I.

I. THE PATHOLOGICAL ANATOMY AND HISTOLOGY OF VARIOLA.

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Introductory. — This paper is based on material derived from fifty-four autopsies. Much of this was obtained during the hospital residence of those engaged in collecting it, a fact which insured prompt study and good preservation. In all cases the examination was as thorough as possible, and, as a rule, all of the organs of the body, regardless of the probable occurrence of lesions, were inspected.

Histological technic. — For histological study material was taken from the skin and from nearly all of the other organs of the body. As fixatives, alcohol, formaline, corrosive sublimate, and Zenker's fluid were used, in a few instances all of these; in the majority of cases, as the best for general histological purposes, Zenker's fluid alone. Material was embedded and cut in paraffine and stained by a variety of methods, chief among which were the eosin-methylene blue stain,[1] Mallory's iron hematoxylin followed by acid fuchsin and picric acid, Mallory's connective tissue stain, and a number of other special stains.

Bacteriological examinations. — Bacteriological examinations were made in several cases by means of cultures from the heart's blood, the spleen, the liver, and the kidneys.

Classification, statistics. — The forms of variola met with in this series of cases may be classified as follows:

A. Variola vera.
   (*a.*) Uncomplicated.
   (*b.*) With hemorrhage.

[1] Pathological Technique, Mallory and Wright, p. 296.

(*c.*) Abortive.
(*d.*) With complications.
B. Variola pustulosa hemorrhagica.
C. Purpura variolosa.

A. Variola vera (*a*) uncomplicated, presented in thirty-seven cases, nineteen males and eighteen females. Grouped according to age there were under five years of age, eleven; from five to twenty years, four; from twenty to fifty years, twenty; over fifty years, two. Grouped according to the duration of the disease, these cases fall into three periods: (1) of less than ten days' duration, seven cases; (2) from ten to thirteen days' duration, twenty-seven cases; (3) over thirteen days' duration, three cases. These periods correspond very closely with the first, the second, and the third weeks of the disease.

(*b.*) Variola vera, with hemorrhage, met with in two cases, both males about thirty years of age, who died on the tenth day of the disease.

(*c.*) Variola vera, abortive, met with in two cases, a female infant who died on the eighth day, from anemia, and a woman of forty-seven years who died on the thirteenth day from acute mania.

(*d.*) Variola vera with complications, represented by a group of six cases, in age ranging from infancy to thirty-nine years, fatal between the fourteenth and thirtieth day of the disease from such complications and sequelæ as noma, gangrene of the lung, pleuritis, broncho-pneumonia, and nephritis.

B. Variola pustulosa hemorrhagic, manifest in two cases, both males, one twenty-five years of age who died on the fourth day, and one thirty-seven years who died on the ninth day of the disease.

C. Purpura variolosa,[1] present in four cases, three males

[1] We include under this heading all cases of variola in which the purpura precedes the development of the eruption, and place in the class of variola pustulosa hemorrhagica those cases in which the eruption develops with or antedates the purpura.

and one female, from twenty-five to forty years old, who died between the fifth and seventh days of the disease.

The anatomical and histological findings will be presented under the head of the following organs:

I. Skin.
II. Mucous membranes.
III. Lungs.
IV. Liver.
V. Spleen.
VI. Lymph nodes.
VII. Bone marrow.
VIII. Testicles and ovaries.
IX. Kidneys.
X. Adrenal glands.
XI. Pancreas.
XII. Heart and arteries.

THE PATHOLOGICAL ANATOMY.

I. THE SKIN.

Variola vera (a) uncomplicated. — The lesions of the skin differ widely according to the duration of the disease at the time of death. Inasmuch as nearly seventy per cent of fatal cases die during the latter half of the second week, the general post-mortem picture is that of the late pustular or crusting stage. Seven of our series of thirty-seven cases were fatal during the first week. In the earliest of these the skin lesions consisted of papular elevations,[1] two to three millimeters in diameter, very slightly raised above the general level of the skin, and "shotty" to the feel. These lesions were fairly numerous on the forehead, cheeks, neck, shoulders, and the upper part of the chest, and were abundant on the backs of the hands and on the inside of the thighs; they were sparse on the abdomen. The palms and

[1] In the anatomical descriptions, the classical terms "papule" and "papular" will be used, although, as will be seen from the histological descriptions, the specific skin lesion of variola is from the first a vesicle.

the soles showed none. At this stage of the disease, about the fifth day, the lesions to the naked eye are not vesicular, but are opaque, reddish papules. Somewhat later the lesions on the face and the upper part of the trunk are vesicular, and papules appear on the lower legs. Toward the close of the first week confluence of the lesions on the face may be apparent. Edema of the face and the formation of crusts about the nostrils and the lips may also be observed at this time. In children who die during the first week the premature formation of crusts, due to the early, and in many instances the traumatic, rupture of vesicles formed in tender skin, is of frequent occurrence. In several children we observed the tendency of lesions upon the lower extremities to develop in groups, and also to differ in their size; in one instance the lesions upon the arms varying from one to four millimeters in diameter. A similar variability in size is also apparent in old people.

The second week includes what may be regarded as the lethal period of the disease, that from the tenth to the thirteenth day; within this, twenty-seven of our thirty-seven cases of variola vera died. At this time the face shows edema, often so marked as to produce great deformity. The prominent skin lesions of this region are crusts, which in size and in extent depend upon whether the pre-existing pustules were discrete or confluent. The face may show discrete crusts and scattered, filled out, or ruptured pustules, or a mask-like mat of crusts covering the face and the neck. Purulent conjunctivitis is sometimes present.

The skin of the trunk during this period presents as the predominant lesion the intact pustule, seldom umbilicated, interspersed with occasional ruptured pustules and crusts. The pustules are in general more numerous upon the upper than upon the lower part of the body. Upon the back they are evenly distributed. The axillæ, the flanks, and the groins are usually devoid of lesions. The number of the pustules depends on the severity of the case, and their condition in some degree on their position,—those on the dependent parts being ruptured earlier than others.

The skin of the extremities at this time presents likewise the pustule. Upon the arms the lesions are more abundant than elsewhere on the extensor surfaces and on the backs of the hands and wrists, in which position they show a marked tendency to confluence, a condition occasionally accompanied by the formation of large blebs filled with serous fluid. Palms, which possess a thick horny layer of the epidermis, show lenticular, copper-colored discs; those of children and others in whom this layer is thin show pustules, often more or less flattened. Upon the legs the lesions are most numerous on the inside of the thighs and upon the ankles and the dorsum of the foot, where they show a tendency to confluence and to the associated formation of blebs. Next in order to the regions named, the lesions are most numerous about the knees. They are few in number on the backs of the legs. The soles, like the palms, present discs, but elevated pustules are here comparatively rare.

Certain cases within this group presented characteristics differing from those of typical severe variola vera. In three such, an eruption of vesicles confluent in distribution was delayed in its evolution; the lesions did not fill out, and had failed to become pustular at the time of death. In these cases the lesions were small, about three millimeters in diameter, and so close-set as to leave practically none of the skin intact. Instances were observed of the grouping of lesions about an abrasion received during the stage of incubation, and in one case of the occurrence of numerous pustules in the flanks and the groins. The grouping of lesions along lines of pressure upon the skin, as beneath a waist-band, was repeatedly observed.

The third group of cases includes those fatal in the third week of the disease, and later. The skin of the face at this time is marked by copper-colored or reddish areas, at first more or less elevated and scaly, later becoming colorless pits.[1] The skin of the trunk and of the extremities shows

[1] This primary, irregular elevation of the skin at the site of the healed lesion was most marked in the negro.

markings of similar character, which gradually lose their color. Immediately after the falling off of the crust the sites of the lesions are somewhat elevated and rough. The palms and soles show usually reddish-brown discs, the color depending upon thickness of the epidermis.

The following are protocols of autopsies on typical cases of variola vera:

CASE NO. XLVIII. — Clinical diagnosis: variola vera (twelve days' duration).

Anatomical diagnosis. — Variola vera (late pustular, crusting); erosions of the palate; focal lesions of the testicle; edema of the lungs; cloudy swelling of the kidneys; sclerosis of the epicardium; chronic adhesive pleuritis.

BODY. — That of a man forty-five years of age; slender; length one hundred and seventy centimeters; fairly well nourished; rigor mortis present; some post-mortem lividity of dependent parts. Eyelids firmly interadherent; edges somewhat crusted. The skin lesions are fairly evenly distributed, and consist in general of umbilicated pustules, with occasional crusts.

The scalp and face present flattened and more or less umbilicated pustules, fairly thickly set, of an average diameter of five millimeters; the forehead and nose show many dry, yellowish crusts. The neck presents closely-set, umbilicated pustules without crusts.

The trunk is covered with pustules of the same general character as those above described, the frequency of the lesions is about one to every centimeter square; upon the back the lesions are evenly distributed; upon the anterior aspect of the body they are most abundant upon the upper part of the chest and the shoulders; the abdomen presents few lesions, about fifty pustules occurring upon the skin of the epigastric region; there are but few lesions in the flanks, and none in the groins. The prepuce, glans penis, and scrotum show flattened pustules and crusts.

The arms present pustules all more or less flattened and umbilicated, of an average diameter of five millimeters, most thickly set upon the forearms, where they are in places confluent; the back of the right hand shows an old abrasion covered by a hard, red crust; around this lesion pustules are crowded and confluent. The palms are covered with very thick epidermis, and show many brown discs.

The legs present lesions of the same sort as those upon the trunk, thickly set upon the front of the thighs, about the knees, and upon the dorsa of the feet. In the latter position some of the lesions are of large size, six to eight millimeters in diameter. The soles show a few discs, most numerous upon the hollow of the instep.

Upon section, subcutaneous fat three-tenths centimeters in thickness; muscles red and firm. Vermiform appendix normal.

Mesenteric lymph nodes normal.

THORAX. — Diaphragm in normal position.

Pleural cavities: left normal; right partially obliterated by old fibrous adhesions to the diaphragm, and in the anterior part of the cavity.

Pericardial cavity normal.

Heart: size, normal; upon the anterior surface is a circular white patch, three centimeters in diameter. Upon section, myocardium red and fairly firm; auricles contain a moderate amount of red and yellow clot. Valves and cavities normal. Coronary arteries normal.

Lungs: alike, present moderate carbon pigmentation; general color, gray-red; crepitant throughout; upon section, cut surface under pressure yields a moderate amount of bloody, frothy fluid, surface gray red and homogeneous. Bronchi upon section contain frothy mucus; mucous membrane red. Bronchial lymph nodes black.

ABDOMEN. — Peritoneal cavity normal.

Spleen: weight two hundred grams; capsule smooth; surface blue red; upon section cut surface presents a mottled appearance, the large and more irregular areas gray red, the smaller and round, or oval, intervening areas deep blood red; consistence slightly lax; pulp not increased.

Stomach and intestines negative.

Pancreas normal.

Liver: weight one thousand six hundred grams; surface smooth; general color brown; upon section markings visible; consistence normal. Gall bladder distended, with thin bile.

Kidneys: weight of both three hundred grams; capsule strips easily from a smooth surface; upon section, markings distinct; cortex six-tenths centimeters in thickness; glomeruli visible as pink points; cut surface, gray red, slightly opaque. Adrenal glands normal. Bladder normal.

Testicles: size, normal; to the touch they are distinctly nodular; upon section the cut surface presents multiple, not very sharply-defined areas which project above the level of the surface about one millimeter; these areas are of an average diameter of two to three millimeters; they are fairly evenly distributed throughout the body of the testicle, and their frequency is about one to the centimeter square; their contour is round or oval, sometimes irregular; in appearance they differ but little from the surrounding substance of the testicle.

ORGANS OF THE NECK.— The mucous membrane of the palate, pharynx, tonsils, and the root of the tongue is overlaid with thick, tenacious, yellow mucus; upon removal of this, the mucous membrane of the palate is thick and white, presenting here and there shallow erosions which have a reddish base. Similar conditions are present upon the uvula. Esophagus normal. Trachea shows a mucous membrane dark red, and overlaid with tenacious mucus. Larynx normal.

CASE NO. XV. — Clinical diagnosis. —Variola vera (twelve days' duration).

Anatomical diagnosis. — Variola confluens, crusting on face, pustular and vesicular elsewhere; edema of the lungs; focal necrosis of the testes; focal lesions of the pharynx, trachea, esophagus, and urethra; acute laryngitis, tracheitis, and bronchitis; phlegmonous inflammation of neck and anterior mediastinum.

Body of a well-developed and well-nourished man, thirty-six years of age. Rigor mortis present and fully developed.

The face and neck present a confluent mass of soft, moist, brown crusts. The nostrils are almost occluded by crusts. Left eye is absent (old injury). Right eye and conjunctiva normal, pupil of normal size.

Over the trunk there are numerous late vesicles and early pustules. The lesions are four to eight millimeters in diameter, are of the color of the skin, show a marked umbilication, and sometimes have a slightly oval outline. These lesions are not very closely set (about one to a centimeter square).

On the arms and legs are many lesions like those on the body, but they are more closely set and somewhat larger, particularly on the dorsum of the hands. On the penis and scrotum are a considerable number of similar lesions.

On the thighs are closely set, umbilicated vesicles like those described on the body. The lesions here are about two or three to the centimeter square. On the legs and dorsa of the feet the lesions are fewer in number and are less umbilicated. There is no clustering of the lesions, and in the groins and flanks they are comparatively few in number. There is a purulent balanitis.

On section, subcutaneous fat three centimeters thick. Muscles deep red. Mesenteric lymph nodes and appendix normal.

THORAX. — Pleural cavities: surfaces normal. Pericardial cavity normal, contains a few centimeters of clear, straw-colored fluid.

Heart: weight, two hundred and sixty grammes. Myocardium pale brown red. Right ventricle flabby and filled with yellow clot. Left ventricle firmly contracted. Valves and cavities normal.

Lungs: on the outer aspect of the left lower lobe is an area of thickened pleura one and a half centimeters across, which is of a pearly-white color and with a serrated border. Lungs alike. Crepitant throughout. On section, cut surface mottled light and deep pink with distinct carbon markings. Surface, on gentle pressure, yields considerable clear fluid containing innumerable bubbles of air. Bronchial mucosa normal. Bronchi contain stringy mucus.

ABDOMEN. — Peritoneal cavity normal.

Spleen: weight, two hundred grams. Color, deep purple. On section cut surface deep red, Malpighian bodies visible as gray points; trabeculæ normal. Consistency is firm, and little substance adheres to knife on gentle scraping.

Pancreas normal.

Stomach: some diffuse ecchymoses along lesser curvature. Mucosa normal.

Intestines: lower part of ileum normal.

Liver: weight, two thousand six hundred and fifty grams. Surface smooth and of a yellow-brown color. On section, markings indistinct. Consistency normal. On the surface are irregular yellow areas which are contoured in such wise as to suggest aggregations of fatty lobules. On section similar markings are found. Gall bladder normal.

Kidneys: weight, three hundred and fifty grams. Surface yellow-brown. Capsule strips readily, leaving a smooth surface. On section markings are indistinct. Glomeruli visible as gray points. Cortex of normal thickness and of a yellow-brown color. Pyramids reddish brown.

Adrenals normal. Bladder normal.

Genitals: urethra. About midway in the penile portion is an elevated area two millimeters across, with an irregular, oval outline and with a central depression. Elsewhere urethra is normal. Seminal vesicles and epididymis normal. Prostate normal. Testes: Tunica vaginalis normal, slightly nodular to the feel. On section the markings are distinct, but scattered over the cut surface are nodular elevations one to three millimeters across, which are redder than the surrounding tissue. These areas are not sharply circumscribed, and in them the tubular markings are visible.

Lymph nodes of the groin are enlarged, red, and somewhat hard. (Largest, two centimeters across.)

Aorta normal.

ORGANS OF NECK. — Soft palate, uvula and pharynx show low, gray, nodular elevations, some of which present a central superficial loss of substance.

Epiglottis thickened and similarly beset with nodules.

Larynx contains much gray mucus and its mucous membrane is reddened. In the trachea are numerous elevations from one to three millimeters in diameter, surrounded by a red ring. These elevations are conical and are occasianally eroded. About thirty such lesions of various sizes are present. Esophagus, upon its mucous membrane, presents many pale gray, oval or circular elevations from one to three millimeters in diameter. The largest of these is a low cone of a translucent gray color surrounded by a narrow elevated rim like the hull of an acorn; this surrounding rim is red.

The deep tissues of the neck on the right side are infiltrated with a grayish material, and on section a considerable amount of turbid, slightly blood-stained fluid exudes. The jugular vein is filled with a yellow clot and its wall appears normal. The muscles close about the larynx are in part friable and of an opaque, yellow-brown color. The fibrillary markings are indistinct. The tissue of the anterior mediastinum is edematous, and on section a cloudy, faintly blood-stained fluid exudes. This condition is most marked over the precordium and about the remnant of the thymus. Left side of neck normal.

Bone marrow: in general yellow with many areas of deep red color.

Variola vera (*b*) *with hemorrhage* (two cases, adult males, death on the tenth day). — Under this head we group cases in which the lesions of typical severe variola vera are complicated by hemorrhage. In one case the skin lesions were chiefly pustular, and in one vesicular. In the latter the lesions were for the most part filled with blood or bloody fluid, and scattered petechiæ were present on the legs. In the other, in addition to the close set pustules, were bullæ, two to three centimeters in diameter, and three to five millimeters in elevation, of dark reddish-brown or black color, filled with cloudy or with bloody fluid, and splitting groups of pustules horizontally.

Variola vera (*c*) *abortive.* — In this form of the disease death is due to some intercurrent cause. The skin lesions are exceedingly few in number, from twelve to forty by actual count in our cases (two), and show a tendency to rapid evolution from vesicle to crust.

Variola vera (*d*) *with complications.* — In four of the six cases falling within this group death occurred during or later than the third week; in the remaining two, fatal on the fourteenth day, the lesions of the skin were such as have already been described.

Variola pustulosa hemorrhagica (two cases, adult males; death on the fourth and on the ninth day). — The skin of the face is edematous; in the early cases it shows a bluish-gray pallor or a pale, gray-red or blue-red flush, together with red and blue petechiæ, one to five millimeters in diameter; in the later cases it presents gray-white papules and vesicles. Crusts are present about the eyelids, nares, and lips. The skin of the trunk shows vesicles, close-set and white, present on the chest and on the abdomen. The skin of the shoulders and the arms resembles that of the trunk; in the early cases petechiæ occur on the inner side of the arms. The palms in each instance showed no lesions. The skin of the lower extremities in the earliest cases is of a deep, purple-black

color, due to the presence of close-set petechiæ, many of which are surmounted by gray vesicles. In both cases the skin of the lower legs was marked by punctate hemorrhages, which in some instances bore small vesicles. In the later cases the vesicular character of the lesions is more apparent. In all cases the soles showed no lesions.

The following is a protocol of an autopsy on a typical case of variola pustulosa hemorrhagica:

CASE NO. XX. — Clinical diagnosis. —Variola pustulosa hemorrhagica; Hematuria.

Anatomical diagnosis. — Variola pustulosa hemorrhagica; multiple erosions of the palate and pharynx; ecchymoses of the stomach; hemorrhagic pyelitis; acute splenic tumor; cloudy swelling of the myocardium, the liver, the kidneys; edema of the lungs; acute bronchitis; acute vegetative endocarditis (mitral); infarction of the kidneys; tuberculosis of the lungs; chronic adhesive pleuritis.

BODY.— That of a man of twenty-five years of age; unvaccinated; length one hundred and eighty-five centimeters; powerfully built; well nourished; rigor mortis present; lividity of dependent parts. Face presents a bluish-gray pallor; the rest of the body shows a dusky bluish-red flush. The face is swollen, and there are numerous excoriations about the alæ nasi and lips. The skin of the face is thickly studded with grayish-white, extremely confluent, papular elevations two to four millimeters in diameter, in some instances slightly umbilicated; nearly all of these upon section contain a small amount of clear fluid. The skin of the neck and shoulders, and the upper and front part of the chest presents lesions similar in character to those upon the face, the vesicles so closely set that no normal skin intervenes; these regions present also occasional bluish-red elevations of about the same size. The lesions are sparse on the abdomen; they are infrequent in the flanks and in the groins; on the hands they are large and closely set, and are here notably transparent. Upon the prepuce the vesicles are large, thickly set, transparent, and more or less umbilicated.

The skin of the arms is thickly studded with papular elevations one to four millimeters in diameter, no normal intervening skin apparent. The skin of the thighs and legs presents lesions for the most part papular, two to eight millimeters in diameter, gray red, in some instances vesicular and umbilicated; interspersed with these are small, pale elevations about one millimeter in diameter; the larger vesicles are surrounded by a prominent red zone. The lesions are very closely set about the knees. Upon the legs the lesions are purpuric in character, consisting of red macules from pin-point size to four or five millimeters in diameter; some of them slightly elevated; they are most numerous upon the front of the legs. The dorsa

of the feet show papules one to six millimeters in diameter. The palms and soles are negative.

Upon section, subcutaneous fat three centimeters in thickness; muscles thick, red, and firm. Vermiform appendix and mesenteric lymph nodes normal.

THORAX. — Height of diaphragm fifth rib on right side, sixth on left.

Pleural cavities: both partially obliterated by old fibrous adhesions, which are most marked in the upper part of the right cavity.

Pericardial cavity normal.

Heart: estimated weight three hundred and seventy-five grams; upon section, myocardium red, and somewhat opaque. The free edges of the curtains of the mitral valve present small, pink, granular elevations; otherwise valves and cavities normal. Coronary arteries normal.

Lungs: right upper lobe presents extensive thickening of the pleura, and is closely adherent to the wall of the chest; this part of the lung upon section shows several areas of caseation about three centimeters in diameter, invested in a tough, fibrous connective tissue; no tubercles are apparent. Both lungs upon section show considerable edema; the bronchi are of a dirty, gray-red color, the mucous membrane apparently thickened; upon pressure they yield considerable muco-purulent material.

ABDOMEN. — Peritoneal cavity normal.

Spleen: moderately enlarged and somewhat flabby; upon section, markings vague, pulp a little increased.

Stomach: upon section the mucous membrane presents numerous red areas, evenly distributed, two to eight millimeters in diameter; otherwise negative.

Intestines negative.

Pancreas normal.

Liver: size normal, brown red; upon section markings vague; surface of section opaque; consistence rather friable. Gall bladder normal.

Kidneys: rather large; upon section capsule strips easily from a smooth surface; markings distinct; surface of section opaque and pale, somewhat edematous; the pelvis of the right kidney contains a small amount of bloody fluid; its mucous membrane is smooth, glistening, and of a deep cherry-red color, upon section showing extensive hemorrhage into the submucosa; the left kidney shows a small, recent, cortical infarct; its pelvis normal.

Adrenal glands normal.

Bladder normal.

Testicles: upon section no focal lesions apparent; tubules unravel easily.

Aorta normal.

ORGANS OF THE NECK. — The mucous membrane of the soft palate, the tonsils, the uvula, and the upper part of the pharynx is swollen, rough, of a dirty, grayish-green color, and in places shows shallow erosions.

Larynx and trachea: mucous membrane red and edematous; that of the

trachea presents appearances similar to those seen in the pharynx. Esophagus negative.

Bone marrow: that of the femur yellow, mottled with reddish areas of small size.

Bateriological examination. — Cultures from the heart, liver, and kidney show the streptococcus pyogenes.

Purpura variolosa (four cases; all adults, three males, one female, duration five to seven days). — The skin of the face shows a dusky, bluish-red flush, deepest about the neck and ears; a few small crusts may be present about the alæ nasi. The skin of the trunk presents a general terra-cotta-red or bluish-red flush, deepest upon the upper part of the chest and upon the dependent parts, together with sparse, vague, bluish splotches, two to four millimeters in diameter, rather more numerous than elsewhere in the flanks. The skin of the arms shows a faint red mottling; in one case that of the upper arms showed five or six small papular elevations. The palms in all showed no lesions. The skin of the legs resembles that of the arms, and like the palms, the soles are negative. The epidermis strips off readily in large sheets, leaving a moist, glistening surface.

The following are protocols of autopsies on typical cases of purpura variolosa:

CASE NO. XLIII. — Clinical diagnosis. — Purpura variolosa (five days' duration).

Anatomical diagnosis. — Purpura variolosa; subserous punctate hemorrhages; cloudy swelling of the heart, liver, and kidneys; punctate hemorrhages of the stomach; hemorrhagic pyelitis.

BODY. — That of a man about forty years of age; length one hundred and seventy-five centimeters; powerfully built; well nourished; body warm; rigor mortis absent; pupils equal and widely dilated.

The skin of the entire body is of a dull, bluish, brick-red color; this color is somewhat deeper upon the dependent parts than elsewhere, and the dusky blue tinge most marked about the ears and upon the sides and back of the neck. The skin is dull and lusterless and presents a somewhat velvety appearance, although it is not especially rough to the touch. The epidermis is readily separable from the cutis, leaving a raw, moist surface.

Upon the arms and legs there is a suggestion of fine red mottling which upon pressure becomes more apparent. Here and there upon both trunk and extremities are faint bluish spots of irregular outline, three to five millimeters in diameter; these are most prominent in the flanks. No other lesions are present upon the surface of the body.

Upon section, subcutaneous fat one and five-tenths centimeters in thickness; muscles well-developed, red, and firm. Mesenteric lymph nodes normal. Vermiform appendix normal.

THORAX. — Height of diaphragm fourth rib on right side, fifth on left. Pleural cavities normal. Pericardial cavity normal.

Heart: estimated weight three hundred and seventy-five grams; the epicardium presents multiple punctate hemorrhages, most numerous along the course of the right coronary artery. Upon section, myocardium red, opaque; blood, fluid; valves and cavities normal. Coronary arteries normal.

Lungs: alike; crepitant throughout; the visceral pleura presents many punctate hemorrhages, most numerous upon the interlobar surfaces; upon section, moderately edematous; bronchi pink, containing frothy mucus.

ABDOMEN. — Peritoneal cavity normal.

Spleen: size normal; free surface bluish red; upon section dark red, follicles visible, but not prominent; surface moist; consistence firm; pulp not notably increased.

Stomach: the peritoneum presents fairly numerous punctate hemorrhages; upon section the mucous membrane is mottled with cherry-red spots two to three millimeters in diameter, and fairly thick set; these are distributed throughout the whole organ and apparently extend into the submucosa. Intestines negative. Pancreas normal.

Liver: surface smooth, presenting here and there small punctate hemorrhages; upon section, brown-red, cut surface opaque; markings vague; consistence normal. Gall bladder normal.

Kidneys: estimated weight three hundred and twenty-five grams; upon section capsule strips easily from a smooth surface; cortex five-tenths centimeter in thickness; markings fairly distinct; cut surface opaque gray-red. The pelvis of each kidney presents a deep, cherry-red surface, slightly roughened; the mucous membrane thickened and edematous; no free blood is present in the cavities. Adrenal glands normal. Bladder normal.

Testicles: upon section no focal lesions apparent. Aorta normal.

ORGANS OF THE NECK. — Mucous membrane of the pharynx and soft palate, uvula, and larynx injected and overlaid with mucus; no focal lesions apparent. Esophagus normal. Trachea shows injection of mucous membrane. Cervical lymph nodes somewhat enlarged and red.

Cranium: brain, moderately congested, otherwise not remarkable.

Naso-pharynx: mucous membrane normal.

Bacteriological examination. — Culture from the heart's blood shows streptococcus pyogenes.

CASE NO. LIV. — Clinical diagnosis. — Purpura variolosa (five days' duration).

Anatomical diagnosis. — Purpura variolosa; punctate hemorrhages of the serous membranes, stomach, intestines, bladder, and kidney; hemorrhagic pyelitis; hemorrhagic endometritis; multiple cysts of the ovaries; corpus hemorrhagicum; fatty degeneration of the kidneys.

BODY. — That of a woman about thirty-five years of age; length one hundred and sixty centimeters; well-developed and nourished; rigor mortis present; slightly warm; post mortem lividity of the back and other dependent parts; eyelids interadherent; conjunctivæ blood-shot; pupils equal three-tenths centimeter in diameter.

The skin of the face and neck presents a faint, general bluish-red flush, most marked in the lateral cervical region; the lips are covered with dry blood clot; the skin of these parts is further marked by rather sparse red spots from pin-point to five millimeters in size; interspersed with these are larger, somewhat vague, bluish areas two to four millimeters in diameter; these are rather more numerous than elsewhere upon the cheeks and beneath the chin.

The skin of the trunk shows upon the anterior aspect of the chest and upon the abdomen closely-set, punctate areas, pin-point to two millimeters in diameter, red, and without sensible elevation. The abdomen is marked by numerous striæ atrophicæ; the striæ are the seat of confluent areas of the same sort, so closely set as to give the appearance of red, interlacing bands, two to three millimeters across. Interspersed with punctate areas are bluish-red spots, ill-defined, two to seven millimeters in diameter, placed four to five centimeters apart; more numerous than elsewhere upon the abdomen, between the striæ. The skin in these regions exhibits, in addition, a faint, general, terra-cotta-red flush.

The skin of the arms is similar to that of the trunk; the forearms show a great number of bluish-red spots; in this region these occur at intervals of from one to two centimeters.

The lower extremities show upon the thighs confluent areas of red macules, the larger areas from five-tenths to one and five-tenths centimeters in diameter. These areas show a slight degree of elevation, and are sensibly rough. The fronts of the thighs, in addition, show, in the larger of these red areas, faint pearly elevations from one to two centimeters in diameter, barely visible, but distinct to the touch. The groins and the upper part of the thighs show a diffuse terra-cotta-red flush. The knees are free from lesions. The legs show sparse punctate areas, from one to two millimeters in diameter, interspersed with which are other lesions, some not hemorrhagic, slightly elevated, pearly, and of the same size. The backs of the legs are shotty to the touch. The ankles and dorsa of the feet show scattered punctate hemorrhages. The lesions are more numerous upon the inner than upon the outer aspect of the legs.

Upon section, subcutaneous fat two centimeters in thickness; vermiform appendix normal; mesenteric lymph nodes slightly reddened.

THORAX. — Position of diaphragm natural.

Pleural cavities normal.

Pericardial cavity contains about thirty cubic centimeters clear, straw-colored fluid.

Heart: weight, two hundred and seventy-five grams; epicardium shows sparse punctate hemorrhages; upon section cavities contain yellow clot; myocardium pale red, firm; wall of left ventricle shows an area of hemorrhage two millimeters in diameter. Valves and cavities normal. Coronary arteries normal.

Lungs: alike; pleural surface presents numerous areas, mostly cherry red, some blue-red, two to four millimeters in diameter, numerous upon the interlobar surfaces; the backs show a faint, general bluish-red color; crepitant throughout; upon section, red and moist; bronchi show some general reddening of the mucous membrane, with occasional areas of diffuse hemorrhage.

Diaphragm of the left side shows diffuse hemorrhages into its substance.

ABDOMEN. — Peritoneum shows sparse punctate hemorrhages.

Spleen: size normal; capsule tense; upon section dry, beefy red; trabeculæ visible, follicles indistinct, pulp not increased.

Stomach: upon section the mucous membrane shows evenly distributed punctate hemorrhages, from one to two millimeters in diameter; it is overlaid with tenacious brown mucus. The peritoneal surface of the anterior aspect near the pylorus shows an area of hemorrhage three centimeters in diameter, extending down into the duodenum.

Intestines: upon section, the lower part of the ileum shows faint punctate hemorrhages at the site of the solitary follicles; elsewhere the mucous membrane shows diffuse reddening. The colon shows fairly numerous areas of hemorrhage from one to three millimeters in diameter at the site of the solitary follicles; the follicles present no sensible elevation.

Liver: size normal; surface smooth, save at the anterior border where it is slighlty granular; upon section markings visible, general color liver brown, consistence normal. Gall bladder contains thick, dark bile.

Kidneys: size normal; free surface shows occasional capsular hemorrhages, from one to two millimeters in diameter; upon section capsule strips easily from a smooth surface; markings vague, pale; cortex seven-tenths of a centimeter in thickness; surface of section opaque; mucous membrane of the pelvis dark cherry red and slightly thickened; consistence flabby.

Adrenal glands normal.

Bladder: upon section mucous membrane shows sparse punctate hemorrhages, with a larger spot of cherry-red color, four millimeters in diameter, at the trigonum.

Genitalia: uterus upon section shows the endometrium overlaid with dark red clot. Ovaries, both cystic; the right contains a corpus hemorrhagicum.

Aorta upon section shows a few small yellow plaques just above the aortic valves.

ORGANS OF THE NECK. — Tongue: the outer half shows marked dessication of the dorsum, the surface dark brown-red, and crusted. Pharynx, soft palate: mucous membrane dusky gray-red, overlaid with brown mucus; no erosions present. Esophagus: mucous membrane shows oval, diffuse, bluish red areas, two to five millimeters in diameter. Larynx negative. Trachea: mucous membrane of the dorsal aspect shows extensive areas of hemorrhage, two centimeters above the bifurcation. Thyroid gland normal.

Bone marrow of femur for the most part yellow, flecked with red.

Cranium: brain shows moderate injection of the vessels of the pia; upon section normal. Spinal cord negative.

II. THE MUCOUS MEMBRANES.

Naso-pharynx. — Examination in three cases of variola vera fatal during the first week showed in two, some injection of the mucous membrane; in the other, and in one case fatal during the lethal period, the examination was negative. Examination in one case of purpura variolosa likewise gave negative results.

Palate, uvula, pharynx.[1] — In variola vera, in cases fatal during the first week, the mucous membrane of these regions is swollen and edematous, usually overlaid with tenacious mucus, and of a dirty, gray-red color. It may further show papules, more commonly shallow erosions, about two millimeters in diameter and slightly elevated. These may occur upon the uvula. In cases fatal during the second week the erosions are somewhat larger and more prominent; they are variously distributed, but are somewhat more numerous than elsewhere on the soft palate and on the posterior and lateral walls of the pharynx. In the later stages of the disease the conditions may be normal, or the lesions be limited to superficial erosions.

In variola pustulosa hemorrhagica the mucous membrane of these parts presents appearances varying between simple injection and edema to marked swelling with multiple erosions, occasional vesicles, and more or less general necrosis.

[1] In one case, that of a child, diphtheria was present as a complication.

In one case of purpura variolosa the mucous membrane was injected and overlaid with tenacious mucus.

Esophagus. — Early cases of variola vera usually show no lesions of this organ; in one such fairly numerous, grayish-white, papular elevations from two to four millimeters in diameter were distributed over the mucous membrane of its upper half. Of twelve cases fatal during the second week, in nine the esophagus was normal; in three it presented papular elevations, more or less eroded at the center. In the late stages erosions were seen once or twice.

In variola pustulosa hemorrhagica the esophagus is either negative or marked by injection and occasional small submucous hemorrhages.

In purpura variolosa no lesions were observed.

Larynx and trachea. — In the earlier stages of variola vera the mucous membrane of these organs is either normal or is swollen and injected. In those of our cases fatal during the lethal period the larynx was either normal or more or less edematous, and occasionally the seat of shallow erosions. Erosions upon both surfaces of the epiglottis were noted in a case dying on the twelfth day. The trachea is usually normal, in some instances its mucous membrane is injected and covered with frothy mucus; in others it presents either nodular elevations from two to three millimeters in diameter, or small, superficial erosions. The latter conditions were observed in four of our cases. In the later stages of the disease these organs are usually normal; lesions, if present, take the form of erosions.

In variola pustulosa hemorrhagica the trachea presents erosions and ecchymoses of its mucous membrane; in one instance it showed an extensive area of submucous hemorrhage just above the bifurcation.

In purpura variolosa these organs were negative.

Gastro-enteric tract. — The mucous membrane of the stomach and of the intestines in variola vera was normal in all but

four of our cases; in three, fatal during the second week, punctate hemorrhages were present in the stomach along its lesser curvature, and in one the mucous membrane of the cardia showed slightly elevated, opaque, yellow areas, two to three millimeters in diameter.

In three cases of variola pustulosa hemorrhagica, in one the stomach and the intestines were negative; in two the stomach presented punctate hemorrhages two to eight millimeters in diameter, scattered over its mucous membrane; and in one similar hemorrhages appeared in the solitary follicles of the ileum and colon.

In purpura variolosa the mucosa of both the stomach and intestines shows thickly set, evenly distributed, punctate hemorrhages about two millimeters in diameter.

Bladder. — In variola vera the mucosa of the bladder is uniformly normal; in a case of variola vera, complicated with hemorrhage, it presented together with punctate ecchymoses red pointed elevations one to two millimeters in diameter. The latter may also be present in variola pustulosa hemorrhagica, although in two out of three cases of this form of the disease the bladder was normal. In purpura variolosa no lesions of the bladder were found.

Urethra. — Examination of the urethra in one case of variola vera fatal during the second week showed, in the penile portion, a colorless elevation of the mucosa two millimeters in diameter.

Uterus. — In general no lesions were apparent. In a case of variola vera, fatal from metrorrhagia, on the fourth day of the disease the uterus contained a moderate amount of red clot, the greater part of which was closely adherent to the endometrium. In purpura variolosa our single case of this type of the disease in the female showed submucous hemorrhages of the endometrium.

III. THE LUNGS.

Variola vera (a) severe. — In the cases fatal during the first week broncho-pneumonia (macroscopic) was observed twice, edema three times, and atelectasis with acute bronchitis once. In the cases grouped within the lethal period, the following pulmonary conditions occurred with the frequency indicated: edema (6), acute bronchitis (1), atelectasis and broncho-pneumonia (3), broncho-pneumonia (4), atelectasis (4), lobar pneumonia (2), peribronchial tuberculosis (1), broncho-pneumonia with multiple abscesses (1), atelectasis and edema (1), atelectasis and abscess (1), subpleural ecchymoses (1). In one instance a vesicular elevation in the mucosa of a bronchus was observed.[1]

In the later stages of the disease, constituting fatal complications, were seen pleurisy, broncho-pneumonia, and gangrene.

Variola vera (b) with hemorrhage. — In one instance the mucosa of the bronchi showed small, indefinite, pale yellow, slightly elevated areas.

Variola pustulosa hemorrhagica. — Among the cases of this group occurred broncho-pneumonia (1), edema (1), subpleural punctate hemorrhages (2), edema of the bronchial mucosa (2), occasional diffuse hemorrhages into the bronchial mucous membrane (1).

Purpura variolosa. — In this form of the disease the lungs show sub-pleural punctate hemorrhages and moderate edema, with some reddening of the bronchial mucosa.

IV. THE LIVER.

In every type of variola the liver may be somewhat increased in weight; in some instances this condition is well marked.

Variola vera. — In the uncomplicated form of the disease cases fatal during the first week present either no changes in

[1] Microscopic examination showed this to be an elevation of the epithelium caused by exudation, and not a specific lesion.

the liver, or cloudy swelling and fatty metamorphosis. During the second or lethal period these degenerated changes are more common and more pronounced. In rather less than one-third of the cases falling within this period the liver was normal. Later in the disease occur fatty metamorphosis and small, opaque areas suggesting focal necrosis. The gall bladder was normal in all cases. In abortive cases the liver showed no lesions. In variola vera complicated with hemorrhage the liver shows some cloudy swelling and fatty metamorphosis. In cases of variola vera with later complications the liver showed usually the same lesions.

Variola pustulosa hemorrhagica. — In this type of variola the liver shows few changes; in two of our three cases it presented cloudy swelling.

Purpura variolosa. — In one case the liver was of a dull, olive green color; in all it showed cloudy swelling.

V. THE SPLEEN.

Variola vera. — Of the cases fatal within the first week of the disease, in five the spleen showed no changes; in two slight enlargement. Of those fatal within the second week, in ten it showed no changes; in seventeen some enlargement, and in twelve enlargement, diminished consistency, and increase in pulp. The appearance of the follicles is not characteristic. Sometimes they are of ordinary prominence; sometimes vague. The color is within normal limits, varying from bright red to purple. Late in the disease the spleen is generally normal.

In the abortive type the spleen is normal.

In variola vera complicated with hemorrhage some increase in pulp and in the size of the follicles was observed.

In cases with late complications a moderate degree of splenic tumor was noted.

Variola pustulosa hemorrhagica. — In two cases the spleen showed some enlargement; in one the organ was normal.

Purpura variolosa. — In this type of the disease the spleen may show hemorrhages into the capsule and some increase in size.

VI. THE LYMPH NODES.

Variola vera. — In uncomplicated cases which died during the first week of the disease the mesenteric nodes were usually normal; in two instances they were somewhat enlarged; the cervical nodes in one case were tuberculous. When death occurs in the second week the mesenteric nodes, and occasionally the cervical, the aortic, and the inguinal, may show some swelling. In cases fatal during the third week changes in the lymph nodes are rare; in one the cervical nodes were somewhat enlarged.

In the abortive form of the disease the lymph nodes were normal.

In variola vera with hemorrhage the inguinal and cervical lymph nodes were in one case enlarged and red.

In variola vera with complications similar conditions were occasionally noted in the cervical and in the aortic lymph nodes.

Variola pustulosa hemorrhagica. — The bronchial and the cervical lymph nodes in two instances were enlarged and red; in other cases the lymph nodes in general were negative.

Purpura variolosa. — In this form of variola the cervical and inguinal lymph nodes presented conditions similar to those found in variola pustulosa hemorrhagica.

VII. THE BONE MARROW.

The marrow of the femur was examined in many of our cases, but, as a rule, segments of the vertebræ were relied upon for histological study, and these showed no macroscopic lesions.

Variola vera. — Uncomplicated cases fatal during the first week of the disease, in four instances presented changes in

the bone marrow. The marrow of the femur was red, brown to reddish yellow in color, or was mottled with large, gray-red, soft spots. When death occurs in the second week the marrow may be normal. In nine cases fatal within this period it was of a gray pink, or dark pink color, or was marked by red streaks, or mottlings, occasionally with grayish-yellow areas two millimeters in diameter. Similar mottlings were observed in one case fatal in the third week.

In abortive variola the marrow was negative.

In variola vera with hemorrhage the yellow marrow in one case showed grayish red mottlings.

In variola vera with complications the marrow in three cases was red, and in two red and soft.

Variola pustulosa hemorrhagica. — The marrow in this type of variola is red, mottled with yellow splotches.

Purpura variolosa. — In this form of the disease no changes in the bone marrow were observed.

VIII. THE TESTICLES AND THE OVARIES.

Variola vera. — Among cases fatal during the first week the testicles in two instances were normal, and in one showed focal lesions apparent upon the cut surface in the form of slightly elevated, pink areas about two millimeters in diameter. At this stage of the disease the ovaries were in all cases normal. With death during the second week, the testicles in about half the cases showed focal lesions. These, in general, appear as areas from one to four millimeters in diameter, pink, gray, or grayish yellow, opaque, and slightly elevated above the surface of section; they are not sharply defined from the substance of the organ, are evenly distributed, and may have a shotty feel. The ovaries in four out of thirteen cases showed focal lesions of the same general character as those in the testicles. Among cases fatal late in the disease, focal lesions of the testicles occurred in two out of six; the ovaries were normal.

Our cases of abortive variola vera were females, and the ovaries in these were normal.

In variola vera with hemorrhage the testicles in both cases showed lesions; in one the surface showed nodules three millimeters in diameter and one millimeter in elevation, sharply defined, yellow and hard, upon section vague in outline, with a reddish center. In the other case, one testicle showed small, shotty nodules of the same sort.

Variola pustulosa hemorrhagica. — In one case of this type the testicles showed doubtful lesions in the form of small, opaque areas. In this form of the disease no lesions were noted in the ovaries.

Purpura variolosa.— In this type of variola the testicles and the ovaries were in all cases negative.[1]

IX. THE KIDNEYS.

The lesions of the kidney in variola consist mainly in diffuse parenchymatous degenerations and in cellular infiltrations, conditions macroscopically so indefinite as to render difficult their recognition by the naked eye. The changes in the organ will, therefore, be considered chiefly from a histological standpoint. (Vide p. 100.)

The only distinctly anatomical change in the kidney is seen in the hemorrhagic types of variola; in both variola pustulosa hemorrhagica and in purpura variolosa there is extensive hemorrhage into the submucosa of the pelvis.

X. THE ADRENAL GLAND.

In no form of variola were changes observed in the adrenal gland.

XI. PANCREAS.

The pancreas was invariably normal.

XII. THE HEART AND ARTERIES.

Variola vera. — Cases fatal during the first week of the disease occasionally show cloudy swelling of the myocardium;

[1] The results of the microscopic examination of the testicle and of the ovaries show that lesions in these organs cannot always be detected by naked eye examinations.

one such presented punctate hemorrhages of the epicardium. Of the cases which died within the second week, or later, about one-half showed cloudy swelling of the myocardium.

The aorta and the coronary arteries were normal, save in one case where slight arteriosclerosis was present.

In abortive variola vera the heart and the aorta in both of two cases were normal.

In variola vera with hemorrhage both of two cases showed cloudy swelling of the myocardium, and no changes, save sclerosis, in the arteries.

Variola pustulosa hemorrhagica. — Among cases of this type cloudy swelling of the myocardium was invariably present; punctate hemorrhages into the pericardium and epicardium occurred twice, and hemorrhage into the myocardium and acute mitral endocarditis each once. In two of these cases there was early arteriosclerosis of the aorta.

Purpura variolosa. — All cases of this type showed cloudy swelling of the myocardium and punctate hemorrhages of the epicardium, the latter usually most numerous in the vicinity of the right coronary artery.

THE PATHOLOGICAL HISTOLOGY.

I. THE SKIN.

In the pathological anatomy of the infectious diseases there is no other organ in which the specific lesions of the disease are so characteristic in appearance, in situation, and in development as they are in the skin in small-pox. But little work has been done on the histology of the skin lesions, notwithstanding their striking character and the abundance of material given by the numerous epidemics in almost every country.

The literature of the histology of the lesions really begins with the great epidemics which appeared in Europe in the sixth and seventh decennia of the nineteenth century. The article by Auspitz and Basch may be said to mark the beginning of the study of the finer anatomy of the process.

They describe the vesicle as formed by a reticulum which includes in its meshes fluid exudate and cells. The reticulum is formed from the epithelial cells, and the contained pus cells are also formed endogenously from the epithelium. They also describe the formation of the central depression of the pock as due primarily to changes in the epithelium, and secondarily to removal of the exudate from the center or oldest portion of the lesion by evaporation.

Klebs, also, speaks of the reticular character of the lesion. The process begins in the middle layers of the epidermis, and the reticulum is formed by cells which are separated from one another by fluid and cellular exudate. The most valuable of these earlier articles is that by Weigert, who made two hundred autopsies in Breslau in the epidemic of 1871 and 1872. His description of the lesions remains the best, and is further interesting in that it formed the basis for his further studies on necrosis, and marks the beginning of the study of bacteria in relation with anatomical lesions. Weigert found that in every case the primary lesion consists in a peculiar degeneration of the lowest layer of the epithelial cells. The center is composed of irregular, reticular or thread-like masses formed of cells which have lost their nuclei. These cells have undergone a form of necrosis which he calls diphtheroid degeneration, which is distinguished from the ordinary forms of necrosis by the non-disintegration of the necrotic material. He regarded it as analogous to the degeneration of the epithelium described by Wagner in the formation of the diphtheritic membrane. This degeneration of the epithelium forms the primary and central focus of the pustule, and around it there are secondary lesions consisting chiefly in an exudate, which collects between the cells. The central depression or dell is due to the rigidity of the cells, which have undergone the primary necrosis, the tissue around this being distended by the collection of exudate. In the pustules without central depression there may be elevation of the connective tissue, or the depression may be obliterated by the rupture of the epithelial threads. The primary necrosis he regards as due to

the direct action of the small-pox virus on the epithelial cells, the virus being brought to the cells by the blood. He opposes the views of Luginbühl, who asserted that the infection producing each pustule came from the outside. To this primary action of the virus is added a secondary or irritative action which leads to the production of the exudate and to proliferation of the epithelial cells. Weigert also was the first to describe and depict the cell inclusions which have such an important place in the later descriptions.[1] The newly-formed epithelial cells are more transparent than the others, and sometimes have a number of nuclei resembling giant cells.

In his first article on the structure of the pock, Unna regarded the primary lesion as due to hypertrophy and inflammatory swelling of the epithelial cells. The stratum lucidum is swollen and the cells separated, the whole changing into a transparent body shaped like a convex lens. Small cavities are finally formed in it. The diphtheroid change described by Weigert he found only in one case. Cornil describes a reticulum formed by the epidermis, the cavities are formed in the interior of the epithelial cells, and the reticulum represents the remains of the protoplasm. The cells in the cavities are due in part to emigration, in part to proliferation of the epithelium. He was the first to describe changes in the corium consisting in swelling of the lining endothelium of the capillaries. The vessels so altered offer little resistance to the passage of the leucocytes.

Renault gives an excellent description of the process. In the corium in the papular stage there is edematous infiltration with dilatation of the lymph capillaries. The reticulum first appears in the prickle cell layer and is due to distention of the clear circumnuclear part of the cell, the peripheral portions becoming united and forming the network. The

[1] In anderen Fällen finden sich ganz ähnliche kleinere, im ungefärbten Zustände glänzendere, im gefärbten dünklere, runde Körnchen neben den hell gefärbten Kernen. Ihr Glanz resp. ihre Fähigkeit, die Haematoxylinfarbe anzunehmen, steht gerade im umgekehrten Verhältnisse zu ihrer Grösse. Die kleinen, übrigens ziemlich seltenen Körnchen, gleichen etwa den kernen der weissen Blutkörperchen, aber sie sind kleiner, werden niemals von einem besonderen Protoplasma-Mantel umbegen und finden sich stets nur neben den grossen Kernen der Epithelien.

dell is formed by the atrophy of the upper epidermis cells in the center of the pustule, while those in the periphery undergo the same changes as the cells lower down. The cylindrical cells in the Malpighian layer undergo cloudy swelling, but form a continued layer, the lymph for the vesicle passing between them. The cells in the pustule are chiefly emigrated leucocytes. He describes the cell inclusions as round, refractive bodies in the interior of the distended epithelial cells, and thinks that they stand in causal relation with the anatomical changes. He was the first to regard these bodies as parasites. He also says that he has seen them germinate in the moist chamber.

With regard to the dell formation, Rindfleisch at first held the view that it was the result of the formation of the lesion around a resistant skin gland. Later he regarded the depression as really below the pustule and due to the destruction and depression of the corium. The pus cells, he thinks, are formed within the epithelial cells.

The latest work which deals with the histology of the complete process is that of Unna. In the formation of the pustule there is liquefaction of the swollen, edematous reticulum. The reticulum is formed by a series of epithelial cells compressed between the primary liquefied areas. The chief contribution of Unna is his description of a peculiar degeneration of the epithelial cells, to which he has given the inappropriate name of "balloon degeneration" (ballonartige). It affects chiefly the cells of the lower prickle layer. They become separated from one another and converted into large, round, solid masses staining with eosin, and the nuclei undergo degeneration. There is a gradual transition between these cells and the flattened cells of the upper layers which form the reticulum. Most of the cells finally undergo fibrinoid degeneration and give the reaction for fibrin. The dell-formation is due to the reticular degeneration and to the edema, which is most marked in the periphery of the pustule. Under the pressure of the peripheral edema, the papillæ gradually disappear, while in the center they are not only preserved, but generally edematous, and

project into the middle of the pock. During the stage of vesicle formation the emigration of leucocytes is scanty, but becomes abundant with the conversion of the vesicle into the pustule. There is an accumulation of plasma cells in the adventitial sheaths of the vessels of the corium, which constantly increases with the change of the vesicle into the pustule. The abundance of these plasma cells, which are ordinarily found in the more chronic inflammations, is remarkable when the acuteness of the process is considered. Although Unna gives a good description of the process of healing, he does not mention the cell inclusions.

All of the more recent work, with the exception of Unna's, refers directly to the cell inclusions in variola and in vaccinia and will be considered in connection with that subject.

In our study of the skin lesions, a number of pieces of skin showing the most distinctive lesions were taken from every case. From the material hardened, a further selection of pieces was made, and these were embedded in paraffin and the sections stained with alkaline methylene blue and eosin as a matter of routine. Eight sets of complete serial sections were made through typical vesicles and pustules. The pieces for these serial sections were embedded in celloidin and the sections stained with hematoxylin. After a primary examination further sections were made when necessary.

In going over so large an amount of material as this, comprising, as it did, a number of sections from each case, in addition to the serials, there is an embarrassment from the variety of the lesions presented. It seems possible, in the first place, to distinguish two groups of lesions which are generally marked by distinctive histological changes: (1) lesions which are sharply circumscribed, and are characterized by a structure and a mode of development which, in whole or in part, are so frequently repeated that it is possible to construct a type. These lesions we regard as due to the direct action of a specific cause, and it is only in these that the various forms of the parasite of the disease are found. They are analogous to the tissue reactions which we find

associated with the presence of bacteria. (2) Lesions which are more diffuse in character, which present more variations, and which we regard as due to more or less accidental conditions, possibly to the action of soluble-toxic substances, may be produced, either by the specific cause, or by bacteria. The same is true of the clinical aspects of the skin lesions. The preliminary rash appearing on the skin of the lower abdomen and the groin would certainly seem to be due to a cause different from that of the typical exanthema, which appears later, and which tends to avoid the places in which the rash has appeared.

The Pustule.[1] — The factors concerned in the production of the small-pox pustule are degeneration of the epithelial cells, associated with or followed by exudation. In the number of cases and sections at our command it was possible to trace the earliest and the simplest form of degeneration. This was found in three cases of purpura variolosa without vesicle formation; it was possible to find the same conditions also in the periphery of a growing vesicle. The

[1] Four layers of cells may be recognized in the epidermis, which though passing by gradations into one another, present types differing in structure and in relation. In the deepest or Malpighian layer the cells are placed perpendicular to the corium; they have relatively large, well-staining, vesicular nuclei with abundant chromatin, and a finely granular protoplasm. Between the cells are small channels crossed by fine protoplasmic prolongations, but these are not so distinct here as in the next or prickle cell layer, into which the Malpighian layer insensibly passes, the cells becoming larger, the nuclei rounder. Here the spaces between the cells are wider, and the connecting protoplasmic processes more pronounced. Above this layer the cells are flatter, and the nuclei pale and poor in chromatin. The protoplasm is homogeneous, and contains granules of kerato-hyalin. Above this the individual cells are fused together, the nuclei no longer stain, and the fused cells form a homogeneous mass, with continual disintegration on the surface. The mass of cells so arranged is permeable to fluids coming from below, the permeability gradually decreasing; the homogeneous, horny layer on the surface is but little or not at all permeable. The various epidermic appendages in the corium beneath are connected with the surface by ducts passing between these cells. The cells forming these ducts are closely connected with the epithelial cells in their vicinity, so that in these places the cells of the epidermis are more closely bound together. Beneath the epidermis is the corium, composed chiefly of white fibrous and elastic tissue, arranged in fine bundles, closely interwoven, and containing numerous epithelioid cells embedded in it. It is extremely rich in blood vessels and lymphatics. The portion of the corium which is in immediate contact with the epithelial cell is composed of closely compacted, very fine fibrillæ, and is analogous to the membrana propria of some mucous membranes.

same case of small-pox often showed in one section beginning vesicles, macroscopically not apparent, and more advanced vesicles.

What we regard as the earliest form of degeneration takes place in the nucleus. This becomes swollen, more vesicular, and the clumping of chromatin in the center more marked than in the normal. This condition was particularly apparent in one of the hemorrhagic cases, the nuclei here appearing as vesicles with but little chromatin around the periphery, and with a large, irregular mass of it at the center. This was more refractile than the normal chromatin, and in specimens stained with alkaline methylene blue it often assumed a distinct greenish tinge. It could not be said that this degeneration would always be followed by the further changes leading to vesicle formation. Cytoplasmic inclusions were often found in cells with such nuclei. Similar nuclei were often found in advanced lesions, together with cells in which were advanced forms of degeneration.

Associated with this in most instances, and always present in the lesions leading to vesicle formation, is a reticular degeneration of the cytoplasm with more advanced degeneration of the nucleus. This may affect all the lower cells of the epidermis, but in the typical vesicle it is best seen in the cells above the Malpighian layer. The cells are swollen, and the cytoplasm loses its normal character and becomes either a faintly-stained, pale mass, or distinct spaces may be formed in it.

The nuclei may lose their form and become irregular and shrivelled, assuming peculiar shapes. This shrivelling is apparently due to the passage of the intranuclear fluid into the space around the nucleus. The irregular rim of the nucleus is preserved, and in the early stages the chromatin does not seem to be diminished and the large central mass is seen. Advanced forms of cytoplasmic inclusions are common in the nuclear space and in vacuoles in the protoplasm. The protoplasmic processes connecting the cells disappear. The periphery of the cell remains and seems to undergo a peculiar condensation and may stain deeply with iron

hematoxylin. It is this degeneration which causes the peculiar reticular appearance of the early vesicle. It is always better seen in the periphery than in the center of the vesicle. With the increase of the exudate coming from below, the spaces within the cells enlarge, finally rupture, and a network is formed by the coalescence of the cell borders. The typical small vesicle is always fan-shaped. The bottom of the vesicle may be seated on the corium, or be separated from this by a layer of comparatively intact cells. The lowest cells have undergone the hyaline fibrinoid degeneration, and form the handle of the fan. Above this and extending widely laterally is the reticular degeneration with the formation of large spaces. A section which does not go through the stalk of the lesions shows nothing but the spaces with an almost intact epithelium below. The cells of the kerato-hyaline layer take but little part in the formation of the reticulum, though they may become separated to some extent by the exudate. As the exudate increases the tension becomes so great that the adherent cell-remains rupture, and large spaces are formed, with the cell-strings extending irregularly between them. In other cases this typical process does not take place, and the spaces are formed by the exudate separating cells which preserve their characteristics. In yet other cases an indefinite degeneration affects all of the cells of the epidermis, and section of the vesicle shows degenerated epithelial cells lying in the exudate, in part adherent in masses or strings, in part separated.

A later form of degeneration is that to which Unna has given the name "ballonartige," and which may best be regarded as a hyaline fibrinoid degeneration. The Malpighian cells are chiefly affected. They become swollen, their protoplasm loses its granular character, becomes homogeneous and refractile, and stains more intensely with the acid dyes. The single cells so altered may be separated from each other, or masses of them may be joined together and lie more or less free in the exudate. In some cases, instead of such a total conversion of the cell into hyaline, droplets of this may appear, and, by their coalescence, fill the cell. The nuclei

may entirely disappear, apparently undergoing the same change as the cytoplasm. In sections stained with carmine, followed by Weigert's fibrin stain, the homogeneous nucleus may be distinguished in the cell by its redder tinge. The periphery of the nucleus often forms a homogeneous red line. The nuclear chromatin rarely undergoes fragmentation. In cells in which the degeneration is slight and shown only by a more homogeneous appearance of the cytoplasm, degenerative direct division of the nucleus may take place, the chromatin first becoming arranged around the nuclear membrane. Cells may be found containing as many as four pale vesicular nuclei formed by direct division. In addition to the masses, lines of cells so altered may be found passing through the vesicle. These may give, with more or less distinctness, the reaction for fibrin, and in specimens stained with iron hematoxylin a dark band may be found around the periphery of some of the cells. This degeneration is found in the older and central parts of the lesion. It is not distinctive of smallpox. It has been best described by Unna, and is found in varicella and in other skin diseases associated with vesicle formation. In the only section of varicella which we were able to study it was not distinctly shown. Very much the same condition is found in diphtheria in the cells of thick mucous membranes, and is the main change leading to the formation of the hyaline diphtheritic membrane. (Councilman, Mallory, and Pearce, 1901.)

The fluid exudate begins early and in most cases probably simultaneously with the degeneration. In the smallest papule which is visible the swelling is due chiefly to the presence of exudate, and in no case have we found degeneration without any evidence of exudation. The character of the exudate varies. In the early stages of the lesion it is clear, without any admixture of cells, and may be very poor in coagulable constituents. In sections hardened in Zenker's fluid we have frequently found perfectly clear spaces in the epidermis without any granular precipitate. On the other hand, the exudate may have a peculiar appearance due to its being filled with small, definite circles; a similar condition is

often seen in the kidney and in other places where an exudate comes in contact with epithelium. These small circles, which must be due to the presence in the exudate of globules which differ from the fluid around them and which do not give a granular coagulum, were almost constantly found in the exudate when it had lifted up the entire mass of epidermis. One of the things which is most impressive in the study of the small-pox process everywhere is the extreme paucity of cells in the exudate. We have found cases in which there was extensive degeneration of epithelium and abundant fluid exudation without a single foreign cell in the epidermis. The cells appear only in a late stage of the process, and are always fewer than would be found in any analogous process of degeneration and exudation due to bacterial infection. The condition commonly found in all sorts of skin lesions, that of polynuclear leucocytes advancing between the epithelial cells to the area of lesion, was never met with.

In the examination of all of the sections of the skin particular attention was paid to the character of the cells in the exudate. It seems probable that the cells appear when the specific character of the process has passed, they being then attracted by the necrosis. The cells in the exudate vary extremely and represent the different varieties of leucocytes. Polynuclear neutrophiles were the most numerous of the exudation cells. In but few cases were pustules found with a perfectly frank, purulent exudate within them. In the later stages of the process, all the cells, both those in the exudate and the degenerated epithelium, undergo fragmentation and give rise to granular masses which cannot be identified. One form of degeneration of the polynuclear leucocytes was particularly noticeable. The cell becomes swollen and clear, the granular contents seeming to have dissolved or passed out. The irregular nucleus is swollen, and the chromatin arranged in small masses, often of the same size, at the periphery of the nuclear membrane, in some cases assuming the form of rosettes.

The study of the vessels in the corium from which the

emigration must take place, shows what we should expect from the character of the cells in the exudate. The mural accumulation of polynuclear leucocytes, which is such a common feature in inflammation, was never found in them. In the early lesions but few polynuclear leucocytes were found in the tissues about the vessels. In the late pustules, and in cases in which there is extensive necrosis extending deeply into the corium, they are found in larger numbers. In the late lesion there are accumulations around the vessels of the varieties of lymphoid cells which are so prominent in the lesions in internal organs, and which Unna has identified as plasma cells. These cells were rarely found in the early vesicles. Small lymphoid cells were often found in the intact epidermis between the cells and in the vesicle and the pustule. Mononuclear cells with phagocytic properties were found both in the corium and in the vesicle. Eosinophile cells in any considerable numbers were rarely found, either in the exudate in the vesicle, or the pustule, or in the corium, except in one case, that of an infant. As the result of our study of the cellular exudation in the small-pox lesion of the skin, we must conclude that there is no positive attraction between the virus and the polynuclear leucocytes. They are present in any considerable numbers only in the late stages of that lesion in which there is extensive necrosis, and in which a secondary infection with pyogenic cocci has in most cases supplemented the action of the small-pox virus. The diminution in the number of polynuclear leucocytes in the blood cannot account for the small numbers found in the skin, for in the lesions in the lungs and in the mucous membranes due to streptococcus infection the cellular exudate has the usual character.

Structures were occasionally found in the epithelium at the edge of both vesicles and pustules which were regarded as necrotic leucocytes. These were hyaline, structureless bodies of the size of leucocytes, showing no trace of nucleus, and found between the epithelial cells. A single such body sometimes extended between several adjoining cells and had an ameboid appearance. There was no difficulty in

distinguishing these structures from the specific parasitic inclusions.

Red blood corpuscles were rarely found in the exudate in the youngest vesicles, nor in such had any hemorrhage taken place in the corium around the vesicles. In the cases of purpura variolosa red blood corpuscles were found in considerable numbers in the papillary layer, but were not present in the epidermis. Extensive hemorrhages were found in the corium, and numerous red corpuscles were found in the exudate in the marked hemorrhagic cases. In the exudate the red corpuscles were in some cases well preserved and stained in the usual manner, in others they were represented by shrivelled shadows. A peculiar staining reaction of the corpuscles in the exudate was often present, shown particularly well by the Weigert fibrin stain. The periphery was sharply stained, leaving an unstained homogeneous center. We must disagree with Ewing in reference to the importance of the part which red corpuscles play in the process.

Fibrin, in varying amounts, was always present in the exudate in the advanced vesicle and in the pustule. It was usually absent in the beginning vesicle. The greatest amount of it was formed in immediate contact with the papillary layer, and this was often connected with fibrin filaments in the pustule contents.

Repair of the lesion begins early. In an early stage of vesicle formation there is slight hyperplasia of the surrounding epidermis and an increase in the thickness of the horny layer. These newly-formed horny cells are edematous and swollen, and their nuclei are faintly visible. The contents of the vesicle or the pustule undergo condensation from the evaporation or absorption of the fluid, becoming finally changed into a solid, granular mass in which nothing can be recognized. While these changes in the pock contents are going on, regeneration of the epithelium is taking place. In the less severe cases the destruction of the epithelium is not complete, and there may be rows of cells at the bottom of the lesion little or not at all affected. New epithelium is constantly being produced from these cells, or is growing in

from the sides beneath the outlying edges, where the process never extends to the papillæ. This regeneration is never absent in late lesions. In the most extensive processes, with great exudation and degeneration involving large areas of the skin, the destruction extending deeply into the corium, the ingrowing epidermis will always be found at the edge of the lesion. This regeneration is accompanied by nuclear figures, often abundant, in the surrounding intact epidermis. Few are found in the early stages in the ingrowing cells. Until these become established on papillæ and their relation becomes normal, proliferation is not active. In some of the newly-formed cells a degenerative, direct division of the nuclei may be seen. All layers of the skin are not formed simultaneously in the process of regeneration. The cells of the horny layer are formed in great numbers in the periphery of the lesion, and from this gradually extend over the deeper cells which have already been formed. The appearance is often given as though the horny cells were being formed only in the periphery, and from this were being pushed over the lower cells which are already in position; but the differentiation, although beginning at the edges, undoubtedly extends continuously over the base of the lesion. In the regenerated epithelium the formation of kerato-hyaline extends from the edges in the same way. In consequence of this regeneration, the mass of necrotic cells and exudate, which has become solid by evaporation and by absorption of the fluid, becomes enclosed within two layers of horny cells: the old layer which is elevated by the exudate, and a lower layer which is newly formed. The old horny layer is finally broken through, and the pustule contents, now a scab, comes away as a whole or in fragments. This process is somewhat modified in the lesions of the palmar and plantar surfaces. In these places the layers of horny cells are very thick, and the dried exudate enclosed within the mass of horny substance is not easily removed. It may remain for a long time, and becomes converted into a more or less translucent, firm mass, of the form of a lenticular disk, by the removal of which from

the soles of each other patients while away the tedium of hospital sojourn.

A complete regeneration without cicatrization is possible when the lesions are not extensive and do not involve the entire epithelium, and also when the entire epithelium is destroyed over a small area only, the papillary bodies remaining intact. When the destruction extends into the corium and the entire architectural arrangement is destroyed, complete regeneration does not take place. This is usually the case in lesions more than one-half centimeter in diameter, the base or stalk of the lesion being one-half or one-third of this. These large lesions rarely show intact epithelial cells below them; the area to be covered by the epithelium growing from the edge is more extensive, and destruction of the papillæ is more apt to result than in the smaller lesions. Even in very small lesions there is sometimes destruction of the papillæ with inevitable cicatrization. After recovery the papillæ are absent or very imperfectly developed, and the connective tissue beneath has the characteristics of cicatricial tissue.

There are some very interesting minor modifications of the process, which are due to the character of the different parts of the epidermis. All parts of the epidermis, with the exception of the horny layer, are more or less penetrable by fluid, and the horny layer is more easily detached from its connection than are the other layers. It happens from this that when the exudate is abundant, further distention being prevented by the interlacing and connected reticulum, the tension within the vesicle may be considerable. In the larger vesicles, and always in the pustules, the reticulum is ruptured and large spaces are formed. In rare cases (in four only of the hundreds of lesions examined) space for the exudate is gained by its passage through the stratum lucidum and the elevation of the horny layer in mass. In this way a secondary vesicle may be formed on the surface of the true vesicle. Figure 1 (Plate III.) shows this process in a vesicle in which, judging from the extensive rupture of reticulum, the tension must have been considerable. The character of the

exudate in the two places is interesting. In the true vesicle there is a great deal of detritus and of granular precipitate. In the secondary vesicle there is only a faint cloud of precipitate. In other cases the exudate in the primary and the secondary vesicles had the same characteristics. A condition just the opposite to this was found in one section. In this there was a typical vesicle in an early stage, but with a broad base. The entire vesicle with the lower layer of adherent Malpighian cells had been elevated by the exudation. The exudation beneath the epithelium contained more cells than the vesicle, Figure 2 (Plate III.). In three cases, all of them severe, and of vesicular type, there were numerous false vesicles due to the lifting of the epidermis by exudation. Some of the vesicles so formed were circumscribed and considerably elevated, most of them were not sharply circumscribed. No cell inclusions were found in such lesions. The secondary vesicle may form the more important feature of the lesion. Figure 3 (Plate I.) shows a small vesicle in the vicinity of a large one, but not connected with it. There is very little reticulum. Almost the entire exudate is contained beneath the elevated horny layer. This was in a child two and one-half years old, in whom the disease was very acute, and it is possible that the epithelium in the child is more penetrable than it is in the adult.

In going over the literature of the disease, we have found no mention either clinical or anatomical of this modification of vesicle-formation. The small elevation filled with clear fluid on the surface of the vesicle or the pustule should be apparent on close observation. An extreme type of this is seen in the formation of large bullæ. These were found in a number of the more severe cases. They occurred on various parts of the body, but were more common on the wrists and ankles than elsewhere. The epidermis was elevated over considerable areas by the accumulation of a serous or bloody fluid beneath. That it was the entire epidermis and not merely the horny layer which was elevated was shown by the presence in the elevated layer of well-marked, umbilicated pustules. No tissue from such lesions was obtained in a condition suitable for study.

The dell-formation or umbilication. — This is almost constantly present in the circumscribed typical lesions. It appears at a very early stage in the formation of the vesicle, and becomes accentuated as this increases in size. When the contents of the vesicle becomes purulent it is often especially evident, and it may persist when healing is taking place. The only lesions in which the umbilication is always absent are those on the palmar and plantar surfaces. Elsewhere there appears to be no difference in the umbilication of the discrete lesions. We have studied the sections with especial reference to the umbilication, and have here found the serial sections of typical lesions especially useful. In all of the other material examined, the sections were made in most cases through the center of the nodule. In the few figures given of sections through entire lesions, it happens that the umbilication is not present or is not marked, but this is not usual. In Weigert's studies of the lesion he regarded the umbilication as due to the diphtheroid degeneration of the epthelium in the center, which was the earliest lesion and prevented the distention of the center by the exudate. Weigert, however, was not able to exclude the part which the hairs or the ducts of the skin glands played in its formation. Before Weigert's work it had been generally assumed that the umbilication took place at such points. The mode of formation described by Weigert has been generally accepted.

We have not been able to attribute the umbilication to the action of any single cause, and in view of its almost constant presence it is remarkable that several factors should take part in its formation. The mode of formation described by Weigert is undoubtedly the correct explanation in many instances. In the early stages of vesicle formation the spaces containing the exudate are usually larger in the periphery than in the center. The reticulum may be absent in the center, all the cells here undergoing the other form of degeneration. Figure 4 (Plate I.), which shows one of the earliest typical lesions we have seen and one which would not have been apparent clinically, shows this very well. In the center

the papillary layer is very close to the surface, and the epithelium is adherent and has undergone the hyaline fibrinoid degeneration. Outside of this the tissue is distended by the collection of the exudate in spaces. Such a condition as this was more often found in the chance sections than in the serials. Even in this figure it is not certain that further sections would not have shown either a hair or a sweat gland in the center, although there is no indication of this in the corium beneath. In the serial sections the presence of hairs and sweat glands at the point of umbilication was rarely missed. It might be supposed from this that the primary lesion was most often in the vicinity of one of these structures. This is not the case. All of our studies of primary lesions have shown the absence of any such relation. The hair follicles play a more important role than do the sweat gland. Where the latter are very numerous, as on the palmar and the plantar surfaces, they simply form a part of the reticulum, and rupture with the increase of tension. They are never sufficiently resistant to draw in the dense horny layer under the tension. The umbilication does not always correspond exactly with the center of the lesion, although it usually does. The serial sections even of small lesions often show several hair follicles or sweat ducts, those in the periphery having ruptured, while one in the center remains. It is possible that there may be a connection between the two conditions, a naturally more resistant center, which makes its resistance more manifest when it is further strengthened by the hair sheath. Where the hair passes through the epidermis the cells of the sheath form a compact layer closely connected with each other and with the surrounding cells. The same is true to a lesser degree of the ducts of the sweat glands. In one case a section through a large vesicle without umbilication showed a hair duct in about the center which had been pulled partly out of the corium where it had broken off. Without serial sections it is impossible to determine whether what appears to be a central depression may not represent the junction between two lesions. The specimen which best shows the relation

between the hairs and umbilication is Figure 1 (Plate IV.), which represents a flat section of a small vesicle. The periphery of the vesicle is shown on one side, most of the section representing the space of the vesicle. In the center of this is a lanugo hair, apparently cut just beneath its exit from the skin and surrounded by the horny cells of the sheath.

The sweat glands may take part in the umbilication in another way, and the depression be formed in the secondary vesicle. We have seen this only in one instance in which serial sections were cut. Macroscopically there was well marked umbilication, and the section showed extensive separation of the horny layer and the formation of a secondary vesicle. At the center, corresponding to the depression, the duct of a sweat gland is seen, and at its emergence the horny layer was not separated, being apparently more firmly connected with the layer beneath. In some very small lesions which are but slightly elevated the central depression may be accentuated by the hyperplasia and swelling of the surrounding epithelium in the healing stage. That the hairs are not the exclusive agents in the umbilication is shown by the frequent presence of this in the lesions of the glans penis. Umbilication is not present in the typical lesions of the muçous membranes, for reasons which we will consider in connection with the description of these lesions.

So far we have described that lesion of the skin only which is the most typical of the disease, and which, in the lighter cases, is the only lesion present.

More extensive lesions, conforming to the type described, arise by confluence of adjoining areas, or by the simultaneous affection of large areas of the skin, and it is not always possible to determine by sections in which of these ways the lesions arise. In the large confluent areas the several points of umbilication may be preserved, or the surface may be smooth or irregular. Often vesicles, apparently confluent, will not be found to be so on examination, the apparently continuous vesicle being separated by a number of small partitions. This was often seen in the large lesions on the palmar and plantar surfaces. In some of the severe early

cases very extensive lesions were found, due apparently not to confluence, but to the simultaneous affection of a large area. Some of those examined extended over an area two and one-half centimeters in diameter. In these large areas there is great irregularity, the process being more advanced in some places than in others. There is always a much greater degree of involvement of the corium. The entire papillary layer is destroyed, its place being indicated by a dark line composed of fibrin and degenerated epithelium. There is cellular infiltration extending throughout the entire thickness of the corium around all the vessels, hair follicles, and glands. In places the cells are entirely of the small lymphoid type, in others a mixture of these and large basophilic cells. There is rarely any extensive necrosis in the glands in these cases.

Edema of the corium, so far as could be estimated from the microscopic appearance, was generally absent. When acute exudation takes place in the corium it seems usually to find its way either into or beneath the epidermis or into the subcutaneous tissue. When edema was present it showed more in the papillary layer than elsewhere. In several cases the fibers of the tissue here were separated by clear spaces due to fluid. Fibrin, though often abundant in the vesicles, was rarely found in the exudation in the corium. When present it was found chiefly in the papillary portion, the entire tissue of this having undergone the same fibrinoid metamorphosis which is found in diphtheria. In the typical discrete lesions there was very little extension downwards along the hair follicles. In the severer lesions the cellular infiltration, combined with destruction of epithelium, may extend deeply into these. In one of the cases there was purulent infiltration with masses of streptococci in a hair follicle. In rare cases the same primary lesions as in the epidermis may take place in a hair follicle. We have seen hyaline fibrinous degeneration combined with numerous cell inclusions in the outer cells of the hair sheath.

The blood and lymphatic vessels of the skin show but little change The lymphatics were usually dilated and

contained granular precipitate, some red blood corpuscles, and a few large mononuclear cells. The nuclei of the lining cells in some were large, the cells projecting into the lumen and apparently increased in number. No nuclear figures were found in them. The blood vessels showed less change than we expected to find. We have already alluded to the absence of accumulations of polynuclear leucocytes in them. Occasionally blood vessels were found which contained numbers of large and small lymphoid cells. Thrombi composed of fibrin or blood plates were found in the most superficial blood vessels, when the tissue around them was destroyed and had undergone fibrinoid degeneration. The thrombus-formation in these cases was secondary. The walls of the vessels underwent the same hyaline change as was found in the vessels beneath the diphtheritic membrane. They gave the fibrin stain and were connected with the fibrin around them.

The lesions in the four cases of purpura variolosa were much alike. Macroscopically they showed diffuse hemorrhages of the skin and an absence of characteristic lesions, save in two cases in which a few vesicles were visible. From the absence of typical eruption, from its extraordinary rapid and different clinical course, and from the alleged greater frequency in vaccinated subjects, some authors have considered it doubtful if this is a form of small-pox. In none of these cases were the hemorrhages circumscribed, but were so diffuse that they gave a dark plum color to almost the entire skin, the color being accentuated at certain places. We have not found in the literature any detailed anatomical study of the skin lesions, though a great deal of clinical study has been devoted to them. Numerous sections of the skin from all cases were examined, and all showed much the same condition. In two cases a few small beginning vesicles were found. There was no doubt, however, about the character of the process. The skin almost everywhere showed the earliest stage of true lesions. The lesions were extremely diffuse. Often the entire area of a large section showed the same condition, in other sections small areas of normal skin were found. The general condition was that of

swelling and reticular degeneration of all the lower cells of the epidermis. There were large vacuoles in the cells, but rarely spaces between the cells resulting from their rupture. In the Malpighian layer there was some separation of the cells by the exudate, and in one section the entire epidermis over a small area was separated from the corium. The nuclei were degenerated, shrunken, and lay in large spaces. In all the cases there were numerous parasitic inclusions. In the earliest cases only early stages of the cytoplasmic inclusions were found, and in the later cases nuclear inclusions as well. Many of the degenerated nuclei had undergone direct division, and the nuclear space often contained several shrunken nuclei with almost no chromatin in them. In the cells least changed the clumping of chromatin in the nucleus was obvious. In the few areas of unchanged epidermis there were numerous nuclear figures. The corium showed little change, all the vessels were dilated, and there were numerous hemorrhages chiefly in the papillary layer. There was some edema particularly about the sweat glands and slight infiltration with mononuclear cells. The lymphatics were dilated. The most striking condition found in the corium was the enormous numbers of streptococci in the lymphatics and blood vessels and in the tissue. None were found in the epidermis. There was entire absence of polynuclear leucocytes in the epidermis, and but few were found in the corium.

On the microscopic examination of sections of both the vesicles and the pustules bacteria were generally absent. Every section was examined with reference to their presence, and the routine staining in methylene blue and eosin stained them vividly. The Gram-Weigert and other stains were also used in an attempt to demonstrate some bacterium which could be considered to stand in causal relation to the lesions. Cocci, usually definitely arranged in chains or in pairs, were the organisms usually found. In but six cases were organisms found in any considerable numbers in vesicles or pustules, — in all of these the organisms were streptococci. In one case it seemed possible that the skin might

have been the point of invasion for a general septicemia. One section showed the corium laid bare, probably by the rupture of a pustule, necrosis of the corium extending a considerable distance; on the surface and in the necrotic tissue were masses of streptococci. Occasionally single threads of streptococci were found in pustules from the other cases. In one case streptococci were found in the deep lesions around a hair follicle. Organisms were found much more frequently in the corium than in the epidermis. We have already referred to the great numbers found in the purpuric cases. They were usually seen as embolic masses within the vessels, and occasionally in the tissues outside of them. They were not found more frequently, or in greater numbers in the vessels of the corium than in the vessels of any other part of the body. In order to show any possible relation between the skin lesions and the ordinary bacteria, we have preferred to place the chief reliance on the histological examination, rather than on cultures. As we shall see later, a general invasion of the tissues by cocci seems to be one of the most characteristic features of the disease. Bacteria were found much less frequently on histological examination than in either smears of pustule contents or cultures made from them, and it is probable that they were frequently missed in the study of the sections. In no case were they found in such relation with the early epithelial lesions that they could have been considered as a causal factor. When they are present they are brought to the lesions by the blood. As we shall see later, streptococcus septicemia is so generally present in fatal cases that it can almost be regarded as a part of the disease. It did not seem that the skin lesions were the usual place from which the streptococcus infection takes place.

We had one opportunity to investigate the lesions in a case of fetal small-pox. We have not been able to find in the literature one record of the histological examination of the skin lesions in a similar case, although fetal infection is probably more common in small-pox than in any other of the acute infectious diseases. The child, evidently at full term, was in process of birth at the death of the mother. It was

not known whether the child was already dead when the labor began. The mother had given birth to five still-born children. There was no anatomical evidence of syphilis, either in the mother or the child. The mother died in the thirteenth day of the disease, dating from the onset, with chill. There was an abundant pustular eruption, partly confluent, which was crusting in most places. The child was a male, well developed and nourished. The appearance of the skin at autopsy was described as follows: "The skin of the neck, shoulders, arms, chest, and back presents small, closely-set elevations, from pin-point to one-half millimeter in diameter, with a transparent, vesicular center, and a white, opaque border. The lesions are largest and most marked upon the backs of the hands. The general surface of the body is covered with a moderate amount of vernix caseosa. The general color of the skin is dull violet." The other organs, with the exception of the testicle and bone marrow, which, on microscopic examination, showed characteristic lesions, presented nothing normal, save small petechiæ on the serous surfaces. Considerable tissue was saved from the case, which was regarded as important for the study of earliest lesions. We were greatly surprised to find an entire absence of typical lesions in the skin, and it was only after lesions of the same character were found in other cases in connection with typical lesions, and after finding characteristic lesions in the testicle and bone marrow, that we could be sure that the skin lesions were those of small-pox. Microscopically, what appeared as vesicles were represented by clear spaces within the horny layer, which was split, and the surface of the vesicle was formed by a thin layer of adherent horny cells, Figures 2 and 3 (Plate VI.). A great number of sections were examined, and they all showed the same formation. Often a row of vesicles, separated by thin partitions, was found. In addition to this, there were numerous areas where the epidermis was elevated with a granular coagulum filled with small, clear spaces beneath it. All the vessels of the corium were greatly dilated, and the fibers, particularly at the papillary border, separated by edema. There was no

hemorrhage, and no cells were found in the exudate. The vesicles were never umbilicated. A close search was made for bacteria and cell inclusions. No bacteria were found, and nothing which we could be sure was a cell inclusion. In one cell, in the vicinity of a small vesicle, an enclosed body was found in the protoplasm adjoining the nucleus, but we could not be sure of its character. The vesicle formation beneath the horny layer, and the numerous cases in which the entire epidermis was elevated by the exudation, showed a similarity between this case and certain of the lesions in the others. In the absence of all characteristic lesions in the epidermis, and the absence of cell inclusions, it seemed probable that these changes, and similar ones in other cases, may have been due rather to the action of soluble toxines than to the direct action of parasites. The lesions were due entirely to the serous exudate, which in some cases passed through the lower layers of epithelium collecting in the horny layer, and in other cases lifted the entire epidermis from the corium. One of the vesicles in a child of two years was formed chiefly by the elevation of the horny layer, though the other characteristic changes accompanied it. This probably does not represent the usual condition in fetal small-pox. Characteristic vesicles, pustules, and cicatrices have been described, which could not have arisen in this way.[1]

II. THE MUCOUS MEMBRANES.

Eppinger was the first to call attention to the frequency and gravity of the lesions in the mucous membranes in small-pox, though their presence was known to the early investigators. Kendall, in 1881, described three forms of laryngitis which might appear: One pustular, with discrete pustules; another confluent pustular, with extensive

[1] In some sections of the skin of fetal small-pox, kindly shown me by the late Dr. Englemann, lesions of the same character were found consisting, in some degree, of hemorrhage and cellular infiltration of the corium, with lifting of the entire epidermis by a non-cellular exudation. The sections were made thirty years ago, and were not adapted for the study of the finer histological details, but the general character of the lesions was the same as in our case. Professor Hektoen also told me that in a case of fetal small-pox examined by him the lesions were similar.

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inflammation of the submucous tissue; and the third, the most serious and dangerous of all, a croupous or diphtheritic inflammation. Huguenin gives especial attention to the lesions in the mucous membranes of the nose, mouth, palate, and pharynx, which may all be affected at the same time. He also says lesions have been found in the rectum, urethra, and vagina. He thinks that the bronchitis and capillary bronchitis with the accompanying atelectasis of the lungs may be referred to the specific action of the small-pox virus. He says pus organisms are always present in the lesions, which run a more rapid course than they do in the skin. Roger says the eruption in the mouth and pharynx often precedes or at least appears at the same time with the skin eruption and passes through its evolution more rapidly. The eruption may produce dysphagia, and a tendency to the hemorrhagic form is often seen in the lesions in the throat, which may be sprinkled with small, black points. He found otitis media rare.

The lesions in the mucous membrane histologically showed a general resemblance to those in the skin, although the process is modified by the nature of the tissue. The epithelial cells are in much looser relation with one another than they are in the skin, and the impervious, horny layer which in the latter plays an important part in binding the mass of cells together is absent. There is also a greater vascular supply and a more active permeation of the tissues with fluid.

This being the case, the specific character of the lesion is lost in a very early stage. The epithelial cells which are affected and those which are adjacent are thrown off by the increasing exudate, leaving an area bare of epithelium. This takes place very much more easily on mucous surfaces covered with cylindrical epithelium, such as the trachea, than on such a surface as that of the tongue, lips, and vagina. The pharynx stands about midway between.

The mucous membrane was examined histologically from every case in which lesions were apparent, and was also taken in several of the cases in which no lesions were found at autopsy. In each case the mucous membrane from a number

of different places was examined. From all these examinations it is possible to form a general conclusion as to the nature and progress of the lesions in the mucous membranes. Only in the earliest cases of the disease, in which the skin lesions were in the vesicular or in the very early pustular stage, were lesions found in a sufficiently early condition for their specific character to be recognized. They presented a widely varying degree of intensity. As far as could be seen, the earliest change consisted in an exudation into the epithelium leading to separation of the cells. Only small spaces, however, were formed between the cells in this way. The extensive fan-like arrangement of spaces, which is so characteristic of the skin lesion, was never seen in the mucous membranes. Even in this stage, numbers of superficial cells were exfoliated. Along with this there was degeneration of both cells and nuclei. Many of the changes in the cells corresponded with those seen in the skin. The same form of hyaline fibrinoid degeneration was found here as occurs in the skin (page 43). In other cases there was the same shrivelling of the nuclei of the cells with more or less disintegration of the cytoplasm. Complete necrosis extending over considerable areas was also found.

In connection with these early changes in the cells, the same forms of parasites were found as in the skin. The cytoplasmic parasites in the various stages leading to gemmule formation were the forms most commonly found, but they were usually not so numerous as in the skin. In one case, however, that of a woman dying on the fourth day of the disease, the lesions in the pharynx were very similar to the lesions of the skin in the cases of purpura variolosa. In this case there was a general swelling and distention of the epithelium over considerable areas by fluid imbibition, and almost every cell of the lower layers contained the large ameboid forms of the parasite. The intranuclear forms were found only in the smaller lesions in the squamous epithelium. They were never found in the lesions in the trachea or in the larynx. The most characteristic forms were found in the squamous epithelium of the tonsil and of the soft palate.

Of all the mucous membranes examined, that of the soft palate and uvula was most affected. It is very probable that it is affected in all cases of the disease. As a rule, however, the lesions which could be regarded as truly specific and due to the direct action of the parasite on the cells were not found. The changes consisted in exfoliation of the epithelial surface with very extensive lesions in the tissues beneath. This was particularly marked in the uvula. In places there were large losses of substance. In all these places there were masses of bacteria, chiefly streptococci. They grew in masses very much resembling the single colonies on a solid culture. Such masses were found on necrotic surfaces and also in tissues apparently but little altered. Large numbers of bacteria were also found between the cells and on the surface in the earliest specific lesions. It is very probable that the destruction of the epithelium and its exfoliation is due in large part to the action of the streptococci.

In connection with these very extensive lesions, small areas were often found showing the specific lesions. It is probable that the deep and extensive lesions in the mucous membrane are always preceded by the true specific lesions which form the atrium for the streptococcus infection. Our conclusions as to the importance and frequency of streptococcus infection in small-pox agree with those of Perkins and Pay, who regard the bronchial mucous membrane as the chief portal of entry. The tissue beneath the necrosis shows various degrees of alteration, the most common condition being extensive edema with a great deal of fibrinous exudate. Not only is the fibrin found infiltrating the edematous tissue, but often large masses of fibrin may be found beneath the surface, filling up the distended lymphatic vessels and forming a coarse network.

The specific lesions in the mucous membrane also differ from those of the skin in the greater number of polynuclear leucocytes which are present. Polynuclear leucocytes were found in every stage of the lesions of the mucous surfaces. There was also extensive infiltration of the tissue beneath with the various sorts of lymphoid cells, particularly with

large basophile cells. The mucous glands of the tissue were variously altered. They were involved in the necrosis of the surrounding tissue and in addition to this lesion showed others closely corresponding to those found in the kidney and in the testicles. In these cases there was an interstitial infiltration of the gland with large basophilic mononuclear cells, which was combined with necrosis of the gland cells. There was no definite relation between the interstitial infiltration and the necrosis. The greatest degree of interstitial infiltration did not correspond with the greatest degree of necrosis. In several of the glands a considerable degree of interstitial infiltration had taken place without any or with but little necrosis. The blood vessels were dilated and contained usually a relatively greater number of polynuclear cells than do those in other situations, save the lungs.

Pyogenic organisms, chiefly streptococci, appear to grow in these lesions in much greater numbers than in lesions produced in any other disease. We have never seen in the lesions in diphtheria or in other infectious processes such masses of organisms as occur here. In one case, all the tissue around the tonsil was edematous, in part necrotic, and contained multiple masses of streptococci. The submaxillary gland in one case was affected, and numbers of organisms were found in the ducts.

It was very difficult to find, either in the larynx or the trachea, lesions which could be regarded as specific, owing probably to the rapidity with which the infected epithelial cells were cast off. In several cases there was very extensive necrosis of the surface epithelium with bacterial invasion. The bacteria in these cases, however, were chiefly bacilli, and formed in the methylene blue and eosin specimens a blue ring immediately above the membrana propria. In certain cases both in the larynx, trachea, and in the primary bronchi small foci of degenerated cells were found, and in these were the cytoplasmic parasite inclusions.

In addition to these lesions, which we regard as specific, vesicles produced by the total elevation of the epidermis by the exudation beneath were frequently found. Such

vesicles were found in pharynx, uvula, tonsils, larynx, and trachea. It is probable that the majority of the unbroken elevations which were described in the mucous membrane at the autopsies are due to such vesicle formation and are not true lesions. There was frequently a great deal of fibrin on the eroded surfaces, in some cases closely resembling the membrane formation in diphtheria. In one case there was evidently a true diphtheria, although examination by culture was not made. In this a characteristic fibrinous hyaline membrane was present, and on the surface and within this were clumps and masses of bacilli, morphologically and in their situation similar to diphtheria bacilli. In this case similar bacilli were found in the bronchi and in the foci of broncho-pneumonia.

Degenerative changes were found in the nuclei of the epithelial cells in connection with the lesions and elsewhere. Within the lesions the grouping of the chromatin masses around the nuclear membrane was frequently found, and there was often direct division of the nuclei so altered, just as in the skin.

The other change which affected the nuclei is a more interesting one, and is difficult to explain. It was found not only in the nuclei in the vicinity of the lesion, but elsewhere, and chiefly in the pharynx and the esophagus. This consisted in a very much more marked degree of the same sort of lesion which we describe in the nuclei of liver and kidney epithelium. The size of the nuclei was not altered. The characteristic appearance of the chromatin was lost, it stained less intensely, and was homogeneous. The main mass of chromatin was collected in the center of the cell, forming there a mass sometimes round or oval, sometimes extremely irregular. What was most peculiar in these cases was the appearance of small refractive vesicles in the interior of the chromatin masses.

Especial interest is attached to the mucous membrane of the eye in small-pox in view of the frequency with which blindness results, especially in children. From the literature

it appears that this must have been much more frequent formerly than it is now.

Adler speaks of the frequency of the eye affections during and after small-pox. He saw pustules appear on the conjunctiva before they appeared on the skin. He doubts whether there is a true pock-formation on the cornea, since the pustular keratitis only appears late in the disease. Hebra found the cornea constantly free from pustules in his cases. Roger found that conjunctivitis was frequent and severe, and that the infection often extended from the conjunctiva to the cornea; the keratitis resulting may be superficial or deep, and may end by perforation of the cornea and hernia of the iris, or by a more extensive infection with destruction or atrophy of the eye. In confluent small-pox he has seen an extension into the anterior chamber.

In our autopsies there was a remarkable freedom of the eye from infection. Purulent conjunctivitis without specific lesions was found in but two cases, and in one, an infant of two years dying in the late stage of the disease, there was an ulcer of the cornea near the scleral edge. Microscopical examination of this showed entire absence of any specific lesion. There was a loss of substance extending about one-third the thickness of the cornea, and the base of the ulcer was densely infiltrated with polynuclear leucocytes and endothelial cells. There was some ingrowth of epithelium from the adjoining edge. No form of the parasite was found in connection with the ulceration.

Certain of the mucous membranes appear to be less susceptible to infection than others. We have never found any lesions in the ureters, nor have we found specific lesions in the bladder; in but two cases were early specific lesions found in the urethra, although the glands were frequently affected. The vagina was also usually found free from lesions. With the exception of hemorrhages in the mucous membrane of the stomach, which were found in all of the cases of purpura and in some of the others, and with the exception of erosions, which were evidently due to these, no change was found in the mucous membrane of the gastro-intestinal canal. In one

case small opaque foci were found in the stomach on macroscopic examination, and these microscopically were found to be foci of necrosis. A few doubtful cytoplasmic inclusions were found in this. We have thought that this lesion was very probably specific, although the fact could not be positively determined.

GENERAL RELATION OF PARASITES TO LESIONS.

We have never found parasites except in the specific lesions of the skin and of the mucous membranes. Difficulty is experienced in determining the relation of the parasites to the duration of the lesions. We have computed the duration of the disease from the beginning of the initial fever. Patients usually came into the hospital with the eruption at various stages, and it was often difficult to determine from their statements or statements of friends the time of onset. Within certain limits the duration of the disease can be determined from the character of the skin lesions. Where it has been possible to determine the duration of the disease we can say with absolute certainty that parasites will be found in skin lesions up to the tenth day of the disease, this corresponding to about the sixth day from the appearance of the eruption. At this time, histologically, the lesions are clear vesicles, or beginning pustules. The uncertainty begins after this. At the eleventh and twelfth day of the disease parasites are sometimes found in the lesions, and rarely on the thirteenth day. When the disease is older than this, and when healing in the skin lesions is advanced, we have never found any parasites. The great majority of cases of smallpox die at about the twelfth day of the disease, and most of these cases are useless for investigation. In these later cases vesicles apparently delayed in their formation may be found, and in these parasites may be present in small numbers, or absent.

The cases which are most suitable for investigation are those of purpura variolosa, in which death usually takes place on or about the fourth or fifth day of the eruption, and the early cases of variola vera. In the fifty-four cases which we

have examined, and which embraced all stages extending to complete convalescence, we have found the parasites present in twenty-nine cases, and in several of these in very small numbers.

The cytoplasmic forms appear first. We have found but two cases in which these appeared alone. These were cases of purpura variolosa in which there was no microscopic appearance of vesicle formation. The skin everywhere showed histologically the cell degeneration with edema, which precedes the formation of vesicles. In more advanced cases of purpura variolosa numerous early intranuclear forms accompanied the cytoplasmic. In nearly all of the other cases the intranuclear forms were found generally accompanied by the cytoplasmic forms.

When the vesicle is formed, the cytoplasmic forms of the parasite are found in the cells of the rete mucosum at the edges where the vesicle is extending. There is evidently a continuous infection of the surrounding epithelium by gemmules formed by the proliferating cytoplasmic forms. The intranuclear forms of the parasite are found in the epithelial cells at the bottom of the vesicle, this being the oldest portion. A point may be found where both forms are seen in the same field of the oil immersion lens. Parasites are rarely found in any of the epithelial cells above the rete mucosum, and they are often limited to the lowest cells of this layer.

III. THE LUNGS.

The frequency of bronchitis and broncho-pneumonia in small-pox is generally mentioned in the text-books. There have been but few articles which especially treat of the condition of the lungs. Ivanowski, in 1876, found in the lower parts of the lung small grayish or red nodules up to the size of a pea. The lung alveoli were filled with cells resembling white blood corpuscles, and also contained epithelial cells with granular, cloudy protoplasm. There were also red blood corpuscles in the alveoli. He regarded these nodules

as true-small pox foci resulting from the inhalation of the germs of the disease.

Breynaert found that the bronchitis in small-pox was sometimes due to the development of definite pocks in the bronchi, which frequently did not reach the pustular stage. He described the pustules as becoming progressively smaller with the diminution of the bronchi in caliber, and found them even in bronchi of the third order. The pustules are sometimes delled and similar to the lesions of the skin, but may be quickly changed to ulcers with slightly overhanging edges. There is also bronchitis not due to the development of pustules which was marked in bronchi of medium caliber, but may also extend to the finest bronchi. Broncho-pneumonia was found in fifty per cent of seventy autopsies. It was less marked in children than in adults, and affected by preference the right lung. The beginning of the broncho-pneumonia takes place between the twelfth and fifteenth days. He has never seen lobar pneumonia in variola. Atelectasis was common in connection with the lesions. Joffroy found pustules in bronchi. These decreased in frequency with diminishing caliber. Along with these pustules there was an independent bronchitis with marked hyperemia of the mucous surface. Broncho-pneumonia was more common in the right lung. He found no lobar pneumonia; in cases in which it appeared to be present the consolidation was due to confluence of foci of broncho-pneumonia.

Roger says that pulmonary foci may be found which contain very few bacteria, but great numbers of his special parasite of the disease (see page 124). He found lung lesions more frequently and more extensive in infants and progressively less marked up to the adult age. The lung complications vary in different epidemics. He regards broncho-pneumonia as a grave complication. In the epidemic in Paris of 1900 there were twenty-four cases of lung complications, with only one recovery. The lung complications were especially prone to develop in cases profoundly affected with the disease in from twenty-four to forty-eight hours before

death. Pneumococci are commonly found, though other bacteria may be seen, or bacteria may be absent and only his special parasites found.

We have never found in the lungs or in the bronchi any lesions which appeared to be specific for the disease, or which may be compared with the lesion in the skin and mucous membranes. True lesions, though modified by the character of the epithelium, have been found in the trachea, but never in the bronchi, save in one case in which cytoplasmic parasites were found in small necrotic foci in the primary bronchi. With this exception, we have never found in the lungs any form of the parasite of the disease. The most common lesion found in the lungs, and one which is very rarely absent, is bronchitis, usually combined with more or less extensive broncho-pneumonia. This was found microscopically in cases in which there was no macroscopic evidence of it. Both the larger and the smaller bronchi were affected. In all cases there was hyperemia of the mucous membrane of the larger bronchi and an increased secretion. In numerous cases there was a very marked degree of bronchitis, even in the larger bronchi. The lumen was obstructed by cast-off epithelial cells and exudate in which there was little or no fibrin. The epithelial covering in many cases without being entirely cast off is lifted by an exudate beneath it. The lesions in the smaller bronchi are always attended with foci of pneumonia as well. Some degree of bronchitis and broncho-pneumonia was found in forty-three of the fifty-four cases. It did not differ from the forms of broncho-pneumonia so commonly seen in diphtheria, although the exudate rarely contained fibrin in any considerable amount. In two cases lobar pneumonia was found. One of these a child who died on the eleventh day, and the other aged fifteen who died on the fifteenth day of the disease.

The lung lesions differed from the lesions in other organs in the character of the exudate. The exudate in the lungs contained great numbers of polynuclear leucocytes. They were usually degenerated and the nuclei in various stages of

destruction. Along with these there were cast-off epithelial cells from the walls of bronchi and alveoli, and larger phagocytic cells. The basophilic lymphoid cells were rarely contained in the exudate.

In eight of the cases the exudate was largely hemorrhagic in character, and in the four cases of purpura variolosa hemorrhages were found, both within the lung and on the pleural surface, without any evidence of an accompanying pneumonia.

The different varieties of pyogenic organisms were constantly found in the foci of bronchitis and broncho-pneumonia. The most common organism was the streptococcus, and next to this the pneumococcus. These organisms were not only found in connection with the lesions, but also in parts of the lung which seemed normal. Along with the cocci, bacilli were frequently present, and in one case the bacilli had the morphology and characteristic grouping of diphtheria bacilli. This case appeared to be one of mixed infection with the diphtheria bacillus, although the organisms were not demonstrated by culture. In the pharynx of this case a diphtheritic membrane was found which contained similar bacilli.

These lung lesions were found in all stages of the disease, from the earliest to the latest. We should regard them as probably the most common and the most serious complication in small-pox. In many of the cases the lesions of the lungs were so marked that they constituted a sufficient cause for death of the individual without the accompanying specific infection. They were not more common in children than in adults, although atelectasis was much more marked in children.

Interstitial lesions consisting of focal infiltration of the tissue around the bronchi and around the blood vessels of the lung were found in a number of cases. These did not seem to have any relation with the purely exudative lesions. The cells found in these interstitial foci were the large basophilic cells and a small number of phagocytic cells. The lesions, however, never assumed the importance here that

they had in the kidney and in the testicle, and were comparable to the unimportant interstitial lesions which were found in the portal spaces of the liver. In spite of the fact that the large basophilic cells were contained but rarely in the exudate in the lung, numbers of them were often found in the capillaries, and in two cases there were thrombi in the veins which were chiefly composed of these cells entangled in a fibrinous network.

The very small amount of fibrin in the exudation made a marked difference in the histological picture of the bronchopneumonia of small-pox, as compared with similar conditions in diphtheria and other infectious diseases. This was probably due to the character of the blood, for the organisms causing the lesions are the same in small-pox and in diphtheria.

IV. THE LIVER.

The first observations on the condition of the liver in variola are those of Quinquard, in 1870, who describes lobular foci of hepatitis with fatty degeneration of the cells. Wagner found no special conditions in the liver. Curschman found fatty degeneration in such degree that he compares the liver with the phosphorous liver. Weigert describes small nodules of the size of a miliary tubercle formed of cells similar to those in the cutaneous lesions. Barthelemy found extensive fatty degeneration nineteen times in twenty-three autopsies. Siredey found in the earliest cases lesions of the interstitial tissue and cloudy swelling of the liver cells which later gave place to fatty degeneration involving all the cells of the lobule. The most recent article is that by Roger and Garnier. They found the liver in the pustular cases enlarged up to thirty-one hundred grams; the average weight was two thousand. In hemorrhagic cases the weight was less, but still above the normal. They think that the over-weight is due to an increase in the quantity of hepatic tissue, "la suractivité fonctionnelle aboutit à une proliferation anatomique active." In the interstitial tissue, particularly in the portal spaces, they found foci of infiltration with mononuclear leucocytes, and, in several

cases, large foci of hemorrhage. In addition to fatty degeneration, they found vitreous or hyaline degeneration and dislocation and separation of the cells. In the less intense cases of fatty degeneration the fat is found chiefly in the periphery of the lobules; later it extends to the centers.

In all of our cases the liver was examined microscopically in the usual way. Only the outer portions of the sections where the tissues was immediately exposed to the action of the hardening fluid were considered, as Zenker's fluid gives perfect preservation of the liver not more than two millimeters from the edge.

At the autopsy enlargement of the liver was generally noted. The average weight in twelve adults was two thousand two hundred and sixty-six grams. The greatest enlargement of the liver (one thousand five hundred grams) was found in a child ten years old. In considering the weights in these cases, it must be remembered that the subjects, as a rule, were otherwise healthy, and that the weights would, therefore, be higher than those found at ordinary hospital autopsies. Orth gives one thousand five hundred and seventy-four grams as the average weight of the liver of adults. This must be considered as below the weight of the liver in acute infectious diseases. In sixty-four cases of typhoid in adults the weight of the liver averaged one thousand eight hundred and ninety-three grams. It is to be regretted that the conditions of the autopsies did not allow accurate weights of the organs to be taken in all instances. The largest livers were found in the late pustular and crusting stages.

It is difficult to understand the condition producing this increased weight of the liver. In one liver which weighed two thousand seven hundred and fifty grams there were large fat vacuoles in the cells, in addition to intense degeneration with numerous small vacuoles in the very granular protoplasm. In the other cases there was but little fat. The over-weight was not due to distention of the vessels, for there was no evidence of this in the sections, and at autopsies the livers were generally described as pale. The only condition to which the increased weight could be ascribed was

the very evident swelling of the cells. The cells are larger and more granular than normal. The granulation of the cells has generally no particular character and represents only an intense degree of cloudy swelling. We have been accustomed to regard the liver in typhoid as the type of cloudy swelling, but the increase in weight in typhoid is slight as compared with the increase in small-pox. In most of the large livers there is no edema shown by dilatation of the pericapillary space. We think this enlargement of the liver to be a practically constant condition in the typical small-pox autopsy, which commonly occurs when the skin eruption is in the pustular and crusting stage. It was less marked in the earlier cases.

In seven cases a peculiar and intense form of degeneration was found to which the French investigators have given the most attention. In this the individual liver cells are separated from each other. The connective-tissue framework about the portal vessels is preserved, and these retain their relative positions, as do also the larger portal veins. In the most advanced cases all the other connective tissue, including the walls of the capillaries, has disappeared. The section represents simply a loose mass of liver cells such as would be given after the maceration and separation of the cells. There was but a small amount of blood in the tissues. The condition was found both in children and in adults and in most cases in the pustular or crusting period. It is not due to ordinary post mortem change. The liver cells and nuclei, though degenerated, gave no evidence of this. The autopsies were made in the winter and at an average of ten hours after death, except in one case in which sixty-five hours elapsed before autopsy. None of the other organs showed evidence of post mortem change. It does not, however, appear to us conceivable that the condition could have been present during life, for in such a liver the circulation would have been impossible. If this had been present in any great degree, the loose liver cells would have been carried in large numbers into the pulmonary capillaries, and in no case were emboli of liver cells found in the pulmonary vessels. We

regard it rather as a post mortem change due to the presence of some substance in the liver which exercised a solvent action on the cement substance between the hepatic cells and on the capillary walls. In the slightest degree the condition was seen first around the hepatic veins. We have found here separation of the liver cells from one another without any lesion of the capillary walls. Embolic masses of pyogenic cocci were common in the livers, showing these changes, as they were in all, but there did not seem to be any relation between the cocci and the condition of the liver cells.

There was but a small amount of fat in the liver. In one adult there were large fat vacuoles, in addition to small vacuoles in the granular protoplasm. Even in the livers of children there was less than the ordinary amount of fat. In but five of the fifty-four cases could the fat be regarded as representing a degeneration.[1]

In five cases hyaline degeneration of the cells was found. In this the cells chiefly at the center of the lobule contain refractive hyaline bodies, staining strongly with eosin, and lying in distinct vacuoles in the cells. They were round, and varied in size from those just distinguishable from the granules of the cytoplasm to those of the diameter of a red blood corpuscle. Two such bodies, attached to one another like diplococci, were often found in the same vacuole. The material resembles the hyaline formed in the kidney epithelium, but is more strongly eosinophilic, and is much smaller in amount, the cells never being filled with it as they are in the kidney. In one case only could the hyaline bodies be regarded as numerous. In this, an adult dying in a late stage of disease, the central cells of every lobule contained them in considerable numbers. The periphery of the bodies often stained more strongly than the center. The liver of this case weighed two thousand eight hundred and seventy grams. This degeneration is a condition not confined to small-pox, but seems to be more common in this than in other diseases. We are ignorant of its significance and character.

[1] By fatty degeneration we mean degeneration of the cytoplasm associated with the presence of fat.

In six cases necrosis varying in extent was found. In three this took the form of the ordinary central necrosis of the lobule, and in one case only was it extensive. The necrotic cells were small, eosinophilic, devoid of nuclei, the pericapillary space dilated. In two of the cases the necroses differed from those found in the liver in other diseases in the absence of polynuclear leucocytes in the necrotic cells. In one case, which died in a late stage of the disease, leucocytes were found. No local cause for the necrosis could be determined. In three cases there were no foci of necrosis, but single necrotic cells were found, without any relation to the lobule. The very small degree of necrosis was singular, in view of other evidences of degeneration and of the constant streptococcus infection, with which necrosis is so often associated in other diseases. Necrosis probably represents the "dégénérescence vitreuse" of the French authors.

The nuclei showed marked variations from the normal, both with and without evidences of cell degeneration. The most common evidence of nuclear degeneration was clumping of the chromatin. All the chromatin of the nucleus was collected usually into a single large clump lying in the center. Occasionally it was attached to the nuclear membrane, and sometimes two or more clumps were found. The clumps were usually round and stained less intensely than normal chromatin. In a few instances the chromatin was acidophilic. In these large chromatin clumps there were occasionally homogeneous, colorless, small, round or oval intensely refractive bodies. They were usually all of the same size, and few in number. In the nuclei so altered there was a considerable network of granular anastomosing threads which were acidophilic. They were too regular in number and arrangement to be regarded as coagulum. We have regarded this network as representing the linen of the nucleus. It was probably swollen and more than ordinarily apparent from the withdrawal of the chromatin from its connection with it. A similar condition was found in the nuclei of the convoluted tubules of the kidney. In a number of other cases the nuclei were greatly enlarged and perfectly

homogeneous. In some cells the nuclei were to be distinguished from fat vacuoles in the cells only by the presence of the nuclear membrane. The entire contents of the nucleus had disappeared. The membrane of the nuclear vacuole was usually round or oval, but occasionally folded and irregular. A condition was seen, regarded as antecedent to this, in which the nuclear contents were converted into a hyaline material, staining very faintly. This, however, could be recognized as material, because of a small space occasionally discernible between it and the nuclear membrane. In a few cases an irregular, acidophilic mass was seen between the homogeneous material and the nuclear membrane. In many of the nuclei so altered a small, faint, hyaline, round body was found almost always attached to the nuclear membrane. A similar condition of the liver nuclei has been found in leucemia. Both of these conditions have especial interest, in that they are unusual forms of nuclear degeneration, and may present slight similarity to some of the forms of the intranuclear parasites.

In some of the cases dying late in the disease there was more or less central congestion of the lobules, but in general the capillaries contained but little blood. In all instances there was an increased number of white cells in the capillaries, and in one case they were present in great numbers. They were almost exclusively the large basophilic mononuclear cells which have been described in the spleen and in the lymph nodes. Nuclear figures were found in considerable numbers in these cells. In one case, that of a child of eighteen months, these cells were so numerous that small foci were found in which all the capillaries were filled with them. Polynuclear leucocytes were almost wholly absent in the cases dying at the height of the disease. In the hemorrhagic and other early cases degenerated polynuclear leucocytes with fragmented nuclei and free nuclear detritus were found. The numerous other cells in the capillaries were not degenerated. Large phagocytic cells were found, alike free and attached to the walls of the vessels, containing both cells and detritus.

In six of the cases there were interstitial changes, consisting in accumulations in the portal spaces of cells of the lymphoid type.

No parasites were found in the liver. Emboli of cocci were found more frequently in the liver than in any other organ.

V. THE SPLEEN.

Golgi and Ponfick found a difference between the spleen in the pustular form and that of the hemorrhagic forms of variola. In the typical pustular form it was enlarged, and in the hemorrhagic form it was small, hard, and dark. Birsch-Hirschfeld, on the contrary, found the spleen constantly swollen in the hemorrhagic form, while in the pustular forms swelling was slight or absent. Roger found the spleen enlarged in sixteen confluent pustular cases, while in twelve hemorrhagic cases, it was enlarged only in four. The pulp was distended by cells belonging to the different varieties of leucocytes, but the mononuclear forms predominated. Some of these were non-granular and others contained neutrophilic granules. The hemorrhagic form of variola is especially characterized by the presence of nucleated red blood corpuscles. Arnaud found enlargement of the Malpighian bodies and infiltration of the pulp.

In our cases enlargement of the spleen with a maximum of five hundred and fifty grams was found in seven cases, and in most of these death took place in the late pustular or crusting stage.

In one respect the spleen in small-pox differs from that of the other acute infectious diseases, and that is in the great reduction in numbers of the polynuclear leucocytes. The spleen in the hemorrhagic forms of variola and in the early period of the ordinary type of the disease up to the end of the pustular stage contains, in some cases, no recognizable polynuclear leucocytes, in others very few. In the period of desquamation polynuclear leucocytes are fairly abundant, and in one case of death during convalescence they were numerous. Degenerating polynuclear leucocytes and the

nuclear detritus resulting from their necrosis are found in cases of purpura variolosa and in some instances in the vesicular stage of variola vera.

In the spleen, as in the lymph nodes and in the marrow, the formation of large cells of the basophile type is a prominent feature. It was particularly striking in the spleens of children up to the age of seven years in the early pustular stages. These cells are formed both in the spleen pulp and in the Malpighian bodies. The Malpighian bodies, like the follicles in the lymph nodes, are in certain cases almost wholly composed of these large cells. The follicles appear edematous, the cells being separated from each other. In such cases there seems to be a slight difference between the large cells in the Malpighian bodies and those in the pulp, the former being not so granular as the latter. There is also a difference in size between the large basophile cells in the spleen and similar cells in the lymph nodes. The very large cells with a loose, granular, vacuolated protoplasm, which are so common in the lymph nodes, are rarely found in the spleen. Nuclear figures are numerous in the basophile cells, both in the follicles and pulp. Occasionally in these cells there is a separation of the cytoplasm into a loose, outer, basophilic mass and a more compact, neutrophilic interior. Much more evidence of ameboid activity is seen in the cells of the spleen than elsewhere. They are frequently found engaged in the walls of the sinuses.

The numbers of eosinophile cells vary, but they are more numerous in the spleen than in either the lymph nodes or the marrow. They are more numerous in the spleens of children than in those of adults, and they usually are of the type of marrow eosinophiles.

Enlargement and multiplication of the cells in the sinuses, leading to the formation of large phagocytic cells, was also seen. Phagocytic cells from this source were found containing cell inclusions. Distinct nodules, similar to those described in the follicles of the lymph nodes, and so commonly found in diphtheria, were found in the follicles in seven cases. They are composed of aggregations of phagocytic

cells formed from the cells covering the reticulum. In some cases they contained much nuclear detritus coming from lymphoid cells. Nucleated red blood corpuscles are rarely found, and only in the spleens of children. They were very numerous in the case of an infant of four months.

The hyaline globules which were described by Arnaud were found in four cases within large phagocytic endothelial cells. These globules are acidophilic, and vary in size. In some cases only one large globule is found, and in others the cell is filled with a mass of globules all of about the same size. Their formation does not seem to stand in any relation to the disease.

In addition to these purely cellular changes there is always a varying, and in some cases a high degree of congestion, but rarely sufficient to produce a considerable enlargement. Hemorrhages into the pulp are frequently found, and the rare cases of considerable enlargement of the spleen seem to be due chiefly to this.

Fibrin, both within the sinuses and diffusely scattered in the tissue, is found with and without hemorrhage. It is not contained within the phagocytic cells as it is in the lymph nodes. In several of the cases in the late stage a considerable amount of pigment was found, both free and enclosed in cells.

Numbers of streptococci were found in twelve cases. The streptococci are both within the sinuses and in the pulp. They are especially prominent in the purpuric cases.

Hyaline degeneration of the arteries of the follicles and the formation of hyaline reticulum in the follicles was found in four cases, the most marked formation being in a child of seven. This formation of hyaline is identical with that found in the spleen in diphtheria, and is not specific.

VI. THE LYMPH NODES.

Very little attention has been paid to the condition of the lymph nodes in variola, notwithstanding the fact that the cellular changes in them are most important and throw much

light on conditions found in other organs. The only special mention of the lymph nodes which we have found is by Wagner in 1872 and by Roger in 1902.

Wagner merely says that the lymph nodes are hyperemic and hypertrophied. The only histological description of the lymph nodes is that by Roger. He says that the changes in them are very analogous to the changes in the spleen. There is hypertrophy in the pustular forms of the disease, but this is little apparent or absent in the hemorrhagic. The swelling is manifest in the beginning of the disease, increases and persists during the period of eruption, and slowly diminishes. Cell forms appear in the sinuses and about the follicles analogous to those which are met with in the marrow. The cells are principally neutrophile myelocytes, basophile myelocytes, and a few eosinophiles. Giant cells and nucleated red blood corpuscles may also be found. In the cellular infiltration about the node is a condition resembling leukemia.

The lymph nodes in our study of the disease were examined in thirty-five cases. In some of these lymph nodes from all regions of the body were examined; in others only those which macroscopically appeared to be the most affected. In the examination of single nodes the cervical were most often selected for study. The changes found varied according to the period and the character of the disease, but they are sufficiently constant to enable us to form a definite idea of their character and progress.

The condition which is most constant, it being absent only in some of the cases which died during convalescence, is a general edema, producing dilatation of the sinuses and separation of the cells. The enlargement of the node is due more to edema than to cellular hyperplasia. All the sinuses of the nodes are dilated, but the peripheral sinuses are most affected. Both the afferent and efferent lymphatics, particularly the former, are also dilated and filled with cells.

Roger has described cells in the sinuses and in the follicles similar to those in the marrow. In the absence of perfectly sharp granule staining, it is often impossible to decide as to

the character of the granules in the cells, and so to differentiate them. In those preparations where the preservation of the tissue is best, the cells are mostly of the basophilic type. They agree substantially with the basophilic cells of the marrow, but are larger, and their nuclei are more vesicular and contain abundant chromatin. The chromatin often shows a peculiar arrangement, there being large masses from which finer filaments radiate for a short distance. One or several such large masses of chromatin are found in the nucleus or may be attached to the nuclear membrane. The cytoplasm has an irregular outline, this being especially marked in those cells which are undergoing division. In many of these there seem to be two kinds of cytoplasm. In the center, around the nuclear figure, the cytoplasm is dense, finely granular, and takes the eosin stain. Outside of this is a loosely arranged mass of blue-staining granules. In other cells, not in division, there is a similar separation of the basophilic part of the cytoplasm. In the nodes from three cases, and to some extent in others, there is a definite blue-staining cap on one or both sides of the cell, in rare cases forming a circle around the cell. The cap in some cases forms a part of the general outline of the cell. In others it gives the impression of a structure added to the cell, forming a crescentic prominence on the periphery. In one such large blue crescent there is a pale, oval area in the middle.

In some of the nodes, particularly in those from children in the early vesicular stage, these cells are the most abundant. The structural separation of follicles and sinuses has completely disappeared, and the node represents a loose mass of cells. In cases not so advanced as this, the large cells, though chiefly in the sinuses, are also in the follicles. Every transition can be seen between the large cells and the lymphocytes. In this transition there is shrinkage and gradual disappearance of the protoplasm. In the large cells it is abundant, contains numerous small vacuoles, and the granulation is not definite. As the cells diminish in size, the vacuoles disappear, and the granulation becomes more evident and more distinctly basophilic. The apparent

separation of the cytoplasm into a neutrophilic central portion and a basophilic exterior disappears, all the cytoplasm being basophilic. The nucleus undergoes somewhat similar changes. Its vesicular character becomes lost, it becomes smaller, and the chromatin becomes arranged around the periphery of the nuclear membrane, forming solid clumps without the radiating filaments. Some of these cells have all the characteristics of Unna's plasma cells. In the smallest cells the cytoplasm almost disappears, forming an irregular outline close to the nucleus, and being without evident granulation. The nucleus is so contracted that it is almost filled with chromatin which is arranged in triangular masses around the membrane. No cell membrane can be distinguished in these cells, but the outline becomes sharper with the reduction in the size of the cell. Nuclear figures are found in great abundance and perfection in the largest of these cells. They become rarer as the cells decrease in size and none are found in the small cells.

Degeneration and necrosis are rarely found in the large cells, and progressively are more frequent in the smaller forms. In one of the late hemorrhagic cases nearly all of the small lymphocytes were degenerated. There are two forms of degeneration: one in which the nucleus becomes irregular, the chromatin less distinct, and finally disappears; and another and more common, in which the chromatin swells, forming a solid mass which assumes peculiar shapes. It is rarely homogeneous, usually it forms a circle with the bulk of the chromatin chiefly on one side, and only a thin rim of it on the other, and with an unstained, homogeneous material in the center. The whole may break up into small fragments, each of which assumes this shape, or perfect circles may be formed with a small, unstained area in the center. In some cases several small, unstained areas may be found, the nucleus representing, on a reduced scale, the masses formed by the degeneration of the cells in the testicle. It was often striking to see the most evident degeneration going on in the small cells with perfectly preserved and rapidly multiplying large cells present in the same field.

With these large basophilic cells and lymphocytes, phagocytic cells are always present. They are most numerous in the later stages of the disease, and are chiefly confined to the sinuses. They vary in size from that of the basophile cells (or smaller) to four or five times their diameter. They are phagocytic for all cells of the basophile type and for other material. They contain large vacuoles in which cells and other substances are included. The vacuole is sometimes out of all proportion to the size of the cell. Single or sometimes several cells are included in the vacuoles and undergo destruction, only fragments remaining. The vacuoles often contain granules which are arranged around the periphery. Granular material in varying abundance is also contained in the sinuses, and is regarded as coagulum or material from broken up cells. The granules within the vacuoles differ from the granules in the sinuses in being more sharply acidophilic, in showing greater irregularity in size, and in being definitely round. It is impossible to say whether the granules in vacuoles represent remains of cells, or granular material taken into the cell, or whether they are formed by the phagocytic cells. Fibrin filaments and beautiful stellate masses of fibrin were frequently found in the vacuoles.

Distinct nodules, composed of epithelioid or phagocytic cells similar to those so frequently found in the follicles of the nodes in diphtheria, are also seen in small-pox. They contain some fragmented chromatin from lymphoid cells, but there is not such a definite relation of these cells to necrosis as there is in diphtheria. Often the nodules are composed of groups of single cells which later undergo more or less fusion. The origin of the phagocytes from the endothelial cells of the reticulum is evident. The cells on the reticulum lining and crossing the sinuses are swollen and increased in number. Cells are found partially detached from the reticulum which agree in all repects with those in the sinuses. Nuclear figures are found in the cells attached to the reticulum, and in those lying in the sinuses It was perfectly evident that only the forming and recently formed cells were undergoing division. When the cell enlarges and

digestive vacuoles are formed in it, and its phagocytic function is established, the reproductive activity ceases. In the largest cells the nucleus is almost unrecognizable, it being formed of a thin, nuclear membrane, and almost devoid of chromatin. Hyaline globules are found in the phagocytic cells, either few in number, or filling the entire cell. There are also a few free hyaline globules.

In the convalescent cases great numbers of polynuclear leucocytes are found both in the sinuses and in the follicles. In all cases more polynuclear leucocytes are found in the nodes than in any other tissues save in the vicinity of the streptococcus infections. Occasionally they are absent. In one node the only polynuclear leucocyte found was within the vacuole of a phagocytic cell. Those in the sinuses often show degeneration and fragmentation. It seems probable to us that many of the polynuclear leucocytes in the sinuses have been brought there by the afferent lymphatics from some focus of bacterial infection. There is no evidence that they are formed in the nodes. Examination of the blood vessels in these cases does not show that they are carried into the node by the blood.

Varying amounts of fibrin are found in the sinuses, and a certain amount is almost universally present. Few of the nodes contain extensive hemorrhages. The cervical nodes of an adult, in the early vesicular stage with extensive lesions in the pharynx, were hemorrhagic in high degree, all the sinuses containing blood. In a node of one of the hemorrhagic cases there was disintegration of the red blood corpuscles leading to the formation of round bodies varying in size, with a bright acidophilic margin. A few scattered red blood corpuscles were also found in the sinuses, either free or enclosed in the phagocytic cells.

Eosinophile cells are fairly numerous, more so than they are in any other situation save in the marrow of children. They are found in all stages of the disease. They are principally of the mononuclear type, though polynuclear cells are occasionally found. In one infant of eighteen months numerous giant cells of the bone marrow type were found in the sinuses of a lymph node attached to the pancreas.

Parasites are never found in the nodes, nor are there forms of degeneration which resemble them. Streptococci are very commonly found in the sinuses. The most marked instance of streptococcus infection was found in the cervical nodes of an early hemorrhagic case. In these nodes the entire peripheral sinus and most of the other sinuses were blocked with them. Occasionally a few were found enclosed in the phagocytic cells, but these, in general, are not attracted by the bacteria. The cells are often found in the sinuses with masses of streptococci about them, yet they show no inclination to incorporate them. No reaction is found around the streptococci; they exert no influence on the number and the varieties of the cells found in the nodes, and they stand in no relation to necrosis, although both streptococci and necrosis are more abundant in early than in later cases.

VII. THE BONE MARROW.

The first investigation of the bone marrow in small-pox was made by Golgi in the epidemic of 1873. He examined the marrow in thirty-five cases and found different types of changes in the suppurative and hemorrhagic forms of the disease. In the suppurative, colorless cells predominated, and in the hemorrhagic, nucleated red corpuscles. Chiari, in 1893, investigated the marrow in twenty-two cases embracing all stages of the disease, and found changes in eighty-six per cent. He described under the name of osteomyelitis variolosa changes consisting in foci of necrosis and hemorrhage, associated with the presence of large cells. He considered these lesions to be of the same general character as the lesions in the skin and in the testicle. The necrosis was most marked in the more advanced cases, and occasionally he found fibrinous exudation associated with the necrosis. He regarded the large cells as formed from the marrow cells, their size being due to the absorption of fat. Mallory studied the anatomical distribution of the foci described by Chiari, and found that the marrow in all parts of the skeleton was affected.

The more recent studies on the marrow in small-pox have

been in connection with the changes in the blood. Roger, Josué, and Weil combined their examination of the marrow with the ante mortem study of the leucocytes in the same individuals. They found in the adult a degree of reaction of the marrow corresponding with the number of leucocytes in the blood. In cases with a leucocyte count of from four to six thousand there was in the adult little or no reaction in the marrow. In children, and in adults with complications, the changes in the marrow were more marked and corresponded with the changes found in the blood. There was an increase in the mononuclear cells and a diminution or complete absence of the polynuclear. The essential condition is that the marrow is incapable of transforming the mononuclear myelocytes into the polynuclear neutrophiles. The authors also note karyolysis and karyorrhexis in the marrow cells. They make no mention of the focal changes described by Chiari. Courmont and Montagard come to essentially the same conclusions. Muir studied the marrow in eleven cases, using that of the rib for both sections and smears. The marrow showed about the normal amount of fat. There was a general diminution in cells, this being compensated for by vascular dilatation. Like other observers, he found the polynuclear cells practically absent. The neutrophile myelocytes were diminished in numbers, a few of them being in mitosis and occasionally degenerated. The eosinophile myelocytes were also scanty, but proportionately less diminished than the neutrophiles. The cell depletion of the marrow is due to the cells being carried off in the blood. He found none of the large necrotic foci described by Chiari.

The marrow was investigated in twenty-seven cases, embracing all ages and all varieties and stages of the disease. The examination was entirely confined to sections of marrow hardened and stained in the usual manner. The marrow was taken from the vertebræ and from the upper third of the femur. The best sections for cell study were obtained from hyperplastic marrow of the femur.

The most striking change, and one which has been noted by all observers, is the marked reduction, even to complete

absence, of the polynuclear leucocytes. This was noted in all the cases, with the exception of one, in which death took place during convalescence. In this the marrow corresponded to that of an active leucocytosis. The absence of leucocytes does not seem to be due to their degeneration and destruction in loco, for, save in the hemorrhagic cases, degeneration forms and nuclear detritus, due to their destruction, are not found. The foci of necrosis are without the usual border of leucocytes, and there are none in the fibrinous exudate occasionally seen in the reticulum.

Extensive degeneration, both in definite foci and a diffuse degeneration affecting single cells, was found in the hemorrhagic and in other early cases. The foci of degeneration, taking the form of complete necrosis of the tissue, vary in size from those easily visible to microscopic areas. In the hemorrhagic cases the necrosis is not circumscribed, and in addition to actual necrosis there is a general diffuse degeneration shown by imperfect staining of cells. In other cases the foci of necrosis are more definitely limited. They are frequently associated with hemorrhages which extended beyond the necrosis. In the early cases there is no reaction around the necrotic areas. In the cases dying in advanced crusting stages, collections of large cells are found in the fat spaces around the necrosis and in the reticular tissue. These foci of necrosis and hemorrhage are the lesions described by Chiari, but the large cells, which he described as occurring in connection with them, do not constitute a necessary part of the process. We did not find the foci so commonly as did Chiari, probably due to the fact that our search for them was not so minute.

The abundance of cells in the marrow varied. It was not hyperplastic in the hemorrhagic and in the early vesicular cases. In the later cases it was generally hyperplastic, but there was considerable variation. In the hyperplastic marrow the most numerous cells were those which could be regarded as premyelocytes. They vary somewhat in size. The protoplasmic contour is irregular, and they are often provided with blunt processes suggesting an ameboid character. The

protoplasm stains slightly pinkish with eosin, and lacks definite granules. The nucleus is round or oval, relatively large, with abundant chromatin, which is often in large masses in the interior of the nucleus. There are also small masses of chromatin attached to the nuclear rim. Definite myelocytes are not numerous, and the forms with incurved nucleus, generally regarded as transitional forms leading to polynuclear leucocytes, are also rare.

In most cases there are present variable numbers of cells of a different and more distinct character. These vary considerably in size. The cell outlines are distinct and sharp. The protoplasm is definitely granular, and has a pronounced blue color when stained with the methylene blue. The nucleus is more brightly stained than it is in the cells first described. The chromatin is abundant, and distributed chiefly at the periphery. The shape of the cells is somewhat irregular, but forms suggesting ameboid activity are rarely found. In some cases these cells are so abundant as to form the predominant type, but generally they are much less numerous than the premyelocytes. They are of the same character as, or are identical with, many of the cells found in the outer part of the follicles and sinuses of the lymph nodes and in the interstitial tissue of organs. Nuclear figures are always abundant in them in all situations. When undergoing division the cell is enlarged, and the granules in the protoplasm become larger and more conspicuous. In some of the dividing cells there may be a distinct line of granules around the periphery, and granules of the same character are often found around the outside of the cells, apparently being separated from the protoplasm. In marked type these cells are easily distinguishable from the premyelocytes, but forms are seen in which neither the granulation nor the color of the protoplasm is so distinct. Many of the cells approach very closely to the character of plasma cells, and occasionally it is possible to distinguish in them the small crescent at one side of the nucleus, in which the protoplasm takes more of the eosin stain. Cells of a typical lymphoid character are found in varying numbers, depending largely

upon age, they being more abundant in children than in adults. They are often simply distributed among the other cells, but there is a tendency towards their occurrence in groups. We have never found groups of them representing definite follicles, such as are often found in the marrow in diphtheria. They are more abundant in those sections in which the large basophile cells are more abundant.

The eosinophile cells also vary greatly in number and are more abundant in children than in adults. They are much less numerous than in the hyperplastic marrow of other infections. In some cases they are absent. In type they correspond chiefly to the eosinophile myelocyte, and those with nuclei of the polynuclear type are as generally absent as are the polynuclear neutrophiles. In the cases in which they were abundant cells similar to premyelocytes were found with a varying number of eosinophile granules in them. These granules were never uniformly distributed in the protoplasm, but were in a group generally near the nucleus.

Nucleated red blood corpuscles are below the number found in healthy individuals of corresponding ages. In some of the latter cases they seem slightly to increase, but it is not possible to make this out definitely. No particular change can be distinguished in the giant cells.

Great interest is attached to the large cells first described by Chiari. He regarded them as formed from the myelocytes and as representing a reaction of the tissue around the areas of necrosis. We are not able to make out any constant relation between the necrosis and their presence. They are occasionally found at the edge of necrotic foci, but are more frequently independent of these. They vary greatly in size. Cells are seen from those of the size of a myelocyte to those nearly filling a fat space. The smaller cells have some resemblance to myelocytes, but could be distinguished from these by their having a more vesicular nucleus poorer in chromatin, and a more homogeneous protoplasm. The nucleus is generally more oval than round, sometimes irregular in outline, and the chromatin seems to diminish with the increase of the cell in size. In the

very large cells, swollen from fat absorption, the faint outlines of the nucleus can with difficulty be distinguished. The protoplasm is distinctly acidophilic, but this is more marked in the smaller than in the larger cells. The outlines of the small cells are often irregular, with knob-like projections. The cells are in part distributed singly among the other cells, but more frequently are found in groups. The most common mode of occurrence is in foci about a number of fat spaces. In no case are these cell-groups large enough to have produced a macroscopic alteration. They often form a line around a fat cell, or the space which this formerly filled may be occupied by two or more very large cells. The sizes of the large cells is evidently due to fat absorption. There is no increase in the cytoplasm. This takes the form of a very fine reticulum enclosing wide spaces which are presumably filled with fat, for the fat cells disappear as these cells become larger. Cells are occasionally found with large vacuoles within them. These large cells often show a distinct line around the periphery where the protoplasm is denser. They are phagocytic for all the cells of the marrow, and cells are taken up which show no evidence of degeneration. When formed around the foci of necrosis, they seem to be absorbing the fat. Nuclear figures are rare, but in one case a tri-polar figure was found. The origin of these cells is obscure. Cells similar to them are found in the blood vessels, both free and attached to the wall. We believe them to be endothelial in origin. Occasionally, rows of smaller cells of the same character were found surrounding a small artery. They are similar to the phagocytic cells found in typhoid fever. They are most numerous in the cases in which the marrow shows the greatest hyperplasia, and it seems probable that their function is intimately associated with the hyperplasia, in that they remove the fat to make place for the multiplying cells. They have not, however, been described in the hyperplastic marrow under other conditions. Not their presence, but their number and their focal accumulations seem to be characteristic of small-pox. Their relation to fat absorption is further shown by the

finding of similar cells in the same relation to the fat in fat necrosis and in inflammation of the mesentery and the omentum. They are also occasionally found in lipomas and in the fat when invaded by a carcinoma.

The blood vessels are generally prominent and filled with blood. Muir calls attention to this and considers it secondary to the cell depletion of the marrow. Thrombi are occasionally seen in the vessels, but this is not a prominent feature. In the cases of purpura variolosa, hemorrhages were found involving considerable areas, without any change in the surrounding tissue. As has been said, hemorrhages often complicated the necrosis. Fibrinous exudation was found both in connection with the hemorrhage and necrosis and without any relation to these.

We have never found any form of cytorycytes variolæ in the bone marrow. In our early investigations particular attention was directed to the marrow, for it was believed that the lesions described by Chiari were characteristic focal lesions, and that the organisms might be found in them. Streptococci were found in the marrow in many cases, particularly in purpura variolosa, but there does not seem to be any relation between their presence and the focal lesions.

VIII. THE TESTICLE AND THE OVARY.

The first definite description of the lesions of the testicle in small-pox was given by Beraud in 1859. He found in a number of cases an inflammatory affection of the tunica vaginalis and foci in the tail of the epididymis, and in one case an affection of the testicle itself, consisting in a parenchymatous inflammation. He describes in this rather dense yellowish foci, in size from that of the head of a pin to that of a pea. Beraud cites Velpeau and Gosselin, each of whom had noted the condition, and the latter says he has never known it to give rise to any symptoms during life. Trousseau says he has frequently been able to make out the condition clinically. Curshmann found orchitis in only four out of four hundred and thirty-two cases. Chiari cites a very interesting observation of Geraud, who found orchitis in a boy

with small-pox, and also bilateral orchitis in two men who had been revaccinated. In all three cases the affection ran a rapid and favorable course. Wagner found in the testicle in a case of hemorrhagic small-pox, in addition to hemorrhages, peculiar, small, grayish red or yellowish, lymphoid nodules. Chiari has made the most thorough study of the condition. He found the lesions in fifteen cases of children, and in a further examination of sixty-three cases, mostly of adults, lesions were found in forty-five. The lesions showed a perfect agreement in their stage of development with the skin lesions. In the early stages of the skin eruption the lesions were slight; they increased in intensity during the pustular stage and diminished during desquamation. In well-marked foci he distinguished a central area of necrosis, around this a line of small cell infiltration, and outside this a broader zone, not so well defined, which he calls the zone of exudation. In the earliest cases the interstitial tissue only was affected, the necrosis appearing secondary to this. Chiari regards the affection as due to the direct action of the small-pox virus carried to the tissue by the blood. He thinks that in the testicle the conditions for the action of the virus may be just as favorable as in the skin. The lesions show in their histological details similarity to the skin pocks.

In his excellent description of the pathological anatomy of small-pox, Roger says that the lesions of the testicle are frequent, but rarely have any clinical importance. Exceptionally, there is slight swelling of the testicle with an increase of fluid in the tunica vaginalis. The fluid is remarkable in the large number of mononuclear cells which it contains, and in the absence of polynuclear cells. On section, the tissue is often reddish and sown with small hemorrhagic foci and yellowish nodules which have somewhat the appearance of small tubercles, and which do not project above the cut surface. The histological examination shows intense congestion of the vessels, and an infiltration of the interstitial tissue, with large mononuclear cells and cells of Turck. The epithelium of the tubules may be destroyed. Roger says nothing of the etiology of the process.

In our cases the lesions were found in such numbers, and in such different stages of their evolution, that it has been possible to follow their development. There is undoubtedly a relation between the stage of the lesions in the testicle and that of the lesions in the skin, the earliest lesions being found in the early vesicular stages of the skin eruption, but the relation is not so absolute as Chiari describes it. The tissue was stained in a variety of ways, none of which gave any advantage over the stain in methylene blue and eosin. The focal lesions were usually visible on macroscopic examination, but were found in a number of cases in which they were not seen at the autopsy.

(1.) Diffuse lesions. — There was absence of spermatogenesis save in the cases in which convalescence was established. This was shown in most cases by absence of normal spermatozoa in the lumina of the tubules, and also by the absence of those appearances in the epithelium which indicate their formation. In the early hemorrhagic cases some normal spermatozoa were found in the tubules and occasionally in the cells, but they were generally degenerated. This absence of spermatogenesis is not confined to small-pox, but may be found in typhoid fever and in other infectious diseases. The absence of spermatogenesis is due to degeneration of the epithelial cells of the tubules, and is most marked in those cells most nearly related to the spermatozoa. In the large basic cells of the tubules the degeneration was absent or least marked. Next to these, the cells with spiral chromatin were least affected. The most marked degeneration was in the smaller inner cells of the tubules. The degeneration affected both cytoplasm and nucleus. The cytoplasmic degeneration was of no special importance. The cells were swollen, the outline ragged, the granules larger and less distinct. Fragments of granular material, evidently separated from cells, were found both in their vicinity and in the lumina. The entire cells were often cast off, either singly or in adhering masses. Hyaline globules in the cytoplasm were occasionally found. In a few cases all the interior cells were lost, the tubules being lined with a single row of swollen, irregular

cells, showing indefinite striæ. In the basic cells, in a few instances, single, small, round, acidophilic bodies were found, varying somewhat in size, and sometimes lying in an indefinite vacuole. They presented a slight similarity to the young cytoplasmic parasites in the skin. They were found most frequently in the epithelium about the focal lesions. They were distinguished from the parasites by differences in staining and by the absence of structure and indications of growth.

The nuclear changes were more striking. The simplest consisted in swelling of the nucleus producing a relative diminution in the amount of chromatin, which stained less sharply. In these swollen nuclei peculiar parallel lines were often found, giving the appearance of rod-shaped structures within them. These structures were inexplainable until fortunate sections showed that they were due to sharp infoldings of the nuclear membrane often extending completely across the nucleus. In some cases several such folds were found, appearing as rods in the optical cross section. Degeneration affecting the chromatin was most marked in the interior cells. There was but little chromatin clumping. The degeneration chiefly took the form of swelling and fusion of the chromatin. The nucleus was converted in some cases into a large, homogeneous mass, which stained intensely with basic stains. In other cases the degenerated chromatin contained clear or slightly stained spaces which sometimes were arranged around a larger, central space. The chromatin was refractive, and differed in no respect in staining and appearance from the chromatin in other forms of nuclear degeneration. These vacuolated masses were sometimes enclosed in cells, at others were free in the lumen, mingled with cell debris. A very similar condition was seen in the chromatin of the spermatozoa. These were swollen, dense, and refractive, and contained vacuoles. Vacuolated bodies of this character present a superficial resemblance to the intranuclear parasites. They are smaller, their framework stains more intensely with methylene blue and is more refractive, and they never lie within a nucleus, being formed of the nucleus and not in it. All these forms of degeneration, including the

vacuolar degeneration of the nucleus, have been found to as great an extent in typhoid fever. They have nothing especial to do with small-pox. The lesions were absent in the undeveloped testicles of children. Even when the focal lesions were numerous and extensive, the remainder of the organ was normal. In a few cases, notably in that of a man of forty-five years dying in the late pustular and crusting stage, small, round, vesicular bodies were found in the nuclei. Only one was found in each nucleus and that generally in the middle. They consist of a ring which stains intensely with iron hematoxylin, and refractive, clear contents. At a certain focus they show a dark dot in the center. In many of the cells, in place of these rings, there are solid masses which stain with equal intensity, and it seems possible that the rings may have been formed by the vacuolization of the solid masses. Probability was lent to this by the fact that the rings were often thicker on one side than on the other. The bodies varied only slightly in size and were a little larger than spores, which, in staining and refraction, they resembled. They were never found in the typhoid and other testicles which we examined, and with the exception of the instance mentioned, very rarely in the small-pox cases. They are different from the rings in the pansporoblast. We are unable to explain these structures. The possibility of their being spores must be admitted, but the weight of the evidence is against this interpretation. We are inclined to think that the rings represent a form of degeneration of some part of the nucleus, possibly the nucleolus. Although we have seen this condition only in small-pox, it is probable that if it be a degeneration, it is not confined to this disease.

In one case of convalescence from small-pox we found old lesions consisting in increase of connective tissue, thickening of the membrana propria, and atrophy and destruction of the tubules. Such chronic lesions were, however, so commonly found in connection with the acute that it was impossible to say that in this case they had been preceded by the specific acute lesions. In the histological examination of the testicles it is remarkable how often chronic lesions are found,

and this in cases which give no macroscopic indication of them.

Accompanying this general degeneration of the epithelium, there is usually some change in the interstitial tissue, consisting in edema and a slight increase in the number of cells.

(2.) Focal lesions. — The focal lesions are more numerous close beneath the tunica than elsewhere. They vary in number, some testicles being thickly sown with the lesions, while in others a single lesion would be found only after a number of sections were examined. The foci vary in size from those which are microscopic to those which are five millimeters in diameter. The smallest lesions, and those best adapted for study, are in the undeveloped testicles of children. In these and in some adult cases the beginning of the lesion is found to consist in infiltration of the interstitial tissue with cells. The infiltrating cells are lymphoid, and large, basophile mononuclear cells. The vessels are dilated, and cells similar to those in the tissue are found in them. Such foci involve only the interstitial tissue between two or three tubules. No change can be demonstrated in the epithelium, beyond the common degeneration. Nuclear figures are found both in the cells in the interstitial tissue and in those in the vessels. No degeneration is found in the interstitial cells. From such lesions as these, which can best be compared with the small interstitial foci in the kidneys, the process extends. In the larger foci the cells in the interstitial tissue are more numerous and closely packed in the dilated septa. The lymphoid cells and the large mononuclear basophiles predominate, but among them phagocytic cells begin to appear. These vary in size here, as elsewhere, and their phagocytic qualities are shown by the red corpuscles and other cells enclosed within them. There is some difference between the lesions in children and those in adults in the greater numbers of eosinophile cells in children. The phagocytic cells seem to be less numerous in children. The blood vessels in and about the foci are greatly dilated, and contain cells of the same character as those in the interstitial tissue, and there is

considerable hemorrhage from them. At the edge of the lesion the interstitial infiltration extends gradually. In those lesions of about the size of a submiliary tubercle some degeneration is seen in the tubules. In the undeveloped tubules of children the epithelium of the tubules, where the interstitial changes are most intense, becomes necrotic, the nuclei are lost, and the entire cell is changed into a smooth, hyaline mass staining strongly with eosin. The necrotic cells retain their connection with one another, and the necrosis is often limited to small groups of cells. Little or no nuclear detritus is formed. In the adult testicle the necrotic cells are cast off, filling the lumen with a mass in which the single cells and nuclei are no longer recognizable. There is usually a small amount of fibrin in the interstitial tissue, particularly in those cases in which hemorrhage is present.

In the larger lesions, embracing all those visible to the naked eye, there is extensive necrosis of the epithelium and to a less extent of the interstitial tissue. The tubules are filled with a mass of necrotic material composed of epithelium and phagocytes, the whole staining so strongly with eosin that the tubules stand out in sharp contrast to the blue intertubular tissue. In addition to the phagocytic cells, which form part of the necrotic mass, others are found containing cells and detritus. The phagocytes are never found in the tubules until necrosis has taken place, and they enter the tubules from the interstitial tissue. The membrana propria of the tubules becomes swollen, fibrillar in character, and the sharp separation between the tubule and the interstitial tissue is lost. With the increase of the intertubular tissue and the encroachment of this on the tubules, the latter may be represented only by the remains of the necrotic epithelium. The tubules are also invaded by the large basophilic cells which likewise undergo necrosis and add to the mass of detritus. The blood vessels in the foci are obliterated in some cases by thrombosis, but chiefly by the pressure of the infiltrating cells. The walls of the small veins are often completely infiltrated with cells; in some the lining endothelium being elevated by them. Endarteritis, marked by an

accumulation of cells beneath the intima, may be found not only in the arteries in and around the foci, but also in those at a distance from the foci. The endothelial cells are hypertrophied, projecting into the vessels, and in many cases lying free. Hemorrhage was found around such vessels. There are always large numbers of nuclear figures, both in the phagocytes and in the large mononuclear basophiles in the interstitial tissue. Thrombi are occasionally found in the larger veins at a distance from the foci. These thrombi are remarkable for the character of the cells within them, polynuclear leucocytes being almost absent. In all the lesions polynuclear leucocytes play no part; it was only rarely that a single one was found either in the vessels, in the interstitial tissue, or in the tubules in any stage of the lesions. The phagocytes acted very much as did the polynuclear leucocytes, being attracted in the same way by the necrotic tissue. In the vessels remote from the lesions polynuclear leucocytes were found in small numbers. In a differential count of the leucocytes in several large veins beneath the tunica vaginalis the large mononuclear cells and lymphocytes formed eighty-three per cent, the polynuclear leucocytes seventeen per cent.

No parasites were found in the interstitial lesions, although careful search was made for them here as in the foci in the bone marrow. It is not absolutely possible to exclude the possibility of their being present, for single gemmules and spores could be overlooked, or not distinguished in the mass of cell and nuclear detritus in both tubules and interstitial tissue.

Streptococci were found in the testicles with about the same frequency as in other organs. They were most numerous in the cases of purpura variolosa. They were usually found in the vessels, and occasionally in clumps in the interstitial tissue, without any reaction of the surrounding tissues. In one case necrosis was found around them, and in the necrotic tissue here were numbers of polynuclear cells. The streptococci cannot be shown to stand in any relation to the interstitial foci. They are occasionally found in the foci, but not more often than in the tissue elsewhere.

Epididymis. — Lesions were found in the epididymis in three cases. In two they were small, but of the same character as those in the testicle. The interstitial infiltration preceded the degeneration of the epithelium. The necrosis of the epithelium was not so extensive as it is in the testicle. The epithelium in places was lifted in festoons formed by the entering of large mononuclear and phagocytic cells. In one case with normal interstitial tissue the lumina of a number of adjacent tubules were filled with phagocytic cells closely packed together. There was no epithelial degeneration and no evidence that these cells had entered the tubules at the place where they were found. It seemed to us that they had reached the epididymis from the lesions in the testicle.

Prostate. — The prostate was examined microscopically in only two cases. In one there were focal lesions of the same character as those in the testicle, and some general infiltration of the intertubular tissue with large, mononuclear, basophilic cells.

It is to be regretted that both epididymis and prostate were not included in the routine examinations.

The ovaries. — The only reference to lesions in the ovaries in small-pox is by Beraud. He gives three cases in which there was exudation on the surface of the ovary with hyperemia of the vessels. We have found nothing which conforms to this description by Beraud.

The ovaries were examined in all cases, and in but two were lesions found which were regarded as part of the disease. In these cases, one dying on the tenth day of the disease and one a case of purpura variolosa, lesions were found very similar to those in the testicle. In the first the ovaries contained a number of small, simple cysts, and the lesions were for the most part in the immediate neighborhood of these cysts. They consisted in an infiltration of the tissues with large basophilic cells similar to those found in the organs elsewhere, and among which were numerous phagocytic cells.

The cells were in places necrotic, but the necroses were not sharply marked and were confined to single cells rather

than to areas. In these places there were a number of polynuclear leucocytes. The cysts were lined with simple epithelium and in the interior there was granular material and a number of large, swollen, epithelial cells, some of them containing hyaline. The foci could not be regarded as due in any way to changes which had taken place within the cysts. In one of the sections from the purpuric case a single similar focus was found. No parasites were found in the lesions.

The examination of the Fallopian tubes showed nothing abnormal, excepting in one case of hemorrhagic small-pox, in which death had probably taken place during menstruation; in this case hemorrhages were found in the lumen and in the tissue without any specific alteration.

IX. THE KIDNEYS.

Little attention has been paid either to the clinical examination of the urine in small-pox or to the anatomical study of the renal lesions. These lesions are extensive and interesting, both in relation to the specific disease and in relation to the general pathological anatomy of the organ.

Hemorrhages in kidney pelvis. — Unruh, in 1872, was the first to call attention to hemorrhage in the pelvis of the kidneys and in the ureters in small-pox. He found this in twenty-eight of two hundred and twelve cases. In sixteen cases the hemorrhage was slight; in twelve marked. The hemorrhage took place both in and below the mucous membrane, leaving the epithelium intact, and in some cases producing no clinical symptoms. This work of Unruh is the only one in which especial attention has been called to this interesting condition, though Ponfick, in 1875, says that hemorrhages may be found in the mucous membrane of the urinary tract.

Such hemorrhages were present in five of our cases. Like Unruh, we found the epithelial surface of the pelvis intact, the hemorrhage taking place in and beneath the mucous membrane. Free blood was present in the pelvis. Microscopically, the epithelium was in part absent, in part necrotic, and a few polynuclear leucocytes were found on or

within it. In places it was fairly well preserved. No parasites were found, but in many sections there were masses of streptococci. Beneath the epithelium the tissue is infiltrated with blood and with cells chiefly of the lymphoid type. Very little fibrin is found in the tissue. This condition we consider as connected with the secondary infections, and not due to the direct action of the parasites. It was found in cases in which there were hemorrhages in other organs. It has no connection with hemorrhagic nephritis, this being a rare condition in the disease. The hemorrhage was confined to the mucous membrane of the pelvis and did not extend into the ureters or bladder, except in one case in which punctate hemorrhage in the mucous membrane of the bladder was associated with the condition in the pelvis.

Huguenin, in 1900, called attention to the cloudy swelling of the kidney and to the frequency of glomerular affections. He thinks that these changes are due to the passage of toxic material through the kidney. In some epidemics albuminuria is rare, in others it is common. Renal affections may appear in late periods of the disease.

Arnaud, in 1898, found albuminuria in ninety-five per cent of his cases. The amount of albumen varied from day to day, making a very irregular curve. As a rule, it was more abundant in the severe cases. He found anatomical alterations of the kidney very frequently. The lesions are diffuse and consist chiefly in interstitial cellular infiltration due to diapedesis, and in alterations of the epithelial cells. The lesions of the epithelium are marked and there may be necrosis. Lesions of the glomeruli are frequently seen. In the acute period, even without any albuminuria, there may be marked lesions both of the interstitial tissue and of the epithelium. He describes both a general acute edema of the interstitial tissue and islands of cellular infiltration. The interstitial lesions predominate. He gives no description of the cells in the interstitial tissue, but says that they come there by diapedesis from the vessels. In eight out of the thirteen cases which he examined the lesions were chiefly of the interstitial type. He has also made the observation that in

interstitial cases the albuminuria may be slight or entirely absent.

Roger, in 1902, found albuminuria not common. It was present in fifteen per cent of the light cases, in twenty-five per cent of the discrete, and in twenty-eight per cent of the confluent. In two cases he saw nephritis appear during convalescence. The lesions of the kidney presented no special features. In a hemorrhagic case the kidneys were large and covered with ecchymoses; there were parenchymatous hemorrhages and the pelves were filled with blood.

Auché et Jouchères, in 1895, found the toxicity of the urine diminished in the state of suppuration. Bowen found focal lesions in the kidney which he compared with the lesions in the skin. They consisted of a necrotic center, surrounded by a zone of pus corpuscles and detritus, and outside of this a zone of epithelioid cells.

In our investigation the kidneys were examined in all cases, sections being made from a number of pieces. The usual methods of hardening and staining were employed.

There is nothing in the condition of the kidney which points to any specific action of the small-pox virus, either as a parasite acting directly on the tissue, or by means of soluble toxine. There is a close analogy between the condition in the kidney in this and that in other infectious diseases, but the changes are more common and more severe in small-pox than they are in any other acute infectious disease which we have studied. It is possible that the lesions are due rather to the concurrent infections than to the small-pox virus.

In our series there were two cases of acute suppurative nephritis, both in adults, and both in late stages of the disease, with crusting well advanced in the skin lesions. There were five cases of acute glomerulo-nephritis which which were also in late stages of the disease, the earliest case being in an infant of nineteen months which died on the fourteenth day of the disease.

In all cases the kidney was affected; the most common change was acute degeneration, often of an intense character,

which occurred in all stages of the disease and at all ages. The kidneys were usually somewhat enlarged, rather edematous, and opaque on section. Leaving out of consideration the cases of acute diffuse and acute glomerulo-nephritis, the greatest weight of both kidneys found was four hundred and ninety grams in an adult of twenty-nine years, dying on the eighth day of the disease, and two hundred and fifty grams in a child of ten years, dying on the eleventh day of the disease. The average of the recorded weights of those kidneys which showed the most degeneration was three hundred and ninety-one grams. In all of these cases death occurred comparatively early in the disease, in the vesicular and beginning pustular stage of the skin lesions. In the cases in which the degeneration was not so marked, the weight of the kidney was only slightly above the normal. The degeneration in these cases differed but little from the degenerations found in other acute infections. The convoluted tubules were chiefly affected. The cells were swollen, almost occluding the lumen; their protoplasm was much more irregular in outline than normal, and the granules coarse and few in number. The striated border of the cells entirely disappeared. The outlines of many of the cells were lost. In some cases the cells contained large, irregular vacuoles, apparently due to edema. There was no examination for fat, and the presence of this was only judged by the appearance of a line of vacuoles along the membrana propria. It is very probable that a considerable degree of fatty degeneration was present in all of the severe cases. The desquamation of cells was not so marked in these as in some of the later cases.

The nuclei showed various changes corresponding with the degeneration of the protoplasm. These changes consisted in an apparent diffusion of the chromatin in the nucleus, giving to it a rather solid appearance. In the nucleus of the normal renal epithelial cells there is a very slight staining of the general mass of nuclear fluid, in which the chromatin lies, and there is no appearance of a nucleolus differing from the chromatin in staining, although there may

be one or more clumps of chromatin in the nucleus. With this diffusion of the chromatin in the nucleus, there were found one or often two masses simulating nucleoli, generally lying at the periphery of the nucleus, and, as the degeneration became more advanced, showing a greater affinity for the acid stains. In the most marked degree of degeneration, the nucleus appeared solid and entirely devoid of chromatin filaments; the peripheral ring was less marked, the entire mass was distinctly blue, and in this there was found a lilac or bright red mass, often taking an indefinite ring form, the interior being less sharply stained than the circumference. The condition is very similar to that described in the epithelium of the testicle. Not infrequently, small, colorless, refractive masses were found in the chromatin clumps.

Hyaline degeneration of the epithelium, consisting in great swelling of the cells, which became filled with hyaline droplets, was often associated with this form of degeneration. In the minor forms of degeneration the condition consisted chiefly in swelling and increased granulation of the cells, with less evidence of destruction.

In certain cases the degeneration affected all parts of the kidney to an almost equal degree. The glomeruli in three cases were not affected, although there was often found a slight amount of granular material in the capsular space. In one case of very marked degeneration an adherent mass of cells was found in the capsular space, which had evidently come from the convoluted tubules, and had been forced into the capsular space by the swelling and tension of the tissue. This condition was first described by Welch in the cantharadin nephritis of the white rat. In the lumina of the tubules there were found hyaline casts, desquamated epithelial cells, and a peculiar circular reticulum, consisting of masses of circles varying in size.[1] Casts, however, were not so common in these early cases as later in the disease.

It is not evident how much such degenerations as these

[1] We have elsewhere called attention to this condition, for which no adequate explanation has been given. These extremely definite circles may form in an albuminous exudate in almost any situation where it is in contact with epithelium.

have to do with the death of the individual. They point to an extensive destruction of the kidney, probably due to the direct influence of a toxin or of toxins on the tissue. From the clinical reports it seems probable that such degenerations may take place without leading to albuminuria.

Total necrosis of the cells was rarely found to any considerable extent. Here and there single necrotic cells would be found, or a small area in which all the cells of a tubule were necrotic. In the two cases of acute diffuse nephritis there was extensive necrosis, and in one of them a beginning abscess. Most of the kidneys were hyperemic, though hemorrhages were not common.

One case in which the kidney was of considerable interest was that of the fetus with congenital small-pox. In this the epithelium of the convoluted tubules was enormously swollen and vacuolated, and the nuclei in the cells usually stained very imperfectly or not at all Post mortem change could be excluded. It is not impossible that the death of the fetus in such cases may be due to degeneration of the kidney from the effect of toxins in the mother's blood.

The interstitial tissue, in addition to containing the foci of cells about to be described, was often distended with fluid. The increased size of the kidney is due to this edema, as well as to the vascular congestion and to the swelling of the cells.

The five cases of glomerulo-nephritis were of the usual types. In the most marked case, in which the kidneys weighed seven hundred grams, a very imperfect history of the duration was obtained, but it was supposed from the character of the eruption that the duration of the disease was only ten days. In this case the glomerular vessels were occluded by cells, and there was extensive proliferation of the capsular epithelium. In another case of glomerulo-nephritis in which death occurred in the period of convalescence, the glomeruli were enlarged and contained great numbers of polynuclear leucocytes, which were present also in the capsular space, evidently reaching there by migration from the glomerular capillaries. This case is of special

interest because it is the only one in which any considerable number of polynuclear leucocytes were found in the kidney. In several of the cases the vessels of the glomeruli contained hyaline thrombi. In two cases, in addition to the hyaline thrombi, true fibrinous thrombi were found in the glomeruli. Occasionally thrombi were also found in branches of the renal veins.

All of these lesions of the kidney, however, are of inferior interest when compared with those which owe their character to changes in the blood. Probably the most striking thing on an examination of the kidney, and that which is most frequently met with, is the appearance of small groups of cells in the interstitial tissue, in various places, but chiefly in the upper portion of the pyramid, in the cortex bordering on this, and around the glomeruli. These cell groups are usually quite small, but they may cover a considerable area. The cells lie both inside the capillaries, which are distended, and outside of them. The cells are almost universally of one sort. They comprise large numbers of lymphoid cells and cells offering every transition between these and the large, basophilic, mononuclear cells.

In addition to their occurrence in these definite interstitial foci, the long vessels of the pyramids are usually dilated and filled with these cells. Great numbers of cells may be found in the vessels without any being present in the interstitial tissue. They are found chiefly in the vessels of the pyramids, but they may be found elsewhere. Often large veins in the cortex contain great numbers of them. In the small foci only cells of this character are found. In the larger, along with them there may be numbers of phagocytic cells. In one case the blood vessels of the pyramids contained large numbers of the mononuclear cells, and in an adjacent lymphatic there were numbers of phagocytic cells evidently derived from the lining endothelium. The large mononuclear cells are distinctly ameboid. We have seen them in the kidney, as in the spleen, in the act of direct migration from the vessels, and in the interstitial tissue they show blunt processes and every morphological evidence of ameboid

activity. Nuclear figures in considerable numbers are found both in the cells inside the vessels and in those in the interstitial tissue. The interstitial cell accumulations and the collections of cells in the vessels were most marked in the cases which died in an early period of the disease, and in one of the cases of purpura of five days' duration.

It seems to us evident that these cell accumulations in the vessels and in the interstitial tissue of the kidney depend directly upon the changes in the blood. Similar cells are present in the blood in large numbers, and for some reason they tend to accumulate in the vessels of the kidney, particularly in those of the pyramids. Here the vessels often present the appearance of those around an area of inflammation, filled with leucocytes. The number of cells found within the vessels certainly show that they continually accumulate, for we know that the circulating blood does not contain them in such proportions. Whether this is brought about by a purely physical condition due to the character of the pyramidal vessels, and the presence of these cells in the blood stream, is uncertain, but in most cases there does not seem to be a positive chemotaxis between the cells and the tissue. They lie at random in the vessels and have no tendency to a mural arrangement. In the interstitial tissue they have no relation whatever to alterations of the parenchyma. There is no special alteration of the parenchymatous cells where they are, and very extensive destruction and necrosis of the parenchyma may be found without them. The vessels in the glomeruli do not usually contain them, or certainly they are never found there in greater numbers than they are in the blood anywhere. Cell degeneration leading to complete destruction, with the presence of nuclear detritus, is not found to any considerable degree in the interstitial foci. In only one instance was there any considerable degree of this, a case of purpura variolosa of five days' duration. In this there was nuclear detritus, which came both from the cells within the vessels and from those in the interstitial tissue.

The absence of polynuclear leucocytes is possibly a more striking feature in the kidney than in any other organ. We

have repeatedly gone over sections of kidney without finding a single polynuclear leucocyte. A few leucocytes were seen in some of the late cases, and, as has been remarked in one case of glomerulo-nephritis, they were present in great numbers. In several of the cases in which degeneration was marked, hyaline masses were found in the capsular spaces of the glomeruli. The hyaline often took the form of a solid ring around the capsule, with irregular projections.

Streptococci were in seven cases found on histological examination, both as distinct emboli and diffusely scattered in the vessels. No especial search was made for them, and they were probably present in a large number of cases. There was no relation between the bacteria and the lesions.

Another point of interest in these cases was the very good condition of the kidneys, as far as the presence of chronic lesions was concerned. In only one case was there a chronic lesion of the kidney, which consisted in slight atrophy of the parenchyma with focal increase of the interstitial tissue; and this was in a man of twenty-five years.

X. THE ADRENAL GLANDS.

The only reference which we have found to the adrenal gland in small-pox is by Oppenheim and Loeper. They describe as the most common lesion foci of interstitial infiltration with large mononuclear cells.

In our investigation the adrenal was examined microscopically in nineteen cases embracing all stages of the disease, and in but five of these could it be regarded as normal. The most common change found was degeneration, which was present in thirteen cases. This affected all parts of the gland, but was usually less marked in the labyrinth than elsewhere. The degeneration was in some cases slight, in others it had proceeded to complete necrosis of the cells. It was either more marked in foci, or assumed entirely a focal character. The degenerative changes affected both nuclei and cytoplasm. The cytoplasm showed the presence of hyaline in droplets or in irregular masses, vacuolation, and disintegration. In the degenerated cells the cytoplasm was

more acidophilic than normal, and in the necrotic cells it was strongly acidophilic.

The nuclei showed nothing of the clumping of the chromatin with degeneration, which was so prominent in the nuclei both of the kidney and the liver cells. The change which was common to all of the degenerated nuclei consisted in an apparent diminution in the amount of chromatin, which for the most part was arranged in small masses around the nuclear membrane. At the same time the contents of the nucleus became more acidophilic and homogeneous. The chromatin after undergoing these changes disappeared and did not give rise to the well-known masses of nuclear detritus. An occasional nucleus was found converted into a homogeneous, sharply circumscribed, acidophilic mass. Another form of degeneration consisted in separation of the cells from their relations to one another in the same way as has been described in the liver. This was found most marked in the same cases in which the separation of liver cells occurred.

The other lesions of the gland consisted in foci of cellular infiltration. The interstitial cells were here, as in other organs, chiefly the large basophilic cells. The foci were usually small and were found chiefly in the medulla of the gland. These interstitial cells were derived from the blood, and in the blood vessels of the foci numbers of similar cells were found. There were no collections of these cells in the vessels in cases in which interstitial lesions were not found. Among the cells there was a varying number of phagocytic cells. Both the phagocytic cells and the basophilic cells were found not only in the interstitial tissue of the gland, but also between the parenchymatous cells. There was no relation between the degeneration of the cells and the interstitial foci. Each occurred independently of the other, although in general the interstitial lesions occurred in cases in which the degeneration was most marked. Neither in the degenerated parenchymatous cells nor in the interstitial tissue were there any parasites found.

XI. THE PANCREAS.

The pancreas was examined in all cases, and no lesions were found. The gland seemed to be especially well preserved, and even in the cases where autopsy was made some time after death the pancreas showed less change, referable to post-mortem alteration, than any other organ. In the course of the routine examinations of other infectious diseases, we have never found such perfect preservation of the pancreas tissue as we have in these cases.

XII. THE HEART AND THE ARTERIES.

We have found but few special references to cardiac lesions in variola. Huchard, 1871, considers that death frequently results from heart paralysis. In the lighter forms of the disease he found little or no affection of the heart. In more severe forms he found affections of both endo and epicardium, and sometimes of the valves. Roger says that there is an exaggerated idea of the frequency of the cardiac affections in the disease; on the contrary, they are extremely rare. Hayem, Desnos, and Huchard, cited by Roger, have described arteritis in small-pox, especially in the hemorrhagic form, in the period of eruption and later, affecting both the aorta and the coronary arteries. Brouardel, in 1874, described changes both in the endocardium and within the aorta consisting in the formation of small elevations, which he regarded as true pocks. The changes which he observed in the aorta were simply the forms of chronic endarteritis.

In our series of cases the heart was always examined. Acute vegetative endocarditis of the mitral valve was found in one case, an adult who died on the ninth day of the disease.

There was no enlargement of the heart save in the cases of acute nephritis. The microscopic examination of the heart gave little more than the macroscopic. There were no examinations of the fresh tissue for the presence of fatty degeneration, the conditions under which the autopsies were made

interfering with this. From the macroscopic descriptions it was probably frequently present, and in four of the cases the examination of the hardened tissue showed the presence of fat vacuoles in the fibers. In three cases, two of them purpura variolosa, there were small, well-marked foci of degeneration of the muscle fibers limited to the region close beneath the endocardium. In two cases, each of them late, rather diffuse areas of necrosis of muscle fibers were found in one case accompanied by hemorrhages and emboli of streptococci.

In four cases there was interstitial cellular infiltration with the large basophile cells. In one case, that of an infant of four weeks who died on the twelfth day of the disease, there was a general infiltration beneath the entire endocardium with these cells. They were also found in small foci elsewhere. The greatest interest, however, was attached to the case of acute vegetative endocarditis of the mitral valve. The vegetations on the valve were composed of fibrin, most of it hyaline. At the base of the vegetations there was some infiltration of the tissue with large cells. The most peculiar aspect of the vegetation was the absence of polynuclear leucocytes. These were not found either within or on the fibrin or infiltrating the base of the vegetation. The blood count in this case showed a very marked diminution of the number of polynuclear cells. Neither parasites nor bacteria were found in the lesion.

Our experience is in accord with that of Roger in showing the infrequency of cardiac lesions in small-pox. The few lesions found were in no sense specific, and were of the same character as those which might be found in any infectious disease. This seems to us rather singular in view of the frequency and intensity of the secondary infection with the pyogenic organisms.

There is little to be said about the arteries. Acute lesions in the large arteries were never found. There was, in a few cases, hyaline degeneration of the arteries of the spleen follicles.

Bacteriological examinations. — In eleven cases cultures were made from the heart's blood at autopsy. The streptococcus pyogenes was found in nine, the pneumococcus in one, and the staphylococcus pyogenes aureus in one. Cultures from the other organs were in accordance with the results of cultures from the heart's blood. Our results agree with the findings of Perkins and Pay as to the occurrence of the streptococcus pyogenes.

PATHOLOGICAL ANATOMY AND HISTOLOGY.

Summary.

The lesions in variola may be grouped as follows:

A. Lesions in character and in distribution fundamentally specific and due to the presence of a parasite peculiar to the disease.

B. Lesions associated with the above, of indeterminate specificity, in kind analogous with those present in many of the infectious diseases, but in degree characteristic of variola.

C. Lesions caused by accessory etiological factors, bacteria, whose presence and activity are conditioned by the specific infection.

A. The specific lesion.

1. The specific lesion of variola is a focal degeneration of stratified epithelium, vacuolar in character, and accompanied by serous exudation and the formation of a reticulum.

2. The fully developed product of these processes is a characteristic multilocular pock, or pustule.

3. The occurrence of these lesions is sharply limited to the stratified epithelium of the skin and of the mucous membranes of the soft palate, the pharynx, and the esophagus.

4. In number the lesions of the skin may be very few or so numerous as to overspread the entire body. In distribution they are fewest on the lower part of the trunk and most numerous on the face and on the hands; they bear no fixed relation to any anatomical structure in the skin. In size,

even when fully developed, they vary widely. Adjacent pocks may become confluent.

5. The lesions appear on about the fourth day of the disease, and passing through progressive stages reach a climax of development on the eighth or ninth day. Their appearance upon all parts of the body is not simultaneous, but begins on the face and hands and extends thence to the trunk and to the extremities.

6. The typical lesion is best seen in the skin. It begins with degeneration of the cells of the lower layers of the epidermis, accompanied by exudation, at first serous, later more or less cellular, the products of which are contained within the spaces of a reticulum formed by the degenerated cells. The exudate increases in amount and the spaces of the reticulum enlarge until its fibers finally rupture, and the lesion becomes a filled-out pustule. This development may take place wholly within the epidermis, and the fluid contents of the pock be separated from the corium by comparatively intact cells; or the corium may form the bottom of the pustule, in which case there is usually necrosis of the papillary border.

7. The subsidence and the repair of the lesion are accomplished by the removal of the fluid portion of the exudate by absorption and by drying, and by the regeneration of the epidermis, in the course of which the residual mass of degenerated epithelial cells, leucocytes, and debris, enclosed between two layers of horny epidermis, the old and the newly-formed, is exfoliated. The complete evolution of the lesion occupies about two weeks.

8. Associated with the lesions of the epidermis may occur edema, cellular infiltration, and hemorrhage of the corium.

9. The lesions of the mucous membranes are in degree proportional to the extent and to the severity of those of the skin. At an early stage of development they resemble the lesions of the skin, but owing to the structure of the mucous membrane, the resemblance is lost in the course of their evolution. In the absence of a restraining horny layer, the degenerated epithelial cells are cast off, and the vesicle within the epidermis is rarely seen, the pustule never.

10. Contained within these lesions of the skin and the mucous membrane and determining their specificity and occurring chiefly in the cells of the rete mucosum is the parasite peculiar to variola; in its younger or cytoplasmic form it is present in the protoplasm of the epithelial cells of early lesions and of such of the older lesions as are extending; in its intranuclear form it is for the most part in lesions more advanced. No parasites have been found in any lesions of the skin in which repair was well advanced.

11. Accompanying the specific lesions and simulating them in form are others, bleb-like, in which the entire epidermis is elevated by fluid exudate; in these the parasite is absent.

12. Variations from that form of the disease which presents typical specific lesions are determined by differences in the character and in the extent of the eruption. On the one hand, the lesions may be few in number or incomplete in evolution, as in the abortive types of variola; on the other, they may, very early in their development and before becoming visible to the naked eye, be accompanied by diffuse hemorrhage into the corium, as in purpura variolosa. In any case, forms exist intermediate between the representative type of the disease and the variation. Thus, between purpura variolosa and variola vera connection is established through types of the disease in which vesicles are developed subsequent to hemorrhage, others in which the specific lesion is followed by hemorrhage (variola pustulosa hemorrhagica), and yet others in which the lesions of a typical eruption after development became hemorrhagic (variola vera with hemorrhage).

B. Associated lesions of indeterminate specificity.

1. Proliferation within the hematopoietic organs is constant and well-marked, and gives rise in the spleen, the lymph nodes, and the bone marrow to the formation of mononuclear, basophilic cells, and in the lymph nodes and the marrow to phagocytic endothelial cells. The former pass into the blood in large numbers. This process is present to some

degree in other infectious diseases, but is here so prominent as to be well-nigh characteristic.

2. Cellular infiltration with the mononuclear basophilic elements above mentioned, focal and interstitial in distribution, occurs constantly in the testicle, and usually in the kidney, in the liver, and in the adrenal glands. In the testicle this infiltration, by pressure and by thrombosis, causes anemic focal necrosis, lesions which seem to be specific of the disease.

3. Degeneration, focal in character, apparently not anemic, but due to the action of toxines, and leading to necrosis, at times with hemorrhage, and accompanied by focal formation of phagocytic cells, is present in the blood-forming cells of the bone marrow, and constitutes a lesion almost pathognomonic, but devoid of parasites. Diffuse degeneration, toxic in character, is present in the liver, the kidney, the adrenal gland, and the testicle; in the liver cloudy swelling is more marked than it is in any other acute infectious disease. Otherwise, the degeneration is not to be distinguished from that due to bacterial infection.

4. Inhibition of cell differentiation by the action of toxines is evidenced in the bone marrow in the absence of complete transformation of antecedent cells into polynuclear leucocytes, and in the testicle in the absence of spermatogenesis. The first-mentioned is a condition seemingly peculiar to variola.

5. The paucity of polynuclear leuococytes, alike in the specific lesions, in the focal degenerations, and in the bone marrow, is a condition so constant and so pronounced as to render it a striking peculiarity of the disease.

C. Associated lesions, bacterial in origin.

Accompanying the lesions specific or characteristic of variola, are others due to bacterial infection through channels created by them or incidental to the lowering of resistance.

1. Acute parenchymatous degeneration of the liver, the kidney, the adrenal gland, and the testicle, already mentioned as associated lesions of the disease, may in part be due to the

action of the toxines of the pyogenic bacteria usually present in severe cases.

2. Inflammatory processes, constituting complications of varied and often of great importance, are present with a frequency dependent upon their position. Boils, erysipelas, and cellulitis are common but unimportant sequelæ. Pharyngitis and consequent broncho-pneumonia are frequent in severe cases, and the latter is often the cause of death. Lobar pneumonia, abscess, and gangrene of the lung occasionally occur. Endocarditis, pleuritis, and empyema are relatively uncommon. Acute lymph-noditis is present in all severe cases.

LITERATURE WITH REFERENCE TO PROTOZOA AND THE CELL INCLUSIONS OF VACCINIA AND VARIOLA.

The first reference to the presence of protozoa in vaccinia or variola is contained in an article of Grünhagen. He described in the lymph of vaccine vesicles, clear, refractive, sharply contoured, greenish bodies which were either free in the fluid or clinging to leucocytes. He was not able to show that they multiplied while being observed.

Following Grünhagen, the next description of organisms other than bacteria is that of Van der Loeff in 1887. He found, on examining animal lymph in hanging drops, ameba-like structures which he regarded as the virus. In a second article, appearing the same year, he describes in the contents of the pustules in two cases of confluent small-pox the same structures which he found in the animal lymph and which he regards as protozoa. There is little doubt that the discovery and the general confirmation of the protozoal origin of malaria at this time had a great influence in directing attention to the possible presence of similar bodies in other diseases. In the same number of the same journal which contained the second article of Van der Loeff there appeared the first of a long series of articles on the subject by L. Pfeiffer. In all there are eight publications of Pfeiffer's on the subject, extending from 1887 to 1896. In Pfeiffer's first article he describes an organism, the " monocystis epithelialis."

It is found in both vaccinia and variola and passes through its first stage of development in the epithelial cells of the Malpighian layer. The smallest examples are nine microns and show a clear nuclear-like spot five microns in diameter. A cyst enclosing several and surrounded by a thick membrane is found. After this encapsulation sporulation begins. The spores enter into the lymph and are converted into the ameba-like bodies ordinarily seen. They were found in the contents of the vesicles and were cultivated up to the third generation.

There can be little doubt that neither Van der Loeff nor Pfeiffer saw the inclusions which later attracted the chief attention, and they probably mistook degenerated epithelial cells, or leucocytes, or fragments of such for the organisms. The second article of Pfeiffer's shows still more clearly the influence of the malarial work. In this, apparently neglecting his first publication, he describe bodies similar to the malarial parasites in the red blood corpuscles of vaccinated individuals. He shows figures in the red blood corpuscles in the vaccinated dog which are in all respects similar to the appearance depicted in the red blood corpuscles in malaria. He was evidently unfamiliar with the appearance of the malarial parasite. The work is important in that it contains the first description of the warm box for the microscope which has so generally replaced the warm stage. In his third article, which contains an admirable contribution to our knowledge of the coccidia, he refers only briefly to smallpox, and is evidently unable to group his supposed organisms in this order. In a further article he considers the specific parasite to be identical with the coarsely granular ameboid elements of the contents of the pock, but says at the conclusion of the work that a classification of the structures in question cannot be given until the histological and staining reactions of the long series of degenerated cells can be ascertained, and the zoölogist can demonstrate motility and mode of reproduction.

These early papers throw little or no light on the subject. The literature with regard to the presence of protozoa really

begins with the publication of Guarnieri in 1892. In this he describes bodies which stain with carmine, hematoxylin, and safranin in the deep epithelial cells of the skin in vaccine and small-pox pustules, as well as in the epithelial cells of the cornea of rabbits which were inoculated either with vaccine or with variola virus. These bodies lie in clear spaces which are much larger than they, and vary in size from that of a micrococcus to the nucleus of an epithelial cell. He thought he could recognize both nucleus and protoplasm in them, and gave them the name of "cytoryctes variolæ," the name having reference to the supposed property of the organism to devour the epithelial cells and in this way form a space around it. He believed multiplication took place by two methods: (*a.*) Binary division.— He saw several times the division of the nucleus in the organism. The chromatin was situated at opposite poles, between which extended indefinite threads. He found several organisms in which there were two nuclei, and others in which there was a cross line indicating a cleft in the protoplasm. (*b.*) Gymnospore formation.— Organisms of a mulberry form were seen by him, the peripheries of which were studded with small masses which he considered spores.

His description of the bodies is perfectly clear. There is no doubt, however, that similar bodies had been seen in the epithelial cells in the variola pustule both by Weigert and Renault. Since the publication of Guarnieri there have appeared a large number of articles which have been, in the main, confirmatory of his description and interpretation, but which, with few exceptions, have added nothing to our knowledge of the bodies. Guarnieri was not the first to use the cornea for the purpose of studying the vaccine process. This was done in 1890 by Straus, Chambon, and Menard, who described the gross changes in the cornea after vaccination without mentioning the inclusions described by Guarnieri. In a second article, in 1894, Guarnieri again gave the results of further investigations on the nature of the cell inclusions. He found ameboid motion in the bodies when they were observed in hanging drops of fluid taken from young vesicles

of small-pox and of vaccinia. In Guarnieri's third article, in 1897, he adds little to his previous work. He describes the bodies as taken up by polynuclear cells, and by adding methylene blue to the fluid in which they were examined, he found in them a slightly stained body of round shape, surrounded by a clear edge. The clear area is not enclosed in a membrane. He thinks that the stained body is a chromatic nuclear substance. He considers the bodies similar to those which he had described in the cornea of a rabbit after vaccination, and places them among the rhizopods. In this communication he regards the spore forms described in his first article as degenerations.

At the same time with Guarnieri's second paper there appeared an important publication of Monti. He found no bacteria in the skin in cases of hemorrhagic small-pox, but in the epithelial cells of the Malpighian layer were corpuscles which stained with Biondi's hematoxylin. On inoculating the corneas of rabbits with pustular contents, there was a formation of transparent, small nodules which healed in ten days; and in the epithelial cells he found the same bodies as in the skin. He regarded these corneal lesions as perfectly characteristic, and inoculated corneas with various tissues from cases of variola with a view to ascertaining the distribution of the virus. He produced successful inoculation with skin, pharynx, larynx, and occasionally with lungs, testicles, and spinal cord. The blood and internal organs gave negative results.

Clarke, in 1894 and 1895, confirms the work of Guarnieri. He found the bodies both in the cornea and in small-pox lesions. In some of them there was segmentation of the nucleus and cellular division. The cornea of the guinea-pig he regarded as more suitable for study than that of the rabbit. He also found similar bodies in syphilis. The plates which accompany his article show the gradual development of these bodies up to the spore stage. It seems improbable, both from the description and the plates, that he has seen the specific inclusions described by Guarnieri. Some of his developing bodies can be regarded as degenerated

cells, some as leucocytes, and the origin of the others it is impossible to determine.

Ruffer and Plimmer described bodies in vaccinia and variola which they regarded as protozoa, mainly because they had ameboid movement. The bodies lie in vacuoles in the epithelium. Piani and Galli-Valerio found in the pustules of small-pox bodies varying in size, partly hyaline and partly granular, and sometimes motile. They were both in and between the epithelial cells. Von Sicherer gives a good description of the cell inclusions, confirming the work of Guarnieri.

The most important work following that of Guarnieri is that of Wasielewski, which is contained in two publications. The article in the "Zeitschrift für Hygiene" may be regarded as the most important confirmatory article which has appeared on the subject. He regards the inclusions as parasites and the etiological factor of the disease, and says that the organism cannot be classified with either the gregarinida or the coccidida. Its first influence on the epithelial cell is to produce an increased nutrition and an enlargement of the cell. He regards the perinuclear space as due to shrinkage in fixation. Wasielewski showed that injuries to the cornea produced by sterile substances did not give rise to changes of the same character as those produced by the vaccine inoculations, and that in them the typical inclusions do not appear. The inoculations with the contents of the vesicles of foot and mouth disease give rise to lesions of a different character from those of vaccinia. He also inoculated corneas with blastomycetes and other organisms, but never found lesions similar to those of vaccinia. He showed that the virus increased in the lesions, for he could inoculate from eye to eye indefinitely, without any change in the character of the lesion. The re-inoculations were successful up to the tenth day, but the most constant results were obtained by inoculating from a lesion from two to six days old. He vaccinated from the cornea of the rabbit to the calf in the fifteenth and the twenty-fifth generation, and in each obtained perfectly typical vaccine pustules and immunity towards

further vaccination. The vaccination of children was interesting. For this a cornea which represented the thirty-sixth generation was used. The epithelium was scraped off, rubbed up with sterile bouillon, and found free from bacteria by cultures made on agar, blood serum, and bouillon. This material, free from bacteria, was found to be perfectly efficacious for corneal inoculation. The amount of material so obtained was very slight, but positive results were obtained in six out of seven children who were vaccinated with it. These children were not further vaccinated to show immunity, the reactions being so typical that the parents would not suffer it. He confirms Guarnieri's observations as to the ameboid movement of the supposed organism.

The general conclusions of Wasielewski are important. The vaccine bodies are the only characteristic structures which can be found in the skin and mucous membrane in variola and in vaccinia. They are absent in normal and in other pathological conditions of the skin. The vaccine bodies appear in the corneal epithelium of rabbits with certainty when active vaccine is placed in an epithelial pocket of the cornea. These structures in the epithelial cells of the rabbit's cornea cannot be produced in any other way. Their origin from leucocytes can be excluded, nor can they originate from the nuclei of epithelial cells. Their origin from the cell protoplasm, in consequence of a specific toxic action, can be denied, because they are retained by filters, because they appear in dividing cells with normal protoplasm, and because we know nothing of specific toxic action affecting certain cells. The changes which these bodies undergo and their granular degeneration have never been observed in degenerating cells. The process cannot be compared with any of the known processes of degeneration. The inactive filtrates of vaccine lymph produce no action on epithelium. Wasielewski leaves untouched the question of the production of immunity in the rabbits by these bodies.

Siegel finds in foot and mouth disease and in the vaccine vesicles of calves structures which he thinks belong to the coccidia, and has photographed these with a power of one

thousand five hundred diameters. The photographs are not convincing.

Gorini, in a series of publications, confirms the work of Guarnieri. He finds the vaccine bodies specific, but thinks it possible that they may be derived from the nucleus, or if the body is to be regarded as a parasite, that it may be a nuclear parasite as well as a cell parasite. In his publication of 1901 he compares the vaccine changes with the changes produced by the inoculation of the cornea with the "plasmodiaphoria brassicæ." Macroscopically, there is a certain similarity, but the changes produced by the plasmodiaphoria develop much more slowly than those produced by vaccinia. Microscopically, the process is totally different. The plasmodiaphoria produces a greater proliferation of the corneal tissue than of the epithelium. His study of the plasmodiaphoria led him to the idea that the cavity in which the vaccine body lies may probably be regarded not as a cell vacuole, but as a part of the supposed organism itself. The work of Gorini on the results of plasmodiaphoria injection was induced by the article of Podwyssotzky on the etiology of tumors. In his last article, 1902, he describes coccus-like forms which precede the specific inclusions. With the appearance of the larger forms the coccus-like forms disappear. He has proved that these forms, as well as the true cytoryctes, are the products of active vaccine and are not foreign organisms. He thinks that the cornea of the rabbit is the most suitable agent for testing vaccine lymph. In the plates which accompany this last article of Gorini's, he shows small bodies of about the size of cocci in and between the cells. These bodies are often united to form tetrads similar to micrococcus tetragenus. Gorini leaves the question undecided as to whether the larger forms are derived from the coccus-like forms.

E. Pfeiffer inoculated the corneas of rabbits and guinea-pigs and investigated them after from one to one hundred and four hours. He found in the sub-epithelial tissue small, dark-staining bodies which afterwards invaded the epithelium, divided, and produced the small cell inclusions. He

inoculated corneas with syphilitic products and obtained the same forms. The plates which he publishes with the article show that he has seen the vaccine bodies, but most of his description and figures refer to things which have nothing at all to do with them.

Lebredo, in 1903, published a series of experiments in which he confirmed the work of Guarnieri and recognized the great practical value of the corneal inoculation as a means for establishing the diagnosis of small-pox in doubtful eruptions.

In addition to these articles, which refer specifically to the cell inclusions found in the cornea, there have been a number of other publications which refer only in part to these, being articles generally of a more ambitious character, in which the attempt is made to construct a life history of a supposed unicellular organism which is regarded as the etiological factor of small-pox and of vaccinia. The most important of these attempts is probably that made by Pfeiffer in various papers, the results of which he brought together in a publication in 1895. In this he compares the lesions produced in the cornea of the rabbit by inoculation with the prepustular stage of variola. The body enters the cornea and produces a specific change in the epithelial cells. On shaving off the infected epithelium and examining it on the warm stage, in a weak methylene blue solution of anterior chamber fluid the bodies inside the epithelial cells show active ameboid motion. The parasites increase by direct division. Around the vaccine point there is a zone of formative irritation which may extend to the membrane of Descemet. He thinks that such a vaccine pustule seven days old can be compared with a variola pustule five days old. In human vaccination and in small-pox the bodies pass from the epithelial cells into the blood. The blood parasites are found in variola, in vaccinated children, and in calves. The ameboid cells, some adherent to the blood corpuscles, others free and sometimes ciliated, are found in the blood. These bodies may form a sort of cyst whose contents divide up into an indefinite

number of spores. He thinks that in variola there may be a mother pustule on the internal epithelial surface of the body. The first fever is due to this and ends with the passage of the germ into the epithelium. The eruption is an embolic affection of the skin. The ameboid bodies in the blood are, in the calf one-half, and in the child one-fourth, the diameter of a red blood corpuscle.

Doehle, in an article embracing the etiology of several of the exanthemata, describes the condition found in three cases of small-pox. He found structures more or less refractive and one-half to one micron in diameter, in the blood. On some of these he found cilia. There were also dark granular structures of two and one-half microns which showed contraction, and, in their interior, refractive granules in irregular arrangement. The development of these parasites can be followed in the contents of the pustule. In the beginning of the pustule they were never in the epithelium. The bodies in the blood were found some days after the beginning of the appearance of the exantheme and continued from five to seven days. In the vesicle there were motile ciliated bodies corresponding to the bodies in the blood. The larger bodies increased in the pustule, and the smaller ciliated bodies disappeared. He found the same thing in the lymph of calves. Illustrative plates accompany the article.

Roger and Weil found in the pustule contents, both between and in the leucocytes, small, round, or oval bodies staining intensely with Loeffler's methylene blue. They found them also in the blood of variola and more abundant in severe cases than in the milder.

In the hemorrhagic form these bodies were found in the hemorrhages in the spleen, in other internal organs, and in the bone marrow. They found similar bodies in the amniotic fluid of two pregnant women who died of small-pox. They were also contained in the blood of variolated rabbits. There is little doubt that the bodies referred to represent degenerated nuclei of leucocytes or fragments coming from these.

The chief part of Bosc's work refers to the sheep-pox or clavelée. He gives a good description of the inclusions and has attempted to cultivate them in various ways. He compares the vaccine lesions with those of small-pox, and believes that they are the same. In his plate of the third-day cornea he shows larger nucleated inclusions and the segmentation of these into spores. Weber, in two articles, has described in the blood of small-pox structures which he regards as different stages of development of protozoa. There are small, round, refractile, greenish or bluish bodies with rotation or with ameboid motion, larger homogeneous bodies which contain in their interior one or two small granules, and also granules which are connected together with threads. He obtained cultures in alkaline agar. Funck found in vaccine lymph and in the contents of variola pustules when examined in hanging drops, cysts filled with small refractile spores. He succeeded in cultivating the spores on agar. The parasite of variola he regards as occurring in two forms, as cysts filled with spores and as free spores. Reed, in 1897, found in the blood of small-pox and in vaccinated monkeys and children small ameboid bodies one-sixth to one-half as large as a red blood corpuscle. Some of them were clear; some of them granular. In one case he found a flagellum attached to the body. He says that similar or closely-allied bodies were found in the blood in several normal children and in a monkey. Dombrowski found in the pustular contents of variola, small bodies, motile and with clear contour, and also larger, sharply-contoured, yellowish bodies. In the fresh blood of small-pox he found bodies similar to the smaller forms.

The work of Guarnieri has also led to a number of articles opposing his interpretation. The first one of these is the article of Ferroni and Massari. They conclude that the supposed sporozoa of Guarnieri are merely derivatives of nuclei of epithelial cells or leucocytes. They obtained the same lesions in a rabbit's cornea by producing inflammation in other ways, but they rarely found the inclusions in such large numbers.

The next article in opposition is that of Salmon. He regards the lesions which are produced as specific in character and as inoculable from one animal to another, but regards the cellular inclusions not as parasites, but as derived from the wandering cells, *i.e.*, the polynuclear leucocytes. He excludes them from the protozoa because they have no nucleus or cell membrane. The shape and size of the inclusions are also too irregular for such an origin. He thinks they are derived from portions of the protoplasm of the leucocytes or portions of their nuclei. The article of Borrel follows that of Salmon. Borrel has grouped a number of exanthemata under the name of infectious epithelioses. He finds inclusions similar to those described by Guarnieri in all of them. In clavelée they are contained not only in the epithelial cells but in cells of mesodermic origin. He regards all these inclusions as originating from polynuclear leucocytes and shows transitions between them all.

The most extensive article in opposition to Guarnieri's view, and one which constitutes a valuable addition to our knowledge of cellular changes, is that of Hückel. He regards the lesions as specific in character, as inoculable from animal to animal, and as conferring immunity, in which he agrees with Straus Chambou and Menard. The work of Hückel was carried out with the utmost detail, and every possible change in the epithelium brought out by various methods of hardening and staining was depicted. Hückel believes that they represent degenerations in the cells brought about by vaccination, but they are not organisms.[1] It is very difficult to understand all of the things which he has described. Some of them are certainly included leucocytes or fragments of them. Some of them seem possibly to be artifacts, but it is difficult from examination of the true inclusions to which he has only given a small space in his second plate (see Plate II., Fig. 58) to see any relation between these and the various

[1] His best results were obtained with the Biondi staining method; he gives the following classification: 1. Naked bodies; 2. Bodies with blue center and erythrophilic mantle; 3. Spherical bodies with red granules; 4. Spherical bodies with threads radiating to cytoplasm; 5. Half moon, sickle or spindle-shaped bodies; 6. Bodies of triangular form; 7. Rare forms; and 8. Bodies in the connective tissue cells of the cornea.

other things depicted. The figures which he gives of the inclusions are not satisfactory because they show no structure within them.

Roux regards the virus of vaccinia and of small-pox as probably belonging to the invisible organisms, and accepts the work of Salmon and Borrel regarding their leucocytic origin. Borrel has filtered the organism of clavelée, the filtrate retaining its virulence, and thinks that vaccinia is probably of the same character, although he does not give any filtration experiments on this. Sikorsky thinks that the bodies do not have specific character and that they may be produced by the injection of various animal fluids and especially by diphtheria toxin. Besredka, who reviews the article, says that the view is universally accepted that there is nothing specific in the vaccine corpuscles. They should be regarded merely as a transformation of the migrating cells. The substances producing them are of the nature of toxins. Ewing found the inclusions present in all stages of the small-pox lesions and their numbers proportionate to the degree of hemorrhage in the lesions. He believes that both in the skin and in the cornea they are derivatives of the red blood corpuscles.

Ishigami has described bodies in vaccinea and in variola which he regards as protozoa and which pass through two stages. In one, the ameboid form, the organism multiplies by simple division. In the other form division takes place by cyst-formation and the production of spores. He has cultivated the organism in a special culture medium, whose chief constituent was epithelial cells. It is impossible to reconcile the description of the bodies which Ishigami has found with the work of any preceding investigator.

In 1903 Councilman, Magrath, and Brinckerhoff published a preliminary communication in which they described bodies similar to those described by Guarnieri in the cytoplasm of the epithelial cells of the skin in both variola and vaccinia. In addition to these and representing a further and complete development of the parasite there are forms which develop only in the nucleus. The cytoplasmic forms precede the intranuclear forms.

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DESCRIPTION OF PLATES.

PLATE I.

FIG. 1. From a case of purpura variolosa. Degeneration of the epithelium preceding vesicle formation with cytoplasmic parasites in the reté mucosum. X 200.

FIG. 2. Degenerated cells showing vacuolation of protoplasm and shrivelling of nuclei. X 1,000.

FIG. 3. Beginning vesicle formation with splitting of stratum corneum by the exudation. X 120.

FIG. 4. Section passing through a young vesicle. X 40.

FIG. 5. Reticular degeneration of epithelial cell. X 1,000.

PLATE II.

FIGS. 1 and 5. Early vesicle showing formation of epithelial reticulum. X 120.

FIG. 2. Later stage showing enlargement of spaces and rupture of reticulum fibres. X 120.

FIG. 3. Early vesicle at edge of hair sheath. X 120.

FIG. 4. Hyaline (Ballonartige) degeneration of epithelial cells at bottom of vesicle with nuclear fragments lying between cells. X 450.

PLATE III.

FIG. 1. Late vesicle with formation of secondary vesicle by elevation of the stratum corneum. X 40.

FIG. 2. Vesicle showing formation of secondary vesicle beneath true vesicle by elevation of entire epidermis. X 40.

FIG. 3. Septa between adjacent pustules. X 40.

PLATE IV.

FIG. 1. Flat section of umbilicated vesicle showing sheath of lanugo hair in centre of vesicle. X 110.

FIG. 2. False vesicle due to uplifting of entire epidermis by exudation. X 110.

FIG. 3. False vesicle showing separation of gland duct from corium by the elevation of the epidermis. X 110.

PLATE V.

FIG. 1. Section through healing pustule showing regeneration of stratum corneum. X 40.

FIG. 2. Remains of pustule showing scab or disk within the horny layer. X 40.

FIG. 3. Section through healed pustule of palm showing hyaline mass, remains of pustule, disk, or scab beneath the dense horny layer. X 40.

PLATE VI.

FIG. 1. Section through healed pustule of plantar surface showing "disk." X 20.

FIG. 2. From case of congenital small-pox showing formation of small vesicle by splitting of the stratum corneum by exudation. This is analogous to the formation of secondary vesicle in Fig. 1, Plate III., and in Fig. 3, Plate I. X 110.

FIG. 3. From congenital small-pox showing elevation of entire epidermis by exudation; analogous to process in Plate IV., Figs. 2 and 3. X 200.

PLATE VII.

FIG. 1. False vesicle in trachea showing separation of epithelium by exudation. X 200.

FIG. 2. Early lesion in mucous membrane showing cell degeneration and invasion by bacteria. X 200.

FIG. 3. Section of trachea showing necrosis of epithelium with masses of bacteria extending along membrana propria. X 200.

FIG. 4. From a section of uvula showing masses of streptococci in lymphatics. X 200.

FIG. 5. Section of uvula showing masses of streptococci in necrotic tissue. X 200.

PLATE VIII AND VIII a.

Cytoplasmic forms of parasite.

FIG. 1. Advancing edge of vesicle under low power showing young forms of parasites in the epithelial cells. X 200.

FIG. 2. From same region showing number and distribution of parasites. X 800.

FIGS. 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, to show growth and differentiation of cytoplasmic parasites. X 1,000.

In Fig. 10 an hour-glass form denoting either ameboid motion, or multiplication by simple division. X 1,000.

FIG. 13. Cytoplasmic parasite preceding gemmule formation. The dark points become the future gemmules. X 1,000.

FIG. 15. A later stage. X 1,000.

FIG. 14. Gemmule formation. A few gemmules are seen within the parasite and in the surrounding tissue. X 1,000.

FIG. 16. Framework of parasite after formation and escape of gemmules. X 1,000.

PLATE IX AND IX a.

Phases of the intranuclear form of the parasite.

FIGS. 1, 2, 3, 4, 5, 6, show young forms and development of intranuclear parasites into sporoblasts.

FIGS. 7, 8, 9, 10. Intranuclear sporoblasts.

FIGS. 11, 12, 13, 14, 15, 16, 17. Free sporoblasts. In Fig. 16, on the right, is a group of pansporoblasts.

FIG. 18. Early intranuclear parasite probably microgammete, from case of purpura variolosa.

FIG. 19. Free spores within nucleus. Fig. 19 is magnified 3,000 diameters Figs. 18, 3, and 6, 2,000 diameters. Figs. 7, 8, 9, 1,500 diameters. The remainder 1,000 diameters.

PLATE X.

FIG. 1. Masses of streptococci in uvula. X 200.

Fig. 2. Area of broncho-pneumonia. X 110.

FIG. 3. Section of pleura and lung in a case of empyema. The pleural surface is covered with a thick mass of streptococci. The lung below is necrotic, and the tissue is covered up by enormous growth of streptococci. X 110.

FIG. 4. Necrotic tissue adjoining submaxillary gland with masses of streptococci. X 200.

FIG. 5. A small area from Fig. 4 showing streptococci. X 1,000.

PLATE XI.

FIG. 1. Section of liver showing large basophile cells in capillaries. X 1,000.

FIG. 2. Section of liver showing hyaline bodies in liver cells with cloudy swelling. X 1,000.

FIGS. 3, 4, 5. Sections of spleen showing character of cells, principally of large basophilic variety in pulp and in sinuses. In Fig. 4, a large basophile cell is shown in the wall of sinus in the act of migration.

PLATE XII.

Fig. 1. Section of cervical lymph node from case of purpura variolosa showing the sinuses of node filled with masses of streptococci. X 25.

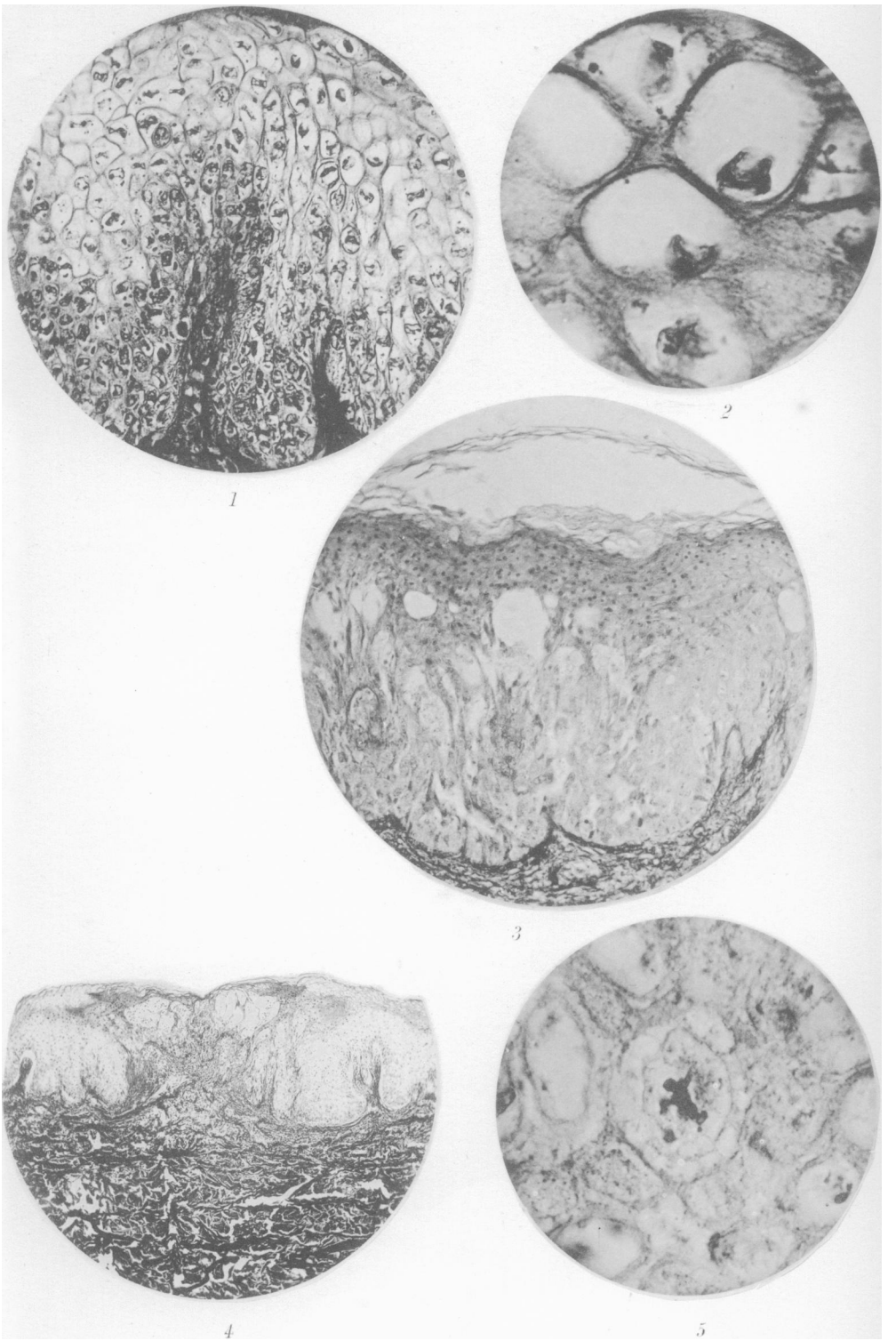
FIGS. 2 and 3. From lymph node showing large basophile cells in sinuses. In the centre of Fig. 2 is a phagocytic cell with cell enclosed in the vacuole. X 1,000.

FIG. 4. Section of bone marrow showing large phagocytic cells in tissue. X 200.

PLATE XIII.

FIGS. 1, 2, and 3. Sections of bone marrow showing groups of phagocytic cells. X 200.

FIG. 4. Three cells of lymphoid type. The cell in the center has the characteristics of a plasma cell. X 1,000.



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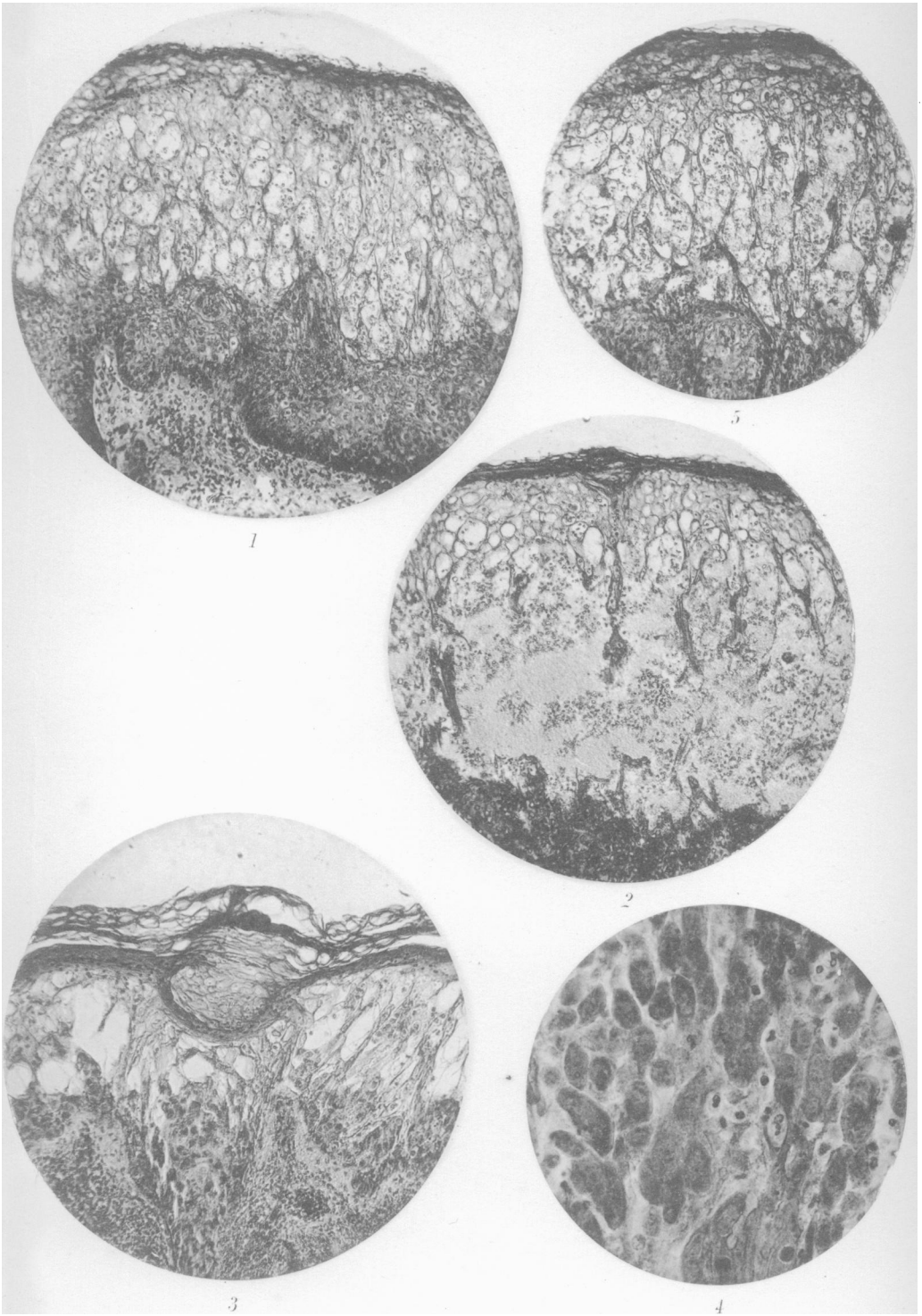

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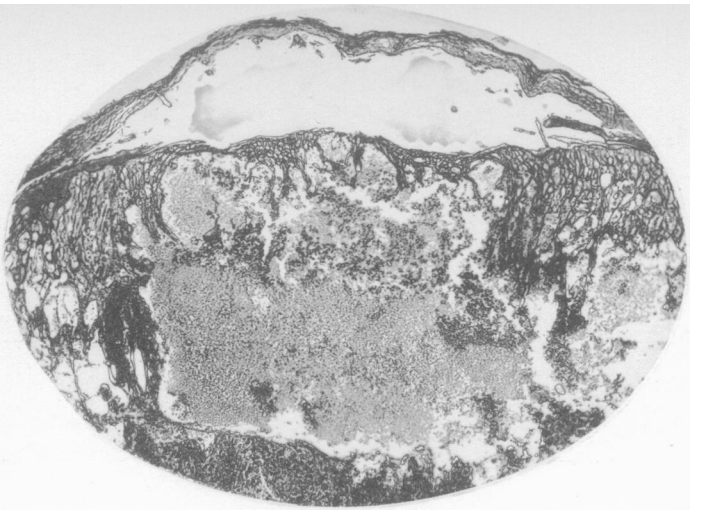

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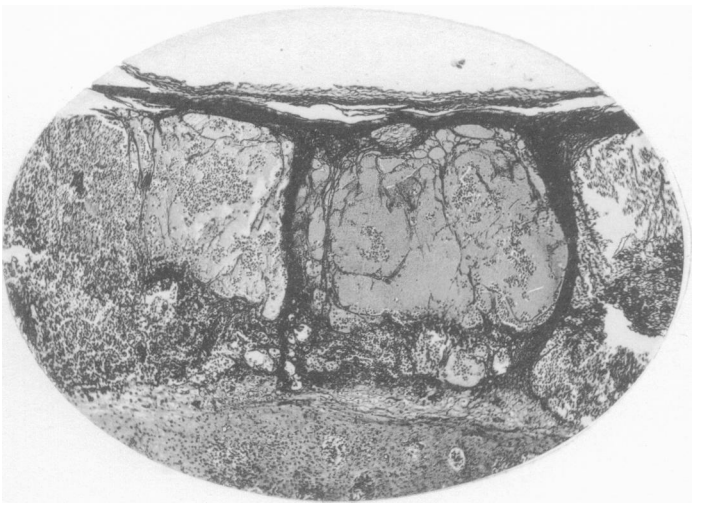

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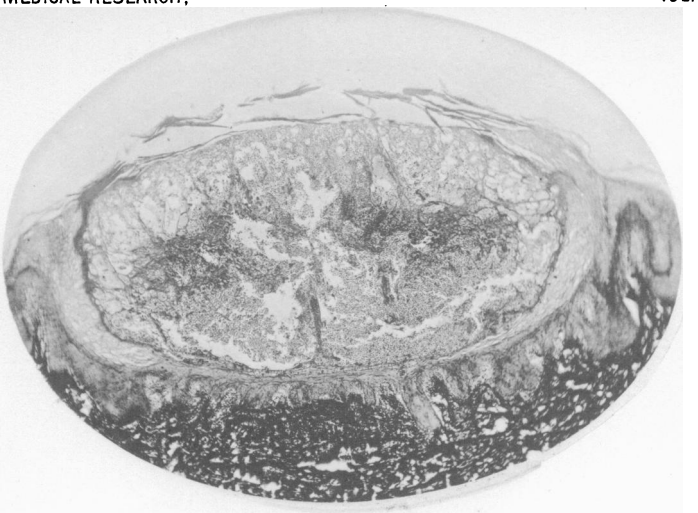

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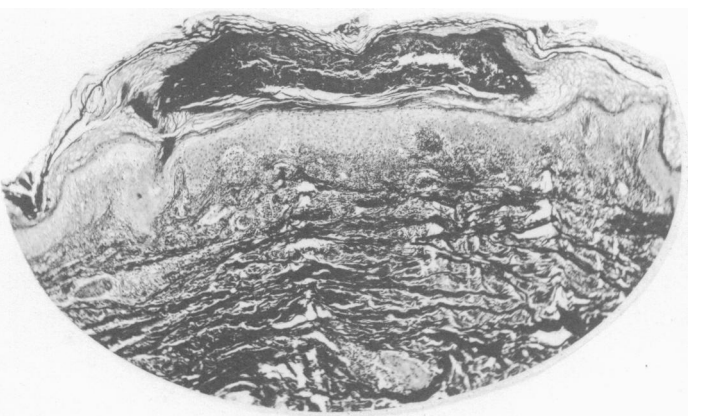

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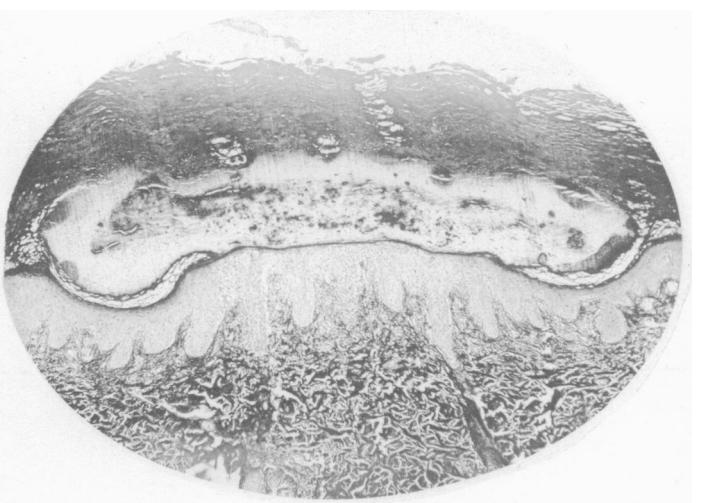

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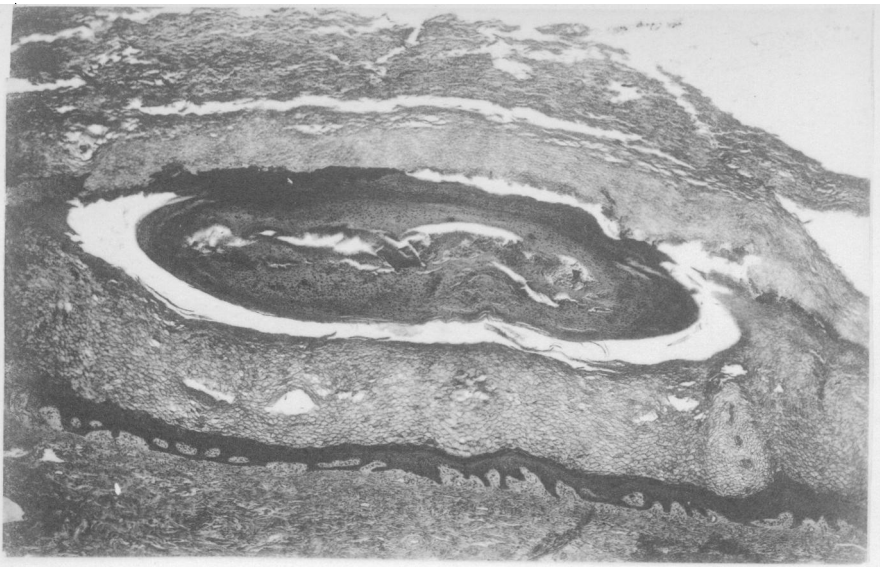

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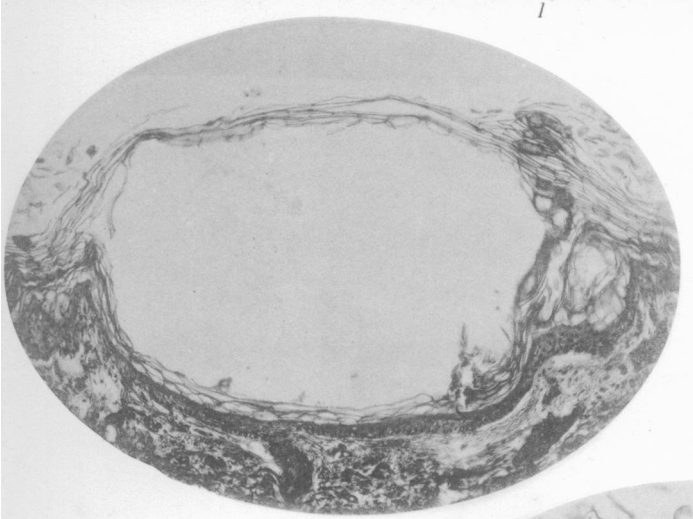

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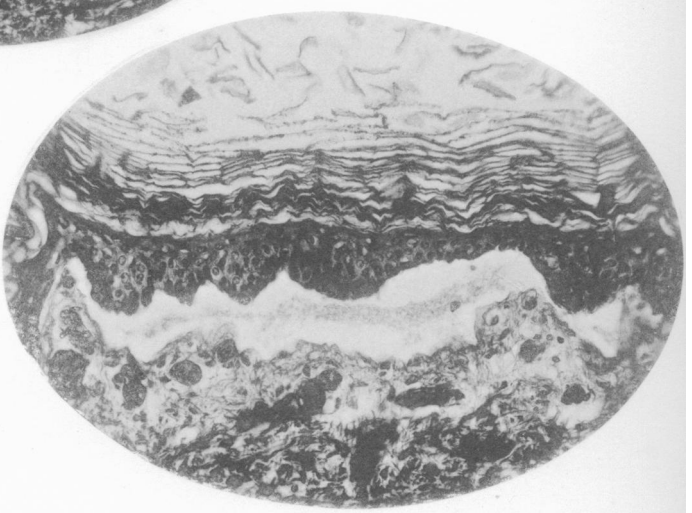

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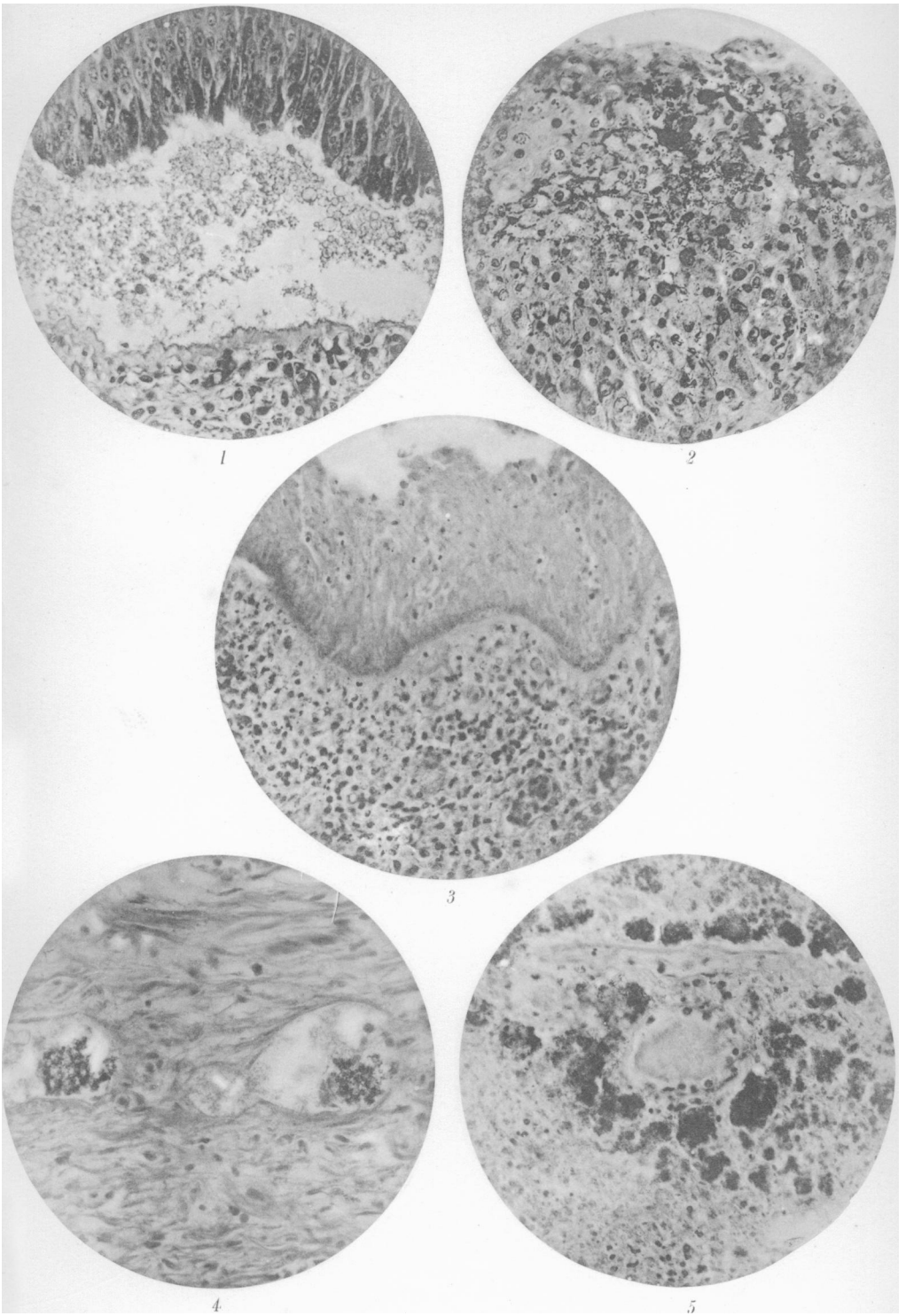

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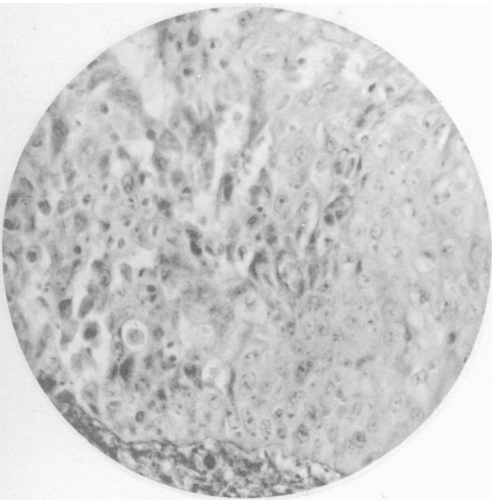

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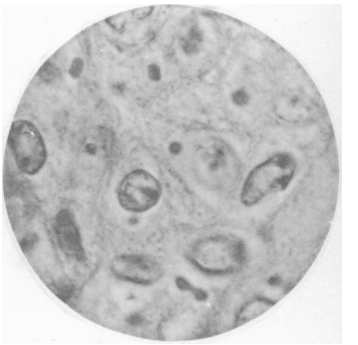

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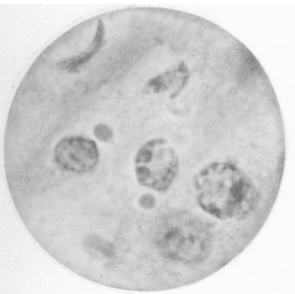

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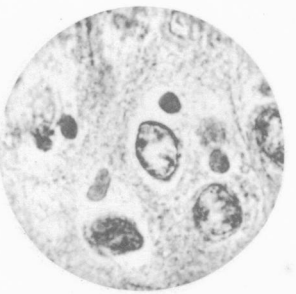

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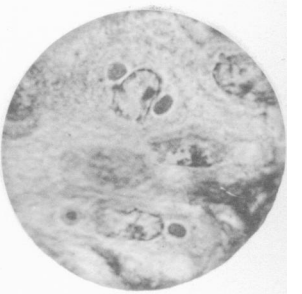

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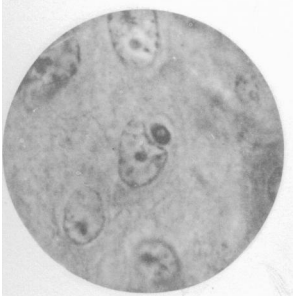

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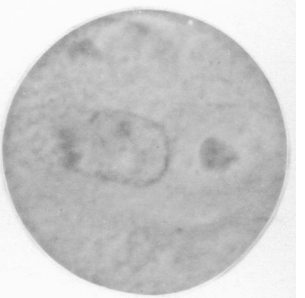

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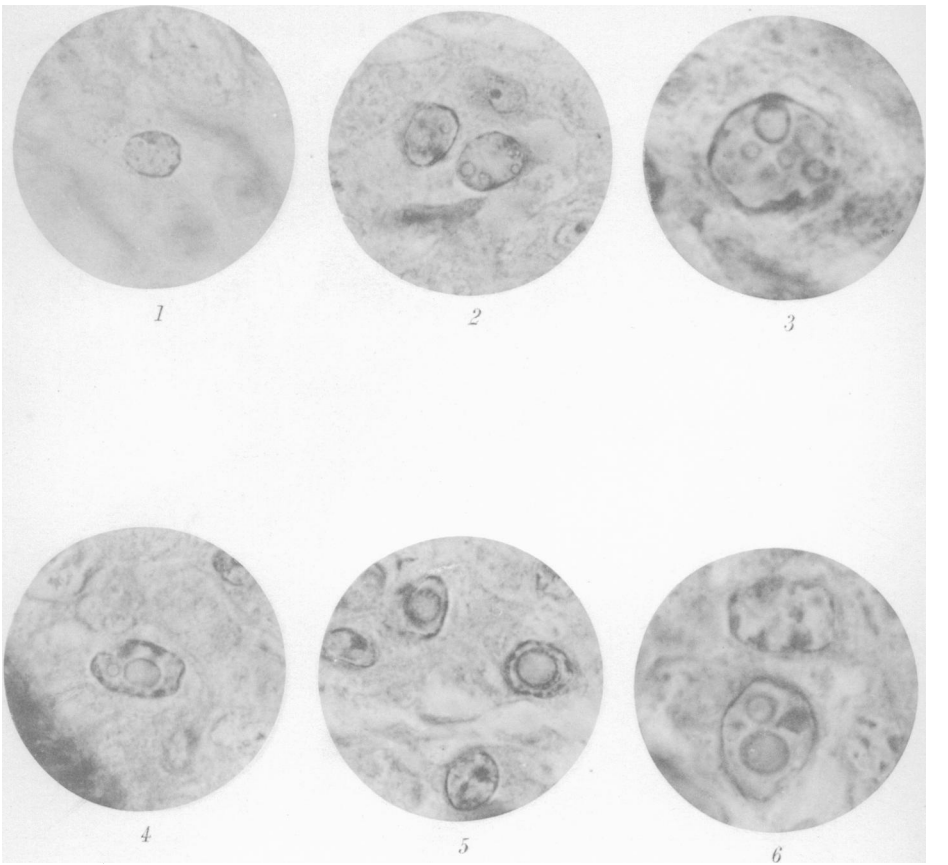

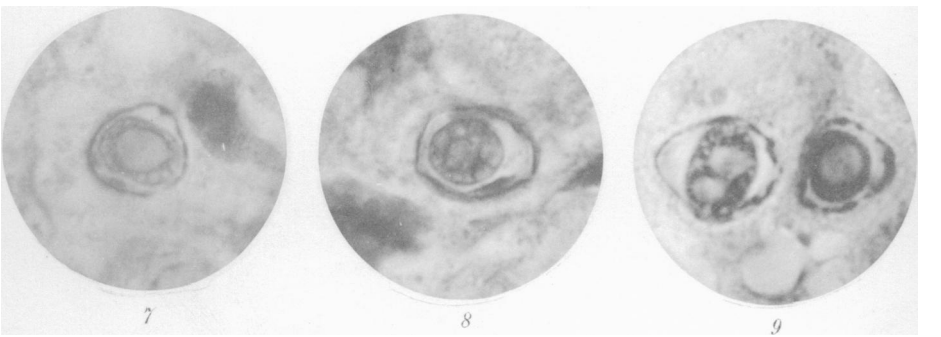

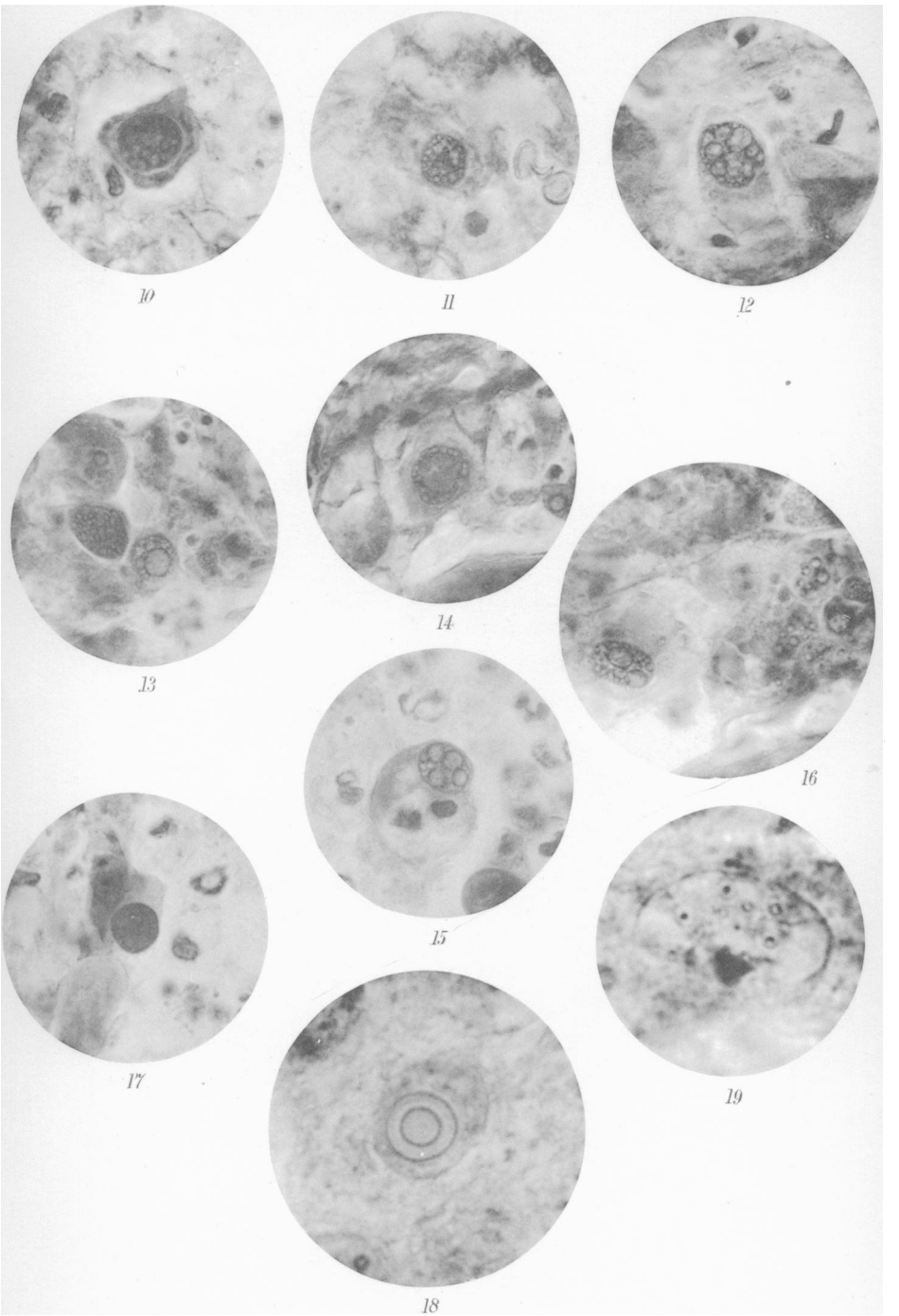

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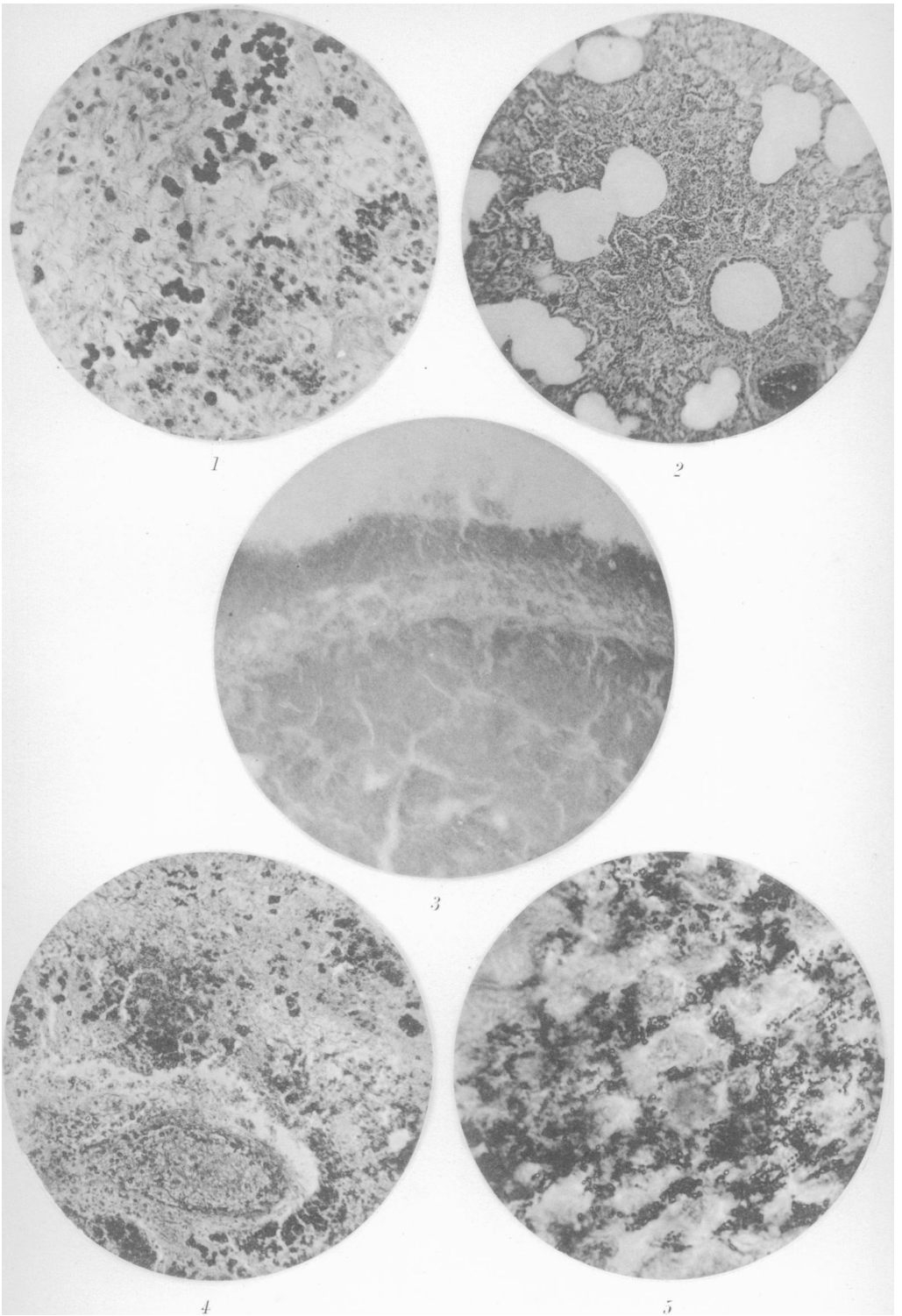

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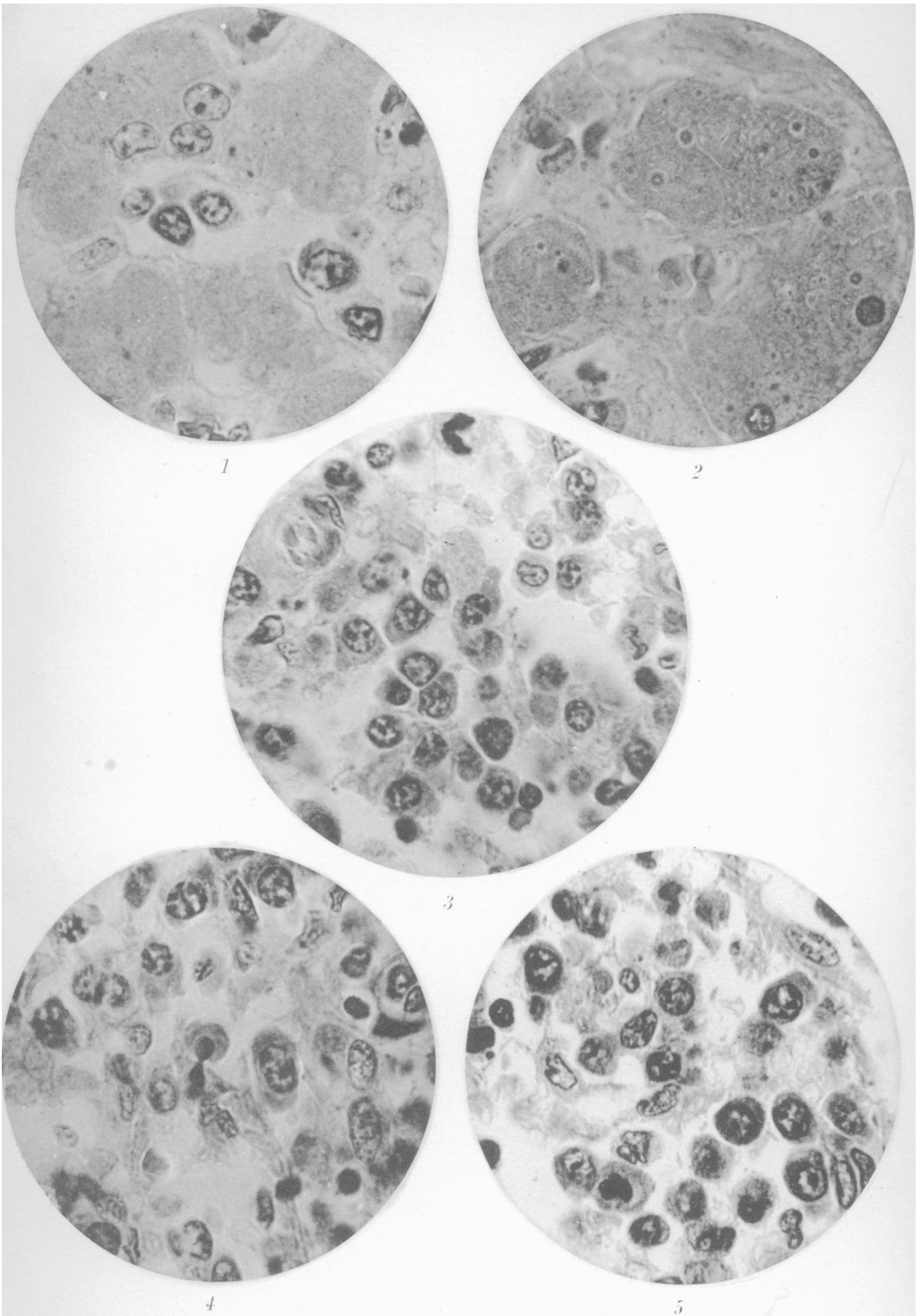

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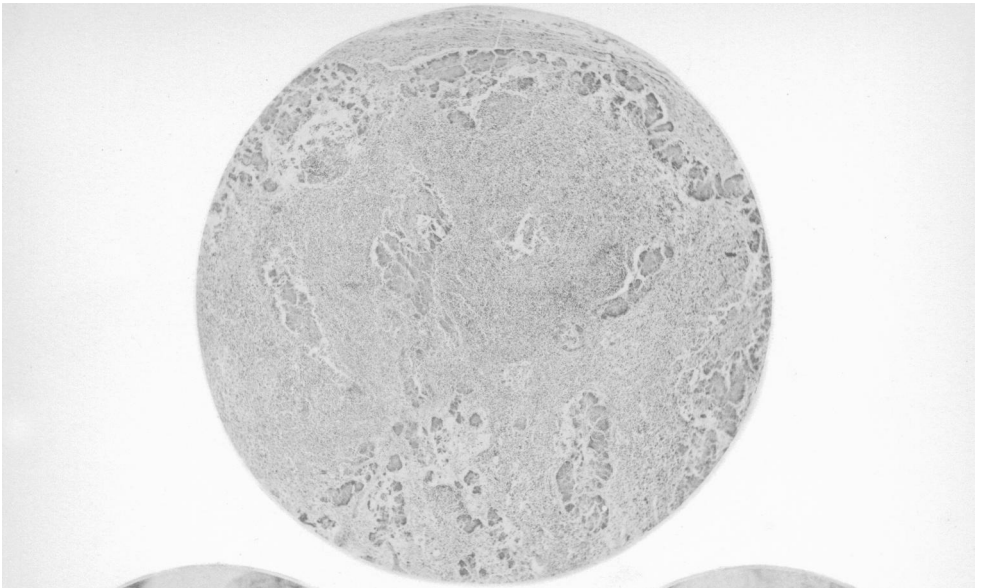

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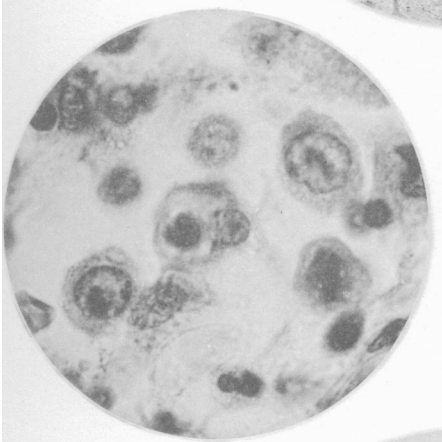

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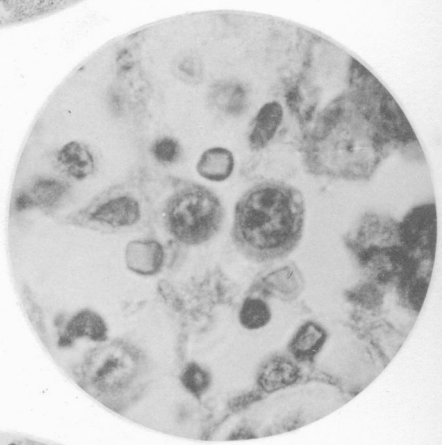

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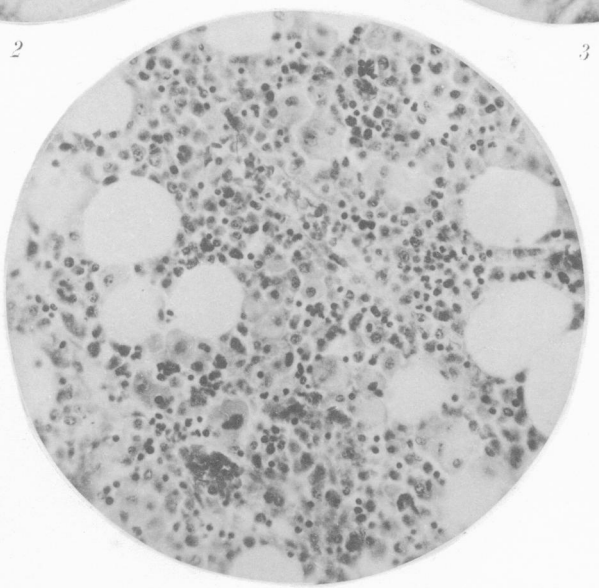

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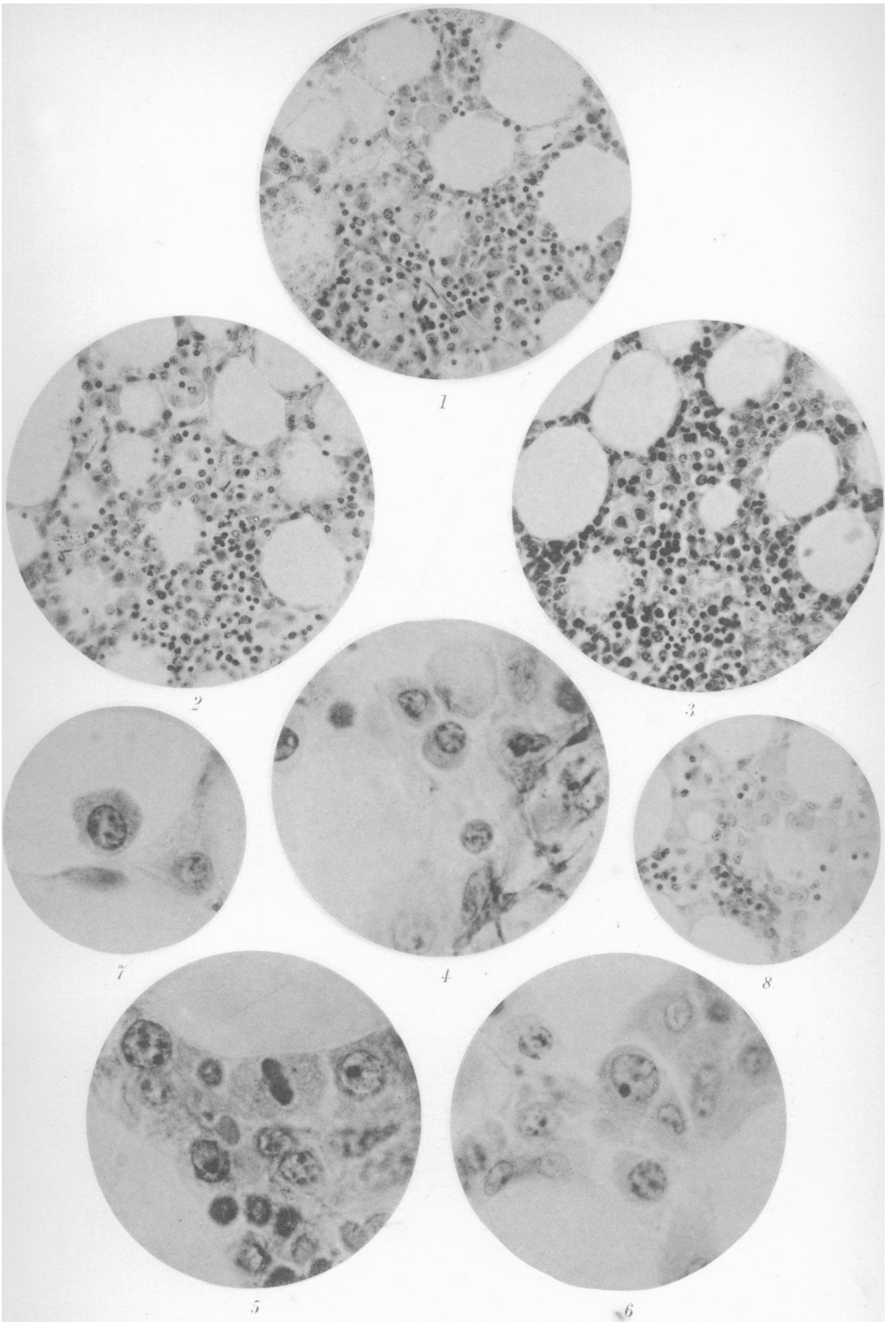

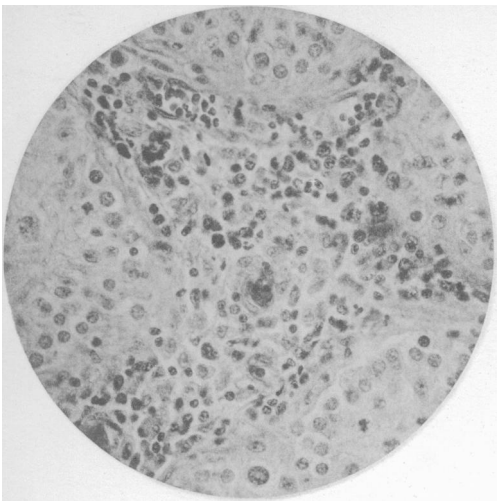

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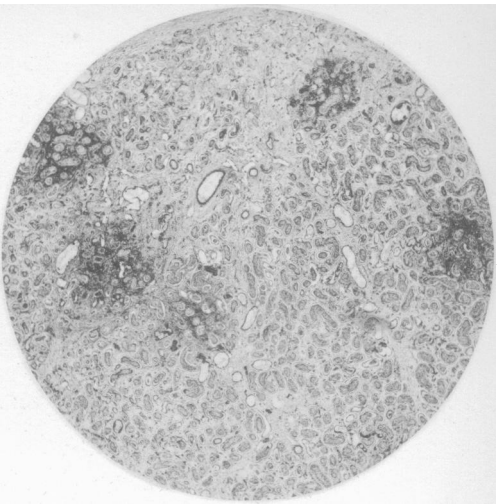

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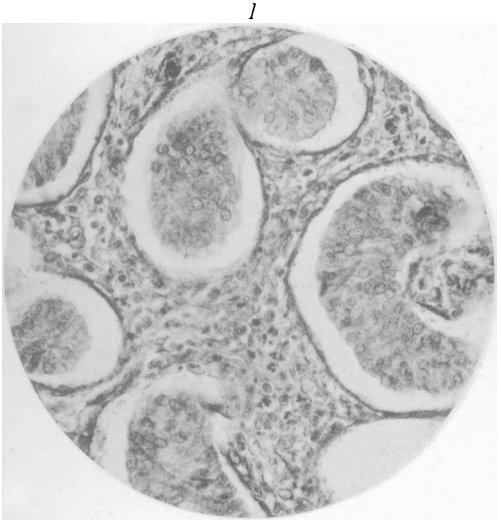

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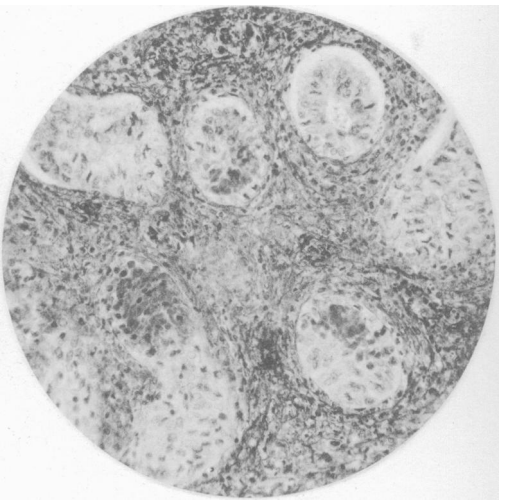

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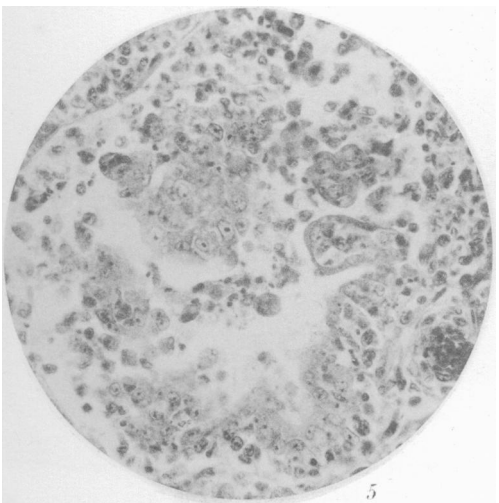

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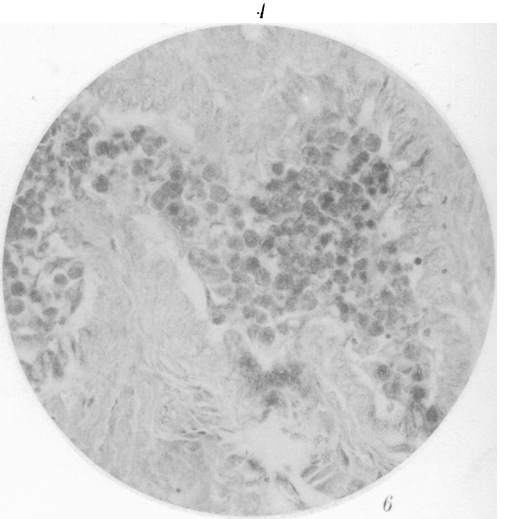
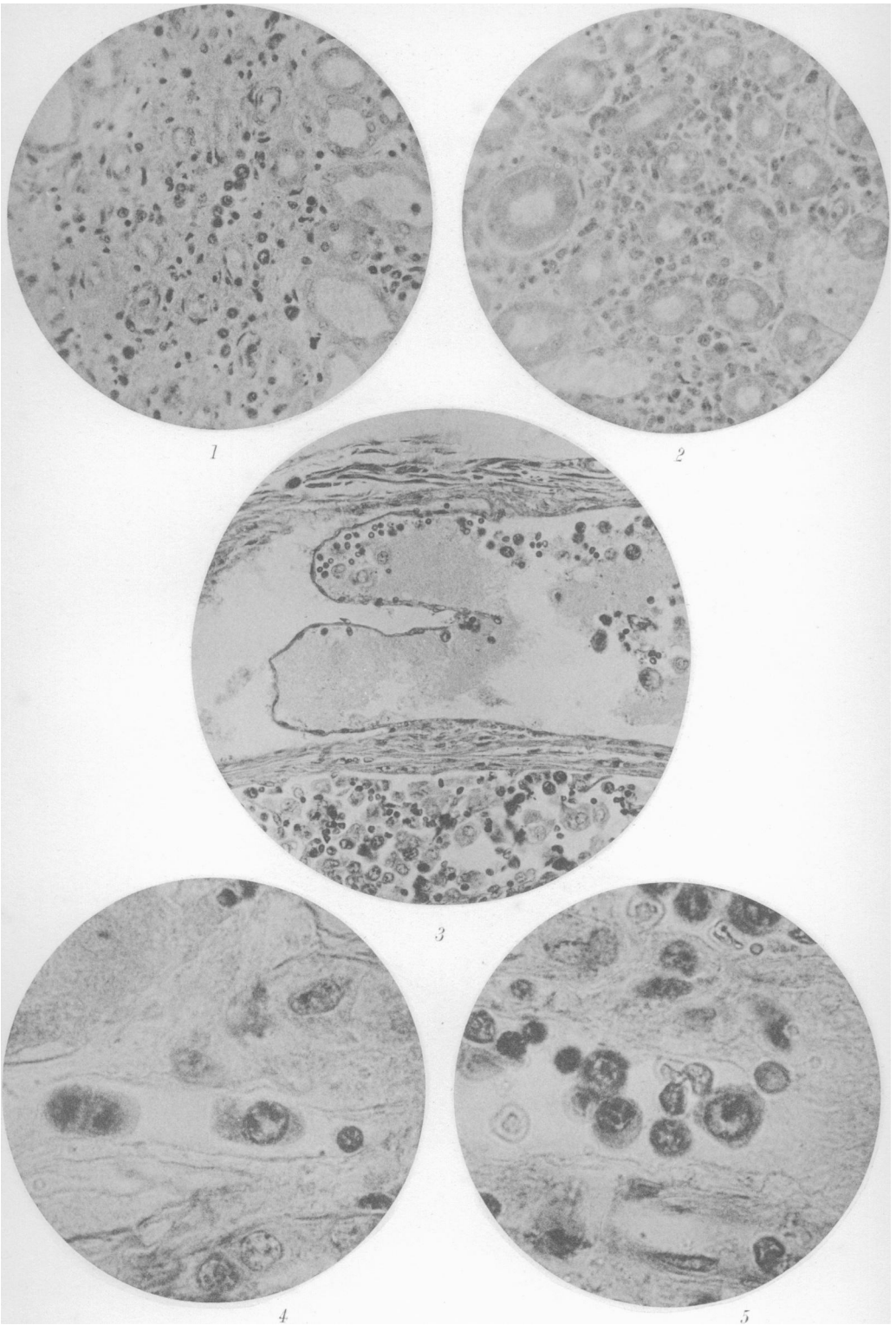


6

Councilman, Magrath and Brinckerhoff — Small-pox

Hollingsworth & Osborne



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Councilman, Magrath and Brinckerhoff Small-pox

FIG. 5. Nuclear figure in premyelocyte. X 1,000.
FIG. 6. Myelocytes. X 1,000.
FIG. 7. Large basophile cell of marrow. X 1,000.
FIG. 8. Group of phagocytic cells around a fat cell. X 200.

PLATE XIV.

FIG. 1. Small lesion in testicle adjoining tunica albugina. The interstitial tissue is dilated, and contains large lymphoid cells. No degeneration in tubules. X 200.

FIG. 2. Several small interstitial foci in testicle with more or less advanced degeneration of epithelium of tubules. X 25.

FIG. 3. From a child's testicle showing area of interstitial infiltration without degeneration of tubular epithelium. X 200.

FIG. 4. More extensive area with fibrin in interstitial tissue and foci of necrosis of the tubular epithelium marked by the darker areas. X 200.

FIG. 5. Cross-section of tubule of epididymis showing infiltration of the tissue with destruction of epithelium. In the lumen of the tubule there are lymphoid and phagocytic cells. X 200.

FIG. 6. Tubule of epididymis filled with large phagocytic cells. X 200.

PLATE XV.

FIG. 1. Section of pyramid of kidney showing cells of lymphoid type in vessels. X 200.

FIG. 2. Small focus of interstitial infiltration in pyramid of kidney. X 200.

FIG. 3. Longitudinal section of lymph node showing afferent lymphatic with valve. Within the lymphatic there are red blood corpuscles, lymphoid, and phagocytic cells. The lower portion of the section shows the peripheral lymph sinus containing phagocytic cells. X 200.

FIG. 4. Capillary in kidney showing two large basophile cells, one of them in mitosis; with typical lymphocyte on the right. X 1,000.

FIG. 5. Section of small vessel in pyramid of the kidney showing varieties of basophile cells. X 1,000.