebral artery piercing the anterior perforated space and going to the striate body, the optic thalamus, and the internal capsule. These arteries, as already stated, are subject to great pressure; they are, therefore, frequently the seat of sclerosis and miliary aneurysm. The hemorrhage may burst through the basal ganglia into the ventricles.

(*b*) *Punctated hemorrhages* occur principally on the periphery of the brain, in the cortical portion, and are usually due to embolism or thrombosis. There is a tendency to the formation of a hemorrhagic infarct, but the latter is not well circumscribed. Embolic hemorrhages are most common in the motor area, the region of distribution of the sylvian artery.

Thrombotic hemorrhage may occur anywhere in the brain.

From the close aggregation of fibers in the internal capsule, a hemorrhage involving it, even if small, will lead to *hemiplegia* of the opposite side, or to *hemianesthesia*, if back far enough. As the fibers spread out in a fan-like fashion toward the cortex, a hemorrhage on the surface of the brain usually produces a *monoplegia*.

Consequences of hemorrhage. The first effect is acute softening, red or yellow. The softened tissue is converted into an

emulsion, the blood pigment being transformed into hemosiderin at the periphery, into hematoidin at the center of the area. Finally, both the pigment and the fatty detritus may be absorbed and be replaced by a cyst or a scar. Usually the cyst or scar contains evidences of pigmentation.

Inflammation of the nerve centers resembles in its early stages the process of softening, in the later, that of sclerosis. In the acute stage we find the same changes as in softening, but in addition the evidences of inflammation—hyperemia, minute hemorrhages, filling of the perivascular spaces, and cell-proliferation. The nerve tissue may break down and a true abscess be formed, which eventually is replaced by a scar or by a cyst.

Suppurative inflammation is common in the brain (*acute suppurative encephalitis*), and gives rise either to a single large or to many small abscesses. The former is usually due to *extension* from disease of the middle ear or the nasal cavities, but it may be produced by the coalescence of several small abscesses. The small abscesses are generally *embolic* in origin, being secondary to ulcerative endocarditis, pneumonia, or other pyogenic processes.

Suppurative myelitis is due either to extension of suppuration from the vertebræ or to septic emboli.

With the naked eye it is often impossible to distinguish between inflammation and ordinary softening. Abscesses usually have a pyogenic membrane, while in softening there is a gradual decrease of the soft character toward the periphery. But there may be abscesses without a limiting membrane; in such cases the discovery of pyogenic micro-organisms will alone aid us.

In some of the inflammations of the nerve centers there is no breaking-down, but a tendency to proliferation of the neuroglia, *i. e.*, to sclerosis. This is best seen in *acute anterior poliomyelitis, or infantile palsy.* This is an acute febrile disease of childhood, probably infectious in origin. In the early stages distinct evidences of inflammation are present, although cases rarely come to autopsy at this period. There is no tendency to suppuration, but there may be some softening. Later the neuroglia becomes hyperplastic and replaces the parenchyma. This disease is, therefore, a sclerosis of distinctly inflammatory origin.

Other varieties of inflammation of the spinal cord are:

Poliomyelitis—inflammation of the gray matter of the cord.

Leukomyelitis—inflammation circumscribed to the white substance.

Transverse myelitis involves the entire cord transversely.

Besides these we have *diffuse*, *focal*, and *disseminated myelitis.*

Tuberculosis presents itself in two forms, (*a*) as a solitary tubercle or tumor (*tyroma*), and (*b*) as miliary tuberculosis.

(*a*) *The solitary tubercle* may be small or as large as a hen's egg. It is irregular, and is found most often on the surface of the brain, involving the pia, but as a rule not the dura. Microscopically, the periphery of the tubercle consists of granulation tissue containing bacilli, while the center is cheesy.

(*b*) *Miliary tuberculosis, or tuberculous meningitis.* In this we find miliary tubercles scattered along the blood-vessels, together with a diffuse inflammation of the meninges. The base is most frequently affected. There is also a tuberculous inflammation in the walls of the vessels.

Syphilis.—Gummata are common in the dura; they are generally smaller than tubercles and do not show the same tendency to cheesy necrosis. Besides gummata syphilis often produces the diffuse arteritis previously described.

The differentiation from tuberculosis is at times difficult and can only be made by staining for the tubercle bacilli which, it should be remembered, however, are not easily found in tuberculosis of the brain.

Syphilis, in addition to causing gummata and vessel changes is also the remote cause of certain degenerations, particularly posterior sclerosis.

Tumors of the brain. The location of brain tumors is as important as their nature. Clinically, *syphilitic* and *tuberculous* growths are considered as tumors, and together with *glioma*, constitute 75 per-cent of all cerebral tumors. These three occur with about equal frequency, and are nearly always found at the periphery of the brain. Gliomas are not encapsulated and resemble the brain substance, but are usually somewhat darker, more translucent, gelatinous, and frequently hemorrhagic. *Sarcoma* is most common in the meninges and is of the alveolar type, or it may be an endothelioma. *Cancer* is usually secondary; it may then be

found anywhere, perhaps most often in the white substance just below the gray matter. Primary cancer is rare; when it does occur, it springs from the surface of the ventricles.

PERIPHERAL NERVES.

It is difficult to separate, in the peripheral nerves, degeneration from inflammation. By some all changes are considered degenerative, while others look upon the vascular changes as inflammatory. Taking the view that there are two different processes, we must admit that it is extremely difficult to say where certain of the changes belong.

The most typical degeneration is seen after separation of the nerves from their trophic centers. Thus, if a spinal nerve be divided, the motor fibers degenerate in the distal part. In the case of the sensory nerves, the processes are more complex—some have their trophic centers in the ganglia on the posterior root, others at the periphery, in the sensory end-organs.

Poisons may produce similar degenerations, although in some cases they cause inflammatory changes.

Among poisons acting on the nerves, we have:

1. *Toxins of infectious diseases.* (*a*) *Beri-beri*, which is an infectious disease, with neuritic and degenerative changes in the nerve fibers, these appearing as the characteristic symptoms of the disease before other phenomena manifest themselves. (*b*) *Diphtheria.* Post-diphtheritic paralysis is due to a degeneration of the nerves brought about by the toxins of the diphtheria bacillus. (*c*) *Yellow fever.* (*d*) *Tuberculosis.* (*e*) *Syphilis.*

2. *Non-bacterial poisons*, as lead, and alcohol.

Macroscopy. The nerves are swollen, and on section appear red and edematous. They are, however, rarely seen in the early stages. *Microscopically*, the appearance is the same as in the white matter of the spinal cord—the myelin degenerates first, then the axis cylinder; but the latter holds its own for a long time.

CHAPTER XI.

DISEASES OF THE DIGESTIVE TRACT.

THE MOUTH.

Inflammation. Stomatitis. — We may look upon all forms of stomatitis as microbic in origin. The mouth is constantly the habitat of many kinds of bacteria which may cause inflammation by becoming more virulent or, what is more probable, are enabled to start disease because the resistance of the mucous membrane is lowered. The lessened vitality may be produced by injuries (hot water or other irritants); even mercurial stomatitis is micro-organismal, the poison in its elimination producing a favorable soil in the mouth for the bacteria.

In the common forms of stomatitis the organisms are not specific, but are the ordinary pyogenic bacteria found in the mouth.

Varieties of stomatitis. (*a*) *Catarrhal*, which is either diffuse or follicular. In the latter the mucous follicles are especially affected and stand out as whitish points surrounded by a red areola.

(*b*) *Ulcerative, or diphtheritic stomatitis*, begins usually about the front teeth, and penetrates to the submucous tissue or even to the bone. It is characterized by a coagulation necrosis, whence the name diphtheritic, but is due to the ordinary organisms.

(*c*) *Gangrenous stomatitis, noma, or cancrum oris.* This occurs when the vitality of the tissues is depressed to the lowest degree. It begins in the cheek, but may extend through and may even involve the entire side of the face. Although at times epidemic, it is probably not due to a specific micro-organism, but to the streptococcus, which renders the tissues a favorable soil for the saprophytic bacteria.

Specific Inflammations.—(*a*) *Aphthous stomatitis.* This is probably due to a specific germ, perhaps the same one that causes foot-and-mouth disease, or murrain, in cattle. The disease is characterized by the formation of minute blebs—*aphthæ*, which are at first clear, but later become opaque and whitish. The constitutional symptoms are slight; the affection may be epidemic.

(*b*) *Mycotic stomatitis, or Thrush.* The cause of this is a fungus standing between the yeasts and the moulds, probably somewhat nearer to the former. It is termed *oidium albicans*, or *saccharomyces albicans*. It grows between the epithelial cells and causes them to degenerate. Whitish patches are produced, consisting of degenerated cells and masses of fungi.

(*c*) *Syphilis.*

(*d*) *Tuberculosis.*

(*e*) *Actinomycosis.*

Malformations.—These are not rare and are due to failure of union of the palatal plates or the branchial arches.

(*a*) *Hare-lip* results from non-union of the palatal plates; the fissure may extend to the hard and soft palate; at times, there is a complete division of the face into two parts.

(*b*) *Cleft tongue* depends on a failure of closure of the branchial arches.

Hypertrophies.—These are usually congenital and are, in reality, tumors, *e.g.*, macroglossia, macrochilia, which are lymphangiomata.

Tumors.—(*a*) *Carcinoma.* (α) *Squamous epithelioma* occurs especially on the lower lip, between the median line and the angle of the mouth, and is usually superficial. (β) *Glandular cancer*—from the salivary glands. Cancer may occur in any part of the mucous membrane of the mouth.

(*b*) *Sarcoma* develops generally from the gums, particularly the giant cell sarcoma (malignant epulis) which grows from the alveolar process.

(*c*) *Cysts.* (α) Retention cysts of the mucous glands; (β) ranula.

THE SALIVARY GLANDS.

Inflammation.—(*a*) *Mumps, or infectious parotitis.* This is a true inflammation of the parotid gland, contagious and epidemic. There is no tendency to suppuration. The infection takes place through the duct of the gland.

(*b*) *Suppuration.* The pyogenic organisms reach the salivary glands through the ducts or the lymphatics. Suppuration is common in scarlet fever and diphtheria, and is usually due to the streptococcus.

(*c*) *Angina Ludovici*—a peculiar suppurative inflammation of the submaxillary glands, at times epidemic.

Tumors.—(*a*) *Adenomatous cancers of glandular type.*

(*b*) *Tubular epithelioma.* This is a peculiar form of epithelioma, occurring in the salivary and mucous glands, in which the nests have a cylindrical shape, extending into the tissues and lymphatics, and resembling to a certain extent endothelioma. The diagnosis may be made by the presence of pearly bodies in the epithelioma. The tumor is usually non-metastatic, but spreads widely locally.

(*c*) *Mixed tumors* are common in the parotid, and are combinations of fibroma, myxoma, and chondroma, and often sarcoma. They bear out Cohnheim's theory of tumors.

FAUCES AND PHARYNX.

Lymphatic tissue is very abundant in the pharynx and is distributed in three groups, (*a*) the lingual tonsil, at the base of the tongue; (*b*) the faucial tonsil, between the pillars of the fauces, and ordinarily referred to as the tonsil, and (*c*) the pharyngeal tonsil in the naso-pharynx. These three sets of tonsils form a lymphoid ring which guards the pharynx and prevents general infection. It has probably been developed as the result of frequent infections in early life.

Inflammation. Pharyngitis.—(*a*) *Catarrhal pharyngitis* is diffuse or follicular. In the latter the glands are enlarged and discharge a creamy secretion. If this spreads over the surface an appearance resembling diphtheria is produced, but the opening of the follicles can usually be seen, and pressure forces out more of the secretion.

(*b*) *Herpetic pharyngitis* is more common than is believed. It corresponds to herpes labialis and occurs most frequently in persons subject to herpes of the lips or prepuce. It has an acute onset, a continuous fever, and a sudden crisis, resembling in these respects croupous pneumonia. Vesicles form, particularly on the tonsils; at first they are filled with a clear fluid, later this becomes opaque and whitish. On breaking a fibrinous membrane is produced—a superficial diphtheritic membrane, differing from diphtheria in the absence of the Klebs–Löffler bacillus. The cause is probably a specific micro-organism.

(*c*) *Pustular pharyngitis* occurs in small-pox.

THE TONSILS.

Of the three tonsils, the faucial or palatine tonsil is generally more markedly involved by disease than the other two. They are, however, also affected, although this fact is frequently overlooked.

Inflammations. Tonsillitis, Amygdalitis.—(*a*) *Catarrhal tonsillitis.* The tonsil participates in acute catarrhal inflammations of the pharynx.

(*b*) *Follicular, or lacunar tonsillitis.* The tonsillar crypts are filled with a yellowish-white secretion composed of broken-down epithelium. When this extends over the surface an appearance resembling diphtheria is produced. The patch is, however, easily removed, the openings of the follicles can be seen, and more secretion can be pressed out.

(*c*) *Herpetic tonsillitis.* It is on the tonsils that herpes of the pharynx shows itself best.

(*d*) *Pustular tonsillitis* is seen in small-pox.

(*e*) *Suppurative tonsillitis, abscess,* or *quinsy.* The tonsils have a special tendency to suppurate, and, considering the number of micro-organisms always present in the crypts, the wonder is that suppuration is not even more common than it is. The abscess may begin in the tonsil or in the peri-tonsillar tissues; it is usually due to the staphylococcus or streptococcus, at times to the pneumococcus.

Chronic Inflammation of the Pharynx.—In the hypertrophic stage the hyperplasia affects either the lymphoid or the mucous follicles, in both cases producing a granular appearance. When the first are affected we speak of *granular pharyngitis,* when the mucous follicles are involved, of *follicular pharyngitis.*

Atrophy in time supervenes and gives rise to a smooth, shining membrane, with cicatricial markings and dilated veins.

Chronic Tonsillitis.—"Hypertrophy of the tonsils." In many cases the hyperplasia involves all the elements; at times the lymphoid tissue is especially affected, at times the connective tissue —in the former the enlargement is *soft,* in the latter *hard.*

The lymphoid hyperplasia of the pharyngeal tonsil ("the adenoid growths of the naso-pharynx") interferes with nasal breathing, and is of great clinical importance—it seems to retard the physical and mental development of the children affected.

Specific Inflammations. — (*a*) **Diphtheria.** — This is due to the Klebs–Löffler bacillus, a facultative, aërobic, non-motile bacillus, not liquefying gelatin, about the length of the tubercle bacillus, but much broader. Its characteristics are *irregularity in shape*, and *variation in staining*. It grows on all media, but best on Löffler's blood serum mixture (*Blood serum 3, bouillon containing 1 per-cent. of glucose, 1*), and on coagulated white of egg.

The diagnosis may sometimes be made by finding a pure culture of the bacillus in the deeper parts of the membrane, usually, however, it is necessary to resort to cultivation. A small cube of coagulated white of egg is placed in a test-tube with a little water, and sterilized by boiling. A bit of membrane is removed and rubbed on the surface of the egg, and the tube then placed into the incubator, at 37°C. In from 14 to 24 hours a characteristic growth appears in the form of circular white colonies with a convex surface. A cover-glass preparation should be made; but the appearance of the colonies is quite diagnostic.

The streptococcus pyogenes often causes false membrane formation, but its growth in culture media is different and much slower, colonies rarely appearing under 48 hours. The angina produced by it is also milder.

Mixed infection is common in diphtheria.

The various phenomena of diphtheria are due to two poisons elaborated by the bacillus, a *nuclein* and a *nucleo-albumin*. The nucleo-albumin is destroyed by proteolytic ferments, the nuclein is not.

The nucleo-albumin gives rise to the acute manifestations of diphtheria, the nuclein to the later symptoms, as the cachexia.

Immunity may be induced in animals (*a*) by feeding them with cultures of the bacillus, (*b*) by employing bacilli grown under unfavorable conditions, *e. g.*, at a high temperature or in culture media containing iodin trichlorid, (*c*) by treating them after the method of intensification, *i. e.*, injecting first attenuated bacteria and then gradually using stronger and stronger cultures.

The blood serum of animals made immune contains an antitoxin, which when the serum is injected into other susceptible animals, renders them also immune.

The pseudo-diphtheria bacillus is now considered an attenuated form of the true diphtheria bacillus. It may be normally present in the mouth, and under certain conditions may produce a mild

inflammation, at times pseudo-membranous. It is non-pathogenic to lower animals.

Diphtheroid inflammations can be produced in the pharynx, larynx, bowel, etc., by other micro-organisms than the Klebs–Löffler bacillus, especially by the streptococcus. Anatomically, the membrane is indistinguishable from that of true diphtheria, but the disease is milder in type. Streptococcus membranes may occur in any infectious disease, particularly in scarlet fever, measles, and typhoid fever. At times both the streptococcus and the bacillus of diphtheria are present together.

Syphilis. — The commonest lesion is the mucous patch; chancre may occur in the pharynx. The gumma is quite frequent and leads to destructive changes, especially in the hard and soft palate. The healing of the ulcers gives rise to stellate scars.

Tuberculosis is not rare in the palate, but is often overlooked. Usually it is a secondary lesion. The tonsil is by some considered a frequent primary seat, but more probably is infected secondarily from the lung. *Lupus* of the face may extend to the pharynx.

THE ESOPHAGUS.

Malformations.—(*a*) *Congenital diverticula.* These are lateral, and are most common in the upper part of the esophagus. They are due to faulty union of the branchial arches.

(*b*) *Acquired diverticula or pouches.* These are not true malformations, but are due to pathologic changes, the causes of which are not always discoverable. They occur on the anterior and posterior wall of the gullet. The *posterior diverticula* are the result of ulceration produced by a foreign body; *the anterior* are due to rupture of a bronchial gland into the esophagus (this may occur without symptoms) and the formation of adhesions which in contracting produce a diverticulum.

Stricture.—Stricture is prone to occur at two points in the esophagus—opposite the cricoid cartilage and the bifurcation of the trachea. At these points the cartilages are complete rings and produce to all intents and purposes a normal stricture.

Causes of stricture. (*a*) *Disease of the walls of the esophagus.* (α) Spasmodic stricture—in hysteria; (β) cicatricial stricture—due to the healing of lesions produced by corrosive poisons, hot water,

etc.; (*γ*) cancerous stricture. The last is the most common, and occurs at the two points of normal coarctation, a fact to some extent supporting the mechanical theory of tumors. The cancer is usually primary; it is squamous in type, and very destructive.

(*b*) *The presence of a foreign body.*

(*c*) *Pressure from without,* as by an aneurysm (most frequent); or by tumors of the neck or mediastinum.

Rupture of the Esophagus.—This may be due to cancer, to perforation by an aneurysm, to ulceration of a diverticulum, or it may occur spontaneously from violent retching and vomiting. In the last, the rent begins at the bifurcation of the trachea, as this was the case in a recent instance.

THE STOMACH.

The most fixed portion of the stomach is the cardiac orifice, which is situated in front and to the left of the last dorsal vertebra. The pylorus and the greater curvature are quite movable; the lesser curvature is relatively more fixed.

Size and weight. The stomach is 20–30 cm. long, 10–12 cm. wide, and weighs 130–140 grams.

The wall consists of four coats, (*a*) the serous, (*b*) the muscular, (*c*) the submucous, and (*d*) the mucous. The mucous membrane is thrown into a series of longitudinal folds, or *rugae*, which, however, are not seen when the organ is distended. The epithelial lining of the stomach consists of tall, columnar cells, which secrete mucus. Two kinds of glands are found in the stomach—the pyloric and the cardiac.

The pyloric consist of a long duct with two or three outgrowths constituting the body of the glands; the cardiac have a short duct which communicates with three or four secreting sacs. The epithelium of the glands is cuboidal, and is of two kinds (*a*) the central, chief, or peptic cells, and (*b*) the parietal, placed between the central cells and the basement membrane, and staining deeply. The central cells are the most important; they secrete the pepsin, while the parietal, which are found only in the cardiac glands, elaborate the HCl.

Lymphoid tissue is abundant in the stomach, and at the pylorus forms a distinct ring. The nodules are well circumscribed but have no capsule, and are often mistaken for inflammatory round cell infiltration.

Physiology of Digestion.—Digestion, not alone in the stomach, but anywhere, depends largely upon the action of ferments. *Ferments* are substances which are capable of starting up chemical changes in certain other substances with which they are brought in contact. They are of two kinds: *organic*, or soluble substances, and *organized*, as bacteria and yeasts. Fermentation seems to be a function of protoplasm; bacteria, which are but cells, have the power in a marked degree. Classified according to their properties, we have the following ferments:

(*a*) *Sugar-producing, or diastatic ferments.* These are found in saliva, pancreatic and intestinal juice, blood, urine, bile, milk, fluids from dead tissues, and solutions of albuminous substances.

(*b*) *Proteolytic ferments.* These act upon albuminous substances, and are found in the stomach (pepsin), in the pancreatic juice (trypsin), in the intestinal juice, and in the urine. The products of albuminous fermentation (albumoses and peptones) may be actively poisonous when introduced into the circulation. In health they do not enter the blood as peptones and albumoses, but are altered in the walls of the digestive tract. Fermentation changes of albumins may take place anywhere in the body —under the influence of cells or micro-organisms. Many disease poisons are produced in this way.

(*c*) *Fat-splitting agents.* These are probably not true ferments; they are found in the stomach and pancreas.

(*d*) *Milk-curdling ferment, rennet, or rennin.* This exists in the stomach, pancreas, and urine.

In the process of digestion proteids are transformed into albumoses and peptones which, however, are not absorbed as such, but are converted into forms of albumin by the epithelial cells, leukocytes, and lymphoid corpuscles of the walls of the stomach and intestine. In the tissues they are further changed into the constituents proper to these, as, *e. g.*, into globulins or myosin. When injected into the circulation or produced in the body in certain forms of chronic suppuration, peptones give rise to toxic symptoms; they act as narcotic poisons, produce fever, and diminish the alkalinity and coagulability of the blood. In certain acute infectious diseases, in which there is an arrest of digestion, some of the symptoms may be due to the absorption of such products.

The gastric juice. The active agents of the gastric juice are pepsin and hydrochloric acid. The former is practically always

furnished in sufficient quantity; the latter may be increased or decreased. The HCl is essential; just enough is normally present to bind the bases and to leave a little free. The normal quantity of free HCl is so small that the chemical reaction is feeble, but distinct.

Hyperacidity. The effects of this are (*a*) rapid digestion of the proteids, which is not an advantage; it may cause disturbances; (*b*) injury to the mucous membrane—at times leading to the formation of ulcers; (*c*) the development of yeast fungi which grow well in an acid medium—they act upon the carbohydrates and produce H, CO_2, CH_4; (*d*) an arrest of the salivary digestion which normally continues for a short time in the stomach. Hyperacidity is rare.

Subacidity. Causes: (*a*) Lesions of the mucous membrane; (*b*) nervous disturbances; (*c*) accumulation and retention of food and of the products of digestion.

The effects of subacidity are the following: (*a*) Proteids, all or in part, pass into the intestines undigested and set up diarrhea. (*b*) Bacteria develop, particularly those producing lactic, butyric, and acetic acids. These give rise to an induced hyperacidity, which in turn favors the development of the yeasts. The amount of lactic acid is insufficient to digest the proteids, although it is capable, in a slight degree, of taking the place of the HCl. The presence of the organic acids is the cause of "acid dyspepsia." (*c*) Putrefactive changes develop, and may lead to the production of ptomains, the absorption of which gives rise to a toxemia. Ordinarily, ptomains and other poisonous substances formed during digestion are destroyed in the liver, but when that organ is disturbed, the poisons are absorbed and cause the nervous symptoms accompanying dyspepsia. (*d*) The absence of HCl favors infection with pathogenic bacteria. The majority of noxious micro-organisms are prevented from entering the intestines by the antiseptic action of the gastric juice. This is especially true of cholera. Experimentally, it is impossible to produce that disease in lower animals on account of the acidity of the gastric juice. But if the acid is neutralized with sodium carbonate, and if, at the same time, peristalsis is checked with opium, cholera can be given to the lower animals.

The muscular coat is also an important factor in digestion. When weakened the organ becomes dilated. *Causes of dilatation:* (*a*) Fermentation of the food, leading to distention of the stomach with gas. (*b*) Obstruction at the pylorus. (*c*) Nervous disturbances.

Given any one of these, the others soon supervene, all acting together in a "vicious circle."

Post-mortem Lesions of the Stomach.—These may simulate true lesions or conceal disease previously existing.

(*a*) *Post-mortem digestion of the stomach wall.* This may be distinguished from ante-mortem lesions (*a*) by being limited to the posterior wall of the stomach, in the region of the fundus—ante-mortem lesions being most marked toward the pylorus; (*b*) by extending only as far as the upper level of the gastric contents.

Two forms of digestion are described, the white and the brown. In the former the mucous membrane is converted into a whitish, gelatinous material, which may easily be mistaken for mucus. Mucus, however, is more readily washed off. In the latter, the same changes take place, but owing to the presence of blood pigment, the color is brownish. Digestion may proceed to perforation of the stomach wall. Putrefactive changes may occur in the stomach after death. The parts are greenish in color and emphysematous.

(*b*) *Hypostasis.* The blood after death gravitates toward the dependent parts of the stomach, particularly the posterior wall toward the fundus. Post-mortem digestion may affect the walls of the distended veins and cause the hemoglobin to pass out, giving rise to an appearance of hemorrhages.

Disturbances of Circulation.—1. *Active hyperemia* results chiefly from the action of irritants, and is best marked toward the pyloric end, on the crests of the mucous membrane.

2. *Passive congestion* is due to liver or heart disease, and is also seen most prominently toward the pylorus.

Both active and passive hyperemia may give rise to petechial hemorrhages which, unlike the post-mortem petechiæ, are distributed anywhere in the stomach, but especially in the neighborhood of the pylorus, and have no connection with the large veins. In passive congestion we often find minute dark or slate-colored spots, due to small hemorrhages.

3. *Hemorrhage.* This may result (*a*) from the entrance of blood into the stomach from neighboring parts—as from rupture of an aortic aneurysm; (*b*) from disease of the vessel walls of the stomach, as in yellow fever, the purpuric diseases, cancer, tuberculosis, and simple ulcer. The vomited blood is generally partially

digested, is dark in color, and resembles "coffee grounds," especially if the hemorrhage has been slow. When the hemorrhage is sudden and rapid, the blood is clotted.

Inflammation.—(*a*) *Catarrhal gastritis.* The mucous membrane is swollen, especially toward the pylorus, the veins are injected, and there is a diffuse redness; the surface is covered with blood-stained mucus, and may show petechial hemorrhages. Swelling of the mucous membrane is not easily discerned; it may be recognized by contrasting the gastric mucous membrane with that of the esophagus. Normally, there is a sharp line of separation at the cardia, the esophageal mucosa being thicker; in catarrhal gastritis this relation may be reversed.

Microscopically, we find filling of the capillaries, and cloudy swelling and desquamation of the central cells of the gastric tubules. The glands are distended by the accumulation of cells and mucus.

Causes. These are innumerable, and are either irritants introduced from without or irritants produced in the stomach.

(*b*) *Diphtheritic gastritis.* This is a coagulation necrosis which is usually most marked on the rugae, appearing in the form of grayish-white lines. The crests may be alone affected; at times the process is more extensive, and we may then have a complete cast of the stomach.

Causes. The coagulation necrosis is generally due to micro-organisms—in rare cases to the diphtheria bacillus, but more commonly it is seen in other infections, as scarlet fever, typhoid fever, pyemia, etc. It may be produced by corrosive poisons.

(*c*) *Suppurative gastritis.* (α) *Submucous abscess.* This dissects along the coats of the stomach, lifting up the mucous membrane, and finally discharges into the stomach through numerous openings like a carbuncle. A large ulcer is left which, if death does not take place, heals with extensive scar formation.

Causes. These are always micro-organismal, but the point of entrance is not in every case discoverable. (1) They are most common in drunkards—(*idiopathic abscess of drunkards.*) (2) Pyemia produces multiple abscesses. (3) Abscesses may occur about tumors and ulcers.

(β) *Follicular suppurative gastritis.* Small abscesses are formed in the lymphoid nodes of the mucous membrane. *Causes.* Small-pox, typhoid fever; tartar emetic when introduced through another channel than the stomach.

Chronic Inflammation.—(*a*) *Chronic catarrhal gastritis.* In this we have a uniform thickening of the mucous membrane, generally most evident in the pyloric region. The mucosa is congested, the veins are prominent, and pigmentation is marked, either in the form of minute dark points or as a diffuse slate-colored deposit. The surface is covered with a thick tenacious mucus.

(*b*) *Chronic productive gastritis.* This is characterized by a marked hyperplasia of the glands and the connective tissue of the mucous membrane. To a certain extent this is present in all chronic inflammations, but in the form under discussion it becomes a very prominent feature and gives rise to localized swellings, particularly of the rugae. Normally, the latter can be made to disappear, but this is not possible in productive gastritis. *Microscopically*, we find the glands elongated, tortuous, and possessing more sacs, while between them we find an embryonal connective tissue. On account of the glandular hyperplasia it is not always easy to distinguish this condition from adenoma. By occlusion of the gland ducts minute cysts are formed.

In some instances the hyperplasia is so great as to give rise to circumscribed projections of the connective tissue covered by epithelium—*gastritis polyposa.* Cysts are very common in this form.

Atrophic gastritis. The hyperplasia of the mucous membrane is often followed by atrophy, brought about by the contraction of the connective tissue. The mucous membrane becomes smooth and resembles a serous membrane. The glands are either entirely removed or remain as mere shallow depressions. There may be cicatricial markings.

In chronic catarrhs, especially in cases where there is distention by gases, the muscular coat is apt to take part in the hyperplasia. This occurs especially toward and at the pylorus and may give rise to obstruction. It is termed *fibroid thickening of the pylorus* by clinicians.

In chronic inflammations congestions are very frequent; these or the cellular proliberation may interfere with the nutrition of the stomach wall and lead to ulceration from digestion.

Causes of chronic inflammation. (*a*) Venous stasis, produced by cirrhosis of the liver, by pressure of tumors on the return circulation, or by heart-disease. (*b*) Bright's disease—probably the inflammation depends on an attempt by the gastric mucous membrane to eliminate excrementitious substances. (*c*) Ingestion of

improper food, *e. g.*, alcohol. (*d*) Tumors. Chronic inflammation is common about tumors, and is also produced by the dyspeptic conditions associated with their presence.

Infectious Diseases.—(*a*) *Acute catarrhal gastritis* is seen in nearly all infectious fevers and probably results from the action of the imperfectly digested food, digestion being arrested. In yellow fever the stomach may be the seat of the specific organism causing the disease. There is generally a catarrhal gastritis in cholera.

(*b*) *Chronic infections.* (α) *Tuberculosis.* This is rare: it may be miliary, but usually is in the form of a tuberculous ulcer situated toward the pylorus. (β) *Syphilis* is very rare.

Tumors.—It is difficult to draw a sharp line of distinction between the hyperplasia of chronic inflammation and adenoma.

(*a*) *True adenoma* occurs especially toward the pylorus in the shape of fungoid masses. Histologically, it is a tubular adenoma with cylindrical epithelium. It may infiltrate and then is termed *adenoma destruens.*

(*b*) *Carcinoma* is common, and may be glandular or cylindrical; at the cardia we may have a squamous cancer coming from the esophagus. The most frequent seats are the pylorus, the cardia, the lesser curvature, and the posterior wall. The cancer may be scirrhous, medullary, or, occasionally, colloid. The last occurs either in the form of nodes or, more commonly, as an extensive diffuse growth.

Cancer of the stomach has a marked tendency to give metastasis, particularly to the liver, but it may go anywhere. To the bones metastasis is rarer than in the case of primary mammary cancer.

Effects of cancer. Cancer of the pylorus causes obstruction, and the concomitant dyspeptic disturbances. Any cancer may give rise to ulceration, to hemorrhage, or to perforation into the peritoneal cavity. The last may be prevented by adhesions.

Free H Cl is greatly diminished or entirely absent in carcinoma.

Degenerative Processes.—(*a*) *Fatty degeneration and atrophy of the epithelium and glandular structure* occurs in marasmus, in inanition, in hysteria from a refusal of food, in phosphorus poisoning, in leukemia, and in progressive pernicious anemia. In regard to the last two, the anemias, the question arises whether the fatty degeneration is primary or secondary. The weight of evidence is in favor of considering it secondary.

(*b*) *Gastric, peptic, simple, or round ulcer.* This is due to digestion of a portion of the stomach wall, the resistance of which has been weakened by some degenerative process. The ulcer may be superficial or deep; it may even extend through all the coats. It is usually round, "punched out," or funnel-shaped, becoming narrower toward the peritoneal coat, and has smooth edges. Generally there is but one ulcer, at times several are found.

As a rule, the borders are pale and show no inflammatory processes, an evidence that the ulcer is due to digestion and not to inflammation. If, however, it has existed for a long time, micro-organismal infection may take place, the ulcer then becoming inflamed; connective tissue forms which may go on to contraction. Healing may thus take place, a stellate scar with a puckered center marking the site of the ulcer.

In some cases instead of being crater-like, the ulcer becomes *undermined* by the digestive processes, a condition most apt to occur when the ulcer has formed adhesions to neighboring parts, as the pancreas, liver, spleen, or abdominal wall. The digestive process may travel along the adhesions producing extensive undermining.

Seats. The most frequent seat is on the lesser curvature toward the posterior wall.

Accidents in the course of ulcer. (*a*) Hemorrhage. (*b*) Perforation. (*c*) Adhesion to neighboring organs with abscess in these organs.

Pathogenesis. The ulcer is due to the action of the gastric juice on a weakened part of the stomach wall.

Causes lessening the resistance of the mucous membrane.

I. *Circulatory disturbances.*

(*a*) *Embolism and thrombosis.* These give rise to a hemorrhagic infarct or an area of coagulation necrosis upon which the gastric juice then acts. This can be demonstrated experimentally.

(*b*) *Petechial hemorrhages,* as in catarrhal inflammations. They give rise to a partial necrosis of the mucous membrane.

(*c*) *Obliterating endarteritis.* This usually acts by inducing thrombosis.

(*d*) *Chronic venous stasis.*

(*e*) *Spastic contraction of the vessels,* causing circulatory disturbances in localized areas. It may be brought about in one of two ways: (1) by an irregular contraction of the muscular coat

occluding certain vessels, (2) by a neurotonic spasm of the vessels. The latter is quite frequent in grave hysteria—there is an ischemia of the gastric mucous membrane analogous to that of the surface of the body.

II. *Inflammation of the mucous membrane.*

III. *Bacterial infection of the mucous membrane.*

IV. *Lessened alkalinity of the blood.*

Apart from the distinct peptic ulcers described above, we may have at the pylorus superficial abrasions which, although frequently overlooked, are important, inasmuch as they cause a condition clinically known as *irritable pylorus*, a spastic contraction, with secondary hyperplasia of the muscular coat and the connective tissue. The closure of the pylorus gives rise to dyspeptic symptoms from the retention of the food, and also to many reflex disturbances, comparable to those produced by fissure of the anus or laceration of the cervix uteri.

THE INTESTINES.

Automy. The coats are the same as those of the stomach—a loose mucous membrane, a submucous, two muscular, and a serous coat. The entire intestinal tract, except the lower third of the rectum, is lined by columnar epithelium. Two kinds of glands are found—racemose glands (Brunner's glands), confined to the duodenum, and simple tubular glands (crypts of Lieberkühn). Throughout the intestines we find lymphoid follicles possessing a distinct wall. In the lower part of the small intestine they are gathered in groups to form 10 to 15 large, oval plaques (Peyer's patches, or agminated glands), placed opposite the attachment of the mesentery. The villi are covered by columnar epithelium; they are chiefly concerned in absorption.

Functions. In the intestines the changes begun in the mouth and stomach are continued. Trypsin, the powerful proteolytic ferment of the pancreatic juice, completes the digestion of the proteids; another ferment acts on the carbohydrates, and another breaks up the fats and assists in their emulsification. The bile also contributes to the formation of the fat emulsion, acts on the mucous membrane in a way to favor the absorption of the fats, and is the natural antiseptic of the intestines.

The *reaction* of the intestinal juice is alkaline, hence putrefactive changes readily take place, especially in the large intestine,

where the alkalinity is well marked. In the upper part of the small intestines the reaction of the juice is also alkaline, but the contents, especially in their interior, are acid. For this reason putrefaction is less apt to occur.

Composition of the feces. (*a*) Undigested food. This may, in a small part, be digestible substances that have escaped digestion; the greater part consists of undigestible material, such as cellulose, nuclein, chlorophyl, and salts. (*b*) Excretory products of the intestinal tract. A large part of the secretion is reabsorbed.

Diseases. Malpositions.—(*a*) *Hernia.* This is a protrusion of any organ outside of the cavity in which it belongs. The word is, however, generally applied to a protrusion of the intestines outside of the peritoneal cavity.

Varieties of intestinal hernia. (*a*) *Internal hernia.* One which pushes out of the peritoneal cavity without appearing externally, as diaphragmatic hernia. The term is also applied, improperly, however, to a loop of intestine caught beneath a band of adhesion.

(*b*) *External hernia.* One appearing beneath the surface of the body.

In pushing itself out of the abdominal cavity, the bowel carries a part of the peritoneum with it, which together with the muscles, subcutaneous tissue, fascia, and skin, constitutes the covering of the hernia. The peritoneal covering is termed the *sac* of the hernia, and is divided by surgeons into the *body*—the part containing the intestine or omentum, the *neck*—the constricted portion, and the *mouth*—the opening into the peritoneal cavity.

Hernias are also classified into (*a*) congenital, and (*b*) acquired.

(*a*) *Congenital hernia.* One which is present at birth. It occurs wherever the abdominal wall is normally deficient—as at the umbilicus and the inguinal ring, but it may also take place at any point where there is a defect in the abdominal wall.

(*b*) *Acquired hernia.* One developed in after-life; it usually occurs in the same places where congenital hernia is found.

Classifying hernias as to position, we have as the most important:

(*a*) *Inguinal hernia*—one occurring at the inguinal ring. (α) *Oblique*—a hernia traversing the inguinal canal following the track of the testicle. When congenital, the hernia occupies the same

cavity as the testicle; when acquired, it lies outside of the tunica vaginalis. (β) *Direct*—one breaking through the abdominal wall at the external ring.

(*b*) *Femoral, or crural hernia.* This follows the sheath of the femoral vessels and lies to the inner side of the deep epigastric artery. It is common in women.

(*c*) *Umbilical hernia* is usually congenital, sometimes acquired.

(*d*) *Retroperitoneal hernia.* One in which the bowel, usually the duodenum or jejunum, pushes itself back of the posterior layer of the peritoneum.

Contents of hernias. In the common forms, femoral and inguinal hernia, we find the lower portion of the small intestine, sometimes the sigmoid flexure, particularly on the left side. In rarer cases the colon, the duodenum, or the jejunum, may form the hernial contents. The omentum may be present in the sac, either with the bowel or, rarely, alone.

Anomalies of contents. (*a*) The omentum, when present alone or with the intestine, is apt to become hyperplastic; it may originally have been only an epiploic appendage. (*b*) The part of the bowel forming the hernial contents may be a *diverticulum,* either Meckel's or a special one formed by the hernia itself in the following way: A large epiploic appendage becomes the contents of a hernia; it forms adhesions to the sac, through which traction is exerted on the bowel causing a portion of the wall of the latter to come down and enter the hernial pouch.

Causes of hernia. 1. *Exciting*—great efforts increasing the intra-abdominal pressure.

2. *Predisposing.* (*a*) A congenital weakness of the abdominal wall. (*b*) Repeated pregnancies. (*c*) Operations—laparotomy. (*d*) An abnormally long mesentery rendering the intestine more movable.

Changes in the hernial sac. Inflammatory changes are common, but as a rule are slight, leading only to adhesions between the sac and the surrounding tissues or between the sac and the bowel.

The intestine may slip back and leave the empty sac, the neck of which may become obliterated; the sac then remains as a simple cyst. In some cases it disappears entirely through the formation of adhesions.. When the bowel has becomes adherent to the sac the hernia is *irreducible,* a *reducible* hernia being one which can be

returned into the abdominal cavity. In reducing a hernia both bowel and sac may be reduced, or the former only, if the sac has formed adhesions to the surrounding structures.

Changes in the hernial contents. These are principally obstruction of which two degrees are described. (*a*) *Incarceration.* This is due to an accumulation of feces in the intestine, and is as a rule readily overcome. (*b*) *Strangulation.* This is obstruction in which the circulation of the wall of the gut is interfered with, in consequence of which disturbances of nutrition result, which terminate in necrosis. The circulation in a hernia is at all times precarious, and venous engorgement is easily produced. If the obstruction is slight, inflammatory changes set in and give rise to adhesions; severe obstruction leads to gangrene.

Dilatation and Diverticula. (*a*) Dilatation may occur above strictures. (*b*) It may be due to fecal accumulations. These in turn are dependent either upon habitual constipation or upon intestinal dyspepsia. (*c*) There may be a congenital defect, either in the muscular wall or in the innervation, circumscribed to a part of the bowel or involving the entire colon.

In false diverticula only a part of the intestinal wall is comprised in the dilatation. There is primarily a defective condition of the muscular coat, from fatty degeneration or other causes, which permits the mucous membrane to slip through and to bulge the serous coat outward. In time the mucous membrane may atrophy, leaving only the peritoneum. These diverticula occur near the attachment of the mesentery.

Meckel's diverticulum is the remnant of the omphalo-mesenteric duct, the embryonic communication between the intestine and the umbilical vesicle. It is variable in size, and is usually attached about one meter above the ileo-cecal valve.

Volvulus.—This is a twisting of the intestinal coils upon themselves. The condition is rare in a normal peritoneal cavity; as a rule there are bands of adhesions through which the bowel passes. The displacement interferes with the circulation and may lead to sloughing.

Intussusception, or Invagination is a condition in which one part of the bowel is driven into the part beyond. It occurs most frequently at the ileo-cecal valve, the valve and ileum being

invaginated into the colon. We might, indeed, speak of the normal position of the valve as one of intussusception.

The condition is most common in children; it gives rise to circulatory disturbances which may lead to gangrene and sloughing of the invaginated portion of the bowel, the case eventually terminating in recovery in this way. Intussusception is frequently produced during the death agony or immediately after death. It may be distinguished from that occurring under other circumstances by the absence of the signs of inflammation.

Inflammation of the Intestines.—(*a*) *Catarrhal inflammation.* This is due to irritants coming from the stomach or to irritants generated within the intestines. The former are represented by products of imperfect digestion or by noxious substances introduced from the mouth, as the saline purgatives. In the majority of instances an important part is played by the poisons elaborated by bacteria.

Macroscopy. The mucous membrane is soft, swollen, edematous, and covered with a slimy mucus or a fluid resembling pus. The discharges may be very liquid, and when the mucus and purulent matter are suspended in the fluid, the appearance resembles that of "meal-soup." In ordinary cases the redness disappears after death, except perhaps in a few coils that may have found their way into the pelvic cavity. In severe inflammations there may be a diffuse redness, from capillary injection, and an arborescent appearance from the filling of the small veins.

Follicular catarrhal inflammation is really a complication of the diffuse. If the follicles are prominently involved they present one of two appearances: in the early stages they stand out as minute red points; in the later stages, when they are apt to be most prominent, they are light in color from anemia, due to the compression of the vessels by the excessive cellular proliferation.

Superficial ulcers are common in acute inflammations, particularly on the valvulæ conniventes and the ileo-cecal valve.

Peyer's patches may be involved in follicular inflammation, but at times they escape entirely, even in typhoid fever. When affected in ordinary catarrhal inflammation they are prominent and have a smooth surface, differing in this respect from typhoid fever.

Ulcers occurring in follicular catarrh affect the lymphoid follicles and are deeper and somewhat undermined. They occur especially in subacute and chronic inflammations.

(*b*) *Purulent enteritis.* The suppuration is limited to the submucous tissue, and is the result of extension of ulceration in the mucous membrane or of embolism in pyemia.

Special Forms of Inflammation.—(*a*) *Inflammation of the duodenum.* This is readily diagnosed on account of the presence of hepatic disturbances. The inflammation extends up the bile duct and may lead to obstruction.

(*b*) *Inflammation of the cecum and appendix. Typhlitis* or, because most frequent in the appendix, *appendicitis.* The following conditions predispose to inflammation of the appendix. (1) The circulation in the appendix is precarious. Often there is no mesentery, the blood coming from the cecum—any obstruction at the base of the appendix will thus obstruct the circulation. (2) Being a closed sac, bacteria, especially the pyogenic forms, find a favorable nidus for growth in the appendix. (3) The same condition permits of the accumulation of foreign matter which acts as an irritant. (4) In many cases the appendix is bound down by adhesions or is misplaced, not infrequently presenting a condition bordering on volvulus.

In rare cases the inflammation is circumscribed to the cecum. In typhlitis and appendicitis the inflammatory process usually extends through all the coats, inducing a local or general peritonitis—in the local form abscesses are found about the cecum or the appendix. Gangrenous changes, with sloughing of the appendix, may at times occur.

A large number of bacteria are found in these inflammations; principally concerned are the pyogenic organisms and the bacillus coli communis, which may be the only one present in perityphlitic abscesses.

The immediate starting-point of appendicitis is a concrement that has found its way into the appendix from the intestines—usually it is fecal matter containing a large amount of lime salts. In many cases the nucleus is probably a foreign body, as a small seed. That this is not discovered in the majority of instances is probably due to the fact that the body has undergone calcareous change and has become unrecognizable.

Causes of Appendicitis. The following list is based on a review of 112 cases—(*a*) Fecal concretions (24); (*b*) foreign bodies (4); (*c*) tuberculosis (20); (*d*) diphtheritic inflammation (5); (*e*) typhoid fever (4); (*f*) puerperal abscess (3); (*g*) carcinoma (3);

(*h*) caries of neighboring bones (2); (*i*) strangulated hernia (2); cause unknown in 45 cases.

Tuberculosis of the appendix, it should be remembered, is more common than is generally believed.

Inflammation of the rectum. Proctitis. The exciting cause of this is irritants or the introduction of instruments; the tendency to congestion that exists is a predisposing factor. The inflammation is usually chronic and tends to penetrate through the wall, giving rise to periproctitis, with abscess formation or even gangrene. Abscesses, opening into the bowel or externally, lead to fistulæ—these are often tuberculous in origin.

Chronic Inflammation of the Intestines presents two stages—the hypertrophic and the atrophic.

(*a*) *In the hypertrophic stage* there is a hyperplasia of the mucous membrane; the crypts become tortuous, lengthened, at times branching, and in some cases cystic. About the crypts we find a round cell infiltration, which in places has been converted into fibrous tissue, and by pressure on the glands has caused the cystic change. The pressure of the connective tissue also leads to atrophy.

(*b*) *The atrophic stage.* In this we find the epithelium removed from extensive areas; the crypts become small depressions only, or are completely destroyed. The portions denuded of their epithelium have a map-like appearance. Pigmentation is common, sometimes in the hyperplastic and sometimes in the atrophic portions. Chronic inflammation is frequent in the large intestine, particularly in the cecum and ascending colon. Very often the hypertrophic and atrophic changes are combined, the former giving rise to polypoid projections, especially in the large intestine and rectum.

Infectious Diseases. (*a*) **Cholera Asiatica**—This is due to the comma bacillus, or spirillum of cholera.

The lesions of cholera are principally located in the intestinal tract; parenchymatous changes may occur in the other organs, but are most marked in the kidney.

The Intestine. Macroscopy. The peritoneum in death from cholera is dry and sticky. The mucous membrane of the bowel is diffusely injected and swollen, and presents here and there, particularly on the projecting portions, minute hemorrhages. In the early

stage the intestinal contents consist of a flocculent serous fluid—the "rice-water" discharges; in later stages they are more opaque and are described as "meal-soup" discharges.

In some cases the solitary follicles are especially involved, and appear, first as prominent red points, later, in the stage of reaction, as whitish projections on the red mucous membrane. The stage of reaction in cholera is characterized by a marked cellular proliferation in the mucous membrane, with a tendency to necrosis. The last may be circumscribed to the follicles; we then have minute ulcers, or it may be diffuse, affecting the valvulæ conniventes. The ulceration may be simple and superficial, or become diphtheritic—*i. e.*, be characterized by a false membrane, the result of coagulation necrosis.

Peyer's patches may be especially involved and may be the seat of simple or diphtheroid ulceration.

Microscopy. In the early stages we have as a characteristic feature, a marked proliferation of the epithelial cells of the mucous membrane and in the crypts of Lieberkühn, with a desquamation of the cells, and a tendency to hyaline degeneration of the cells and the basement membrane. In the bottom of the crypts, among the cells, we find the cholera bacilli. These penetrate to a slight depth into the basement membrane. They may be present in pure culture, both in the mucous membrane and in the intestinal contents.

The Kidney. The kidney in the early stages of cholera presents the characters of acute parenchymatous nephritis; it is enlarged, of a violet color, and soft; the cortex is swollen, and the entire surface of section looks opaque—as if the organ had been "boiled." The same appearance is met with in yellow fever; also at times in diphtheria, scarlet fever, and other infectious diseases.

Microscopy. The epithelial cells are swollen and almost fill the tubules; they are granular in appearance and some show an absence of the nucleus. Later the cells may break down into a granular mass, which by the aid of a coagulable material is converted into tube casts.

Etiology. The cause of cholera is the comma-shaped microorganism discovered by Koch in 1884. It is introduced with the drinking water, although its presence in water has not often been demonstrated successfully. Apart from this, the fact that the disease spreads down the streams of water is a point in favor of the water-borne theory of cholera.

The *cholera spirillum, or cholera vibrio,* is comma-shaped, shorter but thicker than the tubercle bacillus; its ends are thick, while other vibrios have pointed ends; it is motile, having a single cilium at one end; it is facultatively aerobic, and liquefies gelatin. The last two qualities help to distinguish it from other intestinal bacteria resembling it, since they are usually anærobic and non-liquefying.

Examination of the dejecta or intestinal contents of suspected cases. The examination should always be made as soon as possible. For this purpose it is best to pour the material into a black glass dish. A small flocculus is then picked up and spread on a cover-glass, and stained in the usual way, preferably with a weak solution of carbol-fuchsin. If nothing is found but a few epithelial cells and swarms of vibrios, the diagnosis of cholera can be made. But this condition is exceptional, and it is usually necessary to resort to cultivation, as described below.

In sending suspected material to a laboratory for examination, the use of disinfectants must be avoided. It is best, if the case has come to autopsy, to tie a coil of intestines containing the discharges at both ends, and ship it in a perfectly clean bottle, sterilized with boiling water. The bottle is then placed in a box of saw-dust impregnated with mercuric chlorid or carbolic acid. Specimens for histologic examination should be placed in alcohol or mercuric chlorid solution.

Cultivation. A flake of material is broken up in a tube of liquefied gelatin, and from this tube a second, and from that a third is inoculated; all are then poured into Petri dishes, and the latter placed aside at a temperature of from 20° to 24° C. The colonies will become apparent in 16 or 18 hours, and when examined with a low power lens present a characteristic appearance. They form a slight *concavity* on the surface of the gelatin, this being due to the fact that liquefaction occurs so slowly that evaporation can keep pace with it. The depression acts as a concave lens; when the lens of the microscope is depressed below the focus, the concavity becomes luminous; when it is raised, the image becomes dark. Other micro-organisms that might be present, either do not liquefy the gelatin at all, or liquefy so rapidly that the concavity is filled with fluid.

The concavity is quite characteristic, but not absolutely so, and the positive diagnosis cannot be made as a rule before the end of 24 hours, at which time the colonies become visible to the naked eye.

The surface of the gelatin, especially when the plate is held obliquely to the light, appears as if covered with a large number of *vesicles* that had been pricked with a needle. Between the 24th and 36th hour another characteristic feature appears—the concavity presents, when viewed with the microscope, *a ground-glass appearance*, as if it were covered with fine, shining granules. The colonies are not perfectly round.

In stab cultures in gelatin the cholera vibrio produces in 5 or 6 days the appearance of a small bubble at the upper part of the tube. This is also characteristic, and is due to slow liquefaction with evaporation. Hanging-drop and impression preparations should also be made.

The diagnosis of cholera can also be made by a chemical test. If ten drops of strong sulphuric acid are added to 8 or 10 c.c. of a culture of the cholera vibrio in bouillon or other liquid medium, a rose color, gradually deepening into purple, is developed. This is the *indol-reaction*, and depends upon the fact that the comma bacillus produces indol and also nitrites which are essential for the development of the reaction when sulphuric acid is added. Several other bacteria elaborate indol, but do not produce nitrites, and hence do not give the reaction unless nitrites be also added. The test should be performed as soon as a pellicle has formed on the surface of the culture fluid.

The growth of the cholera vibrio is associated with the production of two poisons—a *nuclein*, which is part of the protoplasm of the organism, and a *toxalbumin*, which is elaborated by it. One of the poisons produces a septic condition with fever—the symptoms of the later stages of cholera; the other gives rise to the great depression and fall of temperature peculiar to the early stage.

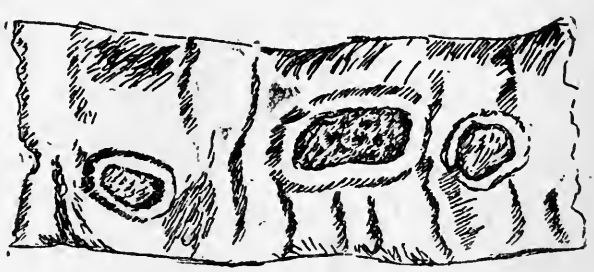
That the cholera vibrio is the cause of cholera has been proved by experiment. Ordinarily, when animals are fed with material containing the organisms, they do not take the disease. But if prior to the administration the gastric juice is neutralized with an alkali, and peristalsis is checked with opium, the animals develop cholera. The period of incubation is 48 hours or less.

Animals can be rendered immune to cholera; in man experiments have not been positive. Vaccination of animals is carried out as follows: A highly virulent culture is obtained by successive inoculations of the vibrio into guinea-pigs (peritoneal cavity), with occasional exposure of the bacterium in culture to the air. Finally,

the bouillon culture, previously heated to 70° C. to kill the bacilli, is inoculated into the peritoneal cavity of a guinea pig—the animal will become immune. *Haffkin* and *Klemperer* have performed experiments upon man. Klemperer found that after inoculating himself with the dead virus, his blood was able to render guinea-pigs immune; but he had not determined whether the blood did not possess the same property before the inoculation.

Typhoid Fever.—The disease is due to the bacillus of typhoid fever (bacillus of Eberth), infection taking place through the food or drink. The period of incubation is not definitely established.

The *lesions* of typhoid fever are most marked in the intestines. On the third or fourth day of the disease we find a general catarrhal inflammation, most pronounced in the region of the ileo-cecal valve. At the end of the first week the specific lesions appear; they consist in a *special hyperplasia and a peculiar necrosis of the lymphoid elements*. Peyer's patches and the solitary follicles become swollen and red; soon, however, in the beginning of the second week, the cell proliferation becomes so great as to compress the vessels and to cause an anemia. The swelling is due to an accumulation of round cells, and as this in the commencement only affects the lymphoid tissue, the latter projects above the connective tissue trabeculæ of Peyer's patches and gives to them a convoluted appearance. Later the trabeculæ as well as the surrounding tissues become infiltrated with round cells, hence the necrotic changes which take place at the end of the second and the beginning of the third week, extend beyond the confines of the plaques. Toward the end of the third week the necrotic tissue is thrown off; during the process perforation of the bowel or of a blood-vessel may occur. The typhoid ulcer has the shape of a Peyer's patch—its axis is usually longitudinal, sometimes transverse; or it may be round from the running together of several follicular ulcers.



Typhoid Ulcer.

The *lymphatic glands* of the mesentery are also swollen, but are not as a rule the seat of necrosis. Here and there a small portion of a gland may become necrotic, but the softened area is usually

absorbed. At times a gland breaks down completely, and by perforating into the peritoneal cavity gives rise to peritonitis.

The spleen is greatly enlarged.

In some cases the lymphoid tissue all over the body is involved, and ulcers form on the various mucous membranes.

Etiology. The cause of typhoid fever is the bacillus discovered by Eberth and subsequently studied by Gaffky. It is about the length of the tubercle bacillus, but much broader, somewhat bent, plump, with rounded ends; it has a large number of cilia projecting from the sides, and possesses a slow, wavy motion. It is facultatively aerobic, does not liquefy gelatin, and grows upon all media, but characteristically only on the potato. It stains easily, but readily yields up the stain; it is not stainable by Gram's method. Inoculations into lower animals have not been satisfactory. Bacteria are found in drinking water and in the intestines closely resembling the bacillus of Eberth; this is especially true of the bacillus coli communis, and it is held by some that the typhoid bacillus is only a modification of this organism. An important differential point is that the bacillus coli produces gas while the typhoid bacillus does not. Another point of distinction between the two, but one not always present, is their difference in growth on potato. The typhoid bacillus gives rise to an invisible film, while the bacillus coli produces a luxuriant visible growth. The main differences between the organisms may be tabulated as follows:

Bacillus of Typhoid Fever.	Bacillus Coli Communis.
Does not produce gas.	Produces gas in media containing glucose, lactose, or saccharose.
Transparent film on potato.	Visible growth.
Does not coagulate milk.	Coagulates milk.
Does not produce lactic acid in media containing milk-sugar.	Produces lactic acid in such media.
Does not produce indol.	Produces indol.
Motile.	Slightly, if at all, motile.

The typhoid bacillus is readily diagnosed in the tissues, the only organisms that might be confounded with it being those of putrefaction. When stained with Löffler's alkaline methyl-blue solution, the bacilli present themselves as deeply-stained blue masses. With an immersion lens it is usually possible to discover individual bacilli at the periphery of these masses.

Distribution in the body. The bacilli are found in the intestinal lesions, in the intestinal contents, in the spleen, in the mesenteric

glands, and in some post-typhoidal cold abscesses. They may also occur in the membranes of the brain, and give rise to certain of the cerebral symptoms of typhoid fever.

Sterilized cultures made in thymus gland bouillon have been injected for purposes of treatment, but without noteworthy results. Sterilized cultures of bacillus pyocyaneus have also been introduced into the body of patients, and seemed to lower the temperature and cut short the disease.

Dysentery.—This is a specific inflammation of the lower bowel that may be due to a variety of micro-organisms. Three forms are described—the catarrhal, the diphtheritic, and the gangrenous.

(*a*) *Catarrhal dysentery* presents no special feature, being the same as catarrhal inflammation in the small bowel. The process affects particularly the folds of the mucous membrane.

(*b*) *Diphtheritic dysentery.* In this, the most common form, we have a marked swelling of the mucous membrane, with coagulation necrosis. The casting-off of the necrotic tissue leaves deep, ragged ulcers. The process is generally subacute. There is a tendency in certain regions to hyperplasia, in others to atrophy, of the mucous membrane. This is quite characteristic and is usually associated with pigmentation.

(*c*) *Gangrenous dysentery* is rare; it leads to destruction of one or more of the coats of the bowel.

Etiology. The disease may be produced by irritant ingesta (*e. g.*, mercuric chlorid), but is usually due to micro-organisms. Many species have been found, but the real cause has not been established. With a certain type of dysentery, especially the epidemic form of the tropics, a protozoan, the *ameba coli*, seems to be intimately associated. This resembles the other amebæ, being a protoplasmic mass, 15 to 30 μ in diameter, therefore larger than a leukocyte. It has a nucleus and a granular protoplasm containing vacuoles, these being especially numerous when the ameba is resting. The ameba may be mistaken for a wandering connective tissue or plasma cell.

Examination. The stools should be examined while still warm, as the ameboid movement of the protozoa is then most active and renders their detection easy. If a portion of the blood-stained mucus is placed in a warmed slide, the ameba will be readily found, often in enormous numbers. The organism has been, it is claimed,

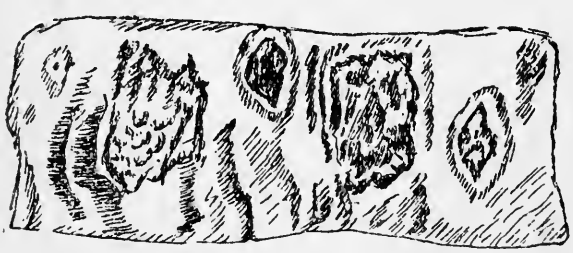
successfully cultivated in hay-infusion; the cultures when injected into the rectum of dogs and cats produced dysentery, as do also the stools of dysenteric patients. As amebæ are found in the normal bowel, they cannot be considered the only cause of dysentery.

The amebic dysentery of our climate is usually severe and apt to recur.

Abscess of the liver is a common complication of dysentery. In this abscess the ameba may be found alone, perhaps because the other organisms have disappeared; in other cases the ameba is associated with pyogenic bacteria; in still others, the latter alone are present.

Syphilis.—Acquired syphilis is common in the lower rectum and about the anus, but rare, if ever occurring, elsewhere in the intestine. Congenital lesions, in the form of extensive gummatous deposits, are at times found in the jejunum of the new-born. In the rectum, syphilis often leads to cicatricial stricture. The anal lesions are most common in women, and are condylomas, the result of infection by vaginal discharges.

Tuberculosis is very common and is probably present in all cases of advanced pulmonary tuberculosis. *Microscopically*, the lesions are the same as in other parts of the body; the naked-eye appearances are peculiar, the common lesion being a chronic ulcer with thickened edges. Gray tubercles can usually be seen on the floor of the ulcer. The outline is as a rule transverse to the axis of the gut; but at times it is irregular and may, especially when near the ileo-cecal valve, resemble the typhoidal ulcer. On the serous coat we find as a characteristic feature minute miliary tubercles which may extend around the bowel, following the line of the lymphatics. Cicatrization is rare, probably because the patients die before the process can be completed. The ulcers show no tendency to perforate. The most common seats of tuberculous lesions are the ileum, in the region of the valve, and the rectum. In the rectum perforation is common, and leads to peri-proctitis, to ischio-rectal abscess, or to fistula.



Tuberculous Ulcer.

Infection is due to the swallowing of sputum by patients suffering from pulmonary tuberculosis.

Tumors of the Intestines.—These occur chiefly on the prominent portions of the bowel, the ileo-cecal valve, the rectum; also at the flexures.

(*a*) *Adenoma* presents itself as a *polypoid* growth, usually due to hyperplasia, or as a *flat swelling*, the latter being most frequent in the rectum, just above the area of squamous epithelium.

(*b*) *Carcinoma* is generally cylindrical, and adenomatous in character. It is most frequent in the rectum, the cecum, and the flexures of the colon. Although rare in the small intestines, it occasionally occurs in the duodenum, at the entrance of the biliary-pancreatic duct. The cylindrical cancer appears either in the form of fungoid masses or as polypoid projections, and has a strong tendency to ulcerate. The epithelium is columnar and nicely arranged in a manner strongly suggestive of adenoma. *Squamous cancer* is found at the lower portion of the rectum and about the anus. It is apt to give metastasis to the inguinal glands.

(*b*) *Sarcoma* is rare as a primary, but more common as a secondary growth.

(*c*) *Lipoma*, and (*d*) *myxoma* grow from the submucous or subserous areolar tissue.

THE LIVER.

Anatomy. The liver is the largest glandular organ of the body, weighing about 1500 grams. It is made up of lobules or acini, in the center of which is the opening of the central vein, a branch of the hepatic vein. Radiating from this we have the liver cells—large epithelial cells containing a large vesicular nucleus and granular protoplasm. At the periphery of the acini we find the branches of the portal vein, the hepatic artery, the bile duct, and the lymphatics, all held together by delicate connective tissue, the capsule of Glisson. There are two currents of fluid in the liver—the one, in the portal vein and hepatic artery, from the periphery of the lobule to the center to empty into the central vein, the other, that of the lymph and bile, from the lobule outward to empty into the perilobular vessels.

Functions. (*a*) The liver elaborates bile which aids in *digestion*, as it contains a fat-emulsifying substance and a diastatic ferment; it promotes the absorption of the products of digestion through the

intestinal walls, stimulates peristalsis, and acts as the natural antiseptic of the bowel. (*b*) The liver has important *nutritive* or *metabolic* functions, which are not yet thoroughly understood. It manufactures glycogen, a starch-like body, which is converted into glucose by a ferment present in the blood. The sugar thus produced is under normal conditions rapidly oxidized, and no excess occurs in the blood. In certain pathologic states, as in diabetes, the blood becomes surcharged with sugar, which in part passes off with the urine. This accumulation of sugar may be due to an increased formation, probably brought about by the blood remaining longer in the liver than normally, or to an imperfect action of the oxidative processes by which sugar is normally destroyed. (*c*) The liver also possesses certain eliminative functions, and (*d*) is concerned in the neutralization of many poisons absorbed from the digestive tract.

Disturbances of Circulation.—(*a*) *Active congestion* occurs physiologically as the result of over-feeding; it is also seen in diabetes, and it is probable that the form of diabetes brought about by injury or disease of the floor of the fourth ventricle, is due to congestion of the liver. A similar congestion results from section of the sympathetic fibers going to the organ.

(*b*) *Passive congestion* is the result of heart and lung disease, and usually appears very early since the hepatic vein empties almost directly into the right auricle. The first effect is the overfilling of the central vein; the surrounding lobule subsequently undergoing various changes. If it becomes fatty, we get the condition of "nutmeg liver," or "fatty nutmeg liver," so-called on account of the contrast presented by the dark central vein and the light periphery. In other cases, the hepatic cells atrophy, either as a primary change or secondarily to the fatty degeneration. We have then a dark center surrounded by a grayish lobule consisting chiefly of connective tissue, the increase of which is partly relative, from atrophy of the parenchyma, partly due to active hyperplasia. Such a liver is known as "atrophic nutmeg liver." Finally, there may be cases in which the peripheral parts of the lobules are also congested and are the seat of the deposit of blood pigment.

Infiltrations and Degenerations.—(*a*) *Pigmentary infiltration* is very common, particularly in the periportal connective tissue; in advanced cases the liver cells are also affected. The pigment consists of reddish-brown or orange-colored granules of

hemosiderin. The causes of pigmentation are (α) malaria and (β) pernicious anemia, both bringing about a destruction of the red corpuscles; also (γ) passive congestion. In pernicious anemia the pigment may be colorless; it contains iron, and therefore turns black when the section is treated with $(NH_4)_2S$.

(*b*) *Fatty infiltration* is normal in the liver, but is also very frequent as a pathologic change. In mild cases the fat is deposited at the periphery of the acini in the form of large, shining droplets, in severe cases all the cells may be filled with drops of fat. The liver is enlarged, anemic, and either uniformly yellow or streaked with pale lines. The causes of fatty infiltration are general obesity, pulmonary tuberculosis, and the abuse of alcohol.

(*c*) *Fatty degeneration* is produced by infectious fevers, poisons, and grave anemias, and also accompanies advanced cases of fatty infiltration. In the infectious fevers it is generally preceded by cloudy swelling.

(*d*) *Amyloid degeneration* is common in the liver and is generally associated with amyloid disease in other organs, being due to chronic suppuration, as in tuberculous and syphilitic bone disease.

Acute Yellow Atrophy is an acute disease characterized by a rapid degeneration of the liver cells, beginning as cloudy swelling and quickly passing on to fatty degeneration, breaking-down and removal of the cells. The liver is greatly reduced in size, soft, almost fluctuating, and variegated in color, presenting areas that are yellowish from fatty change and others red from congestion and hemorrhage. *Microscopically*, we find the evidences of an intense fatty degeneration, the outline of the cells is lost, the nuclei have disappeared, and the protoplasm is converted into fat granules, which may coalesce to form droplets. In places there is marked congestion, with hemorrhage from the capillaries and the deposition of blood pigment. The presence of an excess of blood is quite characteristic of acute yellow atrophy. Crystals of leucin and tyrosin are present.

Etiology. The cause is not definitely known, but it is probable that it is an acute infection. In phosphorus and arsenic poisoning the liver may present a condition resembling that of acute yellow atrophy. The process is, however, less acute.

Inflammations. 1 **Acute Interstitial Hepatitis. Acute Suppurative Hepatitis. Abscess.** — Abscess is always micro-organismal and may be due (*a*) to infection along

the bile ducts, after obstruction of the latter by gall-stones, or by extension of infection from the duodenum; (*b*) to pyemia; (*c*) to extension of a suppurative process from neighboring organs, as the peritoneum, pleura, stomach, or intestines; (*d*) to wounds; (*e*) to dysentery.

The abscess of the liver due to dysentery is usually a single, large, deep-seated abscess, rarely consisting of two or three communicating cavities. As already stated, it may be associated with the presence of the ameba coli or of the pyogenic organisms, or of both simultaneously. The pyemic abscesses are multiple, small, and situated near the periphery of the organ.

Histologically, we find, as in all other organs, that the archiblastic tissues break down rapidly, undergoing first cloudy swelling, later coagulation necrosis and fatty degeneration.

2. **Chronic Interstitial Hepatitis, or Cirrhosis,** is characterized by a hyperplasia of the connective tissue, involving especially the connective tissue between the acini. If the acini become involved, the change affects as a rule only their peripheral portions, the center remaining healthy. Histologically, we find the following: (*a*) round cell infiltration, (*b*) formation of new connective tissue, (*c*) multiplication of the biliary passages, (*d*) atrophy of the liver cells, chiefly at the periphery of the acini.

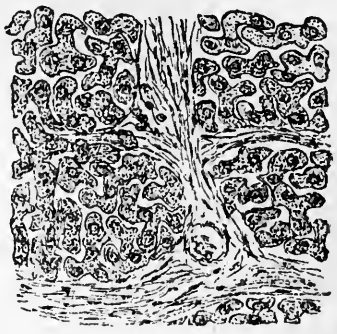
Two forms of cirrhosis are described, the atrophic and the hypertrophic.

(*a*) **Atrophic Cirrhosis.**—In this we have an overgrowth of the connective tissue with a tendency to contraction. The hyperplasia is chiefly perilobular, or "periportal," and does not as a rule penetrate into the acini.

The process is very slow, and although there is a marked round cell infiltration in the early stages, the liver is not made larger, as contraction in one part goes hand in hand with proliferation in another. At an early period, before the cirrhosis has actually begun, the liver may be enlarged somewhat from congestion and fatty infiltration. In the later stages the organ is always reduced in size.

Macroscopy. The surface of the liver is finely granular or marked by coarse projections ("hob-nail liver"), depending upon whether the connective tissue surrounds a single or several lobules. On section we see the acini sharply outlined by grayish bands of fibrous tissue; in the center of the acini the liver cells still preserve

their normal yellowish color. The organ is firm, small, and cuts with considerable difficulty. *Microscopically*, the connective tissue is seen to be rich in blood-vessels, and shows even in the later stages a round cell infiltration. There is also a hyperplasia of the bile-ducts, new tubules being scattered through the connective tissue. This is a strange phenomenon not easily explained. The liver cells at the periphery of the acini are atrophic and may be fatty.



Atrophic Cirrhosis of Liver.

Results. The hyperplasia and contraction affect chiefly the branches of the portal vein running in the perilobular tissue, and necessarily interfere with the circulation through these vessels. Passive congestion in the area drained by the portal vein results and causes the majority of all the symptoms of cirrhosis. There is congestion of the gastro-intestinal tract (hemorrhoids, hemorrhages from stomach or intestines), ascites, and collateral dilatation of small veins in the abdominal wall which attempt to carry the blood from the intestines to the vena cava. The spleen is also enlarged from passive congestion.

The hepatic artery and its branches are not involved; as the biliary passages also escape, jaundice is but rarely present.

Etiology. In regard to the causes of cirrhosis of the liver (as well as of other organs) we meet with the same difference of opinion as that to which allusion was made in the chapter on primary degenerations of the nervous system. According to one theory, the primary change is a degeneration of the liver cells, the connective tissue remaining relatively in excess or undergoing a secondary hyperplasia. According to another theory the connective tissue hyperplasia is primary and the archiblastic changes secondary. Both theories are probably correct, some cases being explicable by the first, others by the second.

Thus in the cirrhosis following phosphorus poisoning there is no doubt a primary degeneration of the cells, the excess of connective tissue being in part relative, in part an actual overgrowth. Again, in the cirrhosis accompanying chronic obstruction of the bile-ducts, there is a primary atrophy of the liver cells from pressure by the distended biliary passages, the connective tissue becoming secondarily hyperplastic. The same thing is true of cirrhotic

conditions following other forms of pressure (tight lacing, pressure of tumors, etc.).

In the ordinary form of cirrhosis, however, there is unquestionably a primary hyperplasia of the connective tissue, the atrophy and degeneration of the parenchyma being a secondary occurrence.

The cause of the connective tissue hyperplasia is usually the presence of irritant substances in the portal blood, the most common being alcohol. In other cases the irritant is not known, the cirrhosis in these instances being a part of a general sclerotic process, affecting the arteries, the liver, kidney, and heart. The irritant is probably of metabolic origin, its elaboration being favored by old age.

Hypertrophic Cirrhosis is an entirely different disease and is characterized by hyperplasia of the connective tissue throughout the organ, without a tendency on the part of the new tissue to contract. The hyperplasia occurs in successive attacks, each attack being accompanied by fever, pain, increase in the size of the organ, and jaundice.

Macroscopy. The organ is enlarged, smooth, firm, olive-green in color, or light-green when fatty degeneration is also present.

Microscopy. There is a prominent round cell infiltration, both periportal and between the liver cells of the acini; the tendency to the formation of connective tissue is slight. There is also a marked hyperplasia of the bile-ducts, greater, indeed, than in the atrophic cirrhosis.

Results. There is no interference with the portal circulation, hence dropsy is absent. The biliary capillaries, on the other hand, are greatly compressed by the presence of the round cell infiltration between the liver cells; jaundice is, therefore, common.

Etiology. The causation of hypertrophic cirrhosis is obscure; the disease is more common in the Southern States, and may be infectious.

Tuberculosis of the liver is not common; when it occurs, it is usually miliary, the tubercles being as a rule so small that they are only demonstrable with the microscope. Cheesy nodes are very rare.

Syphilis is rare in all viscera, but is perhaps relatively more common in the liver than in any other viscus, the usual lesion being the gumma.

Tumors.—Primary tumors are less common than secondary.

(*a*) *Adenoma* is quite a frequent primary growth. It is generally multiple, small in size, rarely larger than a cherry, and as a rule is situated near the periphery of the organ. It is grayish in color or if very vascular, reddish. *Microscopically*, the adenoma is of the tubular variety, which is not strange when we remember that the liver is primarily a tubular gland, as may be seen in the human embryo, in some of the lower animals, and even on careful study in the adult human liver.

(*b*) *Cystic adenoma* springs from the small mucous glands of the bile ducts, is multiple, and as a rule larger than the simple adenoma.

(*c*) *Cancer* is rare as a primary, but very frequent as a secondary growth. *Primary cancer* appears in three forms:

1. *Massive cancer*—single, large, circumscribed masses, resembling secondary growths. When metastasis takes place, the secondary nodes are found also in the liver, in close proximity to the primary tumor.

2. *Diffuse cancer with cirrhosis, or cirrhotic cancer.* The liver presents a marked overgrowth of connective tissue, through the meshes of which the cancer nests are scattered. The disease is distributed uniformly throughout the organ.

3. *Periportal cancer.* This is characterized by the development of cancer about the branches of the portal vein, beginning at the entrance of the vein and presenting the largest mass at the transverse fissure, and thence accompanying the vessel to its finest branches. It is distinguished from cirrhotic cancer by the fact that it begins at the entrance of the large vessels and extends to the smallest, while the latter is first found as a rule in the connective tissue between the acini, in the region of the small portal veins.

The cells of cancer of the liver are generally polymorphous; occasionally cancers containing only cylindrical cells are found.

Secondary cancer appears in the form of multiple, circumscribed, whitish nodes, contrasting markedly with the dark liver substance. The larger nodes possess a capsule. Softening is quite common in the interior of the growths, and leads to a depression of the surface—a condition known as "umbilication"—which is also observed, though more rarely, in the primary cancer of the first variety.

Metastatic cancer is generally secondary to carcinoma of the stomach, in which case the nodes possess the characteristics just given. If the metastasis is from a cancer of the esophagus or the breast, the secondary growths are generally infiltrating and not encapsulated.

Sarcoma is rarely primary; as a secondary growth, the melanotic sarcoma is the most frequent, being generally secondary to a similar tumor in the eye. The metastatic growths are as a rule pigmented like the primary, but, rarely, there may be a kind of double metastasis, some of the secondary nodes being pigmented, others not. In most instances the other abdominal viscera are also involved in the metastasis.

Angioma is the most frequent simple tumor of the liver, and is of the cavernous type. It occurs especially in the old, and does not impair the function of the liver; therefore, it is rarely diagnosed during life. It is small, circumscribed, dark in color, and is generally situated on the surface of the organ. There may be two or three tumors, rarely more.

Fibroma is quite rare. A few cases of *neuro-fibroma*, *i. e.*, a fibroma extending along the nerves of the liver, have been described.

THE BILIARY PASSAGES.

Biliary Calculi.—This is the most important morbid condition affecting the biliary passages. Calculi are most frequently found in the gall-bladder, but are met with elsewhere in the passages, either in the common duct or in the branches higher up. In size they vary from minute granules to large masses. They may be single, when they are round and smooth; or multiple, when they are faceted from mutual pressure. Their color varies from light-yellow to a deep greenish-black. The center is usually dark, even in the light-colored stones, and is surrounded by a paler area having a crystalline or radiating arrangement. The center or nucleus is composed of inspissated bile, which may form the whole of the stone, but as a rule the outer layers consist of cholesterin.

Causes. Two factors appear to be necessary—a central nucleus and an altered composition of the bile. The nucleus is usually a foreign body, either something from the intestines or a mass of loosened epithelial cells. The change in composition, the more important factor, results from stagnation of the bile in its passage to

the intestines. The bile becomes inspissated, and the cholesterin, which normally is held in solution by the salts of the biliary acids, is precipitated on account of a deficiency of these salts. Perhaps bacteria are concerned in the production of these chemical changes.

Effects of gallstones. Pain is the most prominent symptom attending their passage. When they obstruct the duct, jaundice results from absorption of the bile. The irritation of a calculus may lead to inflammation or ulceration of the duct, or even to perforation. Perforation may take place into the bowel, and this is the only way in which the escape of very large stones can be explained. It may also occur into the peritoneal cavity or externally.

The passages above an impacted stone become dilated, and this dilatation is apt to lead to connective tissue hyperplasia, or cirrhosis, around the ducts.

Inflammation of the Bile Passages.—(*a*) Mild or catarrhal forms are very common, being usually due to extension of inflammation from the duodenum. The mucosa may be so swollen, or mucus may accumulate to such an extent, that obstruction and jaundice result. Recovery, without permanent lesion, is the rule.

(*b*) There may be severe inflammation, with tendency to suppuration and ulceration. This is apt to occur in cases of gallstone. Bacteria no doubt play an important part in those inflammations. Under normal conditions the bile destroys the bacteria which have ready access to the bile passages from the intestines. In cases of disease, however, many organisms are found in the bile. They may be the starting point of the chemical changes through which gall stones are formed.

These severe inflammations may lead to septicemia or pyemia; or obstruction may result from cicatricial contraction and give rise to cystic changes of the gall bladder or ducts, or to a cirrhotic condition of the liver.

Tumors.—Cancer of the liver may spring from the bile passages.

CHAPTER XII.

THE RESPIRATORY ORGANS.

THE NASAL CAVITIES.

The nasal cavities are lined by columnar ciliated epithelium; the upper part of the mucous membrane is olfactory, the lower respiratory. Mucous glands are present in great abundance. The submucosa is erectile, particularly in the region of the lower turbinated bones.

Circulatory Disturbances.—(*a*) *Congestion* of the erectile tissue precedes inflammation, but also occurs periodically from obscure causes, and gives rise to curious reflex symptoms, as asthma, cough, epilepsy, ocular and uterine disturbances.

(*b*) *Hemorrhage. Epistaxis.* This may be due to the periodic congestion just described, to passive congestion from heart disease, to liver disease, to the hemorrhagic diseases, like hemophilia and scurvy, to infectious diseases, or it may be vicarious.

Inflammation. Acute Rhinitis or **Coryza.**—All acute inflammations of the nose are of bacterial origin, the bacteria being those that are normally present in the nasal mucus. Even the tubercle bacillus has been found in healthy nasal mucous membranes.

Coryza is characterized by a marked proliferation and desquamation of cells, which undergo a rapid mucoid degeneration. The exudation is at first thin—sero-mucous—containing ciliated epithelium and a few leukocytes. Later it becomes more purulent. The process may extend to the sinuses communicating with the nose or to the larynx and trachea.

Etiology. As already stated, the true cause is bacteria; cold, however, plays an important part, but just how it acts, is not definitely known—perhaps by altering the character of the secretion it prepares the mucous membrane for the infection. The disease is communicable from one individual to another.

Suppurative rhinitis is due to infection with the glanders bacillus or the gonococcus, or to extension of suppuration from the neighboring tissues, as the bones.

Chronic Rhinitis is the result of frequent attacks of acute rhinitis, or of certain infections, as tuberculosis, syphilis, and chronic glanders. Two varieties are recognizable: the hypertrophic and the atrophic. In the *hypertrophic* the mucous membrane is thickened from a hyperplasia of the connective tissue, the epithelium, and the mucous glands. The hyperplasia may be circumscribed and give rise to tumor-like masses termed *polyps*. The atrophic form is a secondary process, being the result of the contraction of the hyperplastic connective tissue or of the healing of ulcers.

Ozena is a form of chronic rhinitis accompanied by fetid discharges. It is generally due to syphilis or tuberculosis involving the bones, but may be the result of an atrophic rhinitis with ulceration.

Syphilis may give rise to condylomata, or to gummata affecting the cartilages, bones, periosteum, or perichondrium, the breaking-down of which produces extensive destruction; it may also lead to a hyperplastic form of rhinitis, which terminates, like the simple hypertrophic, in atrophy and ozena.

Tuberculosis occurs in the form of miliary tubercles or tuberculous ulcers, the latter being more common than is generally assumed. It is possible that these nasal lesions may be the source of meningeal tuberculosis in children.

Occasionally, *lupus* of the face extends inward to the nasal mucous membrane.

Glanders is common in the nasal mucous membrane of the horse; it has a marked tendency to cause suppuration, and runs an acute course, ending in death. In man the disease affects the nose less frequently, and is more chronic.

Tumors.—(*a*) *Mucous polyps* are the most frequent tumors in the clinical sense, but, pathologically, the majority must be considered *inflammatory hyperplasias* of all the structures of the mucous membrane, with myxomatous degeneration in the epithelium. Very often they are cystic from occlusion of the glands and distention of these by mucoid secretion. In rare cases the polyp is a true tumor, a *myxoma*. The most frequent seat of polyps is about the middle turbinated bone. They tend to recur after removal.

(*b*) *Fibroma*, hard and soft, spring from the basilar process of the occipital and sphenoid bones.

(*c*) *Chondroma*, *osteo-chondroma*, and *osteoma*, are rare; they occur most frequently in the sinuses.

(*d*) *Sarcoma* may develop on the septum or the posterior parts of the nasal cavity.

(*e*) *Cancer* is rare, and is usually a squamous epithelioma extending inward from the face.

THE LARYNX.

Anatomy. The mucous membrane of the larynx is covered in greater part by columnar ciliated cells, but on the epiglottis there are patches of squamous epithelium, from which, as a center, processes of squamous epithelium radiate downward toward the true vocal cords; the latter are covered entirely by squamous cells.

Malformations of the larynx are not common. As the result of imperfect union of the branchial clefts, fistulæ may arise, although these are more frequent in the pharynx.

Hypoplasia of the larynx may occur. A condition termed "emphysema of the neck" is due to dilatation of the ventricles of the larynx.

Circulatory Disturbances.—(*a*) *Active hyperemia* is common, but rarely shows after death, on account of the squeezing out of the blood by the contraction of the elastic tissue, which is very abundant in the larynx.

(*b*) *Passive hyperemia* is due to valvular heart disease.

(*c*) *Hemorrhage*, in the form of minute, pin-point size extravasations, occurs in acute inflammations, in death from suffocation, and in the purpuric diseases.

(*d*) *Edema of the glottis* may be due to Bright's disease or heart disease, but most commonly is caused by inflammatory processes, especially when these are deep-seated and accompanied by ulceration. It affects the loose cellular tissue at the base of the epiglottis; also the false vocal cords and the ventricles. This form of edema is not a passive transudate, but is inflammatory and is accompanied by an extensive leukocytic infiltration; in some cases it is purulent.

Inflammation.—(*a*) *Acute catarrhal laryngitis* is characterized by congestion and punctiform hemorrhages in the mucous membrane, by an increased secretion of mucus, and by desquamation and mucoid degeneration of the epithelial cells. Superficial ulcers may form. In some cases the inflammation is chiefly follicular, the swollen follicles standing out first as reddish, later as whitish points. They may break down and form deep ulcers. The follicular form affects particularly the epiglottis, the aryepiglottic folds, the false

vocal cords, and the ventricles. The causes of acute laryngitis are infectious diseases, such as measles, small-pox, influenza, typhoid fever, and irritating vapors; it may also occur in association with chronic ulcerative processes.

(*b*) *Chronic laryngitis* presents itself in two forms: (1) the hypertrophic and (2) the atrophic. In the first the mucous membrane and submucous tissue are greatly thickened, forming in places warty projections, "pachyderma laryngis." The atrophic form is due to the contraction of the new tissue with the formation of cicatricial bands, and is usually secondary to ulceration. Deformity of the larynx may be produced and lead to interference with speech.

(*c*) *Croupous laryngitis.* The formation of false membranes in the larynx is usually due to the bacillus of diphtheria, but may be brought about by irritants, as steam, and by other micro-organisms, as that of typhoid fever. Typhoid fever may also cause a simple catarrhal inflammation.

Diphtheria of the larynx is usually secondary to pharyngeal diphtheria, and is a more superficial process. The larynx does not possess a very loose submucous connective tissue nor an abundant lymphatic supply, hence absorption is not active, and constitutional symptoms not marked. The local symptoms are, on the other hand, very severe, and death often results from suffocation. The disease may extend down the bronchial tubes; by the inhalation of infected particles, broncho-pneumonia may be set up.[1]

(*d*) *Suppurative laryngitis.* This may be (1) a purulent infiltration analogous to edema, or (2) it may be in the form of localized abscesses. The process at times extends to the perichondrium, inducing a suppurative perichondritis which in turn leads to destruction of the cartilages. Portions of these may become separated, and, falling over the glottis, cause death by suffocation. Perichondritis is usually connected with chronic ulceration, as from syphilis and tuberculosis, but may be due to typhoid fever or diphtheria.

Tuberculosis is very common. Although it may be primary, it is in the vast majority of cases secondary to tuberculosis of the lung, infection taking place either through the blood or through the sputum. The lesions usually begin in the posterior wall, between the arytenoid cartilages and in the aryepiglottic folds, although they are not circumscribed to these regions. The tubercles are primarily submucous, and give rise at first to a simple

[1] For details concerning the bacillus of diphtheria see *Pharyngeal Diphtheria*, in Chapter XI

swelling; later, running together, they break down and lead to the formation of slowly-healing ulcers. Eventually the ulceration may extend to the perichondrium and cartilages. That healing of such ulcers is possible, has been proved; but while cicatrization proceeds in one region, the disease spreads in another, consequently complete cure is very rare. This was demonstrated during the tuberculin treatment.

Lupus is a rare form of tuberculosis of the larynx, and is generally an extension of lupus of the pharynx, where it may be primary.

Syphilis is less common than tuberculosis, and differs also in the fact that it is usually a downward extension from the pharynx (like lupus), while tuberculosis begins below and travels upward. The extension is along the anterior wall; this, together with the decided tendency to cicatricial contraction, is quite diagnostic of syphilis.

The disease presents itself in the form of mucous patches, gummy tumors, and simple catarrhal inflammations. The last are not characteristic, but are ordinary catarrhal inflammations, seemingly kept up by the syphilitic poison.

Tumors. (*a*) *Papilloma.* There is in the larynx, as in the nose, a marked tendency to hypertrophy of the mucous membrane; the tumors, however, are not as a rule polypoid, *i. e.*, myxomatous, but are *papillomatous.* Two varieties of papilloma are described, the *hard* and the *soft.* In the former we have a tendency to the formation of hard, horny excrescences, consisting of the hypertrophy of the papillæ and a thickening of the epithelium, and producing a pachydermatous condition (*pachyderma laryngis*). In the soft the hypertrophy affects mainly the papillæ, and gives rise to extensive dendritic growths, covered only by a thin layer of epithelium. These are termed *acuminate condylomata*, or "warts of the larynx." The soft condylomas may at times be true myxomas, and grow from the interior of the ventricles.

Papillomata occur especially about the true vocal cords, but may extend upward to the epiglottis, and also downward, having a tendency to cause "squamous invasion," that is, to induce a transformation of the columnar epithelium into the squamous variety. Papillomata constitute 67 per cent. of all laryngeal tumors, and are usually due to repeated irritation, such as is caused by smoking or speaking, or they may be developed about the borders of chronic ulcers.

(*b*) *Fibroma* may be hard or soft, and grows most frequently from the vocal cords, the aryepiglottic folds, the base of the epiglottis, and the ventricles. It is generally single, but may present numerous excrescences.

(*c*) *Myxoma* is rare.

(*d*) *Sarcoma* is a rare growth in the larynx, but a primary spindle-cell sarcoma sometimes springs from the epiglottis.

(*e*) *Carcinoma* is common, and is either the result of extension from the esophagus, the tongue, or other neighboring part, or is primary, occurring about the true vocal cords, at the entrance of the ventricles. It appears as if the papillomatous tumors at times take on an epitheliomatous formation.

Cancer is usually squamous, but may be cylindrical. The papillomatous excrescences surrounding the cancer may give rise to errors in diagnosis.

THE BRONCHIAL TUBES.

Anatomy. The bronchial tubes are a system of dichotomously dividing tubes lined by mucous membrane, on the outside of which is connective tissue containing cartilaginous plates, smooth muscle tissue, and elastic fibers, the last being especially abundant where the cartilaginous rings are incomplete. The bronchi are abundantly supplied with racemose mucous glands extending deeply, even into the cartilages. The epithelium is columnar and ciliated down until tubes of one millimeter caliber are reached, when the epithelium loses its cilia and becomes cuboidal, while the tubes themselves are deprived of their cartilages and mucous glands. The terminal bronchioles open into the air-passages, which in turn open into the infundibula. In the walls of the latter we find the air-vesicles, lined with a flat epithelium.

Hyperemia may be active or passive—the former occurring in the early stages of inflammation, the latter as a consequence of disturbances in the general or the pulmonary circulation, especially from valvular heart disease. Active hyperemia is apt to disappear after death.

Inflammation. Acute Bronchitis is due to irritants, particularly to exposure to cold. The *catarrhal* form is characterized by congestion, swelling, and opacity of the mucous membrane, an increased secretion of mucus, and punctiform hemorrhages. In rare cases the racemose glands, which usually are invisible,

are especially involved, causing a *follicular catarrhal inflammation.* The exudate is at first thick and tenacious, consisting chiefly of mucus; later it becomes more liquid, and, from an admixture of pus, yellowish in color. In some cases the exudate is liquid and very abundant, and gives rise to *serous bronchitis* or *bronchorrhea.*

Microscopically, we find proliferation, desquamation, and degeneration of the surface epithelium, together with evidences of true inflammation of the submucous connective tissue, namely, a round cell infiltration and a dilatation of the blood-vessels. If the outwandering of the leukocytes is marked, the exudate becomes muco-purulent or purulent.

Croupous Bronchitis may be the result of the extension of a croupous laryngitis, being due to the Klebs-Löffler bacillus, but this form rarely becomes a prominent feature. There is another variety which comes on periodically in certain individuals who may or may not be the subjects of chronic bronchitis. They are suddenly seized with violent cough and dyspnea, which last four or five days, and are relieved by the expectoration of fibrinous membranes, *i. e.* casts of the bronchial tubes. In the substance of these casts we find Charcot-Leyden crystals and eosinophile cells.

In many cases of asthma a similar condition exists—a coagulation necrosis affecting the smaller bronchial tubes, and giving rise to the expectoration of spiral fibrinous coagula having the shape of twisted bands, and containing Charcot-Leyden crystals and eosinophile cells.

Chronic Bronchitis results (*a*) from *frequently repeated acute attacks.*

(*b*) From *disturbances in the circulation* of the lungs. Under this head come (1) the bronchitis occurring in the old. One of the first evidences of advancing age is "loss of wind," associated with imperfect circulation in the lungs. (2) The bronchitis dependent on congestion due to valvular heart disease. (3) The chronic bronchitis of childhood, associated with engorgement of the lymphatic glands and lymphatic channels.

(*c*) *Tuberculosis* of the bronchial tubes or of the lungs.

(*d*) *Peribronchitis.* All forms of chronic bronchitis are accompanied by peribronchitis, and even in the acute there is a slight degree of peribronchial inflammation. In some cases the peribronchitis is primary, and forms the starting-point of a chronic

bronchitis. Two forms of peribronchitis may be described: the *fibrous* and the *suppurative*. Both extend inward from the pleura, either that of the hilum (the bronchial glands) or that in contact with the costal pleura. In the fibrous form there is a marked thickening outside of the bronchial tubes. The suppurative is the result of extension of a suppurative process in the pleura along the lymphatics, the subpleural lymph channels being first involved. A similar appearance is produced by engorgement of the subpleural and pulmonary network of lymphatics, but the lines of injection are somewhat paler, and on section exude clear lymph. The cause of this engorgement is pressure, chiefly by an hypertrophied heart, on the mediastinal and bronchial lymphatic glands. At times the condition resembles miliary tuberculosis in appearance, but is distinguished by the presence of fluid on section.

Chronic bronchitis has two stages: a *hypertrophic* and an *atrophic* stage. In the former there is swelling of the mucous membrane, cellular infiltration of the submucous tissue, hyperplasia of the glands, and a tendency to dendritic formation. The atrophic is a terminal stage of the hypertrophic, and may follow with or without preceding ulceration. There is either complete absence of the epithelial lining or the formation of an irregular cuboidal or even squamous epithelium.

Tuberculous bronchitis affects especially the smaller tubes, and gives rise to a desquamative process, resulting in an abundant accumulation of cells without the presence of much fluid. The cellular masses undergo caseous change, and eventually liquefaction, and are discharged, leaving tuberculous ulcers. The process may then extend to the surrounding tissues and set up a *tuberculous peribronchitis*, or tuberculosis of the lung substance proper.

The macroscopic appearance of the cases in which the disease began in the bronchi is characteristic, and should always be recognized. On examination the cut surface of the lung presents little projecting masses, each with a central opening, which is the bronchial tube. The walls of the tube are thickened from bronchitis and also from peribronchitis. As a rule, the peribronchial hyperplasia shares in the caseation, but in some cases it goes on to the formation of fibrous tissue (fibrous peribronchitis), a process by which healing may be brought about.

Obstruction of the Bronchial Tubes may be acute or chronic. (*a*) *Acute obstruction* is generally due to an accumulation

of mucus and to swelling of the mucous membrane in acute bronchitis. It may lead to atelectasis, to catarrhal pneumonia, or to acute emphysema.

Acute emphysema is brought about in the following way: The obstruction acts as a valve permitting the entrance but not the exit of air. Efforts of coughing, not being able to expel the confined air, will induce a dilatation of the air-vesicles, and at times minute ruptures in their walls, with the production of interstitial emphysema. *Atelectasis*, following obstruction of a bronchus, may be the result of a valve-like action on the part of the obstructing body, which permits the exit but not the entrance of air. This is exceptional; the more frequent cause of the atelectasis is the absorption of the air. The failure of the blood to be aerated leads to stagnation—a condition which predisposes to *catarrhal pneumonia*, since it renders the part a favorable nidus for micro-organisms.

(*b*) *Chronic obstruction* occurs in chronic affections of the bronchial tubes from cicatricial contraction; also from the presence of a foreign body, or from pressure from the outside, as by an aneurysm. The consequences are (1) obliteration of the air-vesicles, the part of the lung supplied by the bronchus being converted into a scar; (2) gangrene; (3) ulceration, the character depending on the micro-organisms present. If the tubercle bacillus is present, it sets up its special lesions. (4) Dilatation.

Dilatation or **Bronchiectasis** may be (*a*) *sacular* or (*b*) *cylindrical.* Two factors are necessary for the production of dilatation: (1) a weakening of the tube, and (2) a distending force. The weakening of the walls is generally due to chronic inflammations, particularly those accompanied by atrophic changes. If it is uniform, the dilatation will be cylindrical. Such dilatations are most common in the lower lobes, and affect especially the larger bronchi. The distending force is nearly always *inspiratory*, and acts upon the part of the bronchus between the obstruction and the trachea. The resistance to the entrance of the air may be constituted by an obstructing body, or there may be an area of atelectasis. According to some authors, the distending force is expiratory, the dilatation occurring behind the obstructing body, which is supposed, in such cases, to have a valve-like action, allowing the entrance but not the escape of the air. *Saccular* dilatation affects chiefly the bronchial tubes of the middle parts of the lung, and is due to a localized weakening in the walls of the tubes, usually brought about

by tuberculous changes. The distending force does not play a prominent rôle in this form of bronchiectasis, which we may compare to a false saccular aneurysm.

Dilatation may also occur in connection with chronic fibroid peribronchitis, the contraction of fibrous bonds extending inward from the pleura exerting traction on the bronchial tubes.

Effects. From their close proximity to the external air, the fluids in the bronchial tubes readily decompose, and may set up ulceration or gangrene.

THE LUNG.

Anatomy. This has in part been described under Bronchial Tubes. The bronchi branch dichotomously until they terminate in pouches, known as *infundibula*, from which spring the *air-vesicles.* The terminal bronchioles, which lead into the infundibula, are called *air-passages* and each of them communicates with from 3 to 5 infundibula, which together constitute an *acinus.* From 9 to 12 acini constitute a *lobule*, which is supplied by a single bronchial tube, and represents the macroscopic unit of the lung. The air vesicles are lined by flat epithelium, resembling both in its appearance and in its behavior under pathologic conditions, the endothelium. In the walls of the vesicles we find an abundant capillary network, held together by connective tissue containing many elastic fibers. The blood-vessels are only separated from the air in the alveoli by the flat endothelial cells, and are exposed to the air on two sides.

Malformations.—There may be absence of a part or the whole of one lung, a condition generally accompanied by a defect in the diaphragm and the presence in the thoracic cavity of some of the abdominal viscera.

Circulatory Disturbances. (*a*) **Active Hyperemia.**—This may be due (1) to active exercise. (2) It may occur acutely after exposure to cold. The origin of this variety is obscure, but by some the condition is considered a form of pneumonia. In many cases the pneumococcus is present, but evidences of inflammation are wanting. A fatal termination may occur, the lung at autopsy being swollen, red, and edematous, and oozing a frothy, blood-stained serum on section. (3) Active hyperemia is best marked in the beginning of croupous pneumonia. (4) Active congestion may be caused by brain lesions, as of the pons and medulla, more rarely

of the cortex. In the latter case the hyperemia is in the lung of the opposite side; when due to lesions of the pons and medulla, it is irregularly distributed on both sides. (5) *Embolic hyperemia.* The congestion due to the lodgment of an embolus may not go on to hemorhagic infarction, but may remain as congestion until relieved.

(*b*) **Passive Hyperemia.**—(1) *Hypostatic congestion* affects the dependent parts of the lung, and occurs in the preagonic period and in the low stages of acute infectious diseases. It is due to failure of the heart's action, to loss of vascular tonus, and to impaired respiration, so that the blood is but poorly aerated.

(2) *Atelectatic hyperemia* is brought about by obstruction of a bronchus, and occurs in the area beyond the obstruction. The blood in this area becomes surcharged with carbon dioxid, and does not readily flow out of the part.

(3) Congestion from *valvular heart disease* of either the left or the right side of the heart.

Appearance of congestion. It is often difficult to distinguish between active and passive congestion. In the former the lung is usually dark-red, swollen, and denser, and at times edematous, at others dry. In passive congestion the organ is bluish or purplish in color, and there is usually a well-marked edema, so that fluid oozes from the cut surface.

Edema is a condition in which the lung is enlarged and the air-vesicles and interstitial tissue are infiltrated with serum. On pressure the cut surface of the lung exudes an abundant frothy fluid. Edema is not always associated with hyperemia—in some cases the lung is anemic. That which accompanies hyperemia is readily accounted for on mechanical grounds, but that found in an anemic lung is more difficult of explanation. There is probably some alteration in the vessel walls, permitting the passing out of a clear fluid.

Hypostasis always plays an important part in all forms of passive congestion.

Results of passive congestion. (1) If long continued it leads to *cyanotic induration* of the lung, an overgrowth of connective tissue, with a deposit of pigment. (2) *Edema.* (3) *Splenization* or *hypostatic pneumonia.* This is a more acute change At first there is an exudation of serum—an edema; after 2 or 3 days the epithelial cells of the air vessels become loosened, and some proliferation of these cells takes place. This gives rise to consolidation, the affected

part, especially the base of the lung, being solid and airless, but oozing a considerable amount of blood on section. This condition of gradual consolidation is called splenization or hypostatic pneumonia, the latter term being used for a more acute process of consolidation, but there is no other difference between the two. The consolidated area is dark-purplish in color, the surface of section is smooth and shining, and small pieces sink in water. On pressure a large quantity of bloody fluid, unmixed with air, oozes from the surface; in true pneumonia such a fluid cannot be squeezed out. Hypostatic pneumonia is very common—it is seen in nearly all fatal cases of acute infectious diseases.

Hemorrhages may be minute or extensive. To the latter the name of "pulmonary apoplexy" is given. Blood may be found in the lung when the hemorrhage occurred higher up, as from rupture of an aneurysm into the trachea or a bronchus.

Causes of hemorrhage. (1) Hemorrhage may result from the various hyperemias. (2) Central disease, especially sudden lesions of the pons. These hemorrhages may be circumscribed and retained within the pulmonary tissue. (3) Traumatism. (4) Tuberculosis. (*a*) Hemorrhages in tuberculosis are most frequent from the walls of cavities, the bleeding occurring either from vessels eroded by the tuberculous process, or from the rupture of small aneurysms. (*b*) In some instances the hemorrhage occurs very early in the disease, before any cavities have formed. The bleeding in such cases is due to ulceration of the bronchial walls with involvement of the bronchial vessels. This form of hemorrhage was formerly believed to be the cause of the tuberculosis in the lung, and to a certain extent this view is correct. The process is often rapid after the hemoptysis, the hemorrhage having made the pulmonary tissues a favorable soil for the growth of the tubercle bacilli; beside this, the blood may carry the organisms to other parts of the lung. (5) Vicarious hemorrhage may be due to suppression of the menses or, more rarely, to an arrest of the bleeding from hemorrhoids. (6) Obstruction in the blood-vessels, *i. e.*, hemorrhagic infarction, from embolism and thrombosis. This is most frequent on the right side, although the difference between the two sides is not great. The infarct is pyramidal in shape, with the base toward the pleura, and the apex toward the root of the lung. It is dark-red in color, elevated, and on section is shining, but less so than is the lung in edema. The tendency is to absorption, the degenerated

tissue being replaced by a scar, which is usually situated at the base or in the middle lobe; scars at the apices are generally of tuberculous origin. If the embolus is specific, an abscess results.

Inflammation of the Lung, Pneumonitis, or Pneumonia, is of several varieties, as follows: (1) Fibrinous, croupous, or lobar. (2) Catarrhal, or lobular. (3) Desquamative, or caseous. (4) Purulent. (5) Interstitial, productive, or fibrous.

Fibrinous, Croupous, or Lobar Pneumonia, is a true inflammation of the air vesicles, characterized by proliferation of the cells, by exudation, and by a coagulation necrosis of the exudate. The epithelial cells of the alveoli in their pathologic behavior are comparable to the cells of the intima of blood-vessels, or those lining the opposing surfaces of a serous membrane. The process of inflammation is divisible into three stages:

(*a*) *Stage of engorgement or congestion.* The capillaries of the intervesicular walls are enormously distended, and bulge into the air vesicles; the lung tissue is in a condition of inflammatory edema, the air vesicles being filled with a serous fluid, some red cells, and loosened endothelial cells from the lining of the alveoli. These cells as well as those in the walls of the vesicle, show evidences of proliferation. The exudate soon undergoes coagulation necrosis, giving rise to the second stage, that of consolidation.

(*b*) *Stage of Consolidation.* This may be divided into two substages: (α) Stage of red hepatization, and (β) stage of gray hepatization.

(α) *Stage of red hepatization.* The air vesicles are now filled with fibrin holding in its meshes red corpuscles and endothelial cells. In some vesicles almost none but red cells are found; in others, both red corpuscles and endothelial cells are present, the latter disposed along the walls of the vesicles.

The affected lobe is enlarged and does not collapse on opening the chest; it is heavy and solid, and sinks in water; it is dark in color and fragile, being easily broken with the finger. The surface of section is dry and granular from the projection of plugs of fibrin from the air vesicles. The pleura over the pneumonic area is also inflamed, whence the name "pleuro-pneumonia." In some cases the pleural changes are slight, the membrane being only dry and sticky; in others the inflammation is of the same nature as that of the lung, being characterized by an exudation of fibrin.

(β) *Stage of gray hepatization.* The change from red to gray hepatization is a gradual one, and is due to the increased outwandering of leukocytes, the destruction and absorption of the red cells, and the anemia of the lung produced by pressure of the exudate upon the vessels. The color of the lung is gray, and the section is granular, resembling, especially on fracture, broken granite. This *granitic* appearance is particularly marked in the lung of adults; in children the color is more uniform and somewhat yellowish.

(*c*) *Stage of resolution.* As the process continues, the exudate begins to undergo fatty degeneration, mucoid change (the epithelium), and liquefaction. The degenerated material is emulsified by the exudation of a fluid, and is in part absorbed by the lymphatics and blood-vessels, in part is expectorated. The lung on section is smooth, and on pressure exudes a pus-like fluid, which, however, is not pus, but a fatty emulsion. Toward the end of the stage of resolution the color of the lung becomes again red, the blood-vessels being released from pressure by the removal of the exudate.

Terminations. 1. *Resolution* is the most frequent. 2. *Abscess.* This is a rare termination, and is usually due to mixed infection, generally by the pneumococcus and pyogenic organisms, sometimes to the pneumococcus alone. The abscess is large, and is apt to involve the whole lobe, and eventually ruptures into the pleural cavity, or into a bronchus. Cicatrization may then take place. 3. *Gangrene.* The disturbances of the circulation in the pneumonic portion of lung may predispose to gangrene, or there may be an infection with some special micro-organism. 4. *Fibrous change.* The changes in this are the same as occur in regeneration anywhere. The cells of the air vesicles proliferate and push into the fibrin meshwork; new blood-vessels form, and, finally, there is organization and the development of fibrous connective tissue. A lung so affected is termed "carnified," an adjective also applied to a compressed lung. This termination is rare, and seems to occur in such cases in which there has previously been a tendency to the formation of fibrous tissue—a fibrous peribronchitis.

Seats. In the majority of cases lobar pneumonia affects one lower lobe, usually the right. Limitation to one apex is rare. At times different portions of the lung present different stages of pneumonia, the lower lobe being generally most advanced. A pneumonia which travels from one lobe to another is termed "wandering pneumonia."

Etiology. The cause of pneumonia, in at least 90 per-cent. of all cases, is the pneumococcus or diplococcus of Fränkel. It does not occur in the normal lung, but in pneumonia is found in the exudate in the air vesicles, both within and between the cells, and in the vesicular walls, and also in the sputum.

It is normally found in the saliva of certain persons, and was discovered there by Sternberg. In reality it is not a coccus but a lanceolate bacillus, with pointed ends, occurring in twos, fours, or in chains. In the human body, but not in cultures, the organism is surrounded by a capsule, which is best demonstrated by the following method. The prepared cover glass is treated with a 1 per-cent. solution of acetic acid, washed in water, and stained—perhaps best with fuchsin. The pneumococcus also stains by Gram's and by Weigert's method. Its property of taking the stain by Gram's method distinguishes it from an organism somewhat similar in appearance, at times found in pneumonia, the bacillus of Friedländer, which is not stained by Gram's method.

Cultivation is difficult, and cultures present nothing characteristic on any medium. The organism soon loses its virulence when grown artificially.

That the pneumococcus is the cause of pneumonia has been proved by experiment on the lower animals. These are very susceptible, and when inoculated with a fully virulent culture die of septicemia in 24 to 48 hours, the micro-organisms being present in the blood. If the virulence is reduced—and this is readily accomplished by successive cultivations or by cultivation at a temperature of 41° or 42° C.—pneumonia can be produced in animals by inhalation.

The organism in its development elaborates certain poisons. At the same time the system manufactures an antitoxin, and it has been found that the serum of convalescent patients is capable of immunizing animals. With regard to man the results have not been positive.

The pneumococcus is also found in certain cases of pleurisy, meningitis, middle-ear disease, endocarditis, and disease of joints.

Normally, it occurs, as has been stated, in the saliva, and also in the mucus of the nose and throat. It seems that predisposing causes are necessary to render it virulent—of these causes cold appears to be one.

Pneumonia may at times be contagious, and epidemics have occurred in hospitals, prisons, and barracks. In such cases there is often a mixed infection of the pneumococcus and the streptococcus. Clinically, these epidemic pneumonias seem to be connected with erysipelas (Guitéras).

Catarrhal, or Lobular Pneumonia is characterized by an exudate in the air vesicles consisting of fluid, red and white corpuscles, and epithelial cells. The exudate has no marked tendency to coagulation necrosis, though there may be a few threads of fibrin. The fluid can be demonstrated by plunging the lung into boiling water, when it is coagulated.

Macroscopy. Catarrhal pneumonia is a lobular process; rarely, from the confluence of neighboring lobules, a whole lobe may be involved, but in such a case the affected lobules present different stages, and the consolidated area is not uniform as in croupous pneumonia. The inflamed lobules are plainly visible, particularly under the pleura; they are generally pale and surrounded by congested but healthy lung tissue. At times, especially in the early stages, the affected areas are dark from congestion.

On section, the surface is smooth, *i. e.*, not granular as in croupous pneumonia; the lobules stand out prominently, are firm and of the size of hazel-nuts or larger. The center of the lobules is usually paler than the periphery. The surface of section is moister than in croupous pneumonia and on pressure exudes a frothy serum from the healthy portions, and a thicker, grayish-yellow fluid, from the diseased areas.

Etiology. The disease is micro-organismal in origin, being in some instances due to the pneumococcus, especially in the young and old, in others to mixed infection, while certain forms are caused

by the streptococcus or the staphylococcus alone. Pure cultures of the pneumococcus are rarely found.

Three varieties of catarrhal pneumonia are distinguished as to their etiology, although they are not different anatomically.

1. *A bronchial form.* The pneumonia is the result (*a*) of direct extension of a bronchitis or peribronchitis, or (*b*) of the aspiration of irritant particles which act *mechanically* as emboli, setting up atelectasis and subsequently pneumonia (*atelectatic pneumonia*), or as direct irritants to the air-vesicles, or as specific emboli, when containing micro-organisms. The first variety is common in children, occurring frequently in the course of measles, diphtheria, and whooping-cough; it is, indeed, present in nearly all fatal cases of these diseases.

2. *A hypostatic form.* Hypostatic pneumonia is due to the infection, probably by aspiration, of areas the seat of intense hypostatic congestion. It occurs in low fevers and in the preagonic period, states in which there is a tendency to the aspiration of irritant materials, which from a paralytic condition of the bronchi are not coughed up. Section of the pneumogastric nerves in animals leads to the same form of pneumonia by inducing a similar paralytic state of the air-passages, which favors aspiration.

Terminations. Catarrhal pneumonia has a marked tendency to recovery, nevertheless there is a general belief that it is a very fatal disease. This arises from the fact that it is so often combined with grave affections like tuberculosis, diphtheria, measles, and whooping-cough, in which the superaddition of the catarrhal pneumonia to the original disease is apt to prove fatal. Another cause of the misconception is the confounding of caseous with catarrhal pneumonia. Catarrhal pneumonia is a benign process, tending to early fatty degeneration and removal of the exudate, and resolution.

Rarely, it terminates unfavorably, in abscess or gangrene.

Purulent Pneumonia is of several varieties.

(*a*) The suppuration may be diffuse, affecting the walls of the air-vesicles—*purulent catarrh.* (*b*) There may be a true abscess of the lung. The single large abscess usually involves an entire lobe, is oval or spindle-shaped, the long axis being transverse, running in the direction of the bronchi and blood-vessels. (*c*) There may be a purulent lymphangitis and perilymphangitis.

Causes. (1) Aspiration of material containing pyogenic organisms, from suppurative processes in the upper air-passages, as in diphtheria; or the inspiration of infected matters from without, as in the pneumonia of the new-born. The abscesses are usually multiple and circumscribed. (2) Metastatic abscesses. These are small and multiple, and are secondary to suppuration elsewhere, as in the abdominal cavity. (3) Extension from neighboring organs —the mediastinum, the pleura—the suppuration traveling along the lymphatic vessels. (4) Extension of a suppurative bronchitis; or of suppurative peribronchitis from the hilum of the lung. This gives rise to multiple small abscesses. (5) Abscess following lobar pneumonia. This is single, large, and usually involves the lower lobe. (6) Traumatism. (7) Rupture of a liver abscess through the diaphragm into the lung.

Desquamative, or Caseous Pneumonia resembles catarrhal pneumonia in appearance, but while the latter is acute and tends to recover, caseous pneumonia is a subacute or chronic process, tuberculous in nature, and goes on to destructive ulceration and cavity formation.

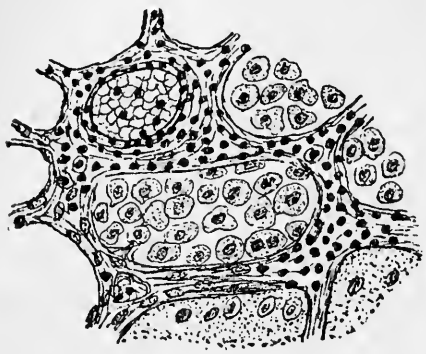
The process is characterized by a congestion of localized areas, followed by an exudation of an albuminous fluid, and a desquamation of the epithelial cells, and a proliferation of these cells and of the connective tissue cells of the intervesicular septa. The entire exudate, fluid and cells, subsequently undergoes a coagulation necrosis, which, however, is not a fibrin formation.

Macroscopy. The process is confined to lobules, several of these being usually involved together. They appear as pyramidal, grayish, translucent nodules, elevated, and harder than the surrounding tissues, and communicate with a bronchus, which is also involved, hence the term caseous broncho-pneumonia. The bronchus is always prominent on section.

The extent of the area affected varies from a single lobule to the involvement of an entire lobe—lobar caseous pneumonia—brought about by the running together of neighboring lobules. The appearance of this lobar form differs from that of croupous pneumonia, in that it presents a distinctly mottled appearance due to the lobules being in different stages of inflammation.

Microscopy. There is a marked proliferation and desquamation of the epithelial cells of the air-vesicles, together with a proliferation

of the connective tissue cells of the septa and of the blood-vessels. The air-vesicles become filled with cells which press upon the blood-vessels and exclude congestion. The defective blood supply leads to necrosis, but is not the sole cause, a very important factor being the tubercle bacillus, since caseous pneumonia is nearly always tuberculous.



The coagulation necrosis is followed by fatty and cheesy changes. The necrosis gives rise to a disappearance of the nuclei, and also obliterates the boundary lines between the air-vesicles. The blood-vessels are obstructed by arteritis, presenting a proliferation and degeneration of their endothelial cells.

Etiology. The cause of caseous pneumonia is the tubercle bacillus.

Terminations. (*a*) If the involved area is large, and mixed infection takes place, a rapid suppurative softening will follow—a condition termed *acute phthisis*, *galloping consumption*, or *phthisis florida*. The suppuration affects first the periphery of the involved lobules and produces a large number of minute cavities which give rise to pyemic symptoms. (*b*) A more frequent termination is the coalescence of the lobules and a slow softening, with the formation of cavities of larger size than are seen in phthisis florida. (*c*) Fibrous change—the formation of a capsule around the caseous mass which subsequently becomes calcified. (*d*) Resolution may occur, but it is difficult to say to what extent. When the involved area is large and there are tubercles elsewhere in the lung, the tendency is undoubtedly to softening. Yet it is probable that small areas, embracing two or three lobules, may get well. We must suppose this from the frequency with which small patches of caseous pneumonia are seen on the autopsy table. If destructive phthisis followed in every case, the death-rate from pulmonary tuberculosis would be much greater than it is. The frequent presence of caseous areas also shows how common infection with the tubercle bacillus is, especially in hospitals.

It is sometimes difficult to distinguish between groups of miliary tubercles and lobules of caseous pneumonia, but the diagnosis can generally be made (*a*) by finding in the latter the

involvement of the bronchial tube, the minute opening of which can be seen with a magnifying lens; (*b*) by the distribution of the lesions—miliary tubercles being scattered irregularly, while nodules of caseous pneumonia radiate from a bronchus as a common center; (*c*) by the fact that on pressure on a caseous lobule particles of cheesy material can be squeezed from the bronchial tube. Both forms of tuberculosis often occur together, and the one may be the starting-point of the other.

Fibrous, Interstitial, Productive, or Indurative Pneumonia is one in which the cellular proliferation becomes permanent connective tissue. In time this contracts and gives to the lung a puckered appearance. Nearly all cases show a marked participation of the peribronchial tissues. Several forms are described:

(*a*) A *parenchymatous* form, one in which the air-vesicles are primarily affected, and which may be due (α) to the inhalation of irritant particles, as dust (pneumonokoniosis); (β) it may be a termination of lobar pneumonia; (γ) it may be due to congenital syphilis (fibroid or white pneumonia).

(*b*) Those forms in which the air-vesicles are *secondarily* involved, and which are due (α) to extension of the fibroid process from the pleura, in cases of chronic fibroid pleurisy; (β) to extension along the peribronchial tissues or blood-vessels, beginning at the root of the lung, and extending outward in a radiating manner —this form may be due to syphilis; (γ) to the healing of gummata; ( ) to the healing of tuberculosis; and (ε) to the healing of wounds.

Tuberculosis gains access to the lung in one of three ways: (*a*) by the blood, (*b*) by the lymph, or (*c*) by inhalation.

(*a*) *Hematogenous tuberculosis* is a secondary process, the bacilli being brought from a primary focus, as the lymphatic glands or the bronchial tubes. It gives rise to *miliary tubercles*, the specific lesion of tuberculosis. The distribution may be local in the lung, affecting a lobe, or general, affecting both lungs. In the latter case the patient is apt to die of toxemia before secondary changes can occur. The lung in acute miliary tuberculosis is intensely congested, and also presents an acute bronchitis, particularly of the smaller tubes. The tubercles are small, grayish, translucent, and not readily seen unless examined by oblique light.

(*b*) *Lymphatic extension* is very common, and is secondary to disease of neighboring organs, as the lymphatic glands of the neck,

the mediastinum, and the throat; also to tuberculosis of the pleura. The lesion produced is the miliary tubercle. The infection may travel forward to the lymphatic glands, or backward into the lungs.

(*c*) *Inhalation* is the most frequent mode of infection of the lung, a fact proved both by animal experiments (causing animals to inhale dust laden with tubercle bacilli) and by clinical observation. The bacilli, when inhaled, lodge in the larger or smaller bronchi; in the former they set up a *caseous bronchitis;* in the latter they are apt to cause obstruction with the production of *nodules of caseous broncho-pneumonia.* From these primary lesions the surrounding lung tissue may become involved (α) by extension by continuity, the tubercle bacilli being carried by leukocytes and wandering connective tissue cells; (β) by extension along the lymphatic vessels, either forward or backward; (γ) by extension along the blood-vessels with the blood; (δ) by inhalation—which may consist in the aspiration of blood containing bacilli, or of the material from a broken-down tuberculous ulcer.

These different modes of infection may give rise to miliary tuberculosis or to caseous processes—the former resulting from extension, the latter from aspiration. It matters not which process is first; caseous pneumonia may give rise to miliary tuberculosis, and *vice versa.* In chronic cases all types of lesions are usually present, though one as a rule preponderates.

All lesions have a tendency to spread and to degenerate. First, there is a coagulation necrosis; later, fatty and cheesy changes; and finally, liquefaction necrosis. As the lung tissue contributes to the cellular accumulation, it also participates in the destructive changes; hence the formation of cavities. Cavities vary in size and number, are most frequent in the upper lobes, and generally communicate with bronchial tubes. The walls may be the seat of caseation and softening, these processes contributing to the contents of the cavity, and also causing it to increase in size. In other cases there is a tendency to the formation of fibrous tissue, by which the spread of the tuberculous process is limited.

Tuberculous lesions may heal, being replaced by a cicatrix; at times the cheesy material becomes calcified and encapsulated. But these apparently healed lesions always constitute a source of danger; though they may be quiescent for a time, the tubercle bacilli or their spores remain active.

Inhalation tuberculosis begins most often at the apex of the lung, although it is probable that the bacilli find their way to the middle and lower lobes as frequently as to the apices, but do not succeed in developing. The circulation of air is less active in the apices than elsewhere, which may explain the more frequent localization in them. Lymphatic and hematogenous infection may begin at the center of the lung.

Mixed infection is common in tuberculosis, and leads to other forms of pneumonia. The pyogenic bacteria are very commonly present and not only cause suppuration, but frequently produce catarrhal pneumonia. Croupous pneumonia, especially when epidemic, may complicate tuberculosis. The mixed infection may cause toxemia or pyemia.

The tubercle bacillus alone is capable of producing suppuration; the dead bacilli have been shown to be actively chemotactic. The toxins of tuberculosis—tuberculin—produce cachexia; the sudden injection causes fever and local congestion about the tuberculous areas. In this congestion lies the explanation of the tendency of tuberculous lesions to spread, and also the danger connected with the use of tuberculin. On the other hand, the hyperemia is also a favorable condition, since it may become the basis of a healing process. Patients suffering from tuberculosis are constantly absorbing tuberculin produced within them, and the same processes follow as after the artificial injection.

The effect of the tuberculous process on the blood-vessels. The large vessels are quite resistant, and may be seen in the walls of cavities or running across them. In the smaller vessels the tuberculous process gives rise to miliary aneurysms, the rupture of which leads to hemorrhage, or to ulceration and rupture without the previous formation of aneurysm.

Changes in the pleura. The pleura is the seat of changes similar to those of the lung, viz., either miliary or caseous tuberculosis. Tuberculosis may be primary in the pleura, and may be miliary or caseous. At times it takes the form of a miliary tuberculosis associated with pleuritis; the pleura is greatly thickened, and there is a large amount of fluid, but the miliary tubercles are scattered and not readily seen.

Pneumothorax or pyopneumothorax may result from the breaking down of a tuberculous focus in the lung.

Syphilis.—As a demonstrable lesion, syphilis is rare in the lung of the adult, but is quite common in children, particularly as a manifestation of congenital syphilis. Two kinds of lesions are met—(*a*) the *gumma*, which is usually multiple, and either subpleural or mediastinal (the gummy tumor is also the lesion of syphilis in the adult lung); (*b*) *syphilitic pneumonia.* This may originate *in utero* and interfere with the development of the lung. Histologically, there is an overgrowth of connective tissue in the walls of the air-vesicles; when this is associated with fatty degeneration of the epithelium, the so-called "white pneumonia" is produced. The lung is solid, and if the condition is of intrauterine origin, it does not expand after birth, being in a state of "carnification." A more frequent cause of carnification is, however, pressure by a pleural effusion.

Actinomycosis and **Glanders.**—Of internal viscera, the lung is one of the most frequent seats of these diseases.

Emphysema signifies an excess of air in the lung. It is of two kinds, (*a*) acute and (*b*) chronic.

(*a*) *Acute emphysema* is either vesicular or interstitial.

1. *Acute vesicular emphysema* is simply a dilatation of the air-vesicles. Its causes are (1) obstruction of the bronchial tubes, the obstructing body having a valve-like action which permits the entrance but not the exit of air, the consequence being a mechanical distention of the air-vesicles. (2) Collapse or atelectasis of parts of the lung, producing a compensatory or vicarious dilatation in neighboring parts.

The condition is transient as a rule, and the lung returns to normal; in some cases pneumonia, gangrene, etc., follow, but not as the result of the emphysema.

Appearance of the lung. The areas are pale, rose-colored, 2 to 3 cm. in diameter, and surrounded by congested lung tissue. To a certain extent they resemble areas of catarrhal pneumonia, but when incised they collapse at once. The middle lobe and anterior borders are the most frequent seats.

The clinical causes are different forms of bronchitis, especially those associated with violent cough, as whooping-cough.

2. *Interstitial emphysema* is similar to subcutaneous emphysema In a general way it is always due to traumatism, either internal or external, causing a rupture of the air-vesicles.

Appearance. The outline of the area is irregular, the emphysema not being circumscribed to the air-vesicles. The characteristic feature is that the air can be pushed from place to place. As a rule interstitial emphysema is transitory. By extending along the septa, the air usually reaches the subpleural space, and in some cases causes serious results by pressing on the lung. It may travel along the bronchi to the mediastinum and press upon the structures there, or along the fascia to the neck and even throughout the body. In such cases septicemia and pyemia sometimes follow.

(*b*) *Chronic emphysema, or substantial emphysema.* This is a vesicular emphysema, and affects especially the anterior borders of the upper lobes. The lungs are enlarged and meet in front, covering the heart; the outlines are irregular from the projection of large bullæ. The affected areas are pale, and seem to contain a large amount of coal-dust; but the increase is only apparent, and is due to the striking contrast between the pale lung and the pigment. The bullæ vary in size, and may correspond to single or to several lobules that have joined. The air-passages and minute bronchial tubes are also dilated, even before the air-vesicles are affected.

Microscopy. The disease is characterized by an atrophy of the pulmonary tissue, involving the septa between the air-vesicles, and even between the infundibula. The tissues undergo a slow, fatty degeneration, and are gradually removed; the blood-vessels take part in the degeneration.

Secondary effects. The enlarged lung presses on the surrounding structures, compressing the heart and displacing the abdominal viscera downward. Very important are the *circulatory disturbances.* The right heart, having to force the blood through a diminished area, becomes hypertrophied; the pulmonary artery also enlarges, at times reaching the thickness of the aorta. As a result of the disturbance in the pulmonary circulation, venous engorgement develops, which, together with the diminution in breathing area, gives rise to dyspnea.

Etiology. Two factors are concerned in the production of emphysema—an *impaired resistance* and a *dilating force.* The impaired resistance of the pulmonary tissue may be inherited or acquired. Acquired lessened resistance depends usually upon inflammatory changes—chronic bronchitis—impairing the elasticity of the lung. The dilating force is, as a rule, expiratory. During expiration the air is forced into those parts that are least protected

by the chest wall, viz., the anterior borders, the apices, and the diaphragmatic wedges.

Senile, or atrophic emphysema is similar to the preceding form. There is also an atrophy of pulmonary tissue; but as there is no dilating force, there is no stretching. The lung is not enlarged; there are no bullæ. In advanced age there is always a tendency to this condition, but it produces no symptoms, since the individual at that time of life requires less breathing space.

Tumors.—Primary tumors of the lung are rare. *Chondroma* is more frequent than in other viscera. All other connective tissue tumors may occur, especially *fibroma*. *Primary cancer* is very rare, but sometimes springs from the bronchial tubes (the mucous glands). *Secondary sarcoma* and *secondary carcinoma* are quite common, the former more so than the latter. Cancer is most often secondary to cancer of the liver; in such cases the hepatic veins are always found involved. Chondroma of the lung is frequently secondary to chondroma of other parts.

THE PLEURA.

The pleura is a serous membrane, and is subject to the same processes as other membranes of this class.

(*a*) *Passive congestion*, with a tendency to dropsy—*hydrothorax*—is seen in heart disease, Bright's disease, etc. Both cavities may be filled with fluid, but usually one contains more than the other. If the hydrothorax persists for a length of time, changes are produced in the pleural membrane; it becomes thickened, both from condensation by pressure and from hyperplasia of the connective tissue.

(*b*) *Hemothorax* is due to traumatism or to the spontaneous rupture of a blood-vessel, as an aneurysm of the thoracic aorta. If the hemorrhage is not fatal, the blood is rapidly absorbed.

(*c*) *Pneumothorax*. The presence of air in the pleural sac is due to external trauma or to rupture of the lung, the latter being, in turn, caused by rupture of the pleura in interstitial emphysema or by ulcerative processes of the lung—tuberculosis, abscess, gangrene. When the rupture is due to ulceration, *pyopneumothorax* is apt to develop.

(*d*) *Inflammation*—pleuritis, pleurisy—is serous, sero-fibrinous, fibrinous, or purulent. The appearances are the same as in pericarditis. In fibrinous pleurisy there is a layer of yellowish lymph

on both surfaces which can be readily removed, leaving the pleuræ dry, opaque, and rough. At times, as in some forms of lobar or lobular pneumonia, there is very little exudate, and nothing is detected save that, when the lung is taken to the light, the pleura is found to have lost its shiny appearance.

The *sero-fibrinous* is the form commonly described as acute pleurisy. It is characterized by the exudation of considerable fibrin and a large quantity of an opaque, pale-yellow fluid, containing flakes of lymph and tending to coagulate.

In *serous* pleurisy there is little fibrin, but a large amount of fluid. This form is generally subacute or chronic, and is frequently tuberculous in origin.

Fibrinous pleurisy is apt to terminate in adhesions between the two layers and the obliteration, partial or complete, of the pleural sac. The terminations of pleurisy in general are: (1) Absorption of the exudate, with the formation of a few light adhesions; (2) extensive adhesions; (3) suppuration—pyothorax, empyema.

Etiology of pleurisy. (1) Simple idiopathic pleurisy, which was formerly attributed to cold, but which is undoubtedly micro-organismal. The micro-organisms are principally the pyogenic bacteria; next in order of frequency, the pneumococcus. The pyogenic organisms may set up an ordinary sero-fibrinous pleurisy, which may or may not terminate in empyema. (2) Traumatism: here it is also the pyogenic organisms which cause the pleurisy. (3) Extension from neighboring organs—the bones, lung, and abdominal viscera. (4) Rheumatism. The rheumatic pleurisy is probably also micro-organismal. (5) Infectious diseases, as measles, scarlet fever, influenza, typhoid fever. The pleurisy is usually caused by the pyogenic bacteria, but may be due to the specific organisms of the disease, as at times in influenza and typhoid fever. Tuberculosis may give rise to a latent, chronic, serous pleurisy or to an empyema. (6) Pyemia.

Etiology of empyema. Empyema may be (*a*) a termination of an ordinary pleurisy; (*b*) it may be due to direct pyogenic infection, or (*c*) to rupture of the lung. Empyema is not rarely primarily tuberculous, or is secondary to tuberculosis of the bones or lymphatic glands.

Effects of pleural effusion on surrounding organs. (*a*) The pressure flattens the dome of the diaphragm. (*b*) The lung is compressed and becomes carnified. If the compression continues, the

connective tissue of the air-vesicles becomes hyperplastic, a true fibrous pneumonia being established, which leads to obliteration of the air-vesicles. (*c*) The heart is pressed upon, and also (*d*) the opposite lung.

Tumors. Primary tumors are rare. Some cases of fibroid thickening have been described as diffuse *fibroma;* they are on the border-line between inflammatory hyperplasias and tumors. *Endothelioma* is comparatively frequent as a primary growth. *Secondary carcinoma* is quite common, being secondary to cancer of the mammary glands.

THE THYROID GLAND.

Anatomy. The thyroid is a compound tubular gland consisting of two lateral lobes joined by a middle lobe, called the isthmus, which lies in front of the trachea; the weight of the gland is 30 to 60 grams. Histologically, the organ consists of numerous closed acini, lined by a low columnar epithelium.

Function. The gland is held at present to subserve one of two functions: (*a*) to aid nutrition; (*b*) to manufacture substances which act as antitoxins. The latter theory is the more reasonable one; the first really is not an explanation at all.

Malformations. Absence of the thyroid body is rare; the gland may be congenitally small or large. At times *accessory thyroid* glands occur, and have been found behind the trachea, inside the trachea, and in other places. Their existence has in some cases explained the non-occurrence of myxedema after extirpation of the thyroid gland in monkeys.

Circulatory Disturbances.—*Graves' or Basedow's disease, or exophthalmic goiter.* This is characterized by an active dilatation of the blood-vessels, with some degree of hypertrophy of the gland structure, due to a disturbance in the nerve centers controlling the circulation of the gland and the body in general.

Inflammation.—(*a*) *Acute thyroiditis,* though called idiopathic, is probably an infectious disease similar to mumps. The gland is greatly swollen, and causes serious pressure symptoms; resolution is, however, the rule.

(*b*) Suppurative thyroiditis is due to embolic processes or to direct infection from without.

Chronic enlargement of the thyroid gland—goiter. Anatomically, the enlargements are of two forms: (*a*) an hypertrophy with

marked tendency to degeneration; (*b*) an adenoma. It is not always easy to separate these forms, whence arises the claim of some authors that all enlargements are hypertrophies, while others hold that they are all adenomas. We are dealing with an ***hypertrophy*** when there is enlargement of the follicles with an increase in their number. The enlargement is either uniform (the perfect type of hypertrophy) or irregularly distributed, but without giving rise to a localized enlargement. In *adenoma* there is a localized enlargement—a tumor formation in a part of the gland. The follicles lose their normal outline, and have a marked tendency to the formation of cylinders lined by epithelial cells in which colloid change is taking place. Pure hypertrophy is rare.

The majority of goiters are associated with an impairment in the functional activity of the gland, and show various degenerations. These are:

(1) Colloid change. This is normal to a certain extent, but is very marked in hypertrophy, and may give rise to "cystic goiter." (2) Fibroid change presents itself in the forms of bands of connective tissue, which may contract and cause atrophy of the gland structure. (3) Hyaline change of the walls of the blood-vessels and other connective tissue. It is frequently associated with colloid or mucoid change. (4) Cystic change, from colloid or mucoid degeneration. (5) Telangiectatic change. (6) Hemorrhages. (7) Calcareous infiltration.

All these changes may be found in different parts of one goiter at the same time.

Myxedema is a nutritional disease due to interference with, or loss of the function of the thyroid gland. That such is its cause may be inferred from the following facts: (*a*) myxedema develops frequently in goitrous persons; (*b*) surgical interference with the thyroid gland in man, and (*c*) experimental removal in some animals have been followed by general disturbances similar to, if not identical with myxedema.

One of the most striking features of myxedema is a swelling of the subcutaneous tissue. It is a pale, translucent swelling resembling edema, but it does not pit, and affects especially the face and hands. In some cases the new material is myxomatous, but in the majority it does not contain mucin, but a substance that resembles it.

Nervous disturbances are always present in myxedema, and are (*a*) a peculiar tremor affecting chiefly the upper extremities, and occurring especially after sudden removal of the gland; (*b*) slowness of muscular movements; (*c*) mental impairment, eventuating in idiocy, particularly in cases where the abolition of the gland function occurred early in life or was congenital. In the last class of cases the mental and trophic phenomena are most marked, consisting in idiocy and arrested growth of the bones (*cretinism, or the cretenoid state*).

Myxedema is progressive, and terminates fatally.

It is not definitely known how the changes noted in myxedema are brought about, but they are thought to depend on the failure of certain poisonous substances, which normally are neutralized by metabolic products of the thyroid gland, to be destroyed. This view is supported by the fact that the introduction of thyroid gland or of its juice into the body after the symptoms of myxedema have developed, produces relief of these symptoms.

Etiology of goiter. Goiter is endemic in certain localities, and affects individuals of all ages. Its cause is supposed to be something in the drinking water, perhaps a micro-organism. Children in the goiter districts often present congenital myxedema, a condition called *cretinism*, or the *cretinoid state*.

CHAPTER XIII.

DISEASES OF THE KIDNEYS.

Anatomy. The kidney is 11–12 cm. long, 5–6 cm. wide, and 3–4 cm. thick, and weighs 150 grams, the left being from 3 to 5 grams heavier than the right. Both kidneys hold a ratio to the body weight of 1 to 200, and to the heart of 1.1 to 1.

The kidney is a compound tubular gland. Each tubule begins in a closed sac, the *capsule of Bowman*, which is invaginated and surrounds a tuft of blood-vessels—the glomerulus. Tracing a tubule from the capsule, we first have the *proximal convoluted tubule*, then a narrow straighter portion, the *loop of Henle*, consisting of a

descending and an ascending portion; then another *convoluted portion*, and finally the *collecting tubule*. With the naked eye we can distinguish in the kidney a cortical and a medullary portion. The *cortex* occupies the outer third, is granular in appearance, and consists of the labyrinth and the medullary rays. The former contains the glomeruli and the proximal and distal convoluted tubules. The latter are small pyramids apposed with their bases to the bases of the medullary pyramids, and are composed of the primary collecting tubules. The *medulla* makes up two-thirds of the organ, and consists of from 8 to 18 striated pyramids, which contain the loops of Henle and their limbs, and the large collecting tubules. Projections of the cortex extend down between the pyramids as the *columns of Bertini*.

Character of the epithelium. (*a*) In the capsule, a single flat layer; (*b*) in the convoluted tubules, a granular, striated, polyhedral epithelium; (*c*) in the descending loop of Henle, flat cells, with large nuclei, alternating in their position on opposite sides of the tubule; (*d*) in the loop and ascending limb, faintly striated, polyhedral cells; (*e*) in the collecting tubules, columnar epithelium.

The *renal epithelium*, being highly specialized, is easily disturbed in its metabolism. The *blood-vessels* of the kidney divide into two sets—one for the cortex, and one for the medulla.

Functions. The kidneys secrete from 1000 to 1500 c.c. of urine in 24 hours, containing solids to the amount of 1 gram to 1 kilogram of body weight. The amount of urea excreted is 30–40 grams; of uric acid, ½ gram. The important waste products excreted by the kidney are not elaborated by the organ, but are produced in all tissues of the body—in greatest part by the liver. By a process of osmosis, the kidney allows certain substances to pass from the blood into the urine, while it retains others. In addition, the renal epithelium actively takes up from the blood certain substances and discharges them into the uriniferous tubules. When the epithelium is diseased, components of the blood which should be retained, pass out into the urine, while the excrementitious matters, which should be eliminated, are not removed, and, accumulating in the body, cause poisoning.

Malformations.—One kidney may be absent or hypoplastic; a more common anomaly is the horseshoe kidney, in which the two kidneys are joined at one end, usually the lower.

Circulatory Disturbances.—(*a*) *Passive congestion* is usually due to valvular heart disease and leads to the condition termed *cyanotic kidney*. The kidney is swollen, dark, and firmer than normal; the blood-vessels are sclerotic, and there is a slight degree of interstitial inflammation, especially about the blood-vessels.

(*b*) *Infarction.* The hemorrhagic infarct is more common than the anemic.

Inflammations.—*A. Parenchymatous Inflammations.* 1. *Acute parenchymatous nephritis.* This is an inflammation in which degeneration of the epithelium is a prominent feature.

Macroscopy. The organ is enlarged, especially in thickness, and feels hard, the result of being swollen within a non-yielding capsule; when cut open it is really softer than normal. The capsule strips readily, and the surface of the organ is congested, the stellate veins being prominently marked. On section, the kidney shows a diffuse redness, with punctate points in the cortex corresponding to the glomeruli. In some cases there is considerable hemorrhage into the cortical substance, giving rise to *hemorrhagic nephritis.* The swelling affects particularly the cortex, which is usually also paler than the pyramids, but shows prominently the medullary rays. The pyramids are not swollen, but are intensely congested. The organ presents an opaque appearance, as if it had been cooked.

Microscopy. In mild cases, as after anesthetization, or in jaundice of short duration, the cells of the convoluted tubules are in a state of slight cloudy swelling, the normal granulation being intensified. In severer cases the nuclei of the cells cease to stain, and the cells become flayed out and break down into granules. At the same time an albuminous fluid is poured out, which coagulates in the lumen, and together with the granular material forms tube-casts. The broken-down cells are replaced through karyokinesis by new cells; these, however, are smaller and flatter than normal; they may remain or may also break down.

In very severe inflammations all parts of the kidney are affected; in ordinary cases, however, it is especially the *convoluted tubules.* Some cases present chiefly involvement of the *glomeruli—glomerulo-nephritis.* The cause of this is not distinctly understood; probably there is an antecedent circulatory disturbance. The flat epithelium lining the capsule of Bowman shows active hyperplasia, but degeneration is not marked. The tuft is also affected and is infiltrated with a large number of nuclei.

In another group of cases the *collecting tubules* are chiefly involved, a form termed *catarrhal nephritis*, which is characterized by desquamation of the epithelium. The cells do not show any great tendency to degeneration, but are discharged bodily. There is also some proliferation. By pressure it is possible to squeeze out little plugs from the ends of the tubules of the pyramids.

The tendency of acute parenchymatous nephritis is to recovery, although some cases become chronic.

Etiology. Catarrhal nephritis is usually an extension of an inflammatory process from the bladder, ureter, and pelvis of the kidney. Parenchymatous nephritis of the convoluted tubules and the glomeruli results from the circulation of poisons in the blood. These poisons are: (*a*) those of the acute infectious fevers—especially, yellow fever, Asiatic cholera, diphtheria, and scarlet fever; (*b*) poisons such as alcohol, arsenic, phosphorus, cantharides, ether, and chloroform; (*c*) certain unknown poisons which produce the nephritis formerly attributed to cold. Acute Bright's disease is probably an infectious process, the special lesion of which is in the kidney.

2. *Chronic parenchymatous nephritis* is due to one of two causes. It is the result (*a*) of an acute attack which does not go on to complete recovery, as after scarlet fever or diphtheria, or (*b*) of the continued action of irritants, such as in large doses give rise to acute nephritis. We know but little of the nature of these poisons. It has been said that their presence in the blood is due to faulty elimination by the kidneys, but it is probable that they are primarily the cause of the kidney changes. To these poisonous substances are then added the retained waste products. Alcohol used for a long time may produce the lesion, either by directly acting on the kidney or by affecting metabolism in such a way that poisons are elaborated which act on the kidney.

Macroscopy. Very often we find the features of the acute form, because many cases terminate fatally from an acute exacerbation of the disease—this obscures the lesions of the chronic form. When we can distinguish, we find that the organ is pale and on section presents a variegated appearance, yellowish areas of fatty degeneration being surrounded by reddish zones. The typical appearance is the *large white kidney*—a large, flaccid organ, the capsule of which strips readily, and the surface of section of which is gray or yellowish, especially in the cortex.

Microscopy. The epithelial cells, especially those of the convoluted tubules, have undergone fatty degeneration. They contain large refracting granules or even oil-drops; these may also be seen in the tubules and on the tube-casts. Some of the tubules have lost their epithelium entirely and are shriveled up.

The *duration* of the pure form of chronic parenchymatous nephritis is very short—a few months. When interstitial changes are present, the course is slower.

It is a question not yet settled whether the changes in chronic parenchymatous nephritis are properly to be called inflammatory.

B. Interstitial nephritis. 1. *Acute interstitial nephritis*, or suppuration of the kidney. Its causes are: (1) Extension of suppuration from neighboring organs—perinephritis, peritonitis, etc. (2) Hematogenous infection—pyemic emboli. (3) Extension of suppuration from the urinary tract.

In the hematogenous form there are multiple foci, especially in the cortex. That due to extension from the urinary tract affects primarily the pyramids, giving rise at first to a true catarrhal nephritis, then to abscesses of the pyramids. Eventually the whole kidney may be converted into a pus sac.

This form is connected with obstruction to the outflow of the urine, from disease of the urethra (stricture, hypertrophied prostate), the bladder, ureter, or pelvis of the kidney. The urine becomes infected with micro-organisms which travel upward against the current of the urine.

When infection does not take place, the fluid accumulates and distends the ureter and pelvis, causing *hydronephrosis.* A catarrhal nephritis follows, but not suppuration. Finally atrophy of the kidney substance takes place. Calculi are the most frequent cause of this condition, but they often lead to suppuration—*pyelonephrosis.*

2. *Chronic interstitial nephritis.* (1) *Circumscribed form*—scars of the kidney. These are generally found on the surface of the organ and are due either to the healing of syphilitic gummata or to the healing of infarcts. Syphilitic scars are usually stellate and not as deep as embolic scars. The latter are very deep and may affect an entire section of the kidney, dividing the organ into two parts.

It is not always possible to differentiate between the two forms of scars, and it is then necessary to look for other evidences of syphilis or for sources of emboli.

(2) *Diffuse interstitial nephritis* appears in two forms. (*a*) The one is a later stage of chronic parenchymatous nephritis. The large fatty kidney undergoes atrophy, the degenerated cells are thrown off, and connective tissue is substituted. The organ is reduced in size and its capsule adherent.; its size may be smaller than that of the red contracted kidney. This is the most frequent form of Bright's disease.

Under the microscope a diffuse round cell infiltration is noted; many of the tubules are empty, in others the cells are preserved; still others show swollen cells. This variation gives rise to a mottled appearance on the surface of section—yellowish islands are seen surrounded by congested connective tissue; the yellow color, however, predominates.

(*b*) *A primary chronic interstitial nephritis*—the contracted or gouty kidney. The causes of this are obscure—it is due to irritants circulating in the blood; often it is associated with arteriosclerosis. Alcohol and other poisons, introduced from without or generated within, may produce it, especially the uric-acid group of compounds. There is also an hereditary tendency to the disease in certain families.

In the early stages the organ is slightly enlarged, of a reddish-gray color, and firmer than normal. Contraction follows, and the kidney eventually becomes small and indurated; the color is reddish, the surface granular, and the capsule densely adherent. Cysts are frequently present in the cortex from closure of the tubules—they are seen in both forms of interstitial nephritis. The fluid of these cysts may be urinous; after the removal of the cells it is mucoid in nature, or it may be colloid if the cells undergo this degeneration.

Microscopy. In the early stages we find a round cell infiltration about the blood-vessels, the tubules, and the glomeruli. The blood-vessels show endarteritis and periarteritis, and become enormously thickened; the capsule of Bowman is also greatly thickened. The connective tissue contracts and causes atrophy of the epithelium. In both forms the epithelium shows fatty changes, but in that following chronic parenchymatous nephritis this degeneration is prominently marked, while in the primary interstitial form, there is chiefly atrophy of the cells and a slight degree of fatty change.

In some cases in which the overgrowth of fibrous tissue is very great, we may find fibroid tumors in the pyramids of the kidney.

Duration. Chronic interstitial nephritis is a progressive process terminating fatally.

Frequently certain salts are deposited in the kidney structure. Calculi in the kidney itself are rare.

(*a*) *Uric-acid deposits.* These are normal in the newborn and are found at the ends of the pyramids. They consist of sodium urate and usually disappear in two or three weeks. If persistent, they give rise to irritability or uremic symptoms. They are of medico-legal importance, as such deposits are only found after respiration has been established. Similar deposits, but more toward the middle of the pyramids, occur in adults, in cases of gout.

(*b*) *Lime-salt deposits.* These are common in advanced life, and are seen as grayish lines or as an opacity toward the apices of the pyramids. They may lead to calculi in the pelvis or bladder, but usually are of no significance.

Tuberculosis may be embolic, being a part of a general miliary tuberculosis, or it may result from extension of the disease from the pelvis. The second form may be the only lesion of tuberculosis in the body. Cheesy cavities may be formed, involving the pyramids and cortex.

Syphilis is rare in the kidney. When it occurs, it is usually in the form of gummata or scars; although it is possible that it may lead to a diffuse overgrowth of the connective tissue, especially in cases of inherited syphilis.

Tumors. — Benign tumors are rare, although lipomas, fibromas, and adenomas are occasionally found. *Cancer* is rarer in the kidney than in other abdominal organs. *Primary sarcoma* is absolutely rare, but as compared with other abdominal viscera, the kidney is a relatively frequent seat. The tumor is often congenital, and is then usually combined with myxoma or rhabdomyoma.

TUBE-CASTS.

These are a part of the inflammatory exudate which has moulded itself in the uriniferous tubules. They are composed of an albuminous matrix, the exact nature of which is not known, and of elements derived from the renal or the blood cells. There are two chief varieties of casts—(*a*) hyaline, (*b*) cellular.

(*a*) *Hyaline casts.* These consist of an albuminous material of obscure composition; it contains nitrogen and resembles the substance formed in various degenerations—amyloid, hyaline, coagulation necrosis. In some cases the casts are colloid, in others mucoid, or amyloid. *Waxy casts* are a special form of hyaline casts—they are opaque, homogeneous, and are composed of a material of obscure composition. At times they are amyloid.

(*b*) *Cellular casts.* These are fundamentally also hyaline, but have attached to them cells or cellular débris. The following are the main varieties:

(1) Epithelial casts; (2) blood casts; (3) pus casts. Any of these cells, but especially the epithelial cells, may degenerate into granular matter, thus giving rise to (4) granular casts.

Diagnostic value of casts. By themselves casts are insufficient to establish a diagnosis of the form of nephritis. The presence of cellular casts in large numbers indicates a rapid shedding of the epithelium, and hence signifies acute parenchymatous nephritis; the same is true of abundant blood casts. The presence of granular casts alone indicates chronic change—if present in abundance, and if of large size and fatty, we may infer chronic parenchymatous nephritis. When casts are few, and those found are hyaline, the case is probably one of chronic interstitial nephritis.

Cylindroids are long slender casts of a hyaline material, resembling mucus. They are often bent upon themselves, ribbon-shaped, and terminate in a fine whip-like extremity. Their exact meaning is not known; they do not always indicate organic disease, but seem usually to be connected with congestion of the kidney.

CHAPTER XIV.

MICROSCOPIC TECHNIQUE.

Fixation of Tissues.—This has for its object the preservation of the tissues, so that the constituents may retain as nearly as possible the characters they possessed during life. It is, therefore, obvious that tissues should be fixed immediately upon removal from the body. The following agents are employed as fixation fluids.

(*a*) *Alcohol.* This has the advantage that it fixes and hardens the tissues at the same time, whereas when other fluids are used for fixing, the tissues must subsequently be passed through alcohol.

Small pieces of tissue, not more than 2 or 3 cm. thick, are thrown in an excess of 95 per-cent. alcohol, which is changed after 24 hours. The tissue is then placed for 24 hours in absolute alcohol, when it is ready for embedding.

For delicate work, especially for bacteriologic studies, the tissue is best placed at once in absolute alcohol, which is changed in 24 hours, the specimen being ready for the embedding process at the end of the second day. It is advisable in all cases to place a little cotton on the bottom of the bottle, that the lower surface of the specimen may not adhere to the glass and be acted upon by the alcohol.

(*b*) *Müller's fluid.* This consists of

Potassium dichromate	2.5 grams.
Sodium sulphate	1.0 gram.
Water	100.0 c. c.

The fluid should be greatly in excess of the volume of the specimen and should be changed as often as turbid, but during the first few days should be changed daily. The specimens may be kept in the fluid indefinitely, the minimum time being about three weeks, though this limit may be shortened by keeping the bottle in the incubator for a time.

After removal from the Müller's fluid, the tissue is washed in running water for from 4 to 6 hours, and then placed in 70 per-cent.

alcohol, and kept in the dark. Every day it is placed in stronger alcohol, 80, 90, and 95 per-cent., and finally in absolute alcohol. Müller's fluid is cheap and can be used for almost every kind of tissue. Nervous tissue should be placed in it and not in alcohol.

(*c*) *Corrosive sublimate.* The solution is prepared by saturating a warm 5 per-cent. sodium chlorid solution with corrosive sublimate (= 7.5 per-cent.). The pieces remain in the fluid from 4 to 6 hours, are then thoroughly washed for several hours in running water to remove the mercurial precipitate, and then are hardened by being passed through alcohol of gradually increasing strength —40, 70, 95 per-cent., and absolute, being left 24 hours in each.

The method is especially useful for tissues removed from the living body.

(*d*) *Formalin.* This is a 40 per-cent. solution of formaldehyd. Tissues are placed in a 10 per-cent. aqueous solution of formalin, and can remain there for an indefinite time. Afterwards they are hardened in alcohol, beginning with 50 per-cent.

(*e*) *Flemming's solution* is especially adapted for the study of karyokinesis or of fatty changes in the cells. It consists of

1 per-cent. solution of chromic acid	15 parts.
2 " " osmic acid	4 "
Glacial acetic acid	1 part.

The specimens, which should be very small, are allowed to remain in the fluid for 24 hours, in the dark; they are then washed in water for 24 hours, and subsequently hardened in alcohol of increasing strength. Flemming's solution cannot be kept for any length of time.

(*f*) *Osmic acid,* in 1 per-cent. solution, is useful when it is desired to study fatty changes. The tissues are treated as in the case of Flemming's solution.

(*g*) *Erlicki's fluid* consists of

Potassium dichromate	2.5 grams.
Copper sulphate	0.5 gram.
Water	100.0 grams.

This has the advantage over Müller's fluid of fixing in from 8 to 10 days at room temperature, or in 4 or 5 days in the incubator; its disadvantage is that it causes more shrinking and produces a precipitate. The specimens are treated as when Müller's fluid is used.

Embedding.—(*a*) *Celloidin method.* This is the method most generally employed by pathologists. The celloidin is dissolved in a mixture of equal parts of absolute alcohol and ether. It is usually customary to prepare two solutions—a thin one and a thick one of about the consistence of syrup. The pieces, after *thorough dehydration* in absolute alcohol, are placed in the first solution for 24 hours, and for an equal length of time in the second. The specimen is then transferred, with an excess of celloidin clinging to it, to a block of dry wood. More celloidin is poured about the specimen, and the preparation allowed to become firm by evaporation. As soon as an opaque film appears on the celloidin, the block is thrown into 80 per-cent. alcohol.

(*b*) *Paraffin method.* After dehydration in absolute alcohol (24 hours), the tissue is placed for about 12 hours in chloroform, or until the alcohol has been displaced by the chloroform, which is indicated by a subsidence of the specimen below the surface. It is then placed in a saturated solution of paraffin in chloroform and allowed to remain for 12 hours, when it is transferred to pure melted paraffin, the melting-point of which is 50° C. It is kept in this for about 24 hours, or until the paraffin has completely permeated the specimen. Whether this has taken place or not can be determined by plunging a heated iron rod into the paraffin near the specimen —as long as chloroform is still present, bubbles will be given off. At the proper time a paper or metallic box is filled with melted paraffin, and the specimen transferred into the mould with a warmed forceps, care being taken to have the specimen properly placed with regard to the plane of cutting. The paraffin is immediately solidified by placing the mould in cold water. As soon as the paraffin on the surface has congealed into a film, water is allowed to run over the mould.

In hot weather the specimen may be transferred to melted paraffin having a higher melting-point before being placed into the mould.

Section Cutting.—(*a*) For cutting tissues embedded in celloidin, the knife is placed obliquely so as to bring the entire cutting surface of the blade into use, and is kept moist with 80 per-cent. alcohol.

(*b*) Paraffin specimens are cut dry. When ribbon sections are desired, the knife is placed at right angles; otherwise it is set obliquely.

(*c*) *Frozen specimens.* Pieces not more than 3 or 4 mm. thick are placed on the metal plate of a freezing microtome and frozen by an ether-spray, which is made to play against the under surface of the plate. If the tissue has been in alcohol, it should be washed free from the latter with water. The tissue should not be frozen too hard. Sections are received in 80 per-cent. alcohol or in 0.6 per-cent. salt solution.

Tissues fixed in Müller's fluid may be cut on the freezing microtome.

Staining, Clearing, and Mounting.—The methods of staining depend upon the special selective affinity which various tissue elements show for different stains, and in many respects stains are comparable to chemical reagents. By a process known as *differentiation* we are able to produce a staining of certain parts of the tissue, while others are deprived of whatever color they have taken up from the original stain by the differentiating agent. The advantages of differentiation are obvious: First, it brings out more clearly the contrast between different elements, usually between the nucleus and the cell protoplasm; secondly, it permits us to counterstain the decolorized parts by other stains.

No fixed limit can be given for the length of time specimens should be left in the various stains—this must be learned by experience. As a general rule the anilin dyes require less time than the vegetable stains which, as ordinarily employed, stain in from 5 to 10 minutes. It is always necessary to filter the stains before using if not clear.

Clearing. This aims at rendering the tissues transparent, so that light can pass through them. The agents used are chiefly the essential oils, such as oil of cloves, oil of bergamot, oil of origanum, oil of cedar, turpentine, etc., and certain benzine derivatives, such as xylol, either alone or combined with carbolic acid. The clearing agent most widely used is oil of cloves, which has the advantage that it takes up considerable water and completes the dehydration of the sections. It possesses, however, the disadvantage of dissolving the celloidin, which renders the handling of delicate sections, such as lung tissue, difficult. Oil of bergamot has less dehydrating power, but does not dissolve celloidin.

Xylol, or, more frequently, carbol-xylol, is largely employed for sections stained with the anilin dyes, as for such sections the essential oils cannot be used since they, especially oil of cloves,

dissolve the dye. Carbol-xylol (xylol 3, carbolic acid 1) and, more particularly, xylol, have the disadvantage that they are apt to wrinkle the specimens and to render them brittle.

Sections are left in the clearing agent until they are transparent, *i. e.*, until a dark object can be seen through the specimen.

The *mounting medium* most universally employed is Canada balsam dissolved in xylol. For mounting specimens of fatty tissue, stained with osmic acid, pure balsam should be used. In certain special methods sections are at times mounted in glycerin.

Methods of Staining. I. **Staining of Sections.**—Sections that are embedded in celloidin can be kept in 80 per-cent. alcohol until ready for staining.

A. **Hematoxylin.**—This is one of the best nuclear stains we possess. The solution generally employed is that of *Delafield*, which is prepared as follows:

(1)	Hematoxylin (crystals)	4 grams.
	Absolute alcohol	25 c. c.
(2)	Ammonia alum (crystals)	52 grams.
	Water	400 c. c.

Mix (1) and (2), and let the solution stand for 4 days exposed to light and air, but protected from the dust. The fluid acquires a deep-blue color. Filter and add

(3)	Glycerin	100 c. c.
	Methyl alcohol	100 c. c.

Filter after 5 or 6 hours, and keep in a tightly stoppered bottle at least 5 or 6 weeks before using. The solution should be well diluted before staining sections. Better results are obtained by long immersion in a weak solution, than by brief immersion in a strong solution. When sections are overstained, they cannot be satisfactorily decolorized, although it may be done to a certain extent by placing the section in a weak solution of hydrochloric acid, and subsequently washing in water.

Water is the differentiating agent in hematoxylin staining.

Method of staining. 1. Place section in water.

2. Stain until of a deep-blue color.

3. Wash in a large quantity of water until excess of stain is removed. It is often a good plan to allow section to remain in water for 24 hours.

4. Dehydrate in 95 per-cent. alcohol (2 to 5 minutes)

5. Dehydrate in absolute alcohol (1 minute).
6. Clear in oil.
7. Mount in Canada balsam.

B. **Lithium Carmin.**—The solution consists of

Carmin	2 grams.
Saturated aqueous solution lithium carbonate	100 c. c.

For differentiation the following solution is employed:

Hydrochloric acid	1.0 c. c.
70 per-cent. alcohol	100 c. c.

Method of staining. 1. Place section in water.
2. Stain from 3 to 5 minutes.
3. Place at once into differentiating fluid until section is rose-pink.
4. Wash thoroughly in water to remove the acid.
5. Dehydrate in 95 per-cent. alcohol.
6. Dehydrate in absolute alcohol.
7. Clear in oil.
8. Mount in Canada balsam.

C. **Borax Carmin.**—The solution is made after the following formula:

Carmin	2.5 grams.
Borax	4.0 "
Water	100 c. c.
75 per-cent. alcohol	100 c. c.

The carmin and borax are rubbed up in a mortar, and as far as possible dissolved in the water, which should be heated. The alcohol is then added, the fluid is filtered, and kept in a tightly stoppered bottle. The method of using the stain is the same as that for lithium carmin.

D. **Bismarck-brown.**

Distilled water	70.
95 per-cent. alcohol	30.
Heat to boiling and add	
Bismarck-brown	3.
Stir and filter.	

The method of staining is as follows:

1. Transfer section from 70 or 80 per-cent. alcohol into stain. Leave in stain 1 or 2 minutes.

2. Wash section in 70 or 80 per-cent. alcohol until excess of color is removed.

3. Dehydrate in 95 per-cent. alcohol.

4. Dehydrate in absolute alcohol.

5. Clear in oil of bergamot.

6. Mount in Canada balsam.

Double Staining.—This consists in the staining of the sections with both a nuclear and a protoplasmic stain.

(*a*) **Hematoxylin and Eosin.**—The sections that have been stained with hematoxylin and washed in water are dehydrated in alcohol to which a few drops of a saturated alcoholic solution of eosin have been added. They are left in this until the blue color has a slight reddish cast. They are then placed in absolute alcohol, cleared in oil, and mounted in balsam. The eosin may be added to the absolute alcohol instead to the 95 per-cent. The nuclei are blue, the protoplasm and intercellular substance reddish-pink.

(*b*) **Carmin and Picric Acid.**—A few drops of a saturated alcoholic solution of picric acid are added to the alcohol used in dehydrating the sections previously stained with carmin. The nuclei are red, while the protoplasm and intercellular substance are yellow.

Special Stains. A. **Weigert's Fibrin Stain.**—The method of using this stain is given on page 34. Before being subjected to the fibrin stain, the sections may be stained with lithium or borax carmin, being subsequently transferred from water or alcohol to the gentian-violet solution. The nuclei appear red, the fibrin and bacteria blue.

B. **Weigert's Stain** for medullated nerve fibers. The specimen is kept for several weeks in Müller's fluid, which is repeatedly changed. It is then placed, without washing, in 70 per-cent. alcohol in the dark, and the alcohol changed as long as it is made turbid by the potassium dichromate. The specimen is further hardened in stronger alcohol, and finally embedded in celloidin in the customary manner. The block with the specimen attached is then placed for 24 hours in solution No. 1.

Saturated solution cupric acetate.
Distilled water, equal parts.

The block is transferred to 70 per-cent. alcohol, and cut into sections after 24 hours. The sections are stained for 24 hours in the following solution (No. 2):

Hematoxylin	1.0 gram.
Absolute alcohol	100 c. c.
Saturated solution lithium carbonate	1.0 c. c.
Distilled water	90 c. c.

They are then washed in a large volume of water and transferred for differentiation to solution No. 3:

Sodium biborate (borax)	2.0 grams.
Potassium ferricyanid	2.5 "
Distilled water	200.0 c. c.

The sections remain in this for from ½ to 2 or 3 hours, according to the intensity of the stain. They are then washed in water, dehydrated in alcohol, cleared in xylol or carbol-xylol, and mounted in Canada balsam. Given briefly the method is as follows:

1. Fix in Müller's fluid.
2. Harden in alcohol without previously washing in water.
3. Embed in celloidin.
4. Leave block for 24 hours in solution No. 1.
5. Leave block twenty-four hours in 70 per-cent. alcohol.
6. Cut.
7. Stain with solution No. 2, for 24 hours.
8. Wash in large volume of water.
9. Differentiate by means of solution No. 3—from ½ to 2 or 3 hours.
10. Wash in water.
11. Dehydrate in alcohol.
12. Clear in xylol or carbol-xylol.
13. Mount in Canada balsam.

C. **Pal's Modification for Weigert's Method** for medullated nerve fibers. This gives very good results and consumes less time than the original method.

1. Fix in Müller's fluid, harden in alcohol, embed in celloidin.
2. Place in the copper solution (solution No. 1) for 24 hours.
3. Place in 70 per-cent. alcohol for 24 hours.
4. Cut.
5. Stain sections in Weigert's hematoxylin solution for from 24 to 48 hours, for the last hour in an incubator.

6. Wash in water to which several drops of a saturated solution of lithium carbonate have been added, until sections have a deep-blue color.

7. Place for from 20 to 30 seconds in a 0.25 per-cent. solution of potassium permanganate.

8. Place for a few seconds into the following solution:

Pure oxalic acid	1.0.
Potassium sulphid	1.0.
Distilled water	200.0.

9. Wash thoroughly in water. If the stain is too deep, steps 7 and 8 may be repeated.

10. Dehydrate in alchol.

11. Clear in xylol or carbol-xylol.

12. Mount in Canada balsam.

A pretty counterstain is obtained by adding a few crystals of magdala-red to the xylol.

D. **Golgi's Silver Method** for nerve cells and their processes. Harden very small pieces in

2 per-cent. solution potassium dichromate	80 c. c.
1 " " osmic acid	10 c. c.

Transfer directly to

Silver nitrate	0.75 grams.
Distilled water	100.0 c. c.

The solution is changed in an hour's time. The pieces may afterwards remain in the fresh solution as long as desired—24 hours is sufficient. Harden in alcohol, embed in celloidin. Sections are cut, dehydrated in alcohol, cleared in turpentine or oil of cloves, and mounted in Canada balsam.

E. **Golgi's Corrosive Sublimate Method** for nerve cells and their processes. Thin pieces of tissue are hardened in Müller's fluid or in 2 per-cent. potassium dichromate solution and then placed in 0.25 per-cent. corrosive sublimate solution, which is changed as long as it becomes yellow, the strength of the solution being gradually increased to 0.5 or 1.0 per-cent.

Small pieces are stained in from 8 to 10 days; larger ones require a longer time. The sections are thoroughly washed, dehydrated in alcohol, cleared in oil, and mounted in Canada balsam.

F. **Marchi's Method** for nerve fibers:

1. Very small pieces are placed at once into Müller's fluid, and kept in this for from 1 to 4 weeks.

2. They are then placed for 6 or 8 days in

Müller's fluid	2 parts.
1 per-cent. solution osmic acid	1 part.

3. Wash thoroughly in water.

4. Harden in alcohol, embed in celloidin, and cut.

5. Dehydrate in alcohol, clear in oil, mount in balsam.

G. **Van Giesson's Method.**

1. Harden in Müller's fluid or in alcohol.

2. Embed in celloidin, cut sections.

3. Stain for from 3 to 10 minutes in Delafield's hematoxylin.

4. Wash thoroughly in water.

5. Stain for from 3 to 5 minutes in a saturated aqueous solution of picric acid, to which a saturated aqueous solution of acid-fuchsin is added, until the mixture has a deep-red color.

6. Wash in water for half a minute.

7. Dehydrate in alcohol, clear in oil of origanum, mount in Canada balsam.

The sections should be overstained with the hematoxylin, as the picric acid decolorizes them to a certain extent. The method is employed for staining axis-cylinders, and for colloid, hyaline, and mucoid material.

Method of Staining Sections Embedded in Paraffin.—In staining sections embedded in paraffin, it is necessary first to remove the paraffin, but as the sections cannot be handled after this has been done, they are cemented to the slide before the removal of the paraffin. The methods of staining are the same as for celloidin sections. The methods of fixing the section to the slide and dissolving out the paraffin are as follows:

The slide is painted with a thin layer of a freshly prepared mixture of

Collodion	1 part.
Oil of cloves	3 parts.

The section is placed in position, and the slide gently warmed, either over a water-bath or at a considerable height above a naked flame, until fumes of oil of cloves appear. In this way the oil is

driven off and the section adheres by means of the collodion. The paraffin is removed by immersing the slide bearing the section in benzol or xylol, and then in turpentine. The turpentine is dissolved out by means of alcohol; the section is then ready for staining.

For very accurate work the following method of fixation is employed. The section is floated on the slide with a weak solution of gum arabic. The slide is cautiously heated to secure expansion of the section, but never to a point at which the paraffin melts. The excess of liquid is then drained off, the section finally arranged in proper position, and the slide placed in a place where it can dry without being exposed to the dust. To insure complete evaporation of the water, it is advisable to let the slide dry over night.

Sections thus fixed cannot be treated with watery stains, as they are loosened by them. When such stains are to be employed, the sections are best cemented on with a weak gelatin solution. After the sections have expanded and are properly fastened, the slide is soaked in a weak solution of potassium dichromate, which, in the presence of light, renders the gelatin insoluble in water.

II. **Staining in Bulk.**—This is rarely employed in pathologic studies.

The piece of tissue, which should not be more than 2 cm. in thickness, is placed from 80 per-cent. alcohol into borax carmin. The length of time which the piece should remain in the stain varies with its size and the density of the tissue—usually 24 hours is sufficient. From the carmin the piece of tissue is transferred directly to the differentiating solution (see lithium carmin stain), where it remains from 24 to 48 hours. When the fluid is no longer colored red, it is removed, washed in water, dehydrated in alcohol of increasing strength, and embedded.

Staining of Blood Corpuscles on cover-glasses. The finger from which the blood is to be taken is washed with soap and water, alcohol, and ether, and with a needle or a small spear-pointed knife a bold puncture is made in the pulp of the finger. The top of the exuding drop is touched with a *perfectly clean* cover-glass held in the bite of a forceps. This cover-glass is at once superimposed upon another cover-glass, also held in a pair of forceps; the two cover-glasses are then slid apart and allowed to dry in the air.

There are two methods of fixing the blood to the cover-glass.

(*a*) *Ehrlich's method.* The cover-glass is heated on a bar of copper to 120° or 130° C.

(*b*) *Nikiforoff's method.* The cover-glasses, dried in air, are placed for from ½ to 24 hours in a mixture of equal parts of absolute alcohol and ether. This is a very good and simple method.

For ordinary purposes the specimens are stained for one minute in

Eosin	0.5 grams.
70 per-cent. alcohol	100.0 c. c.

They are then washed in water, and stained for one minute in a saturated aqueous solution of methyl-blue, or for a longer period in Delafield's hematoxylin, well diluted with water.

The eosin stains the red corpuscles and the eosinophile granules in the leukocytes; the methyl-blue or hematoxylin stains the nuclei of the white corpuscles.

The *neutrophile* and *eosinophile granules* of the leukocytes may be stained simultaneously by means of Ehrlich's triple stain:

Sat. aqueous solution orange G	125 c. c.
Sat. solution (in 20 per-cent. alcohol) acid-fuchsin	125 c. c.
Add gradually, stirring constantly,	
Sat. aqueous solution methyl-green	125 c. c.
Then add	
Absolute alcohol	75 c. c.

The solution is allowed to stand for several weeks, and is not filtered. In using the solution the quantity needed should be removed with a pipette from near the middle of the bottle.

The specimen is stained from 2 to 5 minutes with the solution, washed in water, dried in air, and mounted in balsam. The red corpuscles are colored orange, the nuclei of the leukocytes and of nucleated red corpuscles green, the neutrophile granules violet, and the eosinophile granules red.

Biondi's mixture is practically the same. The solution consists of

A filtered sat. aqueous solution aurantia	100 c. c.
A sat. solution acid-fuchsin	20 c. c.
Sat. solution methyl-green	50 c. c.

For staining this solution must be diluted with 100 parts of water, and enough acetic acid added to give it a deep-red color.

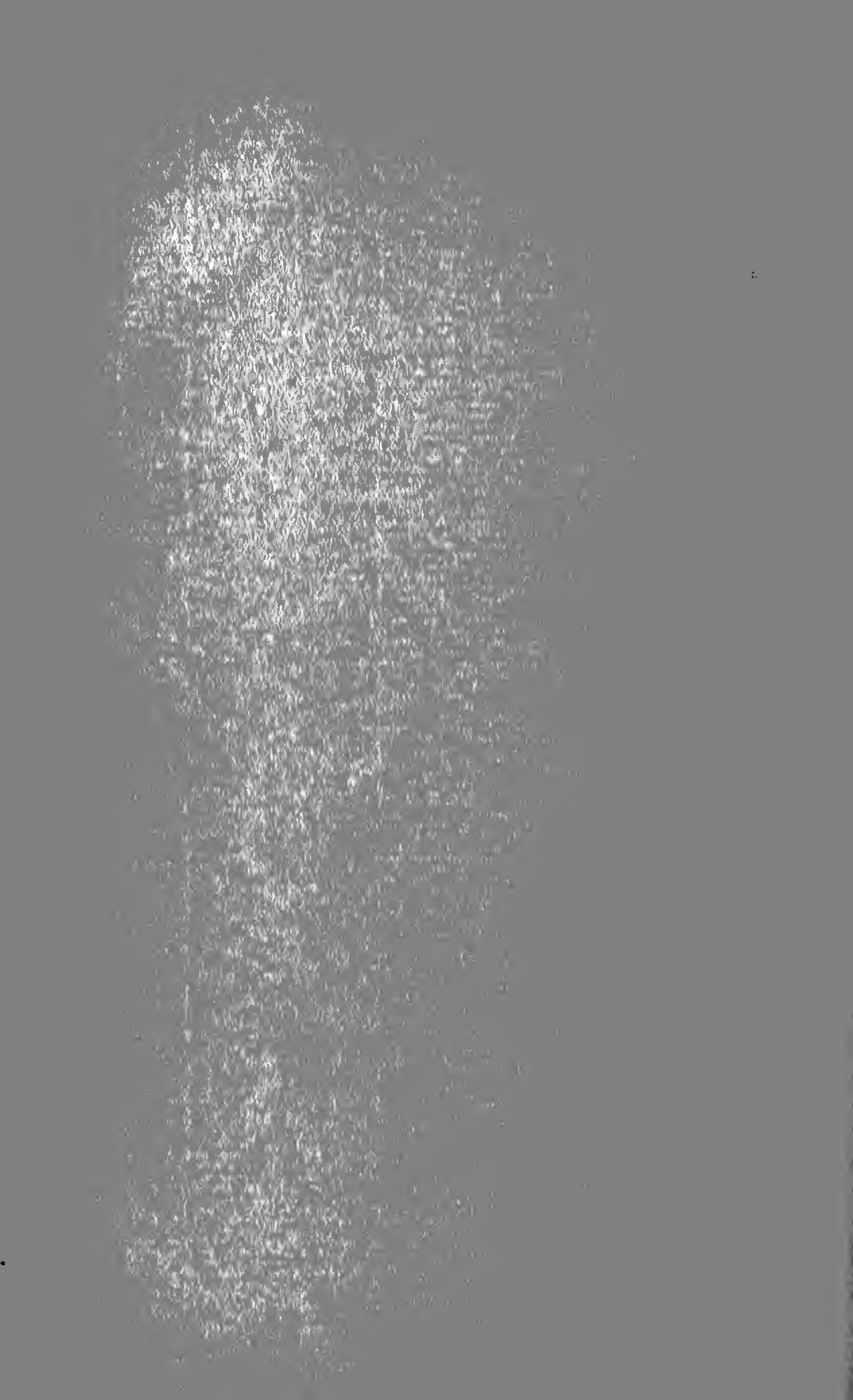
Biondi's stain may be obtained in solid form, and need only be dissolved prior to using.

Basophile granules may be stained with the following solution:

Sat. aqueous solution methyl-blue	40.0
0.5 per-cent. solution eosin in 70 per-cent. alcohol . . .	20.0
Distilled water	40.0

The cover-glasses are stained in this solution in the incubator at 37° C., for from 3 to 6 hours. The eosinophile granules appear red, the basophile granules blue.*

* The most reliable stains are those prepared by Dr. Grübler, of Leipzig. They can be obtained from several firms in this country.



BACTERIOLOGY.

INTRODUCTION.

Although bacteriology is one of the youngest of sciences, we nevertheless find dim suggestions of it in the writings of classical antiquity. It is with the theories of spontaneous generation, fermentation, and putrefaction that its origin seems to be most intimately connected. In regard to the first it was the prevailing belief until a comparatively recent date that life could, under certain favorable conditions, develop spontaneously. Among the early Greek philosophers we find a number (Anaximander, Empedocles, Aristotle, and others) advocating this theory. From their time, down through the middle ages, no one seems to have questioned the possibility of the origin of life *de novo*.

Francesco Redi, who, in 1668, demonstrated that maggots did not develop spontaneously, but were the larvæ of flies, was one of the first to throw doubt on the truth of the theory. The discovery of bacteria by Leeuwenhoek, in 1675, revealed a class of organism the minuteness of which suggested not only a close relationship to the ultimate molecules of matter, but also an easy transition from them, and thus strengthened the belief in spontaneous generation.

Spallanzani, in 1777, found that when organic infusions contained in hermetically sealed flasks were boiled, they did not thereafter become putrid. This was at first explained by ascribing it to the exclusion of oxygen, but Schulze, in 1836, showed that if such flasks were supplied with air that had been passed through sulphuric acid, no life developed, in spite of the admission of oxygen.

In 1837, Cagniard de Latour and Schwann, independently, discovered that the yeast-cell was the cause of alcoholic fermentation. Pasteur, finally, in 1862, brought incontrovertible proof of the fact that the development of life in organic infusions exposed to the air was due to the organized particles floating in the atmosphere and

falling into the fluids. And he also showed that these bodies were capable of causing putrefaction as well as fermentation.

In regard to certain diseases, it was suggested by Henle, in 1840, that they had a living cause, a "*contagium vivum*," probably of a vegetable nature.

Pollender, in 1849, and Davaine, in 1850, observed the anthrax bacilli in the blood of animals suffering from splenic fever, and in 1863, Davaine claimed to have demonstrated by inoculation the causal relationship between the bacillus and the disease. His conclusions were rejected at the time because he had used the blood of the diseased animal, which, it was urged, might have contained some other entity, the bacilli being present accidentally only.

Klebs, in his work on "Septicemia and Pyemia," published in 1872, expressed himself convinced that the causes of these diseases must come from without. In 1873 Obermeyer discovered the spirillum of relapsing fever. The introduction of the anilin dyes, by Weigert, in 1877, made a much more thorough investigation of bacteria possible, and discoveries soon became so numerous and convincing that it was impossible to doubt that micro-organisms were the causes of many diseases. In 1878 Koch published his important treatise on "The Traumatic Infectious Diseases." In 1879 Hansen discovered the bacillus of leprosy, and Neisser the gonococcus. In 1880 Pasteur published his memoir on chicken-cholera, and in the same year Sternberg discovered the micrococcus Pasteuri, now known as the peumococcus.

The typhoid fever bacillus was in this year discovered by Eberth and, independently, by Koch. The year 1880 is also memorable on account of the discovery of the plasmodium malariæ, the cause of malarial fever, by Laveran. In 1882 Koch announced his great discovery of the tubercle bacillus. In the same year Pasteur published his researches on "Rouget du porc," and Löffler and Schütz the discovery of the bacillus of glanders. In 1884 Koch described the comma bacillus or spirillum of cholera; Löffler the diphtheria bacillus, and Nicolaier the bacillus of tetanus. Between the years 1884 and 1892 few important discoveries were made, most of the work done consisting in the perfection of the methods of investigation. In 1892 Cannon and Pfeiffer, independently, discovered the bacillus of influenza. In 1894 Kitasato discovered a bacillus in the lesions of plague.

CHAPTER I.

BACTERIA.

A bacterium is a minute organism consisting of a single cell, principally composed of an albuminous substance called *myco-protein*. In 100 parts of dried bacteria there are found:

Myco-protein	84.20 parts.
Fat	6.04 "
Ash	4.72 "
Undetermined	5.04 "

The myco-protein is generally homogeneous, but may be granular, as in bacillus megatherium; sometimes it contains granules of chlorophyl, sulphur, fat, or pigment. Each cell is surrounded by a cell-wall which in some species gives the cellulose reaction with iodin. With the ordinary nuclear stains it is possible to distinguish between the nucleus and the cell-wall; but when stained with the anilin-dyes, which have a much greater penetrating power, the bacteria appear as solidly colored spheres, spirals, or rods, as the case may be.

Some bacteria are surrounded by a capsule, the formation of which probably depends upon peculiar changes in the cell-wall.

BIOLOGY.

Organisms which take into their bodies particles of food, digest that which is useful, and extrude the remainder, are *animals*, while those that imbibe nutrient fluids only by osmosis through a cell-wall, are *vegetables*.

Bacteria, since they live by osmosis and exosmosis, belong to the vegetable kingdom. Their extremely simple organization places them in the lowest class of the cryptogamia, or flowerless plants, that known as *Thallophytes*. These are divided into three groups:

(*a*) *Algæ*. These are chiefly water-plants containing chlorophyl, and obtaining their nourishment from inorganic substances.

(*b*) *Lichens.* These live upon inorganic matter, generally absorbed from the air; some contain chlorophyl, others do not. By many it is now held that lichens are fungi growing parasitically upon algæ.

(*c*) *Fungi.* These, the lowest group, live upon organic matter, either as *saprophytes*, upon decomposing organic matter, or as *parasites*, upon living animals and plants. They are as a rule devoid of chlorophyl.

The fungi are divided into

1. Hyphomycetes, mucorini, or moulds.
2. Saccharomycetes, or yeasts.
3. Schizomycetes, or bacteria.

Bacteria have been classified in a multitude of ways; the best classification is probably that based on the general shape of the individual.

(1) **Cocci.**—Spherical bacteria.

(2) **Bacilli.**—Rod-shaped bacteria.

All those having one diameter greater than the other should be classed among the bacilli.

(3) **Spirilla.**—Spiral-forms, twisted like corkscrews.

The **cocci** are subdivided into

(α) *Micrococci.* Perfect spheres, except during fission, when they are oval.

(β) *Diplococci.* Cocci occurring in pairs. The contiguous surfaces may be flattened or, as in the gonococcus, slightly concave.

(γ) *Tetragonococci.* Cocci dividing in two directions, on the same plane, forming tetrads. *Merismopedia* is the name given to the entire class of cocci dividing, on the same plane, so as to produce fours, eights, twelves, etc.,

(δ) *Sarcinæ.* Cocci dividing in three directions, so as to produce cubical masses or packages, which resemble miniature bales of cotton.

(ε) *Streptococci.* Cocci dividing only in one direction, the individuals remaining attached to each other, so as to form chains. When diplococci divide in this manner, *strepto-diplococci* are produced.

(ζ) *Staphylococci.* Cocci occurring in irregular groups, resembling bunches of grapes.

(η) *Ascococci.* Cocci arranged in globular or lobulated clusters, encased in a firm, gelatinous substance.

(ϑ) *Leukonostoc.* Cocci occurring in chains or as solitary individuals, surrounded by a gelatinous envelop of almost cartilaginous consistence.

The **bacilli** vary greatly in size; some occur always singly, others form chains; some have rounded, others square ends.

The following names are employed in describing bacilli:

(α) *Leptothrix.* Long chains of bacilli without distinct separation.

(β) *Myconostoc.* Long threads surrounded by a jelly-like material.

(γ) *Drum-stick.* A bacillus with a bulbous end, due to the presence of a spore.

(δ) *Clostridium.* A bacillus distended at its center by a large spore.

Besides these there are a few bacillus-like forms that are not easily classified. These are:

Streptothrix and *Cladothrix.* Bacilli in single or bundled threads, grouped so as to give the appearance of false branching.

Beggiatoa. A form consisting of indistinctly separated threads which are thicker than those of leptothrix.

Vibrio, a term now rarely used, was formerly applied to flexible bacilli possessing an undulating motion.

The **spirilla** are twisted like corkscrews. The name *spirillum* is reserved by some for the inflexible spiral forms, while the spiral, undulating form is termed *spirocheta.*

Other varieties are:

Spiromonas. A ribbon-shaped spiral organism.

Spirulina. A spindle-shaped spiral form.

Ophidiomonas. A variety of spiral forms containing sulphur-granules.

Bacteria vary greatly in size, and on account of their minuteness a special unit of measurement, the *micro-millimeter*, or *micron* (abbreviated μ), has been adopted. It is $\frac{1}{1000}$ millimeter or $\frac{1}{25000}$ inch.

As a rule the cocci are the smallest, the spirals the longest. Cocci vary from 0.15 μ to 2.8 μ; bacilli from 1 μ to 5 μ, in length, and from 0.2 μ to 1.5 μ in width. Some of the spirilla are very long *e. g.*, that of relapsing fever measures at times 40 μ.

Bacteria are changed in appearance by different methods of preparation. The presence of spores gives rise to an alteration of form; while young bacilli are shorter than older ones. The character of the nutrient medium also affects the shape; in old cultures we frequently find distorted shapes, the so-called involution forms. Temperature, air, and light likewise exert an influence upon the development of bacteria. But the effect produced by all these agencies is slight in the case of cocci, bacilli, and spirilli, these groups being subject to the *law of constancy of form.* This law is generally stated as follows: "Although a micro-organism may modify its form and habit of life to accommodate itself to its environment, it is within certain limits only that this change is possible, and under all circumstances one well-defined form exists, which expresses the type of the species."

On account of their constancy of form cocci, bacilli, and spirilla are termed *monomorphic.*

Cladothrix, beggiatoa, and others, which do not present the same form at all times, are called *pleomorphic.*

Reproduction.—Bacteria multiply in two ways:

1. *By direct division.* When the conditions of nutrition are good and growth is active, bacteria multiply by direct division or fission.

2. *By sporulation*—the formation of spores or seeds. When the conditions of growth cease to be favorable, a minute, oval, highly refracting body appears in the protoplasm of the bacterium. This is the spore. It is peculiarly resistant to the action of heat, light, and chemical agents, and to drying, and when transported to a suitable culture-medium, looses its wall and rapidly develops into a bacterium.

There are two kinds of spores:

(*a*) *Endospores*—those formed within the protoplasm of the bacterium. This form of sporulation occurs in bacilli and spirilla, each organism giving rise to a single spore.

(*b*) *Arthrospores.* These are produced by the conversion of the entire organism into a spore, a process most common in cocci.

The general character of spores indicates that they are a protective form which the bacteria assume when the conditions of growth cease to be favorable.

Motion.—Many bacteria possess the power of locomotion. This, as a rule, depends upon the presence of *flagella* or *cilia*, which may project from the sides, from one, or from both ends of the bacterium. Motility is an attribute of bacilli and spirilli chiefly; only one or two cocci are known to move by means of flagella. But the presence of cilia does not necessarily imply motion; thus, the bacillus coli has many flagella, yet it does not move. It has been suggested that, besides serving to transport the organisms from place to place, flagella may stimulate the passage of currents of nutrient material past the bacteria so as to increase the food supply.

Flagellate bacteria are more common in water, and in fermenting and decaying matter than in the bodies of animals.

There is one organism, the bacillus megatherium, which possesses a limited *ameboid movement.*

The cocci and small bacilli sometimes present an oscillating or dancing movement. This is the so-called *Brownian movement;* it is a physical phenomenon, and is not accompanied by any change in the relative position of the bacteria.

Distribution.—Bacteria are very widely distributed, but are not ubiquitous. They live in the air, in water, in our food, on the skin, and in the parts of the body communicating with the exterior. But it has been fully established that *the blood, lymph, and tissues of the healthy animal body are free from bacteria of all kinds.* At high Alpine altitudes no bacteria are found. The upper layers of the soil contain micro-organisms in abundance, but below the depth of one meter their number is very small. The presence of bacteria in the air is generally dependent upon their previous existence in the soil, its pulverization and distribution by currents of the atmosphere. The majority of atmospheric bacteria are saprophytic, but owing to the carelessness and neglect of the public, many pathogenic organisms also infest the air. As long as tuberculous patients expectorate upon the streets and sidewalks, the atmosphere will eontain tubercle bacilli, which are set free from the dried sputum and wafted through the air. The lack of proper disinfection leads also to the perpetuation of such diseases as diphtheria and typhoid fever.

CONDITIONS INFLUENCING THE GROWTH OF BACTERIA.

The growth of bacteria is profoundly influenced by environment.

1. *Oxygen.* Bacteria are divided into two great groups, according to the influence of oxygen upon their growth, (*a*) *aërobic bacteria*—those requiring oxygen for their growth, (*b*) *anaërobic bacteria*—those not growing when oxygen is present, as the bacillus of tetanus and the bacillus of malignant edema. Aërobic forms that grow as well without as with oxygen are termed *optional* or *facultative anaërobic.*

2. *Nutriment.* Bacteria grow best where diffusible albumins are present, but the amount of nutrient material needed varies greatly in different varieties. Sometimes a species with a peculiar affinity for a certain culture-medium can gradually be accustomed to another. Sometimes the addition of glucose or glycerin has a favorable influence in this respect. Thus the tubercle bacillus can be made to grow upon agar-agar to which glycerin has been added, although it does not develop upon ordinary agar-agar.

3. *Water.* A certain amount of water is always necessary, the best growth occurring when the proportion of moisture is about 80 per-cent.

4. *Reaction.* With few exceptions, bacteria grow best in a neutral or faintly alkaline medium. Acid media are good for the cultivation of moulds.

5. *Light.* The direct rays of the sun and, to a less degree, the electric arc-light, retard the growth of and frequently kill bacteria. Certain colors, as blue, for instance, are distinctly inhibitory to their growth. Some chromogenic bacteria produce their pigment only when exposed to the ordinary, diffuse light of the room.

6. *Electricity.* Very little is known about this, but powerful currents are said to check the development of bacteria.

7. *Movement.* Perfect rest is most favorable to the growth of bacteria. A slow flowing movement of the medium has no inhibitory action, but violent shaking disturbs their growth. For this reason, a swiftly-flowing stream, the current of which is broken by falls and rapids, will, other things being equal, furnish purer drinking water than a deep, still-flowing river.

8. *Temperature.* The majority of micro-organisms grow best at the temperature of a comfortably-heated room. Many, however, only thrive at the temperature of the body, 37° C. Below 10° and above 40° very few bacteria can grow. A temperature of 60° kills most bacteria; boiling for fifteen minutes is fatal to bacteria, but not to spores. In order to destroy spores, an exposure to a dry heat of 150° C. for one hour, or to a heat of 175° C. for five to ten minutes, is required. Freezing kills most bacteria, but not all; upon spores it has no influence.

Bacteria are divided into (*a*) *parasitic* forms, those the natural habitat of which is the animal body, and (*b*) *saprophytic* forms, those living on decaying animal and vegetable matter.

The first group is again divisible into the *purely parasitic*, which are never found outside of the tissues or secretions of the animal body, and the *occasionally parasitic*, which live both in the animal organism, where they may produce disease, and outside of it, in water or air. Of the former, the tubercle bacillus, of the latter, the spirillum of cholera, is an example.

Results of the Vital Activity of Micro-organisms.—1. *Fermentation.* Alcoholic fermentation is produced by the yeast-plant, *saccharomyces cerevisiae.* Acetic acid, lactic acid and butyric acid fermentation are brought about by bacilli.

It is very probable that several species of bacteria are capable of setting up each of these latter forms of fermentation, although the *bacillus aceticus* or *mycoderma aceti* the *bacillus acidi lactici*, and the *bacillus butyricus* are most active in the production of their respective acids.

2. *Putrefaction.* This is the decomposition of nitrogenous substances under the influence of bacteria. The process gives rise, during its intermediate stages, to peptone-like substances, to aromatic compounds, and to certain alkaloidal bodies, known as *ptomains.* Many of the peptone-like bodies and of the ptomains are poisonous. A ptomain is a chemical compound, basic in character, formed by the action of bacteria on organic matter (*Vaughan and Novy*). The most important ptomains are methylamin, trimethylamin, propylamin, putrescin, cadaverin, neuridin, saprin, tyroxicon, etc.

3. *Chromogenesis*, or *pigment-production.* Bacteria that produce pigment are termed *chromogenic;* those that do not, *non-chromogenic.* The majority of chromogenic bacteria are saprophytic; a few are

parasitic. All colors of the spectrum are met with. The pigments have been separated into two classes, a soluble pigment, which penetrates the culture medium, and an insoluble one, which does not tinge the culture medium, but is only found in the bacterial growth.

The majority of the pigments are only produced in the presence of oxygen and light.

4. *Liquefaction of gelatin.* This is due to the action of a peptonizing ferment produced by the bacteria. The power of liquefying gelatin is possessed only by certain species.

5. *Production of acids.* Several bacteria give rise to the formation of acids in the culture media, the quantity increasing until the acidity is so intense as to stop the growth of the organisms. The development of acids is detected by adding litmus to the culture medium. Rosalic acid may also be used.

6. *Production of gases.* CO_2, H_2S, NH_3, are the more common varieties of gases produced.

7. *Production of odors.* Some bacteria produce characteristic odors, independent of the gases mentioned above.

8. *Production of phosphorescence.* Several varieties of bacteria produce phosphorescence, as the bacillus phosphorescens of sea-water.

9. *Production of aromatic compounds.* Indol is the most important, and is produced by the cholera spirillum and other micro-organisms.

10. *Reduction of nitrites.* Several bacteria are capable of reducing the nitrites in the soil or in specially prepared culture media into ammonia and nitrogen.

11. *Production of disease.* Bacteria are divided into *pathogenic*, or disease-producing bacteria, and *non-pathogenic*, or those which do not produce disease. The pathogenic bacteria may be parasitic or saprophytic. There is no sharp line of separation between pathogenic and non-pathogenic bacteria, for certain of the former may be deprived of their disease-producing power, and some of the latter may be rendered pathogenic by special manipulations or by combining them with other bacteria. The exact mode in which bacteria cause disease varies. Some multiply so rapidly as to block the blood- and lymph-channels; others merely act as foreign bodies which the tissues attempt to eliminate. More important than either of these effects, however, is the production of poisons—*toxins* or *ptomains*—by the bacteria. These toxic products may cause a widespread

destruction of the tissues immediately acted upon, or, circulating with the blood, produce fever and peculiar nervous phenomena. The pyogenic bacteria induce suppuration by generating a chemotactic substance or by killing tissue-cells, which subsequently unfold chemotactic properties. Bacteria may, therefore, produce disease:

(*a*) By obstructing the lymph- and blood-channels.

(*b*) By acting as foreign bodies.

(*c*) By generating poisons.

(*d*) By inherent chemotactic properties, or by destroying cells which become chemotactic.

Channels of Infection.—Bacteria gain entrance into the body through the following channels:

1. *The digestive tract.* The micro-organisms of many diseases enter the digestive tract with the food and drink. The majority do not pass beyond the stomach, as they are killed by the acid gastric juice. When the latter is deficient or the bacteria are peculiarly virulent, they may reach the intestines and develop in the alkaline juices.

2. *The respiratory tract.* This is the common channel of introduction of the tubercle bacillus, the pneumococcus, and the influenza bacillus.

3. *The skin and superficial mucous membranes.* Few bacteria can penetrate the healthy, unbroken skin or mucous membrane. It is probable that in those experiments in which infection was caused by rubbing bacteria or their spores upon the skin, minute lesions were produced, through which the germs entered.

4. *Distinct wounds.* The entrance of bacteria through wounds is a frequent occurrence; yet the majority of infectious diseases and nearly all the distinctly contagious diseases, arise without the existence of any visible wound.

5. *Heredity.* There is no doubt at the present time that the infectious agent of a number of diseases can be transmitted to the fetus in utero. The infection may occur at the time of conception, and be derived from either parent, or *post conceptionem*, from the mother. This congenital infection has been observed in smallpox, measles, syphilis, typhoid fever, pneumonia, malaria, tuberculosis, and other diseases.

CHAPTER II.

SUSCEPTIBILITY AND IMMUNITY.

Susceptibility is that condition of the animal organism in which it is a fit soil for the growth of pathogenic bacteria or for the action of bacterial poisons.

Immunity is the opposite—it is a condition in which the animal body resists the development of micro-organisms or the action of their poisons.

Immunity is either natural or acquired.

1. *Natural immunity.* This is the constant resistance which certain animals (and human beings) exhibit toward certain diseases. The lower animals are immune to typhoid fever and to cholera. Most birds and reptiles resist anthrax, while man, sheep, cows, rabbits, and white mice are susceptible to it. Morphologic differences may explain variations in immunity among animals of dissimilar families; but as we find marked variations in the species of the same family, other factors must also be present. We find, for instance, that Europeans and Americans are susceptible to the poison of scarlet fever, while the Japanese are generally immune to it. Among the lower animals, the house-mouse, field-mouse, and white mouse, although resembling each other in all respects except color, differ very much in their susceptibility to disease.

2. *Acquired immunity.* This may be naturally or artificially acquired. Naturally acquired immunity is that which remains after recovery from certain infectious diseases. Thus one attack of yellow fever or of typhoid fever protects, as a rule, against a second attack of the same disease. Immunity may be artificially produced in the following ways:

(1) By operations upon the animal:

(*a*) By vaccination, as in the case of small-pox.

(*b*) By injecting blood-serum from an immune animal or from one convalescent from a certain disease, as tetanus, into a susceptible animal.

(2) By manipulation of the specific organism. The pathogenic power of bacteria may be weakened in various ways. The condition

of lessened virulence is called *attenuation*, and may be produced by cultivating the bacteria under unfavorable conditions.

Immunity, it should be remembered, is only relative, and an animal that is immune to a quantity of germs sufficient to kill another animal of similar size, will probably succumb to a quantity sufficient to kill a very large animal.

Susceptibility varies greatly. Young animals are generally more susceptible than older ones. Lowered states of nutrition and exhaustion increase the susceptibility. A susceptible state may be produced in animals ordinarily immune, (1) by altering the body-chemistry, either by a change in diet or by the introduction into the body of certain substances; (2) by changing the environment, principally as regards temperature; (3) by diminishing the strength of the animal; (4) by the removal of certain organs, as the spleen; (5) by injecting combinations of different species of bacteria, each alone of which might be harmless; (6) by intensifying the virulence of bacteria by previous inoculation into very susceptible animals, or by growing them upon special culture media; (7) by introducing large doses of bacteria.

The following theories have been advanced in explanation of the phenomena of immunity:

1. *The exhaustion theory.* In 1880, Pasteur advanced the theory that, by its growth in the body, the micro-organism uses up some substance essential to its life, and that when this substance is exhausted, the body is no longer a fit soil for the micro-organism.

2. *The retention theory.* It was suggested by Chauveau, also in 1880, that the growth of the bacteria in the body might generate some substance prejudicial to their farther and future development.

3. *The theory of phagocytosis.* In 1881, Carl Roser drew attention to the possible relation between immunity and phagocytosis. Sternberg and Koch also observed the phenomena of phagocytosis, but little attention was paid to the subject until Metchnikoff, in 1884, ascribed the production of immunity to these phenomena.

Phagocytosis is the englobing of foreign particles by certain cells called *phagocytes.* These are divided into fixed phagocytes (endothelial cells, connective tissue cells, etc.), and *free phagocytes* (principally leukocytes). Not all leukocytes are phagocytes—*lymphocytes*, or cells with a large nucleus and a small amount of protoplasm, are not phagocytic, while the large uninuclear and

multinuclear forms are. The large uninuclear leukocytes are known as *macrophages*, the small multinuclear forms and those possessing a single nucleus in the process of breaking up, as *microphages.* Phagocytosis is intimately associated with the phenomena of chemotaxis. *Chemotaxis* is the relation or force existing between ameboid cells and food particles. If the cells are attracted to the food particles we speak of *positive chemotaxis;* if they are repelled or not attracted, of *negative chemotaxis.*

Phagocytosis is not a rare phenomenon. In relapsing fever, in erysipelas, and in other infectious diseases, the bacteria can be found within leukocytes at the time of subsidence of the active processes. But the opponents of the phagocytic theory insist on the probability of the bacteria having been dead *before* they were swallowed by the cells. Metchinkoff answered this objection by showing that leukocytes englobed spores, and that when they were conveyed to a proper culture medium, the spores were set free and developed into bacilli.

The micro-organisms which are seized by the leukocytes are carried to the spleen and the lymphatic glands.

4. *The humoral theory.* It was frequently observed that when bacteria were introduced into drawn blood a large number of them were speedily killed. From this fact, and others of a similar nature, such as the death of bacteria placed in blood serum, in aqueous humor, and in other body fluids, Buchner and others concluded that the destruction of micro-organisms in the body was brought about by the bactericidal action of the blood-plasma.

5. *The theory of defensive proteids.* This is a modification of the humoral theory, and predicates the existence in the body of immune animals of proteids possessing the power of destroying the bacteria or of neutralizing the poisons generated by them. Buchner termed these protective proteids *alexins*, while Hankin classified them into two groups, designating those that occur in naturally immune animals, *sozins*, and those found in animals with acquired immunity, *phylaxins.* A sozin capable of destroying bacteria he called *myco-sozin*, and the corresponding phylaxin, *myco-phylaxin. Toxo-sozin* and *toxo-phylaxin* counteract the bacterial poisons. The defensive proteids are now generally termed *antitoxins.* Their existence has been established in tetanus, diphtheria, pneumonia, and other diseases.

None of the theories cited above is entirely satisfactory, and much remains to be done before the subject of immunity is clear.

CHAPTER III.

METHODS OF OBSERVATION.

One of the first essentials for the study of bacteria is a good microscope, the features of which are a set of good lenses, including an immersion-lens with a clear magnifying power as high as 1000 diameters, and a good light condenser.

Rules for using the microscope with the oil immersion-lens:

1. Employ good glass-slides and thin cover-glasses (No. 1).

2. Place a drop of cedar-oil on the cover-glass, rack the body of the instrument down until the oil immersion-lens meets the oil and almost touches the glass-cover, and then find the object by slowly racking up. As soon as the object comes into view, focus with the fine adjustment.

3. Select the light from a white cloud if possible; avoid the direct sunlight.

4. In using the high powers the condenser must be brought near to the object and the diaphragm opened so as to admit a large amount of light. The contrary is to be observed when low power lenses are employed. When the bacteria are unstained the amount of light admitted should be less than when they are stained.

Examination of Unstained Bacteria.—The simplest method is the examination in the *hanging drop*, for which a slide having a concavity in the center is used. With a camel's hair brush a ring of vaselin is smeared around the concavity. A drop of the material to be examined is placed in the center of a perfectly clean cover-glass. If the material is solid, a drop of distilled water is first placed on the cover-glass, and the material then mixed with it. The cover-glass is now placed upon the slide so that the drop hangs into the concavity without touching. The cover-glass is held by the vaselin, and as the latter prevents evaporation, the preparation will keep for days.

The hanging drop should always be studied at its edge, as the center is too thick.

The following points are to be observed :

1. Shape and size of the organisms.
2. Motility.
3. Grouping (chains, threads, etc.).
4. Sporulation.

Examination of Bacteria in the Stained Condition.—For the staining of bacteria we now employ, thanks to the great discovery of Weigert, the anilin dyes. These are coal-tar products, and represent almost every conceivable shade of color. The majority are derived from anilin-oil, a few from the naphthalin group. A good practical division is that into *basic* and *acid* dyes.

Basic dyes are fuchsin, gentian-violet, methyl-violet, methyl-blue, bismarck-brown, etc.

Acid dyes are eosin and acid-fuchsin.[1]

The anilin dyes are always employed in solutions. For the general staining of cover-glass preparations, we first prepare a *stock solution* of the dye. These are saturated alcoholic solutions and are made by adding *one part of the dye to four of alcohol.* The stock solutions do *not* stain bacteria, but are the standards from which the working stains are made in the following simple way: A small bottle with a pipette stopper is nearly filled with distilled water, and enough of the stock solution added until the transparency disappears. Such a watery solution penetrates the protoplasm of the bacteria, while the alcoholic solution does not.

Method of Making a Cover-Glass Preparation.—A little of the substance to be examined is spread upon a clean cover-glass[2] in the thinnest layer possible, and allowed to dry in the air. The material is then *fixed* to the glass—*i. e.*, the albumin in the bacteria is coagulated, so that it adheres to the glass, and will not be removed when the latter is washed. This is accomplished by placing the dried cover-glass for twenty-four hours in a mixture of equal parts of absolute alcohol and ether or, as is simpler and more rapid, by passing the cover-glass, smeared side up, three times through the flame of a Bunsen burner or an alcohol lamp. The preparation is now ready for the stain. The cover-glass being held in a special kind of forceps, enough of the stain is dropped on from a pipette to cover it. The stain is allowed to remain on two to three minutes,

[1] The best anilin dyes are those sold by Dr. Grübler, of Leipzig.

[2] Cover-glasses may be cleaned by placing them for a time in H_2SO_4, then washing them in water and in alcohol. They are kept in ether.

after which the cover-glass is thoroughly washed in water. It is now mounted in water and examined. If found good, it may be removed from the slide, dried, and permanently mounted in Canada balsam.

Synopsis of the method:

1. Spread material on cover-glass.
2. Dry in air.
3. Fix by passing thrice through flame.
4. Stain two or three minutes.
5. Wash in water.
6. Dry.
7. Mount in Canada balsam.

For some micro-organisms special stains, possessing greater penetrating power than the simple watery solutions, are required.

The important ones are the following:

Ehrlich's Solution.—This is a solution of any basic anilin dye in anilin oil and water. It is made as follows:

Anilin oil	4 parts
Distilled water	100 "
Shake well; filter, and add	
Saturated alcoholic sol. of dye	11 "
Filter.	

This is used principally for staining the tubercle bacillus and in staining by Gram's method (*Vide infra*).

As Ehrlich's solution does not keep longer than six to eight weeks, it may be prepared in small quantity by pouring about one cubic centimeter of anilin oil into a test-tube, filling the tube about one-half with distilled water, shaking the mixture well, then filtering into a small dish. To this the saturated alcoholic solution of the basic dye is added until the surface becomes distinctly metallic in appearance.

Löffler's Solution:

Saturated alcoholic sol. of methyl-blue	30
Watery solution caustic potash (1 to 10,000)	100

This is especially useful in staining the typhoid bacillus.

Ziehl's Solution:

Fuchsin	1
Alcohol	10
5 per-cent watery solution carbolic acid crystals	90

This is chiefly employed in staining the tubercle bacillus.

Staining of Bacteria in Tissues.—Unless the specimen of tissue is properly preserved the bacteria rapidly degenerate and lose their power of absorbing the stain. It is best to cut very small pieces and fix them immediately in absolute alcohol or in bichlorid of mercury solution.

Before staining it is advisable to remove the celloidin; if paraffin has been used as the embedding material, it must be dissolved out. The method of staining is briefly as follows:

1. Float the section out in water.
2. Into watery solution of the stain, 5 to 8 minutes.
3. Wash in water, 3 to 5 minutes.
4. Decolorize the tissue in 0.1–0.5 per-cent solution of acetic acid for 30 seconds.
5. Dehydrate in alcohol.
6. Place in absolute alcohol for a short time.
7. Clear in xylol (not in oil of cloves).
8. Mount in Canada balsam.

The tissue may be counterstained after differentiating with acetic acid. If the original dye used was blue, Bismarck-brown or alum carmin are adapted for this purpose.

Instead of the simple watery solution of the stain, Löffler's alkaline methyl-blue solution may be used with advantage.

Gram's Method.—This depends upon the principle that when bacteria that have been stained in Ehrlich's solution, are placed in a solution of iodin and potassium iodid, a new compound is formed in their protoplasm which is insoluble in alcohol.

This insoluble compound (of mycoprotein, basic dye in anilin oil, and iodid) is formed by many but not by all bacteria; there are a number of important species which do not form it, and, hence, are not stained by Gram's method. They are the micro-organisms of Asiatic cholera, chicken cholera, malignant edema, glanders, gonorrhea, relapsing fever, typhoid fever, rabbit septicemia, and the bacillus pneumoniæ of Friedländer.

Gram's method for cover-glass preparations.

Spread material upon cover-glass, dry, and fix. Stain for 2 to 5 minutes with Ehrlich's solution, keeping the stain warm by holding

the cover-glass over a flame. Pour off the stain, and place the cover-glass for ½ to 2 minutes in the following solution:

Iodin	1
Potassium iodid	2
Water	300

Next wash the cover-class in 95 per-cent alcohol until almost no color remains; then counterstain with eosin or Bismarck-brown. Dry, and mount in Canada balsam. Given briefly the method is as follows:

1. Ehrlich's solution, 2–5 minutes.
2. Gram's solution, ½–2 minutes.
3. Wash in 95 per-cent alcohol until decolorized.
4. Dry.
5. Mount in Canada balsam.

Gram's method for sections.

Given briefly, this is as follows:

1. From alcohol or water into Ehrlich's solution made with gentian-violet, 1–5 minutes.
2. Wash in water.
3. Into iodin solution, 2 minutes.
4. Wash in 95 per-cent alcohol until almost decolorized.
5. Dehydrate in absolute alcohol.
6. Clear in xylol.
7. Mount in Canada balsam.

The sections may be counterstained after decolorization, with eosin or Bismarck-brown. Or they may be stained in advance with lithium-carmin or picro-carmin.

Method of Staining Spores.—Spores are not easily stained. The best methods seem to be the following: (*a*) Spread the cover-glass in the thinnest layer possible; dry and fix. Then float on a watch-glassful of Ehrlich's solution, made with fuchsin, and heat until steam arises, allowing the cover-glass to remain in the hot solution 5 to 15 minutes. Transfer it to a 3 per-cent solution of HCl in water, for 1 minute; then wash in water, and counterstain with an aqueous solution of methyl-blue. The spores appear red, the bacilli blue.

(*b*) For the spores of many species the following method seems to give good results: Boil the prepared cover-glass for 15 minutes in a test-tube half full of carbol-fuchsin solution (Ziehl's solution *q. v.*). Decolorize in a 3 per-cent HCl or 2–5 per-cent acetic acid solution; wash in water, and counterstain with methyl-blue.

Method of Staining Flagella.—This is even more difficult than the staining of spores. The best method is that devised by Löffler, for which three solutions are required.

A. 20 per-cent solution of tannic acid 10
Cold saturated aq. solution of ferrous sulphate . . . 5
Alcoholic solution of fuchsin or methyl-violet. . . . 1
B. 1 per-cent solution of caustic soda.
C. An aqueous solution of H_2SO_4 of such strength that one cubic centimeter will exactly neutralize an equal quantity of solution B.

Two cover-glasses are prepared with a drop of distilled water on each. Some of the bacteria to be stained are mixed with the drop of water on the one cover-glass, and from this a small portion is mixed with the second, this being the only one used, as the first contains too many bacteria. After drying, the cover-glass is passed three times through the flame, being held in the fingers instead of in the forceps. Solution A is now poured on and warmed until steam arises; but it must not be boiled. The solution is allowed to act for ½ to 1 minute. The cover-glass is then washed in water, then in absolute alcohol until all traces of the solution have been removed. The real stain—Ehrlich's solution, made with fuchsin—is now poured on, and heated for a minute; it is then washed off, and the cover-glass dried and mounted in Canada balsam. The Ehrlich's solution should have a perfectly neutral reaction. This may be attained by adding sufficient of solution B to change the transparent solution to an opaque one. If the procedure has not succeeded, it is necessary to study the products elaborated by the micro-organism; if they are alkaline, solution B in the proportion of from 1 drop to 1 c. c. is added to 16 c. c. of the mordant A, and the staining repeated again and again until the proper amount is obtained. If the bacterium produces acids, solution C must be added to the mordant in a similar manner.

The staining of flagella is extremely difficult; each bacterium seems to react differently to the stains. Löffler has determined for some of the bacteria the amounts of solutions B and C that must be added to 16 c. c. of solution A to attain the desired result.

Cholera spirillum, ½ to 1 drop of solution C.
Typhoid fever bacillus, 1 c. c. of solution B.
Bacillus subtilis, 28 to 30 drops of solution B.
Bacillus of malignant edema, 36 to 37 drops of solution B.

Bunge's Method of Staining Flagella.

Bunge recommends the following mordant:

Concentrated aqueous sol. of tannin	3 parts.
Sol. of liq. ferri chloridi (1 to 20)	1 "

To 10 c. c. of this solution 1 c. c. of a concentrated watery solution of fuchsin is added. The bacteria are stained with this for 5 minutes, the solution being warmed towards the end. The cover-glass is washed, dried, and finally stained with a warm carbol-fuchsin solution.

STERILIZATION AND DISINFECTION.

The destruction of bacteria by means of heat is termed *sterilization*; their destruction by the action of chemical agents, *disinfection*. The chemical agent which kills the bacteria is called a *germicide*. An object which is entirely free from bacteria and their spores is *sterile*. Substances that prevent the growth of bacteria without necessarily killing them are known as *antiseptics*.

The study of sterilization, disinfection, and antisepsis falls under the following heads:

I. Sterilization of instruments and apparatus used in experimentation.

II. Sterilization of culture media.

III. Disinfection of instruments, ligatures, hands, etc., of the surgeon, and the use of antiseptics.

IV. Disinfection of sick chambers and their contents, as well as the dejecta of patients suffering from infectious diseases.

I. *The sterilization of instruments and apparatus used in experimentation.* This is accomplished either by moist or dry heat. *Glassware* is sterilized by dry heat, in the hot-air oven, at a temperature of 150° C., maintained for one hour. The *platinum wire* and a few other instruments are exposed to the naked flame. *Knives, scissors*, etc., may be heated in the flame, but as a too long exposure destroys their temper, they are best sterilized in the steam apparatus. It is obvious that unless properly protected sterilized objects soon become again contaminated with bacteria. Flasks and test-tubes, before being sterilized are plugged with cotton; this prevents the entrance of germs into the sterilized flasks. Instruments may be sterilized wrapped in cotton, or may after sterilization be wrapped in sterile cotton until required for use.

II. *Sterilization of culture media.* For this purpose the *intermittent, or fractional method of sterilization* is employed. It consists in the exposure of the culture media in flasks or tubes to the action of streaming steam for 15 to 30 minutes, for three successive days. The *rationale* of this method is that streaming steam kills all bacteria, but not the spores. The latter develop in the interval between the first and second sterilization; the newly-formed bacteria are killed by a second sterilization at the end of 24 hours. Lest a few spores remain and develop, the media are sterilized after 24 hours for the third time.

III. *The disinfection of instruments, ligatures, the hands, etc.* Various chemical substances have been used as disinfectants for those objects and parts which cannot be exposed to the naked flame, to dry or to steam heat. Among the compounds employed are mercuric chlorid, hydrogen dioxid, creolin, thymol, potassium permanganate, boric acid, carbolic acid, creasote, alcohol, formalin. The value of disinfectants and antiseptics is relative and varies with the microorganism upon which they act. The action of disinfectants is a chemical one, the destruction of the bacteria being due to the combination of the germicide with the mycoprotein. Some of the disinfectants and antiseptics, such as mercuric chlorid and silver nitrate, are precipitated by albumins, which fact limits the scope of their usefulness. Carbolic acid seems to be the most reliable of all germicides and antiseptics.

Disinfection of the *hands* is carried out as follows: The nails should be short and clean. The hands are washed thoroughly for 10 minutes with brush, soap, and water. The excess of soap is washed off in warm water. The hands are then immersed ½ minute in a warm saturated solution of *potassium permanganate* and then placed into a warm saturated solution of *oxalic acid* until complete decolorization of the permanganate has occurred, after which they are washed in sterile water or salt solution. They are finally soaked for 2 minutes in a 1 to 500 solution of *bichlorid of mercury.*

Surgical dressings are sterilized by superheated steam; *ligatures* and *sutures*, after having been boiled, are kept either in alcohol or in an alcoholic solution of bichlorid of mercury; or, if this renders them brittle, in a watery solution of the bichlorid. *Instruments* are boiled in water and subsequently kept during the operation in a 5 per-cent warm carbolic acid solution. The practice of pouring boiling water over the instruments just before the operation does not sterilize them efficiently.

Instruments, the temper of which is not destroyed by a great heat, may be dipped in alcohol and the latter ignited.

During the operation the *wound* is frequently washed with carbolic acid solution or bichlorid of mercury, 1 to 2000, applied with sterile sponges or pieces of absorbent cotton.

IV. *The disinfection of sick chambers, dejecta, etc.*

(*a*) *The air of the sick-room.* It is impossible to sterilize the air of the sick-room—free ventilation is the best method of purifying it while the patient is in the room, afterward sulphur fumes may be used; but more reliance is to be placed upon disinfection of the walls and floor and wooden parts of the furniture, combined with fresh air and sunlight, than upon fumigation.

(*b*) *The dejecta, sputum, etc.* The vomit, expectoration, etc., in diphtheria, should be received in old cloths, which are immediately burnt. Tuberculous sputum is expectorated into glazed earthen vessels that can be subjected to boiling or disinfection, or into rice paper napkins, which are promptly burnt. The excreta of typhoid fever and cholera patients are received in glazed earthen vessels and intimately mixed with a 5 per-cent solution of chlorid of lime, if semi-solid, or with the powder, if liquid, and allowed to stand for an hour.

(*c*) *The clothing, etc.* All clothing that has been in contact with the patient, should be disinfected by means of steam; when this is not possible, prolonged boiling is the best substitute. When applicable, the clothing should be soaked in 1 to 2000 bichlorid solution before or after boiling.

(*d*) *The walls and floor of the room.* The walls and ceiling should be rubbed with fresh bread, which collects the bacteria, and, if possible, should also be whitewashed. The floors should be scoured with a 5 per-cent solution of carbolic acid, or 1 to 1000 of bichlorid of mercury.

(*e*) *The patient* after convalescence should be bathed daily with a weak bichlorid of mercury solution, or with a 2 per-cent carbolic acid solution, or with 25 to 50 per-cent alcohol. In desquamative diseases, the distribution of epidermic scales may be prevented by anointing the body with a simple unguent.

The dead that have perished of infectious diseases, should be washed in strong disinfectant solutions and speedily buried with great privacy, or, preferably, cremated.

CHAPTER IV.

CULTIVATION OF BACTERIA—CULTURE MEDIA.

For the study of bacteria as well as for the determination of their relation to disease-processes, to fermentation, to putrefaction, etc., it is necessary to isolate the different species from each other, and to observe them in *pure culture*. Very little organic matter is necessary for the growth of bacteria, but considerable moisture—about 80 per-cent of water—is needed. In cultivating the pathogenic forms of micro-organisms, a medium approximating the composition of the juices of the body is most serviceable.

The following are some of the more important culture media:

Bouillon or Meat Infusion. — To 500 grams of finely-chopped lean beef 1000 c. c. of water are added. This is allowed to stand for twelve hours on ice. At the end of that time the liquor is decanted, that remaining in the meat is expressed through a cloth, and enough water added to bring the total amount again to 1000 c. c. To this 10 grams of Whitte's peptone and 5 grams of salt are added, and the whole boiled until the albumins are coagulated. The solution, made acid by the sarcolactic acid of the meat, is now neutralized, or rendered faintly alkaline, by means of a saturated watery solution of sodium carbonate. It is allowed to cool and then filtered. It may be kept in flasks, or be dispensed in sterile test-tubes—about 10 c. c. in each tube—and is finally sterilized by the intermittent method of sterilization previously described. Instead of the 500 grams of meat, bouillon may be prepared with extract of beef (Liebig's) in the following way: To 1000 c. c. of water add 10 grams of Whitte's peptone, 5 grams of sodium chlorid, and about 2 grams of beef extract. Boil the solution, neutralize, and filter when cold.

Bouillon is the basis of culture media; from it gelatin and agar-agar can be readily prepared.

Gelatin.—This is prepared as follows: To 1000 c. c. of meat infusion, or to 1000 c. c. of water containing 2 grams of beef extract, 10 grams of peptone, 5 grams of salt, and 100 grams of gelatin ("Gold-label"), are added, and the whole boiled in a kettle

for an hour over a moderately hot flame. The mixture should be stirred occasionally. It is allowed to cool to 60° C., and then neutralized with a saturated solution of sodium carbonate. The white of an egg beaten up in water is next added, and the mixture boiled for half an hour longer. It is then, while still warm, filtered through a pharmaceutical filter. Finally, it is distributed into sterilized tubes, and sterilized by the fractional method.

The advantages of gelatin consist in that it is an excellent nutrient medium for bacteria, and that it is a transparent solid, which can be made liquid and subsequently re-solidified.

Agar-agar.—This is a peculiar Japanese sea-weed which dissolves in boiling water and forms a thick jelly when cold. It remains solid at temperatures at which gelatin melts, and can be kept in the incubator without becoming liquid.

To 1000 c. c. of bouillon, made as above described (preferably with meat instead of beef-extract), 10 grams of agar-agar are added, and the mixture boiled for an hour, the water lost by evaporization being always replaced. Then it is cooled to 60° C., and after neutralization, an egg beaten up in water is added, and the solution boiled again. It is then filtered through a folded filter. Filtration is somewhat tedious, and the filter-paper has to be renewed. It is best to pour on about half of the solution and add the hot remainder when necessary.

If made from beef-extract the agar-agar nearly always precipitates a considerable amount of urates as it cools.

The agar-agar is dispensed in tubes, and sterilized by the intermittent method. After the last sterilization the tubes, before cooling, are laid on an inclined plane so as to offer an extensive flat surface for the culture.

Glycerin-agar is made by adding about 5 per-cent of glycerin to the melted agar-agar prepared as detailed above. It constitutes an excellent culture medium for the tubercle bacillus.

Blood-serum.—This is obtained from a slaughter-house. The blood is received in a glass jar sterilized by heat or by washing with alcohol and ether.

It is advisable to avoid the first blood which comes in contact with the hair. The clot is separated from the sides of the vessel by means of a sterilized glass rod and the jar placed in an ice chest for from 12–24 hours. The clear serum is then transferred into test-tubes (about 8 c.c. to a tube) by means of a sterilized

pipette. If it is desired to use the serum in a liquid form, it is sterilized by exposing it for an hour on five consecutive days to a temperature of from 60° to 65° C. If a solid medium is wanted the tubes are exposed twice, or three times if contamination is feared, to a temperature just short of the boiling point, for one and one-half hours each time. The tubes should always be inclined before the serum is coagulated. There are a few bacteria that liquefy blood-serum.

Löffler's Blood-serum Mixture.—This consists of

Blood-serum	3 parts.
Meat infusion bouillon containing 1 per-cent of glucose	1 part.

It is placed into tubes and sterilized exactly like blood-serum.

Potatoes.—The most satisfactory method of preparing potatoes for culture media is that devised by Bolton and Globig.

With a cork borer a number of cylinders are cut from large potatoes. They are cut transversely so that several, each about one and one-half inches in length, can be made from a single potato. The skin is removed from the ends and each cylinder cut in two by an oblique incision. The half-cylinders are placed into sterilized test-tubes with their oblique surface up, and the tubes subsequently sterilized by steam for 20 minutes on three consecutive days. The disadvantage of the potato as a culture medium is that it soon becomes dark and dry. Drying may be prevented by placing a few drops of water in each tube before sterilizing.

Milk.—This is a good culture medium but must before using be deprived of its cream. It is best to secure fresh dairy milk from which the cream has been removed by a centrifugal machine. After distribution into tubes it is sterilized by steam.

Litmus Milk.—This is milk to which enough of a watery solution of litmus has been added to give it a faint blue color. Should the milk be acid, it is necessary to add a few drops of a sodium carbonate solution. Litmus milk is used to determine whether bacteria by their growth produce acids.

Peptone or Dunham's Solution.—The composition of this is as follows:

Sodium chlorid	0.5
Dried peptone	1.
Water	100.

After boiling until the ingredients have dissolved, the solution is filtered. It is an excellent medium for the detection of indol. The addition of *rosalic acid* makes of it a good medium for the determination of acids in cultures. A solution of rosalic acid is made by dissolving rosalic acid 0.5 in water 100; of this 4 c. c. are added to 100 c. c. of Dunham's solution. The pale rose color of the mixture fades under the action of acids, and is intensified under that of alkalies.

CULTURES AND THEIR STUDY.

A growth of micro-organisms in which immense numbers are massed together is called *culture*. If such a growth contains but one kind of organism it is known as a *pure culture*. There are three principal methods for preparing pure cultures, those by means of Koch's plates, of Petri's dishes, and of Esmarch's tubes.

1. *Plate cultures.* Half a dozen *glass plates* are cleansed and then sterilized in a hot-air oven. A *moist chamber*, or double dish, is disinfected with 1 to 1000 bichlorid of mercury solution and a sheet of bibulous paper placed on the bottom, and moistened with the disinfecting solution. The plates are then leveled by means of a special leveling apparatus, over a vessel of ice-water. Several tubes, usually three, of melted gelatin at the temperature of about 37° C., are now inoculated with the material containing the bacteria in such a manner as to make what are known as *dilutions*. To do this one of the tubes is inoculated with a sterile platinum loop or *Oese* from the material to be studied; from this tube the second one is inoculated, and from the second the third tube. The last tube contains such a small number of bacteria that the individual colonies, subsequently developed, will not coalesce and can be observed with ease. After the tubes have been thus prepared the stoppers are removed and the ends of the tubes held for a moment in the flame; the contents are then poured out upon the cold glass plates, and after the gelatin is solidified, the latter are placed in the moist chamber. Where each organism falls, a colony soon develops, from which tubes can be inoculated and pure cultures obtained.

2. *Petri dishes.* These are small double dishes that are so convenient that they have almost entirely displaced the glass plates. The dishes are sterilized, the test tubes prepared as described, and the contents poured into the dishes, which are properly marked and set aside for the colonies to develop.

3. *Esmarch Tubes.* The tubes are prepared in the usual way, but should contain a smaller quantity of the culture medium. Several are inoculated and then twisted about in ice-water so as to spread the contents on the sides of the tubes.

Gelatin, agar-agar, and glycerin-agar can be used for plating; blood-serum cannot.

The offspring of each bacterium forms a mass which is termed a *colony.* The colonies should be studied with the naked eye and with a low power of the microscope; drawings of them should be made at intervals.

A pure culture, when it is to be obtained from colonies growing upon a plate, must always be made from a *single colony*, the colony being touched with the platinum-wire under the microscope and then transplanted into a culture tube.

Puncture cultures are made by puncturing the gelatin with the platinum-wire carrying the bacteria all the way down to the bottom of the tubes.

Stroke cultures are made upon agar-agar or blood-serum by drawing the wire over the inclined surface of the medium from the bottom to the top.

The development of bacteria in liquid culture media is of less interest than that upon solid media. The growth generally manifests itself by a diffuse turbidity. Some forms grow most rapidly at the surface of the liquid and produce a distinct membranous pellicle, called a *mycoderma.* Others produce a growth chiefly below the surface and form gelatinous masses which are known as *zooglea.*

Much attention has recently been bestowed upon the preparation of sections of the gelatin growth in puncture culture. One method consists in fixing the gelatin in Müller's fluid. To do this the tube is warmed sufficiently to allow the gelatin to be removed to the fluid; after fixation, the gelatin is passed through alcohols of increasing strength, imbedded in celloidin, cut, and stained just as tissue sections are.

Another convenient method is to bore a hole in a block of paraffin, soak the block for an hour in bichlorid of mercury solution, then to pour the liquid gelatin into the cavity, allowing it to congeal, and afterwards inoculating it. After the growth has developed sufficiently, sections are cut under alcohol and stained with very dilute carbol-fuchsin.

Permanent specimens of plate and puncture cultures in gelatin can be made by treating, simultaneously, the gelatin and the micro-organisms with *formalin*, in spray or in dilute solution.

THE CULTIVATION OF ANAEROBIC BACTERIA.

This is always attended with difficulty, and none of the numerous methods proposed is entirely satisfactory.

The method now generally employed is as follows: The inoculations are deeply made in culture media as free from air as possible, *e. g.*, into freshly steamed agar-agar. The tubes are loosely plugged and placed in an air-tight chamber, the bottom of which contains pyrogallic acid—*pyrogallic acid* 1, *solution of caustic potash* 1, *water* 10. The apparatus is connected on one side with an exhaust pump, on the other with a hydrogen apparatus by which means the atmosphere is removed and replaced by hydrogen. The chamber is then permanently sealed and the germs allowed to grow. Whatever oxygen may have escaped the exhaustion is at once absorbed by the pyrogallic acid.

The *recognition of bacteria* is difficult, and it is often necessary to apply all the methods of bacteriologic technique in order to differentiate one species from another. Only a few possess such marked peculiarities of growth, color, or staining as to be readily distinguished from all others. A series of tables has been compiled by Eisenberg which is a valuable guide in determining the name of a species.

CHAPTER V.

EXPERIMENTATION UPON ANIMALS.

Experimentation upon animals is indispensable for the study of the causes of infectious diseases and for the preparation of curative agents against them. Wanton cruelty to the animal should be, and is, avoided by the conscientious experimenter.

Two principal methods of introducing bacteria are employed, the *subcutaneous* and the *intravenous* injection. Subcutaneous

injections are made exactly as hypodermatic injections are given in man. In the intravenous method the needle of the syringe is introduced into a superficial vein; in the rabbit, for instance, into the vein on the dorsal surface of the ear.

Sometimes *intra-abdominal* and *intra-pleural* injections are made, and occasionally pieces of fresh tissue, such as particles of tuberculous glands, are introduced under the skin or into the abdominal cavity.

The inoculation can at times be made with the platinum-wire through a small opening in the skin.

In making autopsies on infected animals it is necessary to use antiseptic precautions to exclude foreign germs. The animal should be washed with a disinfecting solution and all instruments carefully sterilized.

CHAPTER VI.

TUBERCULOSIS.

Tuberculosis is one of the most common diseases of mankind, and is responsible for an immense number of deaths annually. Its ravages are, however, not confined to man, but extend to most of the domesticated mammalia and also to birds.

Its cause, though long suspected to be a parasite, especially by Klebs, Villemin, and Cohnheim, was not discovered until 1882, when Koch succeeded in demonstrating and isolating the specific bacillus.

The *tubercle bacillus* is a rod-shaped organism with rounded ends and a slight curve, measuring from 1.5 to 3.5 μ in length, and .2 to .5 μ in breadth, and occurring in pairs or chains, often presenting a beaded appearance. The beading was at one time considered to be due to the presence of spores, but is now generally ascribed to contraction of the fragmented protoplasm within the resisting capsule. The organism is not motile and does not possess flagella. The bacillus is peculiar in its reaction to anilin dyes; it is difficult to stain, but also holds the color tenaciously when stained, resisting the decolorizing power of strong mineral acids.

Methods of Staining.—If the material to be examined is sputum, it is advisable to select one of the small caseous granules usually present in the expectoration of tuberculous patients. This is spread on a clean cover-glass; the latter is dried in the air and passed three times through the flame for purposes of fixation. There are two principal methods of staining, the *Koch-Ehrlich*, which is the best, and *Gabbett's*, which is the most convenient.

(*a*) *Koch-Ehrlich Method.* The prepared cover-glasses are placed on, or sections are placed in, *Ehrlich's solution* made with gentian-violet, and kept in an incubator for 24 hours. On removing the specimens they are momentarily washed in water, and then placed for about 30 seconds in *33 per-cent nitric acid*, then immediately into water. They are now washed with *60 per-cent alcohol* until the blue color is almost entirely lost. If desired, they may be counterstained with eosin or Bismarck-brown. The excess of stain is washed off in water, the cover-glass is dried and mounted in balsam, the section is dehydrated, cleared in xylol, and mounted in Canada balsam. The bacilli appear blue, everything else pink (eosin) or brown (Bismarck-brown).

A valuable method for sections is that of Unna. The sections are placed in a dish of Ehrlich's solution 24 hours old, and allowed to remain 12–24 hours at the room temperature or 1–2 hours in the incubator. They are then placed in water for 10 minutes, and afterwards for 2 minutes in 20 per-cent nitric acid, where they become greenish-black. From the acid they are transferred to absolute alcohol, and are gently moved to and fro until the pale blue color returns. They are then washed in three or four changes of water until they become almost colorless. From the water they are removed to a slide with a section lifter. The water is absorbed with bibulous paper, and then the slide heated over a flame until the section becomes shining, when it receives a drop of xylol balsam and a cover-glass. Sections stained in this manner are said not to fade as quickly as those stained by the Koch-Ehrlich method.

(*b*) *Gabbett's Method.* This is more rapid and more convenient. The prepared cover-glass is stained with *Ziehl's carbol-fuchsin solution*, 3–5 minutes, the stain being heated over the flame until white vapors arise; the cover-glass is then withdrawn from the flame for a little while, and then reheated. Care should be taken to replace the stain lost by vaporization. After the staining is completed, the cover-glass is washed in water and then treated for *30*

seconds, for purposes of differentiation and counterstaining, with *Gabbett's solution*. This consists of

Methyl-blue	2
Sulphuric acid	25
Water	75

The cover-glass is now thoroughly washed in water, dried and mounted in Canada balsam.

The method may be applied to sections in the following manner: The imbedding material having been removed, especially if it be paraffin, the section is floated out in water, a clean slide placed beneath it, and the section lifted on the slide. It is then *thoroughly dried* with bibulous paper, by vigorous rubbing, and stained with *carbol-fuchsin* for from 10–20 minutes, the stain being kept hot over a flame. The stain should be replaced as quickly as it evaporates. The section is washed in water, and then decolorized and counterstained with *Gabbett's solution*, this being permitted to act for from *45–60 seconds*. It is now washed by dropping on alcohol from a pipette until a faint blue tinge remains. It is then dried with bibulous paper and mounted in Canada balsam. The method may be epitomized as follows:

For Cover Glasses.

1. Spread, dry, and fix.
2. Stain with carbol-fuchsin, 3–5 minutes, heating stain.
3. Wash in water.
4. Differentiate and counterstain with Gabbett's solution, 30 seconds.
5. Wash in water.
6. Dry.
7. Mount in Canada balsam.

For Sections.

1. Spread on slide and dry.
2. Stain with carbol-fuchsin, 10–20 minutes, heating stain.
3. Wash in water.
4. Differentiate and counterstain with Gabbett's solution, 45–60 seconds.
5. Wash in water.
6. Wash with alcohol.
7. Dry.
8. Mount in Canada balsam.

The bacilli are stained red, everything else is blue.

The tubercle bacillus also stains well by Gram's method, but as this stains other bacteria, it is not adapted for purposes of differentiation.

So far as is known the tubercle bacillus is a purely parasitic micro-organism. It is found only in the bodies of animals affected with tuberculosis and in their excretions and discharges and in the dust that has been contaminated with the latter.

A pure culture is generally obtained as follows: A guinea-pig is inoculated with tuberculous material, allowed to live a month or

six weeks, and is then killed. Under antiseptic precautions a lymphatic gland or splenic nodule is removed, incised, and some of the material transferred with a platinum-wire to a blood serum or glycerin agar tube. The tubes are then closed with a rubber cap placed over the cotton stopper or by a rubber cork above the cotton which is cut off and pushed in. The tubes are then kept at a temperature of 37°–38° C., in the dark. The first growth will be apparent in about two weeks in the form of small, dry, whitish flakes. If now transplanted to another tube, a more active growth is obtained. The tubercle bacillus may be grown upon glycerin gelatin and upon potato, and after it has been grown for many generations on appropriate media, also on agar-agar. But little use is made, however, of any culture media save glycerin agar and blood serum.

The bacillus requires considerable oxygen; it does not grow at a temperature lower than 29° C. or higher than 42° C. Temperatures above 75° C. speedily kill it. Sunlight is also detrimental to its growth.

It was at one time believed that the tubercle bacilli were ubiquitous in our atmosphere and that all persons were constantly inhaling them in large numbers. Cornet has shown that tubercle bacilli exist only in the atmosphere of places frequented or occupied by consumptives. He collected the dust from different localities—streets, houses, hospital wards, etc.—and injected it into guinea-pigs. He found that the dust contaminated with sputum produced tuberculosis in the inoculated animals.

In order to limit the spread of the disease certain hygienic measures are necessary. All tuberculous cases should be registered for the purpose of collecting accurate data; domiciliary disinfection should be practiced, and special hospitals erected, particularly for the poorer classes among which sanitary measures cannot be well carried out. The physician should instruct his patients and their friends concerning the danger of infection and the means of avoiding it. The patient should have his own eating and drinking utensils, his own towels and handkerchiefs; the sputum should be properly disinfected.

Channels of Infection.—(*a*) *The respiratory tract* is the most common channel. The bacilli may for a time remain dormant in the bronchial lymphatic glands.

(*b*) *The gastro-intestinal tract.* The infection is introduced with the food, principally with milk from tuberculous cows, and less

frequently with meat from tuberculous animals. The mesenteric glands are generally involved, with or without the co-existence of intestinal ulcers. At times the thoracic duct becomes affected; general miliary tuberculosis is then readily produced.

(*c*) *The sexual apparatus.* In tuberculosis of the testicle the bacilli may be carried with the semen into the sexual organs of the female and set up tuberculous lesions in them.

(*d*) *Inoculation through wounds.* Infection through this channel is rare. It is seen in the anatomic wart which frequently is tuberculous.

(*e*) *Through the placenta—Heredity.* A few instances of transmission of the bacilli from the mother to fetus through the placenta are on record. The bacilli may remain *latent* in the fetus and cause the development of the disease after birth.

Dead tubercle bacilli are chemotactic, and cause abscesses when injected subcutaneously. Their introduction into the blood produces somewhat different results—results that resemble the effects of living bacilli. The first effect of the bacilli is to cause a proliferation of the connective tissue cells, which, however, soon degenerate. Secondarily, leukocytes are attracted. Aside from the chemotactic substance in the dead bacilli, the necrotic cells also yield chemotactic principles. The substance causing the necrosis is probably not the same as the chemotactic substance, since necrosis is present even when leukocytes are absent. Most tubercles, but not all, are avascular. The necrotic changes also occur when the tubercles are small and vascular, as at times in tubercles of the renal glomeruli. In necrotic areas the tubercle bacilli are not healthy, but show evidences of degeneration.

The tubercle bacilli are carried in the body by the lymph or blood-stream, or by phagocytes, the carrying cells being themselves killed. Tubercles may be healed by the formation of a capsule around them, but they may later break down again.[1]

Koch, in some very important experiments, found that tuberculosis could be cured in guinea-pigs by reinoculating them with tubercle bacilli, or by injecting a 50 per-cent. glycerin extract of a culture destroyed by heat (tuberculin). The active substance of this extract is an albuminous body, which is soluble in glycerin, but

[1] For the histology of the tubercle, see "Notes on Pathology," p. 70.

insoluble in absolute alcohol. It does not act directly on the bacteria, but destroys the tuberculous tissues, and the bacilli perish afterwards from lack of nourishment.

Tuberculin is prepared as follows: Flasks are partly filled with bouillon containing 6 per-cent. of glycerin, and are inoculated on the surface of the medium with pure cultures in blood serum or glycerin agar. They are then placed in an oven for several weeks. The bouillon is finally evaporated on a water-bath to one-tenth the original bulk, and the liquid filtered through porcelain.

SYPHILIS.

Lustgarten has described a micro-organism which is found within the cells of syphilitic lesions. The following stain is recommended:

1. Stain the section in anilin-water-gentian 12 to 24 hours at the room temperature, or 2 hours at 40° C.
2. Wash a few minutes in absolute alcohol.
3. Immerse for 10 seconds in 1.5 per-cent. solution of potassium permanganate.
4. Place in an aqueous solution of sulphurous acid, 1 to 2 seconds.
5. Wash in water.
6. Dehydrate in alcohol.
7. Clear in oil of cloves.

Cover-glass preparations are treated in the same way, except that the distilled water is used instead of absolute alcohol for decolorizing in step 2.

In another method the cover-glasses are immersed in hot anilin-water-fuchsin for a few minutes (sections in same solution, but cold, for 24 hours). They are then placed, first in a weak, then in a strong solution of iron chlorid. The covers are washed in water, dried and mounted; sections are rinsed in alcohol, dehydrated, cleared, and mounted.

The bacilli are not always found in syphilitic lesions, nor are they easily demonstrated.

A micro-organism occurs in the smegma of healthy individuals, which is identical in morphology and staining peculiarities with Lustgarten's bacillus.

As the bacilli of tuberculosis and leprosy can be stained by the same process, it is possible that the few cases in which the

syphilis bacillus has been found in the viscera were cases of mixed infection. The bacillus has never been isolated nor cultivated, and its relation to syphilis must be determined by future experimentation.

ACTINOMYCOSIS.

This disease is almost peculiar to the bovine species, the lesions being found in the jaw and tongue of the animal. It is due to the ray-fungus, or actinomyces, which can be detected by the naked eye. Under the microscope it has a rosette shape, and consists (*a*) of a granular central substance containing small round bodies (spores); (*b*) of radiating mycelial threads extending outward and terminating in (*c*) a zone of club-shaped forms.

Formerly the organism was classed among the pleomorphous bacteria, in the genus cladothrix, but recent researches have shown that it is a bacillus, the round bodies in the centre being spores, the mycelial threads perfect individuals, and the club-shaped bodies involution forms. The actinomyces stains well by Gram's method, and, better probably, by Weigert's fibrin method.

It grows upon artificial media, but produces the rosette shape only in the body, not in cultures. Introduced into the abdomen of rabbits, typical nodules develop in the peritoneum, mesentery, and omentum, and show the ray-like arrangement. Infection occurs usually through grain, particularly barley.

GLANDERS.

The cause of glanders is the bacillus mallei discovered by Löffler, in 1882. It is a bacillus with rounded ends, shorter and thicker than the tubercle bacillus, non-motile, and non-flagellated. Spores have not been demonstrated, although the bacillus can live for a time in the dry state. It always occurs as a parasite.

The disease affects chiefly horses and asses, but is communicable to man. The guinea-pig and field-mouse are especially susceptible to experimental inoculation, while house-mice, white rats, and white mice are immune.

The purulent discharges from the nostrils of horses contain but few bacilli and are greatly contaminated with other bacteria. To obtain a pure culture, a guinea-pig is inoculated subcutaneously with the discharge from a case. The animal dies in 4 to 5 weeks, and a pure culture can then be obtained from the lymphatic glands or the testicles.

The bacillus grows best on glycerin agar or in blood serum, at the body temperature. On potato, at incubator temperature, the growth is characteristic, appearing, at the end of 48 hours, in the form of yellowish, transparent, honey-like drops. Later the transparency disappears and the amber color changes to a reddish-brown. After 4 or 5 weeks' cultivation the bacillus loses its virulence.

Staining. It does not stain by Gram's method; the best stain is that devised by Kühne. The sections are placed for 30 minutes in a solution of methyl-blue 1.5, alcohol 10, and 5 per-cent. watery solution carbolic acid 90. They are then washed in water, and carefully decolorized in a solution of HCl 10 drops to 500 c. c. of water. They are now at once immersed in a solution of lithium carbonate (saturated solution lithium carbonate 8 drops, water 10 c. c.), and then placed in distilled water for a few minutes. Afterward they are dipped in absolute alcohol colored with methyl-blue, dehydrated in anilin oil colored with a little of the blue dye, then washed in the clear oil, then in ethereal oil, and finally cleared in xylol and mounted.

The bacilli are not easily stained, as they give up the stain readily when the tissue is decolorized.

The position of the bacillus in the glander nodules resembles that occupied by the tubercle bacillus in the tubercles. The nodules are composed chiefly of leukocytes; the center rapidly degenerates, and suppurates, leaving an irregular, ragged-edged ulcer discharging an abundant amount of pus.

There is no immunity to the disease. White rats, though immune naturally, become susceptible after glycosuria has been produced by feeding the animals with phloridzin.

Mallein, a glycerin extract of cultures of the glanders bacillus, has been separated in about the same way as tuberculin is obtained. When injected into animals suffering from the disease, a febrile reaction analogous to that following a tuberculin injection in tuberculous individuals, is produced. The substance is used only for diagnostic purposes.

TETANUS.

The tetanus bacillus is an organism, the most striking feature of which is the enlargement of one end produced by a bright spore. It stains readily by the anilin dyes and also by Gram's method. Its habitat is garden earth, dust, manure, and it is sometimes found in the intestinal discharges of animals.

Isolation and cultivation are difficult, as it will not grow where oxygen is present. The spores are very resistant, and the bacillus may be isolated by heating the material to be investigated to 80° C. for an hour. In this time all the bacteria are killed and most of the spores except those of tetanus. The bacilli are also very resistant to disinfectants, being able to withstand a 5 per-cent. carbolic acid solution for 10 hours and one of mercuric chlorid 1 to 1000 for 3 hours. The micro-organism grows on all media and gives off a characteristic odor. Upon gelatin the colonies at first appear like those of the hay bacillus; but later liquefaction takes place.

The bacilli usually enter the body from the soil through a wound, which may be quite small. The period of incubation is often of considerable length, being in man at times 3 weeks.

Men, horses, mice, rabbits, and guinea-pigs are susceptible; dogs are much less susceptible, while amphibians and most birds are immune. The bacilli remain at the seat of inoculation and never enter the blood or lymph. In most cases there is a mixed infection, the other bacteria using up the oxygen and thus aiding in the growth of the tetanus bacillus. The symptoms are due to a poison elaborated by the tetanus organism.

When bacilli, freed from poison, are introduced into the body, they fail to produce any sign of the disease, being at once killed by the phagocytes. When introduced with the poison or when the tissues are simultaneously injured by chemical agents (as lactic acid), the toxin which causes the characteristic symptoms is developed. The amount of poison generated in the body is probably small, but extremely virulent, and rapidly produced. Kitasato found that excision or cauterization of the point of inoculation in mice failed to save the animal unless practiced *within an hour after inoculation.*

Post-mortem examination shows the organs to be normal in appearance except the nervous system, in which there is congestion.

The existence of the toxin has been demonstrated in the blood and urine of diseased animals. The toxin can easily be prepared from cultures outside the body. It is destroyed by exposure to light or by heating to from 60° to 65° C. An antitoxin can be produced in the blood serum of horses, goats, and dogs by the gradual introduction of the toxin, as is done in diphtheria. The antitoxin is obtained in solid form by precipitating the serum with alcohol.

ANTHRAX.

Anthrax, or splenic fever, is not common in this country or in England, but is a frequent and dreaded disease on the European continent. Cows and sheep are most often affected. Among laboratory animals, white mice, guinea-pigs, and rabbits are very susceptible, while dogs, most birds, and amphibians are almost immune. Man is but slightly susceptible, the disease usually being local—*malignant carbuncle* or *pustule;* general infection is rare. The cause of the disease is the bacillus of anthrax.

Anthrax bacilli are large, rectangular rods, 5 to 20μ in length and 1 to 1.25μ in width, and have a tendency to arrange themselves in long threads. They form oval central spores, are non-motile, and have no flagella. They stain readily with the watery solutions of the anilin dyes and by Gram's method. In sections, picro-carmin, followed by Gram's method, gives a beautiful picture. The spores can be stained with carbol-fuchsin, the bacilli being decolorized with a weak acid, and then counterstained with methyl-blue.

On the surface of gelatin plate cultures the colonies appear as minute, round, whitish dots, liquefying the gelatin as they increase in size. Under the microscope they present a tangled center, from which large numbers of curls extend, each composed of parallel threads of bacilli. The colonies make beautiful adhesive or impression preparations. In gelatin puncture cultures the bacilli grow most luxuriantly on the surface where oxygen is plentiful. As the growth progresses, fine filaments extend from the puncture out into the gelatin, giving the culture an appearance of an inverted evergreen tree. Eventually the entire gelatin is liquefied, and the growth precipitates. On agar the growth has few characteristics. On the potato a creamy-white layer is produced; sporulation is marked. Blood-serum cultures lack peculiarities; the medium is slowly liquefied.

The bacillus grows between the extremes of 20° and 45° C., best at 37° C. An exposure to a temperature of 42° or 43° C. for 24 hours destroys its virulence.

The anthrax bacillus is a parasitic organism, but by reason of its spore formation, it can exist in this latent form outside of the animal body until appropriate conditions for its development are presented. Ordinarily infection takes place through the respiratory or the intestinal tract. Men coming in contact with diseased cattle may be inoculated with the germ through a wound, and develop

malignant pustule, which may prove fatal. Those who work with the skins and hair of animals dead of anthrax sometimes suffer from a pulmonary form of the disease, "wool-sorters' disease," caused by the inhalation of spores attached to the wool.

In the laboratory the method of inoculation is to cut away a little of the hair from the abdomen of a guinea-pig or rabbit, or the root of a mouse's tail, make a little pocket with a snip of a pair of sterile scissors, and introduce the virus from a pure culture on a heavy platinum wire, the end of which is flattened, pointed, and perforated. The animal dies in from 24 hours to 3 days, according to the species. At the autopsy the naked eye changes are not marked. When a microscopic examination is made of the tissues, the capillaries are found to be filled with immense numbers of bacilli.

The inoculation of bacilli, the virulence of which has been reduced by growing them under unfavorable conditions, is capable of rendering cows and sheep immune to anthrax subcutaneously inoculated, although such vaccinated animals are not perfectly protected against intestinal anthrax. Immunity can also be secured by introducing simultaneously with anthrax another bacterium not at all related to anthrax.

At one time a discussion was waged how the pastures from which cattle acquired the disease became infected. It has now been pretty conclusively shown that infection is by the discharges—urine and feces—of diseased animals; hence the importance of the prompt destruction, by burning or by deep burial, of all infected animals.

MALIGNANT EDEMA.

This is due to a large slender bacillus, often found to contaminate cultures of the tetanus bacillus; it is almost as large as anthrax, but with rounded ends, and motile by virtue of a number of flagella attached to its ends and sides. It is strictly anaerobic, grows well at the temperature of the room and the incubator, and produces oval central spores. Its habitat is garden earth, but it is also found in dust, in the wash water from houses, and sometimes in the intestines of animals. It is pathogenic to most of the lower animals except cattle. Inoculation should be made subcutaneously, into a pocket of the skin, as when deposited on a surface abrasion, the presence of oxygen interferes with the development of the organisms. If the animal is a mouse, guinea-pig, or rabbit, it

usually dies in 48 hours, the autopsy revealing a general subcutaneous edema, containing immense numbers of the bacilli. In the blood the bacilli are few or cannot be found on account of the presence of oxygen.

Two cases of infection in man are reported; both were typhoid fever patients who had been injected with musk, to which the organisms were probably adherent.

The bacillus stains well with the ordinary dyes, but not by Gram's method. Pure cultures are readily obtained, best from the edematous tissues of rabbits or guinea-pigs inoculated with garden earth.

DIPHTHERIA.

This disease is due to the Klebs-Löffler bacillus, discovered by Klebs in 1883. It is about the length of the tubercle bacillus, but twice the diameter, and has rounded ends. One of its striking peculiarities is its irregularity in size and shape. It is very probable that the markedly irregular individuals represent involution forms, since they are far more plentiful in old than in new cultures. The bacilli stain with the ordinary stains, but best with Löffler's alkaline methyl-blue solution (see page 17). In tissues they are best stained by Gram's method or by Weigert's fibrin stain.

The organisms are optionally anaerobic, do not form spores and are readily killed by heat (50° to 58° C.), but withstand drying for several weeks. Flagella have not been demonstrated. They grow on all media, but most rapidly on Löffler's mixture: Blood serum 3 parts, meat-bouillon, containing 1 per-cent. of glucose, 1 part. On this medium, when kept at 37° C., growth occurs in the form of white colonies at the end of 12 hours. Few bacteria grow so rapidly, and scarcely any that are found in the throat. Gelatin is not liquefied by the organism. Milk is a good culture medium and may be a means of transmission of the infection. In litmus milk the alkaline reaction is replaced by an acid reaction, but as the culture grows old, the medium becomes again alkaline.

In man diphtheria is a local disease, the bacilli being only found in the membrane, and the general symptoms result from the absorption of poisons produced by the bacillus. In animals injected with the virus, the lesions differ from those noted in man. If 0.5 c. c. of a bouillon culture, 24 hours old, is injected into a susceptible animal (guinea-pig, kitten, or pup), a fibrinous exudate

and an extensive edema develop at the point of inoculation. The animal dies in from 24 to 36 hours, the organs, especially the liver, presenting at the autopsy minute white areas of necrosis. In these areas the bacilli are not found. Similar lesions are seen in other infections. The lymphatic glands and the adrenals are enlarged, the latter being also hemorrhagic. Rarely the bacilli are present in the internal organs and the blood. When introduced into the trachea of animals the bacillus produces a false membrane as in man.

The *pseudodiphtheria* bacillus resembles the true diphtheria bacillus very closely, and is probably merely an attenuated form of the latter. It is a little shorter when grown on blood serum, grows more rapidly in bouillon at from 20° to 22° C., and is not pathogenic to the lower animals.

In the human throat virulent bacilli have been found as late as five weeks after the disappearance of the membrane.

A *toxin* can be separated from cultures of the organisms by filtration through a porcelain filter, and can be obtained in such concentration that 0.1 c. c. will kill a guinea-pig in from 24 to 30 hours. Animals can be rendered immune to the bacteria or the toxin—in the blood serum of such animals an *antitoxin* is found.

Preparation of the toxin. The most virulent bacilli obtainable are grown in Löffler's mixture at 37° C. for 3 or 4 weeks, the medium being in a thin layer and exposed to a constant stream of moist air. The material is then filtered through porcelain. The filtrate should possess such a toxic power that 0.1 c. c. will kill a guinea-pig weighing 500 grams, in from 24 to 36 hours.

Immunization of animals. For practical purpose the horse is the best animal. The first injection is 1 c. c. At intervals of 8 days larger and larger doses are introduced, until finally as much as 300 c. c. are injected. As the toxin causes some local reaction, the injections should not be made until that has disappeared. If the injections are made too rapidly in succession, the animal is apt to die of cachexia.

Preparation of the serum. The horse is bled and the blood received in sterile bottles and allowed to coagulate in the cold. The serum is pipetted off, and preserved from decomposition by the addition of camphor, phenol, or trikresol. The serum should protect an animal against ten times the amount of toxin; *i. e.*, 0.01 c. c. antitoxin should neutralize 0.1 of toxin. The strength of

the serum is expressed in "immunity units"—an immunity unit being the amount of antitoxic serum required to protect a 500 gram guinea-pig against ten times the minimum fatal dose of toxin.

CHOLERA.

The cause of cholera is a spirillum discovered by Koch in 1884. It is short, about half the length of the tubercle bacillus, considerably stouter, and distinctly curved on itself, hence the name "comma bacillus." When the conditions of nutrition are unfavorable, so that division is not rapid, long, winding, spiral threads are formed, showing that the organism is a spirillum. The bacteria are actively motile by reason of a flagellum projecting from one end. Involution forms are common in old cultures and sometimes also in fresh ones, the germs from different sources varying in this respect. Spores have not been found by most observers. The spirillum has but little resisting power, although it multiplies with great rapidity under favorable circumstances. It is readily killed by germicides, by a temperature of 55° C., and by drying, although in the moist state it retains its vitality for months. Staining is readily accomplished with the ordinary anilin dyes, best perhaps with a weak aqueous solution of fuchsin; it is not stained by Gram's method. In making a cover-glass preparation from the intestinal discharges, one of the rice-like bodies is smeared on the glass and stained in the customary manner.

Cultures. On *gelatin-plates* the organism produces highly characteristic colonies. The gelatin is slowly liquefied and as the liquid gradually evaporates, the colonies seem to be situated in little pits with sloping sides, the plate appearing to be full of air bubbles. The colonies are not regular in contour, and those which have not yet reached the surface are coarsely granular and yellowish in color. As they increase in size they present a powdered-glass appearance. The growth scarcely resembles that of any other micro-organism. In *puncture culture* the growth occurs along the entire stab, but best at the surface, where liquefaction and evaporation take place so that a funnel-shaped depression is produced. The growth reaches the sides of the tube in from 5 to 7 days. In 8 weeks the germs die and cannot be transplanted.

On agar the growth is not peculiar, but the vitality is retained much longer. The blood serum culture offers nothing peculiar. On potato the growth is active, even when the medium is acid. In

bouillon-peptone solution the organisms grow well and produce a wrinkled mycoderma on the surface, the fluid below remaining clear. They grow well in milk without causing any visible change, but die as soon as the medium becomes acid. In sterilized water they develop with great rapidity and remain alive for months. In unsterilized water they are soon destroyed by other bacteria.

One of the characteristics of the bacterium is its ability to produce indol simultaneously with nitrites. The simple addition of a few drops of H_2SO_4 suffices to produce a red color—the indol reaction. The organism also develops certain toxic substances which have been isolated.

The cholera spirillum is always found in the evacuations of cholera patients, sometimes in drinking water, in milk, and in foods moistened with infected water. They enter the body with the food and drink.

Animals do not suffer from a disease similar to cholera during epidemics, nor does the administration of food to which cholera discharges or cultures are added, produce the disease in them. Hypodermic injections are also without consequences. When, however, the gastric juice of a guinea-pig is neutralized with sodium carbonate and peristalsis is checked with opium, the introduction of a cholera culture kills the animal in 48 hours. The autopsy shows the intestines congested and filled with a rice-water fluid rich in bacilli, a condition like that found in man.

In man and animals the bacteria are found only in the intestines, where they enter the epithelial cells and basement membrane, aiding in the detachment of the cells. They are never found in the other organs or in the blood.

Their detection in drinking water is difficult. Löffler recommends the addition of 200 c. c. of water to 10 c. c. bouillon, allowing the mixture to stand in the incubator 12 to 24 hours, and then making plate cultures from the surface, where development is most rapid because of the presence of air.

THE FINKLER-PRIOR SPIRILLUM.

This was obtained from a case of cholera nostras in 1884, and closely resembles the cholera spirillum morphologically, but differs in its mode of growth, particularly on gelatin and potato. On gelatin plates the colonies are situated in slight depressions, are yellowish-brown, and finely granular, but are surrounded by a zone

of liquefied gelatin. In puncture culture a more extensive and rapid liquefaction occurs—along the entire stab. The absence of the air-bubble and the cloudy nature of the liquefied medium are additional points of differentiation from the cholera germ. It does not produce indol.

The organism grows readily, but without peculiarity, on blood serum and agar. In milk or water it does not grow well. It stains readily with all ordinary dyes, especially with fuchsin. Injected into the stomach of guinea-pigs treated after Koch's method, 30 per-cent. of the animals die, but the intestinal lesions are not the same as in cholera. The spirillum is probably a frequent and harmless inhabitant of the human intestine.

THE SPIRILLUM OF DENECKE.

This occurs in old cheese, and resembles the cholera spirillum in form and staining properties. On gelatin-plates it grows more rapidly than the cholera germ, but more slowly than the Finkler-Prior spirillum. The colonies differ from cholera in the rapid liquefaction, rapid growth, yellow color, irregular form, and distinct lines of circumscription which surround the colonies. Indol is produced at times, but not constantly.

It is not pathogenic, and probably never associated with disease in man, and is only mentioned because of its morphological relations to the cholera spirillum.

THE SPIRILLUM OF GAMALEIA (VIBRIO METSCHNIKOVI).

The organism is closely related to the cholera spirillum, and was first obtained from the intestines of chickens affected with a disease similar to chicken cholera. It is a trifle shorter and thicker than the spirillum of cholera, has also rounded ends, is motile, having a terminal flagellum. It grows well at ordinary temperatures and at that of the incubator. The ends stain more deeply than the center; it does not stain by Gram's method.

Upon gelatin plates the colonies present a marked similarity to those of true cholera, but liquefaction is quite rapid and gives rise to the presence of a turbid fluid in the concavity. Generally a few colonies will be found which resemble the cholera germ by occupying small conical depressions. Under a high power the contents of the colonies are found to be in active motion. In

gelatin tubes the culture is very much like that of the cholera spirillum, but develops more slowly. Upon agar a yellowish-brown growth develops along the whole line of inoculation. No growth occurs on potato at the room temperature, but in the incubator a yellowish-brown or chocolate-colored growth takes place. In bouillon the growth which occurs at the incubator temperature is quite characteristic and very different from that of the cholera spirillum. The medium becomes cloudy throughout, of a grayish-white color, and opaque. A folded and wrinkled mycoderma forms upon the surface.

The addition of sulphuric acid develops the indol reaction.

The organism is pathogenic for animals (chickens, pigeons, guinea-pigs), but not for man.

CHICKEN CHOLERA.

Chicken cholera is a very fatal epidemic disease, which affects chickens, ducks, and geese, and causes a profuse serous diarrhea. The bacteria which have been found to cause the disease are short, broad bacilli with rounded ends, non-motile, without spores, and do not stain by Gram's method. The organism appears to be identical with the bacillus of rabbit septicemia, the bacillus of swine plague, and several others bearing different names.

The *bacillus of hog cholera* resembles it very closely, but differs in being motile, and in producing a straw-colored growth on potato.

TYPHOID FEVER.

This is caused by a short, actively-motile bacillus, 1 to 3μ long and .5 to .8μ wide, with rounded ends. The motility is due to the presence of numerous flagella which project from the sides. The organism stains with the ordinary dyes, but best with Löffler's solution; it is not colored by Gram's method, and in tissues stains with difficulty, as it gives up the stain very readily. The bacillus is much more resistant than most pathogenic bacteria, and can live both as a saprophyte and as a parasite.

It has been found in water, air, on soiled clothing, in dust and sewage, in milk, and on vegetables sprinkled with water. In a number of instances the disease was traced to the contamination of oysters with the bacteria. The bacilli are killed at 60° C., but resist freezing and thawing several times repeated. They have been found alive in linen for from 60 to 72 days, and are known to

retain their vitality when buried in the upper layers of the soil for nearly six months. They can live a long time in distilled water, but in ordinary water are overcome by more vigorous organisms in a few days. The bacillus will grow in media containing as much as 0.1 or 0.2 per-cent. of carbolic acid.

Pure cultures may be obtained from the stools of typhoid fever patients by inoculating gelatin tubes containing 0.05 per-cent. of carbolic acid, and making plates. The carbolic acid prevents the growth of the majority of organisms except the typhoid bacillus and the bacillus coli communis.

The typhoid bacillus does not liquefy gelatin, and its colonies on this medium, as well as upon agar and blood serum, are not characteristic. The growth on potato is peculiar, and will be found described in the table below.

The isolation of the bacillus is difficult on account of the close resemblance between it and the bacillus coli communis, which is constantly present in the intestines. It is similar to the typhoid bacillus in morphology, and grows in the same manner on gelatin, agar, blood serum, and bouillon. The similarity is so great that some claim the two bacilli are identical. The following table presents the differences between them:

Bacillus of Typhoid Fever.	Bacillus Coli Communis.
1. Does not produce gas.	1. Produces gas in media containing glucose.
2. On acid potato produces an invisible growth. (At times growth is yellowish or brownish).	2. On acid potato gives rise to a smeary, elevated, circumscribed, brownish layer, resembling that of typhoid on alkaline or neutral potato.
3. Does not coagulate milk, though producing a slight acidity.	3. Produces a marked acidity, and coagulates milk.
4. Does not produce indol.	4. Produces indol.

The typhoid bacilli enter the body through the mouth, and passing the acid gastric juice uninjured, settle in the solitary glands and Peyer's patches of the intestines. The period of incubation is from 1 to 3 weeks. The organisms induce primarily a hyperplasia of the lymphoid structures, then a necrosis and sloughing. They can be found in the intestinal lesions, in the mesenteric glands, in the spleen and liver, in the kidneys, and in any other local lesions that may be present. Ordinarily they are not demonstrable in the blood, but at times have been found in that obtained from the

rose-colored spots. The local lesions are slight in comparison with the constitutional symptoms, which are now known to be due to a toxalbumin elaborated by the organisms.

Patients at times die with the clinical picture of typhoid fever, but do not show the characteristic lesions; the diagnosis of typhoid fever has been confirmed in these cases by the discovery of the typhoid bacilli in the spleen.

The demonstration of the bacilli in the spleen is often difficult. It is therefore advisable to wrap the organ in a towel impregnated with bichlorid of mercury and place it in a warm room for 3 days, which permits the organisms to develop actively.

Typhoid fever is communicated to animals with great difficulty —they are not affected when their food is mixed with fecal discharges containing the bacilli or with pure cultures. Injections of pure cultures into the peritoneal cavity are without effect, except in the case of mice and rabbits, which die and show the bacilli in the blood in large numbers. In animals which were manipulated after the method of producing cholera, intestinal lesions resembling those seen in man were observed.

An antitoxin for clinical use has not been produced. Animals are easily accustomed to the organism, and seem to develop some antitoxic substance in their blood serum. Good results have been obtained in a few cases by the hypodermic injection of sterilized cultures of the bacillus pyocyaneus.

RELAPSING FEVER.

In 1873 Obermeyer discovered in the blood of patients suffering from relapsing fever a spirillum 20 to 40μ in length and 0.1μ in width. The spirilla are long, slender, have pointed ends, are flexible, and move vigorously by means of flagella. They stain readily with the ordinary dyes, but not by Gram's method. The spirillum appears to be a true parasite, and has never been cultivated artificially. There is no doubt as to its pathogenic power; it is constantly present, and the disease can be reproduced in man and monkeys by injecting the blood of patients suffering from relapsing fever.

During the febrile period the organisms are numerous in the blood, and move actively both by rotation on their long axis and by undulation. At the crisis they are motionless, and most of them

are contained in leukocytes, and are apparently dead. The tendency of the paroxysms to recur has led to a belief in the existence of spores, but they have never been demonstrated.

INFLUENZA.

Canon and Pfeiffer, in 1892, discovered, simultaneously, a bacterium which they look upon as the cause of influenza, and which they found in the blood and in the bronchial discharges. It is a very small bacillus, 0.5μ in lengths, and occurs usually singly, but may form chains, and stains poorly, even with dyes like carbol-fuchsin or Löffler's alkaline methylene-blue solution. One of the best stains is the following:

Concentrated watery solution methyl-blue	40
0.5 per-cent. solution eosin in 70 per-cent. alcohol	20
Distilled water	40

A cover-glass spread with blood is dried, fixed by a 5 minutes' immersion in absolute alcohol, and stained in the solution for from 3 to 6 hours; then it is washed in water, dried, and mounted in balsam. The bacilli are stained blue, and are at times abundant, at others but few are present. They are often enclosed in leukocytes. They do not stain by Gram's method.

The organism is non-motile and, as far as known, does not form spores. It speedily succumbs to drying, and is killed by a 5 minutes' exposure to a temperature of 60° C. Below 28° C. it will not grow.

Cultures. It does not grow on gelatin or plain agar. On glycerin agar, left in the incubator, minute, colorless, transparent, drop-like colonies develop along the line of inoculation in 24 hours. They resemble condensed moisture, never become confluent, and are so small that they cannot be detected without a lens. On bouillon a scant development occurs, appearing as whitish particles on the surface and subsequently sinking to the bottom.

The bacillus grows well on culture media containing hemoglobin or blood, and can be repeatedly transplanted without losing its vitality. It has not been positively demonstrated that it is the cause of influenza, but it has been shown that it is constantly present in all uncomplicated cases of influenza, and only in influenza, and can be found as long as the purulent secretion continues; then it disappears.

MEASLES.

Canon and Pielicke, in 1892, discovered in the blood of measles patients an organism varying in size and shape, sometimes resembling a diplococcus, at others appearing as a bacillus as great in length as the diameter of a red corpuscle. The discoverers employ the following method of staining. The blood is spread thinly upon a cover-glass and fixed by 5 to 10 minutes' immersion in absolute alcohol. The cover-glass is then placed in a solution of

Concentrated aqueous solution methyl-blue	40
0.25 per-cent. solution of eosin in 70 per-cent. alcohol	20
Distilled water	40

and stood in the incubator at 27° C. for from 6 to 24 hours. The bacilli do not stain uniformly; they also do not stain by Gram's method.

They were found not only in the blood, but also in the secretions from the nose and eyes; they are said to persist throughout the course of the disease.

PNEUMONIA.

I. Lobar or Croupous Pneumonia.

The pneumococcus of Fränkel and Weichselbaum is found in at least 75 per-cent. of cases of lobar pneumonia. Discovered by Steinberg in 1880, in his own saliva, and also by Pasteur in saliva in the same year, its relation to pneumonia was not revealed until nearly five years later.

In its typical form it is lanceolate in shape, but its morphology is variable. In bouillon it occurs in pairs or chains, so that some have been disposed to look upon it as a streptococcus. In the fibrinous exudate of croupous pneumonia, in the rusty sputum, and in the blood of rabbits and mice that have been inoculated, they have a distinct lanceolate shape, and occur in pairs, the pointed ends being approximated, and are surrounded by a distinct, clear halo, or capsule, which is thought by some to be a swollen cell wall, by others a mucus-like secretion given off by the organism. When grown on the ordinary solid media, the capsules are absent. It has no motion, is without spores, and is unable to resist any unfavorable conditions when grown artificially. It stains well with the ordinary dyes, and very beautifully by Gram's method.

The pneumococcus is found normally in the saliva of some persons; and when such saliva is injected into rabbits, the latter die of septicemia, the bacteria occurring abundantly in the blood and tissues.

Pure cultures can be obtained by inoculating rabbits with saliva and recovering the organism from the blood, or from the rusty sputum of pneumonia by the method by which tubercle bacilli are cultivated from tuberculous sputum.

The organisms lose their virulence in culture media in a few days, and, unless continually transplanted, die in one or two weeks. Its growth on gelatin is slow, and the medium is not liquefied. On agar and on blood serum minute, transparent, scarcely visible colonies develop. In bouillon the growth is active, the medium becoming clouded. In milk the growth is also active and produces coagulation; no growth occurs on potato.

To maintain the virulence of the micro-organism, it is necessary to pass it frequently through the bodies of susceptible animals.

When a pure culture or a piece of pneumonic lung is introduced into a mouse, guinea-pig, or rabbit, the animal dies in from 1 to 2 days of general septicemia. At the point of inoculation there is an inflammatory edema. The spleen is enlarged, reddish-brown, and firm. The blood contains large numbers of the organisms with distinct capsules. The lungs show no pneumonic change. Even if the injection is made directly into the lung tissue, pneumonia is not produced.

Pneumonia is said, however, to have followed the introduction of the bacteria into the trachea of animals.

Unfortunately the name pneumococcus has been applied to a micro-organism very different from that just described. It was discovered by Friedländer, in 1883, in the exudate in croupous pneumonia, and being thought by its discoverer to be the cause of the disease, was called the pneumococcus, or more properly the *pneumobacillus.*

The two micro-organisms are, however, often confounded. That of Friedländer is distinctly a bacillus, but sometimes closely resembles the pneumococcus, often forming chains of four or more elements, and is also commonly surrounded by a transparent capsule. It is non-motile, has no spores and no flagella, and stains by the ordinary dyes, but *does not stain by Gram's method.*

In cultures great differences exist between the two organisms,

Friedländer's pneumobacillus forms distinct colonies on plates in 24 hours, and produces a luxuriant growth in puncture cultures. It will also grow at a lower temperature than the pneumococcus—at 16° C. On the surface of agar or blood serum it gives a distinct growth, and also a rapid and abundant growth on potato.

The only pathogenic results were obtained in the lung and pleura of mice. Rabbits and guinea-pigs are immune to it.

At present it is looked upon as a very feebly pathogenic organism, which is generally a harmless saprophyte, but may at times produce inflammatory changes in the body.

II. Catarrhal Pneumonia.

This is a localized inflammation about the bronchioles, and is not due to specific micro-organisms. The most common causes are staphylococci and streptococci of suppuration.

Friedländer's bacillus may also be connected with its production.

III. Tuberculous Pneumonia.

At times the tubercle bacilli are distributed to an entire lobe or an entire lung. Such a lobar inflammation may be due to the tubercle bacillus alone, but more often this organism is aided by the staphylococcus, streptococcus, tetragonococcus, pneumococcus, pneumobacillus, or other bacteria.

IV. Mixed Pneumonia.

Often pneumonia occurs during or shortly after influenza. In these cases the influenza bacillus and the pneumococcus are as a rule present together. Sometimes the pneumococcus and the staphylococcus operate simultaneously, purulent pneumonia with abscess formation being the consequence.

Almost any combination of bacteria is possible in the lungs.

GONORRHEA.

The cause of gonorrhea is the gonococcus of Neisser (1879). It is a coccus arranged in pairs, sometimes in fours. The approximated surfaces of the pairs are concave. The organism is non-motile and does not form spores. It stains readily with weak aqueous solutions of the anilin dyes, but not by Gram's method. In the urethral discharges it is found from the beginning until the end of the disease, growing fewer in numbers in the later stages.

It is generally found within pus cells or attached to the surface of epithelial cells, and should always be searched for as a diagnostic feature of gonorrhea.

The cultivation of the gonococcus is not easy; it has been accomplished on human blood serum. A drop of the pus is mixed with the liquid serum and the latter added to an equal part of melted 2 per-cent. agar at 40° C., the mixture being then poured into Petri dishes. As soon as the medium is firm, the dishes are placed in an incubator at 37° C. Within 24 hours colonies develop, having a dark center and a granular periphery. Transferred to coagulated human blood serum, the organism develops gray colonies which later become confluent. The gonococcus has also been grown upon acid gelatin and even in acid urine, where it develops on the surface, while the pus cocci that may be present sink deeper into the medium. Turro has succeeded in inoculating the urethra of dogs with cultures grown on acid gelatin. It was not even necessary to produce a lesion of the mucous membrane in order to cause the disease.

The gonococcus is not only constantly present in gonorrhea, but is frequently found in the sequelæ and complications of that disease, endometritis, salpingitis, cystitis, peritonitis, arthritis, conjunctivitis, etc.

The cocci at first grow in the superficial epithelial cells, but soon penetrate to the deeper layers. The peri-urethral abscesses at times occurring in gonorrhea are generally due to the staphylococcus aureus and albus.

After apparent recovery the gonococci may yet remain latent in the urethra and be capable of setting up a relapse. The gonococcus is not easily killed; it withstands drying very well.

Bumm has found in the urethra a coccus resembling the gonococcus, and claims that the shape and the position in the cells are not positively diagnostic, but that added to these we must have the refusal to stain by Gram's method.

MOUSE SEPTICEMIA.

The bacillus of mouse septicemia was isolated by Koch in 1878 from the blood of mice that had died of septicemia induced by the injection of putrid blood. The organism is very small, 1.0 x 0.2μ, grows well at room and incubator temperatures, and is facultatively anaerobic.

By some observers the bacillus of mouse septicemia is considered identical with the bacillus of swine erysipelas.

Mice die of septicemia in from 40 to 60 hours; guinea-pigs are not susceptible. Swine present paralytic weakness of the hind limbs, and die in 2 or 3 days. In all animals the lesions are the same—the disease is a septicemia. The bacteria can be found in the organs, particularly the lung and spleen, but are few in the blood. They stain well by Gram's method. Of the organs, only the spleen and the lymphatic glands appear abnormal, being enlarged.

Pasteur, Chamberlain and Roux have secured immunity in animals by vaccination, but the vaccinated animals are a source of infection, and should be isolated.

TETRAGENUS.

This is found in normal saliva, in tuberculous sputum, in tuberculous cavities, and sometimes in acute abscesses. It is a large micrococcus, 1μ in diameter, occurring in groups of four, surrounded, in the animal tissues, by a transparent capsule. Gram's method serves best for its demonstration in tissues; it also stains well with the ordinary dyes. On gelatin-plates it produces in from 24 to 48 hours small white colonies which under the microscope appear finely granular and lobulated. In gelatin punctures a large white surface-growth occurs, but very scant development in the puncture. The organism also grows on agar, potato, and blood serum.

White mice rapidly die of tetragenus septicemia when inoculated with pure cultures or with tuberculous sputum. House mice, field mice, dogs, and rabbits are resistant.

The organism, when associated with others in the human body, may hasten tissue necrosis, and contribute to the formation of tuberculous abscesses and cavities; and it may also be a factor in the production of hectic fever.

SUPPURATION.

Suppuration is due to a variety of micro-organisms which enter into wounds usually from the hands or instruments, rarely directly from the atmosphere. The skin is the habitat of a coccus —*staphylococcus epidermidis albus*—which may cause the so-called "stitch-abscesses." It is probably an attenuated form of the

staphylococcus pyogenes albus. The latter is often present on the skin, but is feebly pathogenic to animals.

The *staphylococcus pyogenes aureus* is almost constantly present on the skin, but only in small numbers; it is virulent and the most common organism of suppuration. It is found in the dust of houses and hospitals, especially in surgical wards; on the skin, in the nose, mouth, conjunctiva, and ears. In culture media it occurs in masses or evenly distributed. It stains easily, is facultatively anaerobic, and grows well on all media, producing an orange-yellow pigment. It liquefies gelatin rapidly and coagulates milk.

Its entrance into the skin causes furuncle or carbuncle. In animals the subcutaneous injection produces as a rule abscesses, and often a fatal result, the organisms being found in the blood and in infarcts in the internal organs. In man it is found in carbuncles, abscesses, and furuncles, in osteomyelitis, ulcerative endocarditis, etc.

The *staphylococcus pyogenes citreus* is identical with the former, except that on agar and potato it produces a lemon-yellow growth. It is less common and less important than the other pyogenic staphylococci.

Streptococcus Pyogenes.

This grows in chains, is non-motile, and does not form spores. It stains readily with the ordinary dyes; also by Gram's method. On gelatin it forms small colonies, without liquefaction of the medium; on agar and blood serum it produces a slow, pale, transparent growth; it does not grow on potato. In milk it grows readily; it coagulates and and then digests the medium. It is not very pathogenic to lower animals and subcutaneous injections in mice and rabbits are usually without effect. Rubbed into a rabbit's ear, a patch of erysipelas is produced, which soon disappears.

In man the organism is found in phlegmonous suppuration, ulcerative endocarditis, puerperal endometritis, and at times in the throat as the cause of a false membrane like that produced by the Klebs-Löffler bacillus.

The streptococcus pyogenes is believed to be identical with the *streptococcus of erysipelas.* The latter can be obtained in pure cultures from the serum secured by puncture of the margin of an erysipelatous patch. It is a small coccus forming chains, and grows best at a temperature of from 30° to 37° C. Its cultures are identical with those of the streptococcus.

The fact that malignant tumors when infected with erysipelas, sometimes slough and disappear, has led to the use of a toxin prepared from cultures of the streptococcus of erysipelas for therapeutic purposes. Cultures of the organism are grown for 3 weeks; the bouillon is then inoculated with the bacillus prodigiosus, kept at room-temperature for 10 or 12 days, and then sterilized by heating to from 50° to 60° C. for an hour. The combined toxin seems to give better results than the pure erysipelas toxin. It has been employed with some success in sarcoma.

Bacillus Pyocyaneus.

This is the bacillus of blue or green pus. It liquefies gelatin and gives to it a greenish color. On agar it produces a growth at first bright-green, later bluish. It is highly pathogenic to animals, but immunity is readily produced. Injected subcutaneously into guinea-pigs, it causes a rapidly-forming edema, suppuration, and death. Immunity is induced by the injection of sterilized cultures (heated to 56° C.). It is common as a saprophyte.

Bacillus Pyogenes Fœtidus.

This gives rise to an offensive odor. It grows on all media, producing grayish-white colonies; it does not liquefy gelatin, and is pathogenic for mice and guinea-pigs.

Besides those named above the *bacillus coli communis*, the *bacillus of typhoid fever*, and the *pneumococcus* should be mentioned as occasional pus producers. The first is found in suppuration in the bile-ducts and the appendix; the last in meningeal suppuration. The typhoid bacillus has been found in bone abscesses, in purulent meningitis, and other post-typhoidal suppurative foci.