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A STUDY

OF THE

BACTERIOLOGY AND PATHOLOGY

OF

TWO HUNDRED AND TWENTY FATAL CASES OF DIPHTHERIA

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INTRODUCTION.

Diphtheria may now be considered as the best known of any of the infectious diseases. It enjoys the singular preëminence that its study has in a marked degree increased our knowledge of pathological anatomy, of bacteriology, and of therapeutic measures in infectious diseases. In no other disease has the discovery of the cause led to measures of prevention and of cure which have been rewarded by such brilliant success.

The literature of the disease is enormous. Since the first pefinite description of the disease by Bretonneau, in 1826, there have appeared numerous articles on the pathological anatomy, on the relation of bacteria to the disease, and finally on the nature of the curative substances produced in the disease and the means of their artificial production. It is possible to select from the literature a comparatively small number of articles, each one of which represents an important increase in our knowledge of the disease, and by which the development of our knowledge may be traced, namely: First recognition of the disease, Bretonneau; its recognition clinically as a specific, contagious disease, Trousseau; anatomical investigation of the membrane, and its mode of formation, Virchow, Wagner, Weigert, Cohnheim, Nasiloff, Peters; pathological anatomy of remote lesions, Bizzozero, Oertel, Babes; discovery of bacilli, their relation to the disease, and study of experimental lesions, Klebs, Loeffler, Roux and Yersin, Frosch, Welch and Flexner, Flexner, Wright; discovery of antitoxin, Behring, Roux; clinical evidence of value of antitoxin, Welch, Ernst, McCollom.

In the following article but little is added to our knowledge of diphtheria. The matter presented is based on the largest number of cases of diphtheria which have been studied in

detail both anatomically and bacteriologically. In great part the work is confirmatory of results which have been reached by other investigators, but in certain points we have been led to advance views other than those generally held. The detailed examination of the cases and the comparison of the results have consumed a great deal of time, a greater amount probably than the value of the work, except to the investigators, would justify. In the histological study of the cases we have derived great assistance from photomicrography by means of which we were enabled to record and use for the purposes of comparison any lesions met with. In photography we have been indebted to Mr. W. R. Brinckerhoff and Mr. F. L. Richardson. We are also indebted to the past and present assistants and internes in the pathological laboratory of the Boston City Hospital and in the South Department; without their hearty coöperation the work would not have been possible.

In the histological examinations we have felt the lack of knowledge of normal histology. This was felt particularly in the study of the changes in the bone marrow, and the material at our disposal has not enabled us to supply this deficiency. In our description of pathological changes of various organs we have ventured to make some suggestions about normal structures and relations of parts which we think simplify the conception of the pathological anatomy. In the lung, for instance, we have introduced the term "acinous pneumonia" to distinguish the pneumonias limited to the group of air spaces into which the terminal bronchus enters. The term is far more descriptive of certain pathological conditions than is "bronchopneumonia."

MATERIAL.

All of the 220 cases on which our work is based have come from the South Department of the Boston City Hospital. This is a hospital of three hundred beds, which is devoted to the infectious diseases of children. It is separate from the main hospital, and except in its general management is a distinct institution. Its patients, nurses, and house-officers do not come in contact with the main hospital. The patients generally are received from the poorer classes and often are brought to the hospital from considerable distances. Quite a number of fatal cases reached the hospital in a moribund condition and died in a few hours. Almost without exception all the cases were treated with antitoxin. The bacteriological diagnosis of diphtheria is thoroughly carried out in the hospital, and in all of the cases which we report the diphtheria bacilli were found. The table gives the age and the duration of the disease. Sex was not considered.

There is considerable uncertainty as to the duration of the disease in these cases. The time was reckoned not from the date of entry into the hospital, but from the onset of the disease as nearly as could be determined from the history. The lack of intelligence in the parents or friends of the children made the time of onset in many cases very uncertain. The ages given can be considered as correct. The oldest cases were two aged sixty-five years each; the two youngest were respectively nineteen days and one month old.

The small square in the upper left hand corner of the table, giving the cases up to ten years of age and up to ten days' duration of disease, includes 113 cases, somewhat over 50 per cent. Sixty-one of the cases were from one to two years old and 40 of these were from one and one-half to two years old. Thirty-seven cases were from two to three years

old. The number of those from four to five years of age was slightly greater than that of those from three to four years of age.

These figures differ somewhat from the following table which Cronemeyer has given of 459 fatal cases:

1–2 years	64
2–3 "	81
3–4 "	61
4–5 "	58
5–6 "	42
6–7 "	26
7–8 "	26
8–9 "	18
9–10 "	12
10–15 "	11
15–20 "	24
20–30 "	8
30–40 "	2

These cases of Cronemeyer from the Kiel Pathological Institute extend from January, 1883, to December, 1887. The diagnosis was not made from bacteriological examination, though that probably is without influence in so large a number of cases.

As a rule the autopsies in our cases were made a short while after death and the tissues were in a good state of preservation. All tissues were rejected for histological examination in which there appeared to be any post mortem change. At the autopsy, routine bacteriological examinations were made from the throat, lungs, heart, liver, spleen, kidneys, and lymph nodes, though this was modified in certain cases. While, in the main, the results obtained from these routine examinations can be regarded as correct, there is no doubt that certain organisms often were overlooked, but the results certainly are correct as regards the presence of diphtheria bacilli and the common pyogenic organisms.

All the cultures were made on slants of blood serum; the material for culture was obtained by searing the surface of

the organs and thrusting a stiff platinum spear (previously heated) into the tissue. In this way some of the fluid and often some of the parenchyma was removed and rubbed over the surface of the medium. This procedure was of course modified in certain situations.

Small pieces of mucous membrane from the throat, and thin sections from the lungs, heart, liver, spleen, kidneys, lymph nodes, and bone marrow, were taken at the autopsy and put into a comparatively large amount of Zenker's fluid, which was changed after a few hours. The tissue remained in this fluid for 24 hours. The tissues were then thoroughly washed in water and hardened in alcohol of increasing strength. Alcohol and corrosive sublimate were used to a less extent for fixation. Various ones of the organs mentioned were frequently omitted from the examination, and in other cases the examination was more extensive, embracing every organ of the body. A sufficient number of organs from cases representing every age and duration of the disease were examined to make sure that no lesions were overlooked. After the tissue was hardened it was cut in paraffin, and the sections stained in various ways. The most satisfactory stains were eosin and alkaline methylene blue, hæmatoxylin and eosin, and the chloride of iron hæmatoxylin and triple (connective tissue) stains recently described by Mallory. In many cases serial sections of the tissues were studied. This is particularly to be recommended in the examination of the lung and kidney. Only in this way can both the character and the topography of the lesions in these organs be accurately ascertained. The anatomical description of the lesions in each organ was written on cards, and from these with the assistance of photomicrographs the lesions in the organ were described. In both lungs and kidneys we have derived great assistance from the photomicrographs of serial sections. By marking the prints and following the same places through we were able to obtain some idea of the usually neglected third dimension.

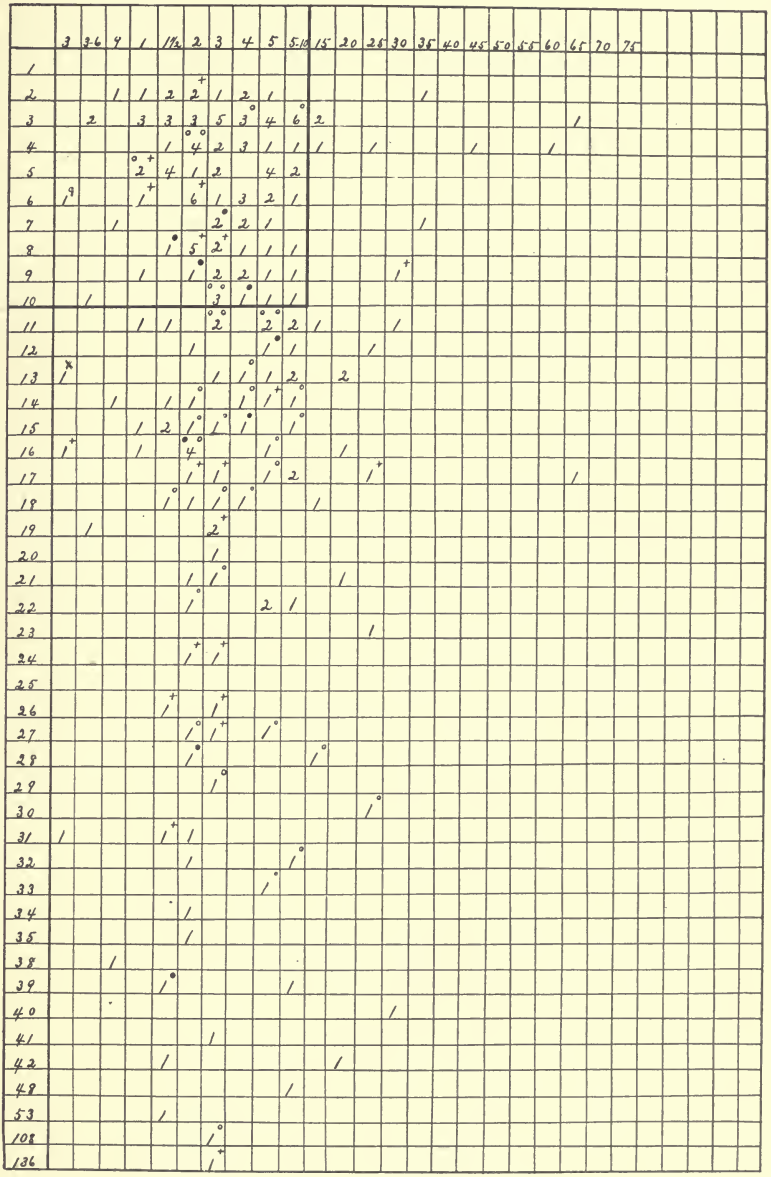
MIXED INFECTIONS.[1]

The largest number of mixed infections was of those with scarlet fever. On the table of cases the 34 cases of this combination are indicated by circles. It will be observed that comparatively few are within the smaller table of 10 squares. In many cases the child was brought to the hospital with evidence of both diseases; in most cases, however, one infection followed the other. The crosses indicate infection with diphtheria and measles, and the solid circles infection with diphtheria, measles, and scarlet fever. What is true of the duration of the cases of scarlet fever is true also of the other infections. If the cases outside of the small square be considered it is seen that these mixed infections occurred chiefly between the ages of two and five years. The small number of cases of these ages in the small square is due to early death from diphtheria and the shorter time given for infection. There is no antagonism between these diseases; if anything, one predisposes to the other. We have made no attempt to consider the pathological anatomy of these mixed infections separately. There were no well-marked differences in the character of the lesions in the cases of pure diphtheria as compared with these mixed infections. In the analysis of the kidney lesions it is seen that certain lesions were more common in the mixed infections, but these lesions were of a more chronic character and the mixed infections were more common late in the disease. The lesions in the organs generally seemed simply to be more accentuated in the mixed infections. The investigations of Pearce on scarlet fever have shown how similar the anatomical changes in this

[1] The clinical records of the hospital show that the large majority of the cases of mixed infection came into the hospital as such. In many of the cases shown on the chart outside of the small square, recovery from diphtheria had taken place and death was due to the other complications.

AGE.

DURATION.



† 1 month old.

× 19 days old.

disease are to those in diphtheria. There were also a number of mixed infections with whooping cough, but these have not been put down in the table. The clinical diagnosis of these mixed infections has been taken in all cases, as there are no lesions on which an anatomical diagnosis can be based. The bacteriology of these mixed infections has been spoken of in another place. There is a greater number of these mixed infections among our cases than has been reported by other writers. Cronemeyer in his analysis of 459 cases found 4 cases in which diphtheria was secondary to scarlet fever, and 7 in which it was secondary to measles.

Mixed infection with tuberculosis. — The frequency with which tuberculosis has been found in connection with diphtheria has attracted the attention of several writers. There does not seem to be any relation between the diseases; the frequency with which tuberculosis is found in autopsies of children is merely an index of the frequency of tuberculosis at an early age. How frequent this disease is is shown by the statistics of Müller in Munich, who found tuberculosis in 41.8 per cent. of all autopsies on children. Berliner found 19 cases of tuberculosis in 107 autopsies on diphtheria in Freiburg, or 17 per cent., certainly a wide difference from the statistics of Müller in Munich. The tuberculous lesions were usually old and as a rule were not influenced by diphtheria. In rare cases, according to Berliner, an eruption of miliary tubercles may be caused by diphtheria, being possibly due to a chemical change in the blood increasing susceptibility. Cohaus in an analysis of 459 cases of diphtheria in Kiel found 95 cases of tuberculosis. He gives the following table of ages:

			Per cent.
22	cases,	1–2 years . . .	23.0
17	"	2–3 " . . .	17.9
13	"	3–4 " . . .	13.6
12	"	4–5 " . . .	12.6
8	"	5–6 " . . .	8.4
8	"	6–8 " . . .	8.4
5	"	8–10 " . . .	5.2
5	"	10–12 " . . .	5.2

		Per cent.
1 case,	12–14 years . . .	1.05
1 "	14–16 " . . .	1.05
1 "	16–20 " . . .	1.05
1 "	20–30 " . . .	1.05
1 "	30–50 " . . .	1.05

Nearly one-half of the cases of tuberculosis could be regarded as definitely healed. In one-third of the cases there was a fresh outbreak of tuberculosis which he attributed to the influence of the diphtheria.

The statistics of Müller show so much larger a percentage of tuberculosis than has been found in the autopsies on cases of diphtheria that it is difficult to explain them.

In nearly all of our cases there were no clinical evidences of tuberculosis and the character of the lesions was not such as would have given rise to symptoms.

Cronemeyer found in 459 cases of diphtheria 60 cases of various forms of tuberculosis, or 13.3 per cent. He thinks that diphtheria both favors new infection with tuberculosis, and fresh extension of old tuberculous lesions, a view which is not favored by the small percentage of cases which he found.

Tuberculosis was found in 35 of our 220 cases, or in 16 per cent. In 3 cases miliary tubercles were found on microscopic examination only. In one case there was tuberculosis of lungs, liver, spleen, œsophagus, intestine, epiglottis, larynx, mesenteric, bronchial, cervical, mediastinal, and axillary lymph nodes, middle ear, temporal bone, and elbow joint. This was in a child one year old, who died two days after entry into the hospital with laryngeal diphtheria. In three cases the lung, liver, spleen, kidney, and mesenteric and bronchial lymph nodes were involved; in one of these cases the cervical lymph nodes, pleura, and pericardium also were involved, and in another there was tuberculous meningitis with a solitary tubercle of the cerebrum. In 3 cases there was healed tuberculosis of the lungs without lesions elsewhere Of the other cases the lung alone was involved in two; lung

with bronchial lymph nodes in two; lung with bronchial lymph nodes and intestine in two; lung with bronchial and mesenteric lymph nodes in two; lung with bronchial and cervical lymph nodes in two; lung with liver in one; lung and mesenteric lymph nodes in one; liver alone involved in one; liver with intestine, and mesenteric and cervical lymph nodes in one; liver with intestine and mesenteric lymph nodes in one; spleen with mesenteric lymph nodes in one; mesenteric lymph nodes alone in seven; mesenteric and cervical lymph nodes in one; mesenteric lymph nodes and intestine in one; bronchial lymph nodes alone in one; cervical lymph nodes alone in one.

It is shown by this analysis that tuberculosis was most frequent in the mesenteric lymph nodes, which were more frequently involved than either the lungs or the bronchial lymph nodes. In 7 cases the mesenteric lymph nodes were affected without tuberculosis elsewhere. In only 6 of the 18 cases of tuberculosis of these lymph nodes was there intestinal tuberculosis. Cronemeyer in his cases found the mesenteric lymph nodes more frequently the only seat of tuberculosis than any other organ in the body; all of these statistics point to the frequency of infection by way of the alimentary canal. The two youngest of these cases were respectively three, and four and one-half months old. In the case three months old the tuberculosis was limited to scattered miliary tubercles in the lungs and liver, and in the four and one-half months' case there was extensive general miliary tuberculosis [1].

In addition to these more common mixed infections the following unusual cases occurred:

1. *Diphtheria after pregnancy.* — March 18, labor took place outside the hospital; manual dilatation and forceps were employed. March 25, patient entered hospital with puerperal septicæmia and with membrane in throat. Diphtheria bacilli found in cultures from throat. Death April

[1] We think that the frequency of tuberculosis in young children without any clinical evidence of its presence is generally underestimated. The rapidly fatal cases of tuberculosis which so frequently follow measles and other infectious diseases are due generally, not to a new infection, but to the extension of an infection which already is present.

9th. Autopsy: Septic endometritis, thrombosis of veins of pelvis and of inferior vena cava, bronchopneumonia. Streptococci in thrombi.

2. *Diphtheria with erysipelas.* — Child five years old, entered with diphtheria. Erysipelas of forehead, scalp, and cheek on fifteenth day. Died on twenty-second day. General blood infection with streptococcus.

3. *Diphtheria in the course of epidemic cerebro-spinal meningitis.* — Child aged six. On the twentieth day of the meningitis developed membrane on pharynx, palate, and uvula. Cultures showed diphtheria bacilli. Died on twenty-third day with acute glomerulo-nephritis and bronchopneumonia.

4. *Diphtheria with typhoid fever.* — Diphtheria not recognized clinically. The autopsy disclosed the following lesions: Bed-sores. Left tonsil swollen, covered with pseudo-membranous exudation; irregular erosion of post-pharyngeal wall. Membrane covering larynx and epiglottis; trachea injected, no membrane. Both lobes of left lung œdematous, congested, with numerous sharply-circumscribed foci of solidification about bronchi. Slight fibrinous exudate over pleura of lower lobe. A few foci of solidification in lower lobe of right lung. Slight fibrinous peritonitis. Spleen enlarged, weight 300 gms., area of necrosis just beneath capsule; over this the exudate is most abundant. One cm. from this necrotic area is an area of suppuration 2 cm. in diameter. Numerous typhoid ulcers in lower portion of ileum. Mesenteric lymph nodes large.

Cultures from the larynx and lungs showed diphtheria bacilli and streptococci. The spleen contains the typhoid bacillus. (This case is not included in the 220.)

5.[1] *Diphtheria with typhoid fever.* — The intestine showed the characteristic lesions of typhoid fever. There was a purulent infiltration of the sub-maxillary and parotid glands, together with a softened thrombus of the external jugular vein, and embolic foci of suppuration in the lungs. Cultures from the purulent infiltration in the neck and from the lungs showed the diphtheria bacillus and the staphylococcus aureus. Microscopical examination of the thrombus showed large numbers of bacilli morphologically identical with diphtheria bacilli, and a few cocci. The abscesses in the lungs had developed around small branches of the pulmonary artery and contained, in large numbers, the same bacilli as the thrombus. There were also in the small branches of the pulmonary arteries emboli composed entirely of these bacilli. It is to be regretted that the thrombus was saved for histological examination and no cultures made from it. The case is an important one in showing an unusual mode of action of the diphtheria bacillus. (This case is not included in the 220 cases.)

6.[2] *Diphtheria, tuberculosis, amœbæ coli.* — Child aged three,

[1] Previously reported (Councilman, Journal Boston Soc. of Med. Sciences, Vol. 1).

[2] Previously reported (Strong, Boston City Hospital Med. and Surg. Reports, 1899).

admitted with laryngeal diphtheria. Was intubed without relief and died on the following day. Autopsy. Characteristic membrane on tonsils, larynx, and trachea. Tuberculous ulcers of ileum, and caseation of mesenteric lymph nodes. Microscopical examination of ulcers showed numerous amœbæ among the cells at the bases of the ulcers.

The following cases as well as case 5 show an action of the diphtheria bacillus very different from that ordinarily found, and bring the bacillus into close alliance with the pyogenic organisms.

7.[1] Jan. 27, 1896, autopsy made on case of diphtheria by Dr. Leary. He was not conscious at the time of any prick or injury of the hand.

February 1 a slight swelling and tenderness around a hair follicle of the middle finger of the left hand. The tissue about the follicle was reddened and slightly swollen. Two days after this a small pin-point pustule developed about the hair. A culture made at this time showed a pure growth of the diphtheria bacillus. The bacilli in culture appeared to be rather larger than the ordinary bacilli, the ends more swollen, and atypical forms were more common than usual. A cover-slip preparation of the contents of the pustule showed cells with a few diphtheria bacilli in them. The finger on February 5 was reddened, a little brawny, scarcely swollen at all. There was nothing in the course of this infection which differed from that of the ordinary pyogenic infections.

Guinea-pig inoculated from the pustule on February 5 died February 7, with the lesions of experimental diphtheria, a great deal of œdema around the seat of inoculation extending down to the belly wall, a fibrino-purulent exudation immediately around the point of inoculation, and on microscopic examination numerous diphtheria bacilli in the pus cells.

8. L. P., employee in the pathological laboratory of the Boston City Hospital, developed a small abscess of the right index finger on the palmar surface. The abscess was opened and the wound healed in a few days. The diphtheria bacillus and the pneumococcus were obtained in the cultures. No inoculation test made.

[1] Previously reported (Leary, Boston City Hospital Med. and Surg. Reports, 1896).

BACTERIOLOGY.

The 220 cases [1] studied in this report may be divided according to the clinical diagnosis into groups, thus:

Group I., 161 cases, diphtheria only.

Group II., 59 cases (diphtheria complicated by scarlet fever 34, by measles 16, or by both 9).

These will be spoken of as Groups I. and II. respectively, and will be taken up in the order mentioned. The bacteriology of the general infections will be considered first, and then that of the various organs and tissues. Each of these divisions will be preceded by a brief review of the literature on the bacteriology of the organ considered.

GENERAL INFECTION.

Frosch was the first observer to note in a series of cases of diphtheria the occurrence of the diphtheria bacillus in the internal organs (heart's blood, liver, spleen, kidney, and lymph nodes). In 1895 he reported that he had found the organism in 10 out of 15 cases which he had examined. Kolisko and Paltauf previously, however, had noted its occurrence in the spleen in 1 case, as had also Schmorl in the cervical lymph nodes in 7 out of 10 cases. Booker in 1 case found the bacillus with the streptococcus in the spleen, lung, submaxillary gland, and heart's blood. Kutscher found it in 1 case in the liver and kidney, and in 8 out of 9 cases in the lung.

Canon found it repeatedly in his post-mortem examination. Kanthack and Stevens found it in the lung in each of 26 cases; in the spleen in 10 out of 21 cases; in the kidney in 2 out of 3 cases. Wright in 14 cases demon-

[1] One hundred and fifty-seven cases have been previously reported (Pearce, The General Infections and Complications of Diphtheria and Scarlet Fever, Med. and Surg. Reports of the Boston City Hospital, 9th series, 1898; also Journal of the Boston Soc. of Med. Sciences, March, 1898).

strated it in the lung 13 times; in the liver 3 times; in the spleen twice; in the cervical and bronchial lymph nodes 5 times; in the mesenteric lymph nodes twice; in the heart's blood once; and in the kidney once. In 7 of these cases there was also a general streptococcus infection. Wright and Stokes in a later series of cases reported 31 cases in which the diphtheria bacillus was found in the lung 30 times; in the liver 9 times; in the mesenteric lymph nodes 7 times; in the spleen and heart's blood each 5 times; in the cervical lymph nodes 4 times; in the brain and bronchial lymph nodes each twice. The streptococcus was present in 20 cases, and the pneumococcus or the staphylococcus pyogenes aureus in 5 cases. Stokes, in 9 cases treated by antitoxin, found it in the lung 9 times; in the kidney 4 times; in the heart's blood and spleen, each once. Nowak in 22 fatal cases found the streptococcus in the internal organs in 21. In 9 of these cases it was associated with the diphtheria bacillus, and in one with a bacillus resembling it except in virulence. Genersisch in the examination of 25 cases of septic diphtheria did not always find the streptococcus in the blood or internal organs, and thinks that the diphtheria bacillus alone can produce the so-called septic symptoms. Reiche in examining 42 fatal cases found streptococci and staphylococci in 64.3 per cent.; streptococci alone in 45.2 per cent.; and the diphtheria bacillus alone twice. Stephens and Parfitt report 3 fatal cases, one with a general infection with the streptococcus and the diphtheria bacillus; the second with the diphtheria bacillus alone; and the third with the diplococcus lanceolatus. In the second case the bacilli were demonstrated in cultures from the blood during life. Flexner and Babes have each in 1 case demonstrated a general infection with the diphtheria bacillus. Dahmer states that he has found the streptococcus in the blood of diphtheria patients in about 50 per cent. of the cases which he has examined. Out of 36 cases he found it in the heart's blood and spleen in 17; in the lung in 30. In 10 of the latter it was associated with staphylococci. He kept no record of the occurrence of the diphtheria bacillus. Mya found the diphtheria bacillus in

the spleen in 2 cases. Infection with the streptococcus and pneumococcus he found, however, to be more common.

In inoculation experiments with guinea-pigs Wright found the diphtheria bacillus 19 times in 155 livers, 15 times in 152 spleens, 4 times in 151 kidneys, and 7 times in the blood of 153 hearts. Abbot and Ghriskey found that by inoculating the testes of rabbits with diphtheria bacilli, small bodies made up of leucocytes and diphtheria bacilli were found in the omentum. Zarniko in a few cases found diphtheria bacilli in the necrotic foci in the liver in animals inoculated with that micro-organism.

Group I. — In this group cultures were taken in all except 8 cases from the heart's blood, liver, spleen, and kidney. The results are as follows:

Heart's blood; the diphtheria bacillus was found 7 times; 3 times alone; twice with the streptococcus; and twice with the staphylococcus pyogenes aureus: the streptococcus alone 22 times; with the pneumococcus once: the pneumococcus alone once: the stapylococcus pyogenes aureus alone 3 times.

Liver; the diphtheria bacillus 30 times; alone 16 times, with the streptococcus 14 times: the streptococcus alone 24 times: the staphylococcus pyogenes aureus alone twice; with the pneumococcus twice: the pneumococcus and the staphylococcus pyogenes aureus alone each 3 times.

Spleen; the diphtheria bacillus in pure culture 16 times; with the streptococcus 3 times: the streptococcus alone 32 times; with the staphylococcus pyogenes aureus once: the pneumococcus in pure culture 3 times: the staphylococcus pyogenes aureus 3 times.

Kidney; the diphtheria bacillus alone 17 times; with the streptococcus 8 times; with the staphylococcus pyogenes aureus twice: the streptococcus alone 27 times; with the staphylococcus pyogenes aureus twice; with the diplococcus lanceolatus once: the diplococcus lanceolatus in pure culture 7 times: and the staphylococcus pyogenes aureus in pure culture 7 times.

Group II. — Cultures were made in all but 3 cases.

Heart's blood; the diphtheria bacillus alone once; with

the streptococcus 4 times: the streptococcus alone 11 times; with the diplococcus lanceolatus once: the staphylococcus pyogenes aureus alone twice.

Liver; the diphtheria bacillus alone 5 times; with the streptococcus 7 times: streptococcus alone 15 times; with the staphylococcus pyogenes aureus 3 times.

Spleen; the diphtheria bacillus alone 5 times; with the streptococcus twice: the streptococcus alone 17 times; with the staphylococcus pyogenes aureus once; the latter alone once.

Kidney; the diphtheria alone 7 times; with the streptococcus 5 times: streptococcus alone 13 times; with the staphylococcus pyogenes aureus 3 times: the latter microorganism alone 3 times; and with the pneumococcus once: the pneumococcus alone once.

In taking cultures from these organs the amount of material used to inoculate the culture medium (Loeffler's blood serum prepared by the Councilman and Mallory method) was that which would adhere to the sides of a sterilized flattened platinum needle thrust into the organ after its surface had been burned. In the case of the heart's blood the needle was thrust into the right auricle after burning the surface and before the large vessels were cut, or into the blood which escaped on cutting the inferior vena-cava. Thus it will be seen that a comparatively small amount of material was used for inoculation. In most cases, nevertheless, the growth of the diphtheria bacillus was fairly abundant, generally from 3 to 15 colonies on each tube, but sometimes many more. Cultures from the liver sometimes showed as many as 25 to 35 colonies. The spleen cultures never showed more than 9 colonies. The kidney cultures in 2 cases showed 19 and 24 colonies respectively. In some cases the growth was only in the water of condensation. This was especially true in cultures from the heart's blood, in which in only 2 cases were there distinct colonies on the surface of the serum. We agree with Kanthack and Stephens, and Flexner that the bacilli can be found when only the usual amount of material for the culture is used. Most observers consider it necessary

to use a large amount of material in order to demonstrate the presence of the bacillus at all. In some of the cultures from these organs involution or degenerate forms were present in considerable numbers.

The clinical significance of this general infection with the diphtheria bacillus is not apparent. It occurred generally but not always in the gravest cases or in those known as septic cases. In this series of fatal cases the number of infections with the streptococcus was but slightly greater than that with the diphtheria bacillus.

Whether the diphtheria bacillus does or does not continue to produce the toxic products wherever it may be in the blood or internal organs it is impossible to say, but from the number of fatal cases with such an infection it would seem very probable that it does. Kanthack and Stephens incline to this opinion, and as previously stated, Genersisch believes many of the so-called septic cases to be due to such an infection, independently of the streptococcus.

In comparing Groups I. and II. the general infection with the diphtheria bacillus appears to be about equal; thus Group II. with 59 cases has about the same percentage of cases in which this bacillus was found as Group I. with 161 cases. General infection with the streptococcus, however, is comparatively more frequent in Group II. This is not surprising, for the streptococcus is the micro-organism most commonly found in a general infection in scarlet fever. Pearce [1] in a recent study of 21 cases of scarlet fever found the streptococcus in 9 out of 11 cases having a general infection.

PERICARDIUM.

Acute sero-fibrinous pericarditis occurred twice in each group. The streptococcus was found in all 4 cases, but associated with the pneumococcus in 1 case of Group II.

In Group I. occurred 1 case of acute purulent pericarditis also due to the streptococcus.

[1] Pearce, R. M. Scarlet Fever: Its Bacteriology, and Gross and Minute Anatomy, Med. and Surg. Reports Boston City Hospital, 10th series, 1899. Also Jour. Boston Soc. of Med. Sciences, Vol. 3, p. 161.

ENDOCARDIUM.

Acute ulcerative endocarditis. — Group I., 2 cases. Group II., 5 cases.

But 2 cases of endocarditis in which the bacillus of diphtheria has been found in the vegetations are on record. The first was that of Howard, who cultivated from the valvular vegetations in the heart and from infarcts in the spleen and kidney a bacillus identical with the diphtheria bacillus in everything except virulence. Wright reports a case in which the aortic and tricuspid valves were affected and in which cultures showed the diplococcus lanceolatus, the staphylococcus, and a bacillus corresponding to the diphtheria bacillus except that it was non-pathogenic for guinea-pigs.

In one case of the Group I. the streptococcus was obtained in pure culture; in this case there existed a general streptococcus infection. In the other case cultures were sterile.

In a case of Group II., on the mitral curtain was a reddish-gray, soft, clot-like mass firmly adherent to the free edge of the valve. Cultures from this mass showed a pure growth of the diphtheria bacillus. Sections of the vegetation showed fibrin with pus and coagulated material, and here and there single bacilli which resembled those of diphtheria, but no clumps of bacilli. There were also a few cocci in indefinite arrangement. This was a case of scarlet fever with diphtheritic rhinitis, tonsilitis, and laryngitis, with bronchopneumonia of both lungs, and marked general lymphatic hyperplasia. The diphtheria bacillus was also present in the heart's blood, liver, spleen, and kidney. In a second case of this group cultures were sterile and in the other three none were taken.

LUNG.

Thaon (1885) appears to have been the first investigator to study the relation of the diphtheria bacillus to the bronchopneumonia of diphtheria. He demonstrated in histological preparations the relation of the bacilli to the inflammatory process. Various cocci were usually associated with the diphtheria bacillus.

In this same year Darier also reported the diphtheria bacillus associated with the streptococcus in 1 case. In 3 other cases which he reported at the same time the streptococcus was present in pure culture in 1, and with the staphylococcus aureus and albus in 2.

The presence of diphtheria bacilli in this complication of diphtheria has been reported by many observers, some of whom consider it to have an etiological relation, while others believe the associated cocci to be of more importance. It is of interest in this connection that Loeffler in his study of the bacteriology of diphtheria (1884) reports the presence of the diphtheria bacillus in the lung, but explains it as a post-mortem invasion.

In the earlier reports the diphtheria bacillus was not found very often and seldom in pure culture. Thus Strelitz (1891) found it in 1 out of 8 cases. In the others the streptococcus, the pneumococcus, and various staphylococci were found. Flexner (1893) found the pneumococcus in 2 cases, in 1 of which it was associated with the diphtheria bacillus. Its presence was confirmed histologically. In 3 cases Mosny (1891) found the streptococcus, associated in 1 with the diphtheria bacillus. The latter organism has also been reported by Johnson (1891) and Booker (1893) in single cases; by Kutscher (1894) in 8 out of 9 cases, sometimes alone, but generally with the streptococcus or staphylococci; and by Frosch (1893), who found it more frequently in bronchopneumonic foci than elsewhere in the internal organs. All his cases appear to have been mixed infections.

Netter (1892) in 7 cases found the streptococcus in all, and the diphtheria bacillus in 4. Mya has found the diphtheria bacillus twice in the lung, but considers the streptococcus and pneumococcus to be the micro-organisms more frequently present.

Horton-Smith (1897) in 2 cases found the diphtheria bacillus, associated with the pneumococcus and the streptococcus in one, and with the former only in the other.

Among those investigators who have found the diphtheria bacillus in a large number of cases are the following:

Wright and Stokes (1895), who found it in 18 of 19 cases, in 8 of which it was in pure culture, in 5 associated with the streptococcus, and in the others with various combinations of the pyogenic cocci and the pneumococci. The streptococcus occurred alone in 1 case. They believe that the diphtheria bacillus can cause a bronchopneumonia.

They also found the diphtheria bacillus in the lung in 12 cases in which no bronchopneumonia was present. Belfanti reports 26 cases, in 21 of which he found the diphtheria bacillus; in 4 it was in pure culture. The streptococcus occurred in 20 cases, the staphylococcus aureus in 10, the pneumococcus in 3. He concludes that the diphtheria bacillus either alone or associated with the other micro-organisms may cause bronchopneumonia.

Kanthack and Stephens (1897) found the diphtheria bacillus in the lung in 26 cases, in 15 of which bronchopneumonia was present. Various cocci were also present; but they believe the bronchopneumonia of diphtheria to be not of pyococcal origin but a true diphtheritic process.

On the other hand, some investigators have found the diphtheria bacillus seldom or never present.

Sims Woodhead (1895) in 50 post-mortem examinations found it in the lung in only 5 cases. Northrup and Prudden (1889) in an analysis of 17 cases found the streptococcus in all (in pure culture in 4), the staphylococcus aureus in 13, the diphtheria bacillus in none.

Woolstein in 14 cases of bronchopneumonia secondary to diphtheria, scarlet fever, and measles found the pneumococcus in 11. In 2 it occurred in pure culture; in the others it was associated with the pyogenic cocci.

In our 220_1 cases bronchopneumonia was recognized macroscopically in 131. Ninety-eight of these were in cases

[1] A portion of these cases have been previously reported:

Pearce. The General Infections and Complication of Diphtheria and Scarlet Fever. (A bacteriological study of 157 cases.) Journal Boston Soc. Med. Sci., March, 1898.

Pearce. The Bacteriology of Lobar and Lobular Pneumonia. Boston Med. and Surg. Journal, Dec. 21, 1897.

of diphtheria only (Group I.); and 33 were in cases of diphtheria complicated by scarlet fever, or measles, or by both.

Group I., 98 cases. No cultures taken in 10 cases, cultures sterile in 6. Of the remaining 82 cases the bacillus of diphtheria was present in 49; the streptococcus in 51; the staphylococcus pyogenes aureus occurred in 27 cases; and the pneumococcus in 10. The diphtheria bacillus occurred alone in 15 cases; with the streptococcus in 17; with the streptococcus and the staphylococcus aureus in 5; with the latter alone in 6; with the pneumococcus in 4; and in the other cases with various combinations of the above. The streptococcus was found alone 15 times; with the staphylococcus aureus 11 times; and with the diplococcus lanceolatus twice. This last micro-organism occurred alone once; the staphylococcus aureus occurred alone 3 times.

In the 10 cases in which no cultures were made sections were stained and examined for micro-organisms. The following results based on morphological characteristics were obtained: In 3 cases the streptococcus was found; in 2 the diphtheria bacillus; in 1 the diphtheria bacillus and the pneumococcus.

In 17 cases of Group I., cultures were taken from the lung, although no inflammatory process was present. In 7 cases with œdema and congestion, the diphtheria bacillus was found alone in 3, and with the streptococcus in 2; the pneumococcus alone once, and with the streptococcus once; the streptococcus with the staphylococcus aureus once, and with the staphylococcus albus once; the streptococcus and the staphylococcus aureus each alone once.

In 3 cases in which small bronchi contained diphtheritic membrane without evidence of bronchopneumonia, cultures contained the diphtheria bacillus. In 2 of these cases the streptococcus was also present, and in 1 the staphylococcus aureus. In a lung with slight diffuse hæmorrhage, the diphtheria bacillus was found; in 1 with tuberculosis the pneumococcus; and in 2 with infarcts the staphylococcus aureus.

Group II., 33 cases. The cultures were sterile in 2, and not taken in 9 cases. In the remaining 22 cases the diphtheria bacillus was present in 20, the streptococcus in 16, the staphylococcus aureus in 10. The diphtheria bacillus occurred alone twice, with the streptococcus 9 times, with the staphylococcus aureus 4 times, and with both 5 times. The streptococcus occurred alone once, and with the staphylococcus aureus once. In 2 of the 4 cases in which cultures were not taken, the pneumococcus and the streptococcus were found each in one case upon histological examination.

In this group cultures were taken in 5 cases from lungs showing only œdema and congestion. The diphtheria bacillus was found in 3 cases, associated in 2 with the staphylococcus aureus, and in 1 with the streptococcus. In the other 2 cases only the streptococcus was found. In the sixth case with an organizing pneumonia, the pneumococcus and the bacillus pyocyaneus were found.

No marked difference is seen between the results in Group I. and Group II. The various organisms occur with about the same frequency. The observation of several investigators that bronchopneumonia is generally due to a combination of bacteria is supported by the results in both groups.

Abscesses of the lung. — These were small, often multiple, and occurred in 7 cases of Group I., and in 4 cases of Group II.

In Group I. the diphtheria bacillus was found 3 times; twice with the streptococcus, and once with the staphylococcus aureus. In the other 4 cases the streptococcus and the staphylococcus aureus each occurred alone in one case, and combined in 2 cases.

In Group II. the streptococcus was found alone in 3 cases, and associated with the diphtheria bacillus in one.

PLEURAL CAVITIES.

Empyema. — Group I., 5 cases. The staphylococcus pyogenes aureus was present in one; the streptococcus alone in 2; and associated with the diphtheria bacillus and the staphylococcus aureus each in one. The cause of the

empyæma in this last case was the rupture of a small abscess near the surface of the lung into the pleural cavity. In cultures from other abscesses in the lung the same micro-organisms were obtained.

Group II., 2 cases. In both the streptococcus was present; in one in pure culture, in the other associated with the diphtheria bacillus. In this second case, which had been operated upon, there was a ruptured abscess cavity on the surface of the lung.

The only reference to the occurrence of the diphtheria bacillus in inflammatory conditions of the pleura is that of Frosch, who found it not only in a pleural but also in a pericardial exudate.

Sero-fibrinous pleurisy. — Group I., 18 cases. Unfortunately cultures were taken in only 6 cases. In these the streptococcus occurred alone in 3 cases, the diplococcus lanceolatus alone in 1, the staphylococcus aureus alone in 1, and with the streptococcus in 1 case.

Group II., 5 cases. In 3 cases the streptococcus was present, twice in pure culture and once with the diplococcus lanceolatus. In 1 case the latter micro-organism alone was present.

MEDIASTINUM.

Acute suppurative mediastinitis occurred in 2 cases of Group II. It was due in one case (diphtheria with measles) to the ulceration and perforation of the larynx as the result of intubation. The area of suppuration was most marked from the third to the sixth costal cartilages. There was a rupture of the sternum at the articulation of the fourth costal cartilage, and the fourth and fifth cartilages were free. Streptococci were found in cultures from the pus; on both sides there was a streptococcus pleuritis.

In the second case (diphtheria with scarlet fever) it was associated with acute bronchopneumonia and sero-fibrinous pleuritis and pericarditis. The streptococcus was found in all these exudates, and there was also a general infection with the same micro-organism.

PERITONEUM.

Acute peritonitis occurred in one case of each group. Both were due to the streptococcus. One was associated with the abscess of the spleen mentioned below. In this case there was a general streptococcus infection, abscess of a cervical lymph node, and suppuration of both middle ears.

ACCESSORY SINUSES OF NOSE.

Until within a few years direct extension of an inflammation due to caries of the teeth, with or without necrosis of the maxilla, was considered the most common cause of inflammation of the antra.

It is now known that inflammatory conditions of the nasal mucous membrane, such as coryza, acute and chronic rhinitis, or of the throat, such as tonsilitis or pharyngitis, may involve the antra by direct extension. It is also known that secondary infection by means of the blood may occur in various infectious diseases such as typhoid fever, meningitis, acute articular rheumatism, pulmonary tuberculosis, pneumonia, and suppurative processes in distant parts of the body.

The only writers who have reported the results of the bacteriological examination of a series of more than ten cases are Dmochowski (1895), Hertzfeld and Hermann (1895), E. Fränkel (1896), and Howard (1898). According to these observers the following micro-organisms are found most frequently in inflammatory conditions of the antra: the streptococcus pyogenes, the staphylococcus pyogenes aureus, albus, and flavus, the pneumococcus, the bacillus of Friedländer, the bacillus fœtidus, the bacillus pseudo-diphtheriæ, the bacillus influenzæ, and the bacillus pyocyaneus.

Except in the work of Wolff there are no references to the bacteriological examination of the antra in diphtheria and scarlet fever; nor has the relation of these two diseases to inflammatory conditions of the antra been noted clinically. Some text-books state that disease of the antra may occur in the course of or follow the acute infectious diseases, but in none are diphtheria and scarlet fever considered as im-

portant factors. In looking over the clinical histories of the reported cases of disease of the antrum it is occasionally seen that the symptoms date back to an attack of diphtheria or scarlet fever. Thus Farlow (1898) reports a case of catarrhal disease of the antral, frontal, and ethmoidal cavities coming on gradually after an attack of scarlet fever from which the patient had suffered several years before. The bacteriological examination was negative.

Of the 10 cases of antral disease reported by Hertzfeld and Hermann (1895) one occurred in a child thirteen years old, who had had nasal obstruction since an attack of diphtheria seven years previous. The antrum contained a fairly clear fluid in which were thick brownish thready masses. Cultures showed the staphylococcus pyogenes aureus, a yellow sarcina, and a non-pathogenic bacillus.

Bryant (1889) states that empyæma of the antrum may occur in the course of the acute exanthemata, particularly scarlet fever and measles.

Sendziak (1898) reports a case of diphtheria of the pharynx and naso-pharynx complicated by numerous abscesses of the tonsils and abscesses of both antra of Highmore. No bacteriological examination is recorded.

Lothrop (1899) states that diphtheria and scarlet fever may cause acute suppuration of the accessory sinuses of the nose.

The only report of a large number of cases with bacteriological examination is that of Wolff (1895). He examined post mortem the accessory sinuses by Shalle's section in 22 cases of diphtheria, 5 of measles, and 2 of scarlet fever, with the following results:

In all of the *diphtheria* cases changes in the antrum were found. Of 15 severe cases the diphtheria bacillus was found in 12. In 2 of these it occurred alone, in 3 was associated with the pneumococcus, in 1 with the streptococcus, in 2 with staphylococcus pyogenes aureus, and in the others with various combinations of these organisms. In the remaining 7 cases a mild catarrhal condition was found. The streptococcus was found alone in 2 cases, and associated with the staphylococcus pyogenes flavus in 1. The pneumococcus occurred alone in 1 case and associated

with the staphylococcus pyogenes aureus in 1. The latter organism was found with the bacillus pyocyaneus in 1 case.

In 7 cases the sphenoidal sinus was involved. In 2 of these a false membrane was found. The bacillus of diphtheria occurred in 6 of the 7 cases, 3 times alone, and in the other 3 cases with the streptococcus, the pneumococcus, and the staphylococcus pyogenes aureus, respectively. In the seventh case the streptococcus and the staphylococcus pyogenes flavus were found.

In 1 case there was an inflammatory œdema of the frontal sinus. Cultures showed the bacillus of diphtheria and the staphylococcus pyogenes aureus.

In 1 of the 2 cases of scarlet fever the antrum of Highmore was involved. Cultures showed the staphylococcus pyogenes aureus and the bacillus pyocyaneus. In this case there was also an inflammatory œdema of the sphenoidal sinus. A culture was not taken. In the second case there were no inflammatory changes, and cultures taken were sterile.

Of the 5 cases of measles examined, cultures from the antrum in 2 showed the streptococcus and the pneumococcus, and in 1 "staphylococci." The sphenoidal sinuses in these cases were not involved.

These accessory sinuses were examined in 63[1] of our cases.

The cases are divided as follows:

I. Diphtheria, 52 cases.
II. Diphtheria complicated by scarlet fever, 7 cases.
III. Diphtheria complicated by measles, 4 cases.

In no case were there any clinical symptoms pointing to disease of the antra or other sinuses. All cases, with the exception of 3, aged nineteen, twenty-two, and twenty-four years respectively, were children. Of the latter, 2 were ten and 1 twelve years old. All others were between two and six years of age. Most of the cases in which the sinuses were invaded died between the fourth and tenth days of the disease; the average was 9 days. The earliest infections occurred in diphtheria on the second and third days after the appearance of the membrane.

Methods. — The nasal sinuses were examined by Harke's section, which consists (after removing the brain) in sawing

[1] Forty-six of these cases have been previously reported: Pearce. The Bacteriology of the Accessory Sinuses of the Nose in Diphtheria and Scarlet Fever. Jour. Boston Soc. of Med. Sciences, March, 1899.

through the base of the skull and forcibly separating its two halves. The frontal and sphenoidal sinuses are thus exposed, and the antra of Highmore are easily reached by chipping away the turbinated bones on either side. This method naturally alters the appearance of the contents of the frontal and sphenoidal sinuses. In this series, however, it has made little difference in the results, for the cases were mostly young children in whom the sinuses were but slightly, or not at all, developed. In those cases in which they were developed, and exudation was found, smears were made at once in order to control the cultures.

In opening the antra the turbinate bones were cleansed as much as possible, and care was taken not to introduce particles of mucus with the knife used to chip away the bone. Cultures were made from the interior of the cavity with a thin platinum needle. Smears for the control of the cultures were also made.

As the chief object of this investigation was to determine the condition of the antra, rather than of the other sinuses, every precaution was taken to prevent contamination of these cavities, and the results here reported are as nearly accurate as is possible by any method of examination. In regard to the frontal, sphenoidal, and ethmoidal sinuses only those cases of infection were accepted as conclusive in which there was a definite exudate and in which the results obtained by smears and cultures were the same.

All primary cultures were made on Loeffler's blood serum.

In some cases the lining membrane of the antrum was removed for histological examination.

Diphtheria. — Fifty-two cases examined. In 33 inflammatory changes were present in the accessory sinuses, as follows:

Both antra, 19.

Both antra, sphenoidal and ethmoidal sinuses, 2; one antrum only, 9; sphenoidal sinuses only, 2; sphenoidal and ethmoidal sinuses, 1.

Of the 21 double antral cases the exudate, on both sides, in 5 was a thick yellow pus; in 3 a seropurulent fluid; in 3

a thin cloudy serous fluid; in 1 a purulent fluid with membrane; and in 8 a thin mucoid fluid.

Excluding for the present the 8 cases with mucoid accumulation, the bacillus of diphtheria was present on both sides in all but 3 cases. In 1 of these 3 cases the streptococcus only was found, and in the other 2 the bacillus of diphtheria on one side and the pneumococcus on the other. In 2 cases the diphtheria bacillus was the only pathogenic organism found; in all others it was associated with one or more of the pyogenic cocci or with the pneumococcus. The streptococcus occurred in 9 cases, the staphylococcus pyogenes aureus in 5, the albus in 2, the pneumococcus in 3, and the colon bacillus in 4.[1]

Of the 8 cases with mucoid accumulation 3 were sterile; 1 contained the streptococcus; 1 the staphylococcus pyogenes aureus; 1 the bacillus of diphtheria alone; and 2 this last organism associated with the pneumococcus and streptococcus respectively.

In 2 of these cases of double anthral empyæma an infection of the sphenoidal sinus was also present. In 1, with a cloudy serous fluid, the streptococcus and the bacillus of diphtheria were found; in the other, with a thick yellow pus, the streptococcus only.

Of the 9 cases with infection of the antrum on one side only, 3 with thin purulent contents contained the bacillus of diphtheria and the staphylococcus pyogenes aureus; 1 with thick purulent contents, the latter organism with the streptococcus and the colon bacillus; 1 with cloudy serous contents, containing shreds of membrane, the bacillus of diphtheria only; and 1 with mucoid contents, a variety of non-pathogenic organisms. In 3 cases no cultures were taken.

In the sphenoidal sinuses of the 2 cases in which that cavity alone was involved a mucoid accumulation was found. Cultures from both showed the presence of the streptococcus.

[1] It is not to be understood that these were the only micro-organisms found. Often non-pathogenic bacteria commonly met with in cultures from the nasal cavities were present. These have been disregarded, for although they indicate that the source of the infection was the nasal cavity, the pathogenic organisms found were sufficient to account for the inflammatory changes.

In 1 case there was a general infection with the streptococcus; in the other a streptococcus infection of the middle ear.

In the case with purulent exudate in the sphenoidal and ethmoidal sinuses, the streptococcus was found.

Diphtheria with measles, 4 cases. The antra in each case contained a sero-purulent fluid. The diphtheria bacillus and the streptococcus were found in 2; the streptococcus alone in 1; and the diphtheria bacillus alone in 1.

Diphtheria with scarlet fever, 7 cases. In 5 of these the antra were normal, and in 2 inflammatory changes were found. Of these 2 cases 1 was unilateral and contained a thick purulent fluid. Cultures showed the diphtheria bacillus and a variety of unrecognized bacteria.

In the second case one antrum contained a thin mucoid fluid and the other a thick creamy fluid. Cultures from both contained the streptococcus, and the latter the staphylococcus pyogenes aureus also. The sphenoidal and ethmoidal sinuses were also involved, containing thick creamy pus in which the streptococcus was found. In this case both middle ears contained purulent contents. Cultures showed the diphtheria bacillus and the streptococcus.

Histological examinations. — In 5 cases in which the contents were mucoid or but slightly purulent, and in 3 in which they were purulent and contained shreds of false membrane, the lining membrane was stripped off for histological examination. In the former the changes were slight. The tissue beneath the epithelium was œdematous, and here and there were a few lymphoid and plasma cells and an occasional polynuclear leucocyte.

In the other 3 cases a definite false membrane composed of fibrin and leucocytes was present.

Conclusions. — The preceding cases indicate that infection of the antrum of Highmore is quite common in fatal cases of diphtheria and scarlet fever. The micro-organisms commonly found are the diphtheria bacillus, the pus cocci, and the pneumococcus. In some cases the exudate was serous or sero-purulent, in others distinctly purulent; in a few cases

a fibrinous membrane had formed. In 7 cases a mucoid accumulation only was found. In the cases here reported the inflammatory changes in the antra did not produce symptoms sufficiently marked to attract attention during life. If symptoms did exist they were probably referred to the primary disease.

The practical point in regard to this subject is to determine whether this infection takes place as commonly in those cases which recover as in those which are fatal; and, if it does, whether it may not lead to subacute or chronic disease of the accessory sinuses. In fatal cases with a diminished resistance to bacterial invasion, as shown by the large number of cases with inflammation of the middle ear and frequent systemic infection, an infection of the antrum is not surprising. It is very probable, however, in view of its frequency in fatal cases, that it may occur in some cases which recover. In most of these cases it probably clears up without any ill effects, but it is very possible that in others it may so alter the condition of the lining membrane that later an acute inflammatory condition in the nose may readily set up chronic antral disease.

That the infection of the antrum with diphtheria bacilli explains the persistence of these bacteria in cultures from the nose long after all evidence of membrane has disappeared seems very probable. Any one who has made routine bacteriological examinations of the throat and nose in diphtheria can recall cases in which positive cultures were obtained from the nose for weeks and even months after all evidence of the disease had subsided. In the laboratory of the Boston City Hospital, where no case of diphtheria is discharged until three negative cultures have been obtained from both throat and nose, cases have been detained for six, seven, eight, and nine weeks, and even three months, on account of the persistence of diphtheria bacilli in the nose.

Le Gendre and Pochon (1895) report a case in which they obtained positive cultures from the nose for fifteen months after nasal diphtheria. Upon douching the nose with antiseptic solutions the bacilli would disappear; but as soon as

the cleansing was stopped the bacilli would appear again in cultures. The writers claim that the bacilli were hidden in the deep glands of the mucous membrane, where the antiseptics could not reach them. In view of the cases here reported it would seem much more probable that they had a case with infection of the antrum. The antrum drains slowly. If it becomes infected with diphtheria bacilli, and its outlet is not obstructed, cultures from the nose would necessarily show these bacilli until the cavity is completely drained or the organisms have died out. In all cases, therefore, in which the diphtheria bacillus persists in cultures from the nose an examination of the antral cavities would appear to be indicated.

MIDDLE EARS.

The diphtheria bacillus has been found in acute inflammation of the middle ear by Councilman and by Wright; each reports 3 cases. In all of Wright's cases the streptococcus, and in one case reported by Stephens and Parfitt the pneumococcus also were present. Lommel reports 25 cases of diphtheria, in 24 of which there was disease of the middle ear. In only 1 of these cases was a bacteriological examination made. The diplococcus lanceolatus was found. Rimini reports a fatal case of pyæmia, the source of infection being a suppuration of the middle ear following diphtheria. "Large numbers of cocci" were found.

Podack in 3 cases of diphtheria complicated by measles found the diphtheria bacillus and the streptococcus in the middle ear. In 1 case there was a definite fibrinous membrane on the membrana tympani; the other 2 cases were purulent.

Baginsky has found diphtheria bacilli usually associated with the streptococcus and the pneumococcus in both outer and middle ears.

The middle ears were examined in 144 of our cases. In 86 cases disease of the middle ear was found. In Group I. an exudate was found in one or both ears in 59 cases. In 44 cases the exudate was purulent. The mastoid cells were involved on both sides in 7, and on only one side in 6. In

12 cases the exudate was more mucoid than purulent, and the mastoid cells were not involved at all. In 4 of these cases the condition was bilateral. In 3 cases the exudate was mucoid on one side, and purulent on the other. Of the 44 purulent cases, 35 were double. In 7 no cultures were taken. In the remaining 28, the diphtheria bacillus occurred in both ears in 9 cases, in only one in 6 cases. The streptococcus occurred in both ears in 17 cases, and in only one ear in 3.

The staphylococcus aureus occurred in both ears in 4 cases, and in only one ear in 3. The pneumococcus occurred in both ears 5 times. The staphylococcus albus occurred in 3 cases. The streptococcus pyogenes alone was found in both ears in 7 cases, the staphylococcus aureus alone in 1 case, and the pneumococcus alone in 1 case. Generally a combination of two or more of these organisms was found, as a rule the diphtheria bacillus with the streptococcus, or with the staphylococcus aureus, or with both.

In the 9 cases with purulent exudate in one ear only, cultures were taken in all but 1 case. The streptococcus occurred 5 times, the diphtheria bacillus and the staphylococcus aureus each 4 times, and the diplococcus lanceolatus once. The streptococcus occurred alone twice, the diphtheria bacillus alone once, and the staphylococcus alone once. In all other cases a combination of two or more organisms occurred.

Of the 4 cases with mucoid material in both ears, cultures were taken from 3. The staphylococcus aureus was found alone in 1 case, and with the diphtheria bacillus in 1 case. The latter occurred alone in the third case.

In the single cases (8) no cultures were made in 2 cases; in the others the diphtheria bacillus occurred 3 times, the streptococcus 5 times (twice in pure culture), the staphylococcus aureus twice, and the bacillus pyocyaneus once.

In Group II. there were 27 cases, 23 of which were purulent, with involvement of the mastoid cells of both ears in 3, and of those of only one ear in 6. Seventeen of the purulent cases were double, and 6 single. In the double cases the diphtheria bacillus occurred in both ears 11 times, in only one ear once. The streptococcus occurred in both ears 10

times; in one ear 4 times. The staphylococcus pyogenes aureus occurred in both ears 3 times; in one ear twice. The bacillus pyocyaneus occurred in 2 cases. In no case did any of the above micro-organisms occur in pure culture. In one case no cultures were taken.

Of the 6 single cases, in 3 no cultures were taken; in 1 the diphtheria bacillus occurred alone; in 1 the streptococcus alone; and in 1 both these micro-organisms were found.

Of the 4 mucoid cases 3 were bilateral; cultures from 1 were sterile; the other 2 showed the streptococcus alone in one, and associated with the diphtheria bacillus in the other; in the single case both these micro-organisms were found.

It is not to be understood that in the above cases the micro-organisms mentioned were the only ones present. In some, various non-pathogenic organisms were associated with those known to be pathogenic. Several of these were isolated and studied, but none showed pathogenic properties when inoculated into guinea-pigs or rabbits. The presence of these organisms is readily explained by the easy communication of the middle ear with the mouth through the Eustachian tube. This also explains the frequency of the occurrence of the diphtheria bacillus. We did not make any histological examination of the mucous membrane, and in the absence of this it is impossible to say that the diphtheria bacilli were the cause of the exudation. The otitis media may have been caused by the associated pyogenic organisms and the diphtheria bacilli may have been only accidentally present.

It is of interest that in only 23 of the 86 cases was the condition recognized during life. For this reason it is difficult to estimate the stage of diphtheria at which involvement of the middle ear is most liable to occur. Of these 23 cases, 6 developed before the fifth day, 8 between the fifth and eleventh days. The remainder developed after two weeks; 2 as late as the thirty-fourth day. With the exception of 3 cases all of these cases were in children under three years of age. Nasal diphtheria was present in 12 of the cases.

LATERAL SINUS.

In 1 case of Group I. *thrombosis* of the lateral sinus followed suppuration of the middle ear and mastoid cells. Cultures from the thrombus showed the streptococcus and the diphtheria bacillus. Cultures from the mastoid showed the same organisms and also the staphylococcus aureus.

PERIOSTEUM.

Acute periostitis. — In a case of Group II. (diphtheria with measles) there was found beneath the periosteum of the parietal bone a small accumulation of pus. In cultures the diphtheria bacillus and the streptococcus were obtained.

ACUTE ABSCESSES IN VARIOUS SITUATIONS.

In Group I., 7 cases were noted: 3 of these were in the cervical lymph nodes, and in 2 of them were found the diphtheria bacillus and the staphylococcus albus. The third case was due to the streptococcus and the staphylococcus aureus, as was also a retropharyngeal abscess. An abscess of the scalp contained the staphylococcus pyogenes aureus, and one in a bronchial lymph node the streptococcus. A tonsillar abscess contained the staphylococcus albus and the diphtheria bacillus.

In Group II. 14 abscesses were examined. Nine were of the cervical lymph nodes, and in 5 the streptococcus was found in pure culture. In 2 the diphtheria bacillus occurred associated in one with the streptococcus and in the other with the staphylococcus aureus. The abscesses in the other two had been opened and dressed antiseptically; cultures, therefore, were not taken. A retropharyngeal abscess contained the diphtheria bacillus, the streptococcus, and the staphylococcus aureus, while a laryngeal abscess contained the streptococcus and the staphylococcus. A retrolaryngeal abscess contained the streptococcus. An abscess of the spleen with an associated peritonitis was due to the streptococcus, as was also an accumulation of pus over the trochanter of the femur.

Acute abscesses containing the diphtheria bacillus have been reported as follows: In abscesses of finger in pure culture by Leary; diphtheria bacillus and staphylococcus aureus in paronychia of toe by Wright; of the larynx by Goris; of the thumb (paronychia) by Müller. The abscesses occurring in the course of diphtheria are generally due, however, to pyogenic cocci, particularly streptococci. According to McCollom, abscesses forming at the point of injection of antitoxin are generally due to the streptococcus pyogenes, although Wright reports one case in which the diphtheria bacillus was found.

PATHOLOGY.

MEMBRANE.

Distribution of membrane. — A definite membrane which varied in its extent and distribution was found in 127 of the 220 cases examined. Membrane was found on the tonsils in 65 cases, epiglottis 60, larynx 75, trachea 66, pharynx 51, mucous membrane of nares 43, bronchi 42, soft palate, including uvula 13, œsophagus 12, tongue 9, stomach 5, duodenum 1, vagina 2, vulva 1, skin of ear 1, conjunctiva 1. The membrane was most frequent in the larynx, and next in order of frequency come the trachea, tonsils, epiglottis, and pharynx. In a number of cases but a small amount of membrane limited to a single situation was found. It was found on the tonsils alone in 7 cases, trachea 2, larynx 3, pharynx 1, soft palate 1, œsophagus 1, epiglottis 2, mucous membrane of nares 1.

In all other cases several structures were involved. These may be divided as follows, according to the extent of the membrane:

Twenty-two cases in which membrane was present on tonsils, on nasal passages, on either pharynx or palate, or both, with extension to some part of lower air passages. These cases were those with the most extensive distribution of the membrane and included the following unusual locations: tongue 6, œsophagus 5, stomach 3, conjunctiva, skin, vulva, and vagina, each 1 case.

Three cases, membrane present on tonsils, nasal passages, and some part of lower air passages. These include 1 case with involvement of stomach and duodenum, and 1 of tongue.

Three cases, membrane present on tonsils, nasal passages, pharynx or palate, or both.

Three cases, membrane on tonsils, pharynx, or palate, including 1 case of membrane on œsophagus.

Sixteen cases, membrane on tonsils, pharynx or palate, or both, and some part of lower air passages. This includes 2 cases in which the tongue and 1 in which the œsophagus were involved.

Ten cases, membrane on tonsils with some part of the lower air passages.

Seven cases, membrane on nasal passages with some part of the lower air passages, including 1 case with involvement of œsophagus.

Seven cases, membrane on pharynx and some part of lower air passages.

Thirty-one cases, membrane on some or all of lower air passages, including 1 case of involvement of œsophagus and 1 of the stomach.

Two cases, membrane on nasal passages, pharynx, and palate; in 1 case the œsophagus was involved.

One case, membrane on pharynx and œsophagus.

One case, membrane on nasal passage and vagina.

The following are the 2 cases with the most extensive and unusual distribution of the membrane:

B. C. H., '97. 184. Woman, thirty-five years old. There is a membrane covering both nasal and buccal surfaces of the soft palate and uvula extending over the vault and back of pharynx, and including the tonsils, which show in addition central losses of substance. On the back of the tongue there are a few patches of membrane which is thick, yellow, rather adherent, and extends over both surfaces of epiglottis where it is very thick, into the larynx, trachea, and bronchi. In the lower air passages the membrane is thin, white, and easily removed; where there is no membrane the surface is deeply injected and granular. The bronchi and trachea are filled with frothy serous fluid, and the membrane is adherent only over small areas.

Lung. — On section the larger bronchi are completely filled with yellowish, purulent, and fibrinous plugs.

The smaller bronchi have softer puriform contents. Associated with this condition is a bronchopneumonia.

In the œsophagus there is a continuation of the membrane from the pharynx. In the upper portion the membrane is thick, grayish-yellow, and rather evenly distributed over the surface. Below it is thinner and

occurs in longitudinal streaks. Approaching the stomach it is found in small patches partly covering longitudinal eroded areas which are deeply injected and granular. The erosion stops sharply at the cardiac orifice.

Genitals. — The inner surface of the labia majora, the labia minora, the vestibule, and the introitus are covered with a thick, greenish-yellow, slimy, opaque pseudo-membrane which is very adherent. This membrane extends for a short distance into the vagina, where it merges into a slightly injected area which is followed by apparently normal mucous membrane. Beyond this the vault is covered by a thin gray semi-translucent membrane which is not adherent, and extends up over the vaginal surface of the cervix. Uterine mucous membrane normal. Membrane stops sharply at the meatus urethræ. Bladder and urethra normal.

B. C. H., '97. 215. Age seven years. Inspection of the upper nasal cavity shows mucous membrane injected, of deep purple color, and middle and lower turbinates covered with yellow, soft membrane. The membrane also involves the nasal surface of the soft palate as well as part of its buccal surface. The tonsils, pharynx, and extreme upper portion of œsophagus are covered by a thick, ragged, greenish pseudo-membrane which is rather adherent. This membrane extends deeply into the follicles of the tonsils, and on section there is deep necrosis of the tonsillar tissue. In the trachea the membrane becomes much thinner. It is smooth, pale yellow, and easily removed. Mucous membrane beneath deeply injected and granular. Membrane can be followed beyond the second divisions of the bronchi. Lung on section shows the large bronchi completely filled with gray fibrinous plugs.

Stomach. Beginning sharply at the cardiac orifice, the mucous membrane is slightly eroded in irregular longitudinal patches. These patches in places are covered by distinct yellow fibrinous membrane which is rather adherent, and leaves a red granular surface on removal.

The following cases of stomatitis and cancrum oris due to diphtheria bacilli are taken from the clinical records:

1. Simple *stomatitis* occurred in 5 cases. Three were cases of diphtheria with measles, 1 of diphtheria with scarlet fever, and 1 of diphtheria only. All were in children under four years of age. Three developed before the ninth day, the other two on the thirteenth and thirty-second days respectively.

2. *Cancrum oris*, 2 cases. Both two years old. Both were cases of diphtheria with scarlet fever and measles. In one case stomatitis occurred on the fourth day, ulceration on seventeenth day, and finally involved the entire cheek and a portion of the upper jaw. Death on thirty-first day. In the other case stomatitis on the sixth day, ulceration of cheek on fifteenth day.

The following cases of conjunctivitis are taken from the clinical records:

1. True *diphtheritic conjunctivitis* (with membrane), 2 cases. In one case membrane disappeared before death. Positive cultures from eye in both cases. Scarlet fever in both cases. Diphtheria of nose in one. One aged fourteen months, the other three years.

2. *Muco-purulent conjunctivitis* with presence of diphtheria bacilli (no membrane), 3 cases. Diphtheria of nose in all three cases. All under three years of age. All developed before the seventh day.

The character of the membrane varies. It may appear as a thick mass of a brownish or grayish-brown or almost black color, or as a thin whitish pellicle. It may extend as a continuous mass over the tonsils, palate, pharynx, epiglottis, larynx, and trachea, or only small isolated patches may be found. It may be granular and easily broken up or dense and elastic, and may be removed in large patches. It is always more easily removed from the trachea than from any other part. On opening the trachea it often appears as a loose wrinkled mass lying in the lumen. Removal of the membrane from the trachea or larynx, even when it is thick and adherent, rarely leaves a loss of substance extending into the subepithelial connective tissue. The tissue beneath the membrane and in the vicinity is intensely injected and often hæmorrhagic. This injection is always evident on microscopic examination, but it may be obscured on macroscopic examination by superficial necrosis, and may be more evident in foci.

The *literature* on the histological characteristics of the membrane and its mode of formation is not extensive. Virchow sharply separated the croupous from the diphtheritic membrane. In the formation of the croupous membrane according to him the fibrin in the plasma is greatly increased, the exudate passes through the epithelial covering and coagulates on the surface. Such a membrane may be formed on all surfaces covered with mucous membrane, but is seen best on the respiratory mucous membrane. In the diphtheritic membrane the exudate consists of coagulated amorphous fibrin and lies in the upper layers of the mucous membrane.

The exudate coagulates between the tissue elements, and if it extends over the surface of the connective tissue it lies beneath the epithelium. There is necrosis of the tissue combined with the exudation and no new cells are formed in the diphtheritic membrane, though they are formed in the croupous.

A material advance in our knowledge of the histogenesis of the membrane was made by E. Wagner. He believed that the membrane formation was chiefly due to a peculiar metamorphosis of the epithelium. In this process the protoplasm and the nucleus of the epithelial cells become enlarged and small vacuoles are formed both in the centre and periphery of the cell. The nucleus disappears and the cells become converted into large thick masses containing round and oval spaces which give to each cell an appearance which he compares with the horns of a stag. From the fusion of adjoining cells a reticular membrane is produced. The croupous membrane is produced in the same way as the diphtheritic, the only difference being that in croup the membrane is composed of finer fibrillæ of fibrin and encloses more cells than the diphtheritic membrane. Cornil and Ranvier confirmed completely the observations of Wagner. They isolated the altered epithelial cells, stained them with picrocarmine, and decided that they did not contain fibrin but a material similar to mucin. Hartman regards croup and diphtheria as identical processes. The plasma poured out in the mucous membrane is forced to the surface by the contraction of the muscles of the pharynx and coagulates, forming a croupous membrane. If the exudation continues, the membrane already formed causes it to accumulate in the tissue and coagulate, producing diphtheria.

Weigert does not recognize the anatomical distinction between croup and diphtheria which Virchow has made. According to him, in croup of the trachea, in which the membrane is easily removed, the exudate is seated on the surface bare of epithelium, though it may extend over the epithelium adjoining. There is a pseudo-diphtheria in which the membrane lies on the connective tissue surface just as in croup,

but is more firmly attached to it. In true diphtheria the superficial layers of the connective tissue are converted into a mass similar to coagulated fibrin. Diphtheria may be found in any of the mucous membranes except the trachea. The membrane formation is due to a combination of coagulation necrosis and fibrinous exudation, both the necrotic cells and the fibrin contributing to it. The necrotic pus cells play a greater part in its formation than do the epithelial cells.

Senator also distinguishes several forms of diphtheria. There is a catarrhal form in which the lesions are the same as in a simple catarrh. The next is a pseudo-croupous form which is found only in the larynx and in which small whitish points, which are easily removed, are seated on the surface in which there is a catarrhal inflammation. The true diphtheria is the third form, and in this the membrane clings firmly, and when removed leaves a bleeding surface.

Peters studied the formation of the diphtheritic membrane under the direction of v. Recklinghausen. He believes that the thick dense refractive membrane in diphtheria is formed by a hyaline degeneration of the cells both of the epithelium and of the exudation. Hyaline formation is seen also in the blood-vessels and lymphatics of the connective tissue beneath the membrane. The croupous membrane is formed by a fibrinous exudation only; the hyaline degeneration takes no part in it. In the ulcerating form of diphtheria but little hyaline is present.

Rindfleisch says that the diphtheritic membrane does not consist of ordinary fibrin. When small pieces of the dense membrane are laid in weak ammonia and teased out, the membrane is found to be composed of degenerated cells united to one another. In the beginning of its formation the cells are round and the membrane often seems to be composed of round balls united to each other. Along with this degeneration there may be interstitial fibrin formation between the degenerated cells. This is more marked in the trachea than elsewhere.

Orth was the first sharply to differentiate two distinct forms

of structure in the membrane, one a membrane formed by exudation, composed of a meshwork of fibrin enclosing leucocytes and most often found in the trachea and bronchi; the other a membrane formed by hyaline fibrinoid degeneration of the leucocytes and epithelium. This latter membrane is thick, elastic, and adherent, and is composed of a thick dense hyaline reticulum similar to young osteoid tissue. Large hyaline balls or irregular masses may be found in the membrane. This dense membrane is found chiefly on the tonsils and pharynx; the reason for this is that more leucocytes are in the exudate in these places. In the trachea the dense basement membrane prevents their passage into the exudate. The adhesion of the membrane on the tonsils and pharynx is favored by the irregularities of the surfaces and the presence of lacunæ. The membrane clings more closely to the surface of the epiglottis than elsewhere in the air passages. The reason the membrane is so easily separated from the surface of the trachea is that it is forced up by the secretion of the mucous glands beneath it.

Ribbert considers the hyaline membrane as due to a hyaline metamorphosis of the fibrin, and says that the hyaline masses may be continuous with fibrillæ of ordinary fibrin. The membrane may be seated on the surface or may extend into the tissue. Leucocytes and epithelial cells are often enclosed in it.

Oertel in his monograph describes the membrane as composed of a coarse reticulum which forms the chief mass, of a finer reticulum with membranous branchings, and of a dense, broad, refractive reticulum which differs from the others in staining strongly with methylene blue and fuchsin. He thinks this membrane is formed by a peculiar degeneration of the round cells. He describes also a direct division of the nuclei of the epithelial cells in the early stage of the process. Heubner investigated the formation of the diphtheritic membrane by removing small pieces from the tonsils and pharynx during life. In the earliest stage of the process he found a coagulated exudation in the upper part of the epithelium between the horny cells, which were pushed

apart. The membrane, at first composed of coagulated exudation, becomes changed at the end of the second day into a peculiar refractive reticulum. Baumgarten comes back to the views of Wagner in giving the chief place in the formation of the membrane to the hyaline metamorphosis of the tissue elements. The fresh diphtheritic deposit on the mucous membrane of the pharynx consists of the swollen elements of the epithelium which have lost their nuclei and become changed into a substance similar to fibrin. The degenerated epithelium becomes converted into a refractive network similar to that described by Wagner. The nodal points in the reticulum are formed from the remains of the epithelial cells. Leucocytes are rare and show no trace of this formation. A fibrinous exudation consisting of fine fibrillæ of fibrin, in whose meshes numerous leucocytes and red blood corpuscles are contained, may be formed beneath this membrane. When the process extends into the connective tissue beneath there is a fibrinoid metamorphosis of the connective tissue similar in character to that taking place in the epithelium. He speaks of this as desmoid pseudo-fibrin. There may be some exudation fibrin in the connective tissue which can be distinguished from the desmoid pseudo-fibrin by the finer fibrillæ and the less marked refraction. After the first membrane is cast off a second membrane may be formed from exudation-fibrin and cells. The connective tissue which has undergone such a fibrinoid metamorphosis is not to be regarded as destroyed, but may again return to the normal condition.

Baginsky recognizes three layers in the membrane: on the surface a layer composed of loose necrotic epithelium and round cells; next to this a wide fibrinous or fibrinoid network, rather denser toward the surface, containing scattered epithelial and round cells; and lastly a layer composed of altered epithelial cells between which there is a dense fibrinous network.

Middeldorpf and Goldman come to the following conclusions: Both in experimental croup and in epidemic diphtheria fibrin forms the essential constituent of the false

membrane and comes as an exudation from the vessels of the inflamed mucous membrane. The formation of the pseudo-membrane takes place after the complete destruction and desquamation of the epithelium. The hyaline material found in the dense refractive membrane is not a special substance, but is a derivative of the fibrin. The croupous and diphtheritic membranes are both in their mode of origin and composition completely homologous structures.

Neuman in an article on the fibrinoid degeneration of the connective tissue says that the diphtheritic membrane may be in large part due to a direct transformation of the upper layers of the connective tissue into fibrin.

With regard to relation of the bacilli to the formation of the membrane Henka has found that a membrane similar to that found in man is produced when the bacilli are rubbed on the mucous membrane of the trachea. Other micro-organisms produced no membrane. Roger and Bayeux found that the diphtheria toxin is in itself capable of producing a membrane. Baumgarten denies that the bacilli alone are capable of producing the membrane, but claims that their action is assisted by the other pyogenic organisms invariably present.[1]

On examination of the membrane from a large number of cases of diphtheria the variety in structure which it presents is striking. The membrane on the tonsils (Plate XV., Fig. 1 a) will be described first because the variations in structure are best seen there. We can distinguish microscopically two distinct varieties of the membrane corresponding to the differences observable macroscopically. The dense, firm, elastic membrane which can be stripped off in large flakes is composed of a reticular structure, with considerable uniformity in the size of the beams which form the reticulum. (Plate XV., Figs. 3 and 4.) Occasionally, particularly in the upper part of the membrane, there are small areas in which the beams

[1] We regret very much that we have had no opportunity of investigating any of the cases of membrane formation which clinically occur so frequently in the pharynx without the diphtheria bacilli being present. In every case of membrane formation on the tonsils or pharynx seen at autopsy the diphtheria bacilli were present.

of the reticulum are large and the spaces extremely small. This tissue is much denser and more refractive both in the stained and in the unstained condition than is ordinary fibrin. The reticulum takes the fibrin stain in most cases, but shows a marked difference when compared with the stain of pure fibrin. With iron hæmatoxylin it takes in some cases the dense black color which fibrin gives with this stain (Plate XV., Fig. 4); in other cases it is tinted only a bluish-gray (Plate XV., Fig. 3), or there may be a difference in the color reaction; the centres of the fibres may be pale, while the outer portions stain intensely. With methylene blue and eosin it takes more of the blue than of the eosin stain; with fuchsin it stains intensely red; and it is deeply but also irregularly stained with Weigert's fibrin stain.

The reticulum in most cases is homogeneous in structure, and the beams composing it have the same size. In other cases nodular projections are found along them, or they may contain small cavities. (Plate XV., Fig. 4.) In one case a membrane was found so dense that it appeared as a solid mass with small canals intersecting it. The spaces enclosed by the reticulum vary but slightly in size. They may be angular or round, for there may or may not be thickening of the reticulum at the points of contact. When this membrane is present, masses of material of the same character as the reticulum and of varying size may be found which are either enclosed in the reticulum or lie in its vicinity. (Plate XV., Fig. 3.) These masses are often continuous with the reticulum. They often stain irregularly, but rarely give the intense fibrin stain which the reticulum does. Usually there is only a small area around the periphery which gives the black stain of fibrin; the centre stains the bluish-gray color which parts of the reticulum take. In some an irregular intensely staining mass is seen in the centre, in others again the centre is unstained. The masses are usually of about the same size as the epithelial cells, and where parts of the epithelium remain they may be continuous with it. In the smaller masses an irregular mass of nuclear material resembling the nucleus of a polymorphonuclear leucocyte may be

found. There would seem to be little doubt from the transitions which may be observed that these masses which have been noted by various observers are epithelial cells and leucocytes which have undergone hyaline degeneration and play an important part in the formation of the hyaline membrane. Very few cells are found in the spaces of the reticulum, although occasionally there is present an entire leucocyte or the fragment of a nucleus. A membrane of this character may cover the entire surface of the tonsil, or only fragments of it may be found enclosed in fibrin, or it may form the upper part only of the entire membrane, being separated from the tissue beneath by fibrin. The upper surface of the membrane is rarely sharp, the reticulum here becomes swollen and more or less disintegrated.

The other variety of membrane which macroscopically is characterized by greater friability is composed of fibrin. (Plate XVI., Figs. 1 and 4, and Plate XVII., Fig. 1.) The difference between the two can be recognized at a glance even under a low power. The fibrin forms a reticulum just as does the hyaline material, but varies greatly in the size of the fibres and the spaces. In general the spaces are larger than in the hyaline membrane and more often oblong than round, with the long diameter parallel with the surface. The reticulum often appears to be arranged in whorls starting from a centre. In the spaces of the fibrin there are numerous leucocytes sometimes well preserved, at others represented only by cell and nuclear detritus. When well preserved they usually can be recognized as polymorphonuclear in character. In some cases the fibres of the network are thick, and extending from these thicker fibres is a network of very fine fibrillæ. This fibrinous membrane often is continuous over the entire surface of the tonsil and extends into every crypt. The hyaline membrane is never found extending from the surface into the crypts, though occasionally small masses of hyaline reticulum are found in them.

The epithelium is usually absent beneath the membrane. In places small masses of epithelium consisting of the lower layers of cells are found (Plate XVI., Fig. 1), and in places

the membrane may extend over a considerable area of epithelium which is but little altered, although the upper layers of cells are always absent. (Plate XVII., Fig. 2.) We have never found a case in which the membrane extended over a large surface of intact epithelium. Both sorts of membrane, but especially the fibrinous, often show areas which differ from the general character of the membrane. Areas are found where the reticulum is broken and forced apart. The spaces thus formed are filled by a fibrinous network, the fibres of which are finer than the remainder, the spaces larger and more irregular and containing large numbers of leucocytes. The membrane proper may be elevated from the surface by such a formation. The line separating the old membrane from the new formation below it is easily seen. It is obvious in these cases that after the membrane is formed an exudation which afterwards undergoes coagulation may enter into it, forcing apart its meshes or elevating it bodily.

When the membrane extends over the epithelial surface it is rarely in contact with it, but is separated from it by a space containing granular material, leucocytes, and nuclear fragments. (Plate XVII., Fig. 2.) The exudation seems in some cases to flow over the surface like lava reaching a certain distance before becoming solidified, but the membrane may be added to by exudation coming through the epithelium and coagulating on contact with it.

In such cases appearances similar to the smallpox vesicles may be seen. The upper layers of the epithelium may be elevated, forming vesicles filled with fibrin and pus cells, or small masses of adherent epithelium. The vesicles are often divided by small septa formed by adherent epithelial cells. (Plate XVII., Fig. 2.) That there is an abundant exudation passing through the epithelium in the vicinity of the membrane is shown by vesicles filled with coagulated exudation with or without fibrin beneath the epithelium or above the first layer of cells.

Almost invariably the epithelium beneath the membrane and in the vicinity of it shows various alterations. It contains numbers of polynuclear leucocytes and lymphocytes. (Plate

XIX., Fig. 1.) These cells are situated between and in some cases in the epithelial cells. Usually the lymphoid cells are found only in the deeper layers of the epithelium. In several cases there were numbers of red corpuscles in the epithelium. These were for the most part between the epithelial cells, but in others they seemed to be directly within the cell and to lie in a cavity just around the nucleus. When red blood corpuscles were found in the epithelium there was more or less hæmorrhage in the tissue beneath, and the corpuscles had evidently been carried by the exudation stream into the overlying epithelium. The greatest number of red corpuscles in the epithelium was found in the uvula in the vicinity of the membrane.

Where the epithelium comes in contact with the membrane and in places on the surface not in contact with membrane there are changes in the cells, which consist chiefly in an enormous multiplication of the nuclei by direct division. (Plate XVII., Figs. 3 and 4.) No nuclear figures are found in these cells and the process appears to be the same as that described by Councilman as occurring in the degenerating cells around a central lesion in the cornea. The nucleus becomes larger and paler, the chromatin becomes arranged around the periphery, and division by constriction takes place. As many as ten very pale vesicular nuclei may thus be formed in a single cell. The protoplasm of the cell becomes paler and its outline indistinct; or the periphery may be preserved, leaving the nuclear bodies in a sort of vacuole in the cell. These changes in the epithelium are circumscribed and limited to the places mentioned. Small connected masses of epithelial cells representing the lower layers of cells or a part of a gland duct are often found beneath the membrane (Plate XVI., Fig. 4), and in these every stage of direct nuclear division can be seen. A short distance from this the epithelium may preserve its normal appearance and nuclear figures in considerable numbers may be found in the cells. The crypts, in places denuded of their epithelium, are filled with necrotic tissue and fibrin (Plate XV., Fig. 2); the necrosis often extends a considerable distance into the surrounding tissue.

In other places they seem but little changed. The epithelium lining the crypts in all cases is loose, œdematous, and infiltrated with cells. In many cases it is difficult on superficial examination to distinguish the epithelium from the tissue beneath. The cells are small, the nuclei resemble lymphoid cells, and where they are separated from one another and infiltrated with cells it is difficult to distinguish the epithelium from the infiltrating cells. In all of these places the flat epithelial cells of the surface are cast off and masses of them lie inside the crypt. Among the lymphoid cells in the epithelium there are numbers of plasma cells, sometimes single, more often in groups. The blood vessels of the papillæ extending into the epithelium are surrounded by lymphoid and plasma cells. The lymphoid and plasma cells, like the red blood corpuscles, seem to be carried for the most part into the epithelium by the exudation stream. They most generally are found in the deeper layers where the epithelial cells are separated from each, though occasionally single ones are found nearer the surface in the same position as the polynuclear leucocytes. In some cases the crypts are dilated, the epithelium almost entirely absent, and the space filled with polynuclear leucocytes. In such places there is but little fibrin.

The tissue beneath the membrane, and beneath the epithelium when this is present, is variously altered — the most profound alteration consists in necrosis with dense fibrinous exudation; in this case the fibrin in the tissue is so mingled with the fibrin on the surface that it is difficult to see where the tissue begins. The fibrin in these cases is in the form of a fine reticulum with small spaces which are either empty or contain nuclear fragments. The fact that this is tissue and not membrane is often only to be recognized by the presence of denser areas representing the vessels. In other cases there is a dense hæmorrhagic infiltration of the surface with masses of red blood corpuscles mixed with the fibrin. The tissue in these places is not evident. In other places again there is a slight extension of the membrane into the tissue in the form of small patches of fibrin. A process very analo-

gous to the hyaline degeneration of the epithelium may take place in the tissue, but is less often found in the tonsil than in the epiglottis and trachea.

In one specimen there were beneath the almost intact epithelium of a crypt small hyaline masses, and masses of fibrin which were applied to the bottom of the epithelium and extended from this into the tissue. The hyaline material could be distinguished from the fibrin by the size of the reticulum, and the manner of staining. (Plate XVI., Fig. 3.) The fibres were larger and more refractive. The hyalin was present, both in the form of a reticulum and in masses. The refractive hyaline material, just as in the formation of the hyaline membrane on the surface, seems to be formed by a direct metamorphosis of the tissue. (Plate XVI., Fig. 2 e.) The first change leading to this is swelling of the tissue accompanied by disappearance of the fibrillar character. The homogeneous mass so formed becomes more opaque and hyaline, and the whole or portions of it take the fibrin stain. Definite fibrin in the form of a fine reticulum passes directly into the hyaline material. A considerable amount of fibrin also is found in the tissue with no connection with the membrane, and often with no apparent connection with necrotic tissue.

This hyaline fibrinoid degeneration of the connective tissue is more marked in the epiglottis than in the other tissues. In this degeneration it does not seem to us that the tissue, as such, is directly converted into fibrin. The fibrin coming from the fibrin factors in the exudation is simply deposited in the tissue, which is probably necrotic, and which has undergone first a hyaline metamorphosis.

This is the desmoid pseudo-fibrin described by Baumgarten. Occasionally both sorts of membrane are found together, the upper part distinctly hyaline, and beneath this a fibrinous reticulum. This seems due to the elevation of the primary hyaline membrane by the accumulation beneath it of a fibrinous exudate. Such an exudate can be distinguished from the primary membrane even when it is of the same character by the large size and irregularity of the fibrin network. In still other cases the membrane is elevated by an exudate

containing no fibrin, and showing only as a granular coagulated material.

The changes in the trachea in connection with membrane formation are in many respects different from those in the other tissues. In general the membrane is distinctly fibrinous. (Plate XVI., Fig. 1.) Only in one instance in an early and very acute case in a child one year old was the membrane hyaline, and this only in places. This hyaline membrane differed from that on the tonsils in the very small size of the spaces in the reticulum. In the fibrinous membrane the reticulum is much closer than in similar membrane elsewhere. The meshes are almost always flattened and the long diameters of the spaces are parallel to the surface. Three more or less distinct layers can be distinguished in the membrane. On the surface is a rather granular mass composed of nuclear detritus and broken-up fibrin in which no trace of reticulum can be seen. Beneath this lies the definite fibrinous reticulum with small and generally flattened spaces. The beam-work of the reticulum offers little or no variation in size. In some cases the reticulum is filled with cells which are almost exclusively polynuclear leucocytes with an occasional red blood corpuscle. The cells in some cases are comparatively well preserved in form, though the nuclei are broken up and degenerated; in other cases only fragments of the cells and nuclei can be distinguished. Between this network and the membrana propria, and frequently separated from the former by a denser mass of fibrin, is a layer in which the spaces in the fibrinous network are much larger. This layer shows a rather definite architecture. Thicker masses of fibrin from the membrane above pass through perpendicularly to the membrana propria, to which they adhere, and from these lateral communicating fibres are given off. In the meshes of this fibrin are numbers of cells, sometimes single, sometimes in slightly coherent masses. (Plate XVI., Fig. 1.) Along the membrana propria they usually are arranged in a row side by side. As a general thing only the nuclei can be recognized, and the character of these shows them to be epithelial. The nuclei also show the swollen vesicular

form and the peripheral arrangement of chromatin which we have described in the tonsil.

In the cell groups nuclear masses resulting from direct segmentation are seen. There seems to be little doubt that in the trachea in most cases there are remains of the epithelium beneath the membrane, but the membrane is never seen extending over large areas of comparatively intact epithelium, as in the tonsils and pharynx. Among the remains of the epithelial cells are a very few red blood corpuscles and an occasional lymphocyte. The very small number of red corpuscles found in the membrane evidently is due to the barrier to their passage which is offered by the membrana propria, for the tissue beneath may show an extreme hæmorrhagic exudation. Abundant hæmorrhage is also often found in the glands and filling up their ducts.

The membrane usually extends over the mouths of the mucous glands without passing into them. In some cases, on the other hand, it passes directly into the mucous glands, the epithelial lining of which is necrotic. The membrana propria in most places is intact and forms a sharp line of separation from the membrane above and the tissue beneath. A few leucocytes can be seen passing through it. In their passage through it they assume the small attenuated shapes which they show when migrating in the cornea and in passing through the wall of a vessel. In most cases they do not seem to pass through in a straight line, but in a rather irregular manner. Here and there along the surface just below the membrana propria there are small areas representing hyaline fibrinoid metamorphoses of the connective tissue. (Plate XVI., Fig. 2.) Usually they are of very small extent and opposite a point where the fibrin is adherent to the membrane. In many of these places the same change can be seen in the membrana propria. This becomes thinner and denser; often it seems to split or spaces appear in it, and it assumes with the iron hæmatoxylin the dark fibrin stain. Where the fibrin is adherent to the membrana propria it often spreads out like a foot stalk, and becomes directly continuous with the fibrinoid metamorphosed membrane and tissue. The fibrinoid

tissue is distinctly reticular. In a few of the specimens examined this change in the tissue was much more marked. A hyaline fibrinoid and fibrinous network was formed just beneath the membrana propria and seemed to be continuous with the membrane over it. Close examination was necessary to distinguish the thin fibrinoid membrana propria which seemed to be a part of the reticulum. In some cases, however, the membrana propria was clearly absent; the reticulum in the tissue was directly continuous with the membrane. The fibrinoid change of the connective tissue is beautifully shown by Mallory's connective tissue stain. This shows also that the first change in the connective tissue consists in swelling of the fibres. They become homogeneous and more refractive. The swollen tissue stains blue, but not so sharply as ordinary connective tissue, and gradually becomes reticular. Later the reticulum takes the reddish-yellow fibrin stain, either wholly or in places. Portions of the reticulum or single fibres still staining blue can be traced into the fibrin bands.

In 9 cases there was a formation of membrane on the tongue due to an extension of the membrane from the tonsils. In most cases the epithelium had entirely disappeared and the membrane was composed of fibrin without any hyaline. The membrane was usually thicker on the apices of the papillæ than elsewhere In one case every papilla in the section was covered by a cap of fibrin (Plate XVII., Fig. 1), and between there was no membrane.

In the œsophagus, in which membrane was found in 12 cases, its formation could be studied better than elsewhere. Macroscopically there were small losses of substance consisting simply of erosions of the epithelium extending longitudinally. These were covered with a thin adherent membrane. Between these erosions there were areas where the surface was thickened and covered with a grayish necrotic-looking mass, alternating with areas of normal mucous membrane all extending longitudinally. On microscopic examination small foci were found in the apparently normal mucous membrane which marked the beginning of the lesions. Here the

cells were swollen, the interior of the cells pale, vacuolated, the nuclei apparently lying in spaces. The contact edges of the cells were more prominent, forming a pale reticulum. Certain of the cells, instead of undergoing this vacuolation or œdema, were converted into refractive hyaline masses. No fibrin was found in these places.

The edges of the erosions were sharply cut. At the edge of the erosions the epithelium was undermined and showed an extraordinary degree of the nuclear proliferation by direct division. In some places there was little at the edge save the mass of partly broken down vesicular nuclei. The adjoining nuclei showed the peripheral arrangement of chromatin and segmentation. In places bare of epithelium there was a small amount of membrane on the surface, and a slight extension of the fibrin into the tissue beneath. In the place where macroscopically there was evident membrane, this was found microscopically to consist of a fibrinous reticulum with here and there small bits of thicker hyaline membrane. In one specimen there was very evident participation of the epithelium in the formation of the membrane. The upper layers of cells seemed to be lost or converted into detritus. Lower down the single epithelial cells were separated, and between them was an irregular fibrinous reticulum. The cells themselves were refractive and hyaline, and around the periphery of many of them was a thin line which gave the fibrin stain. In many places there were vesicles containing masses of such altered cells, together with much nuclear detritus. In the cells which were most altered no nuclei could be distinguished. Where the change was less advanced the nuclei were swollen and either disintegrated to a mass of detritus or segmenting.

The tissue beneath was intensely hyperæmic. Around many of the blood-vessels there was hæmorrhage and infiltration with polymorphonuclear cells and lymphocytes. In the membrane there were numerous infiltrating cells, both lymphocytes and polynuclear leucocytes, principally the former.

In the comparatively intact mucous membrane near the

erosions and the membrane formation there were numerous lymphocytes between the epithelial cells. While the membrane was chiefly fibrinous, hyaline areas were found which extended from the membrane into the tissue beneath. The hyaline membrane had only in places the definite reticulum which was so prominent in the tonsils.

The membrane in the pharynx and palate was in general similar to that described on the tonsils. The soft palate and uvula were particularly good for the study of the membrane. Both the fibrinous and hyaline membranes were found, more generally the former. Small amounts of mucin were occasionally present in the membrane.

Membrane was found on the epiglottis in 60 cases, and in 2 this was the only situation which showed it. Usually it was extensive, covering both sides of the epiglottis as a dense grayish or black mass. Hyaline membrane was found, but not so frequently as in the tonsils. The membrane usually consisted of a fibrinous reticulum, the meshes of which varied in size and which ultimately was connected with a fine fibrinous exudation in the tissue.

The changes in the lymphoid tissue of the tonsils will be spoken of in connection with the changes in the lymph nodes.

There was frequently considerable hæmorrhage in the tissue beneath the membrane. (Plate XIX., Fig. 1.) In many cases large numbers of red corpuscles were found in the membrane. The dark, almost black color of the membrane often found was due to the presence of blood. In all cases the blood-vessels beneath the membrane were more or less affected and the character of the changes in them did not appear to be always the same. Usually immediately beneath the membrane the vessels were occluded by a mass of very much the same character as the membrane. In some the material was obviously fibrin, in others it had the same character as the hyaline membrane. The entire wall of the vessel was swollen, hyaline, and stained with the fibrin stain. The vessels were often surrounded by a fibrinous or hyaline membrane connected with the membrane

above, and were often so altered that their character could not be ascertained. The change seemed to affect both arteries, veins, and capillaries; the latter were represented by dark lines of hyaline. The changes preceding this complete degeneration could often be traced in the small arteries. In these, small masses of homogeneous material giving the fibrin stain appeared in the wall. This material appeared first between the muscle cells of the media, and afterwards the cells were either changed into or covered up by it. (Plate XVIII., Figs. 3 and 4.) The whole change presented a marked similarity to amyloid infiltration of blood-vessels. It appeared to be a hyaline fibrinoid metamorphosis of the same character as that described in the connective tissue. The hyaline material within the vessels sometimes was in the form of a reticulum, at others in large irregular clumps adhering to the wall. In other cases the change affected the internal elastic lamina, which became swollen and hyaline. The most marked changes were found in the vessels nearest the membrane and were less intense in the vessels deeper down. The change was most marked in the epiglottis and tonsils. It was less marked in the œsophagus and trachea. The vessels showing the slightest degree of this alteration were filled with unaltered red corpuscles and an apparently normal circulation was taking place in them. Thrombi were very frequently found in the underlying veins.

Another marked change in the vessels was the proliferation of the nuclei in the small veins, but this was so much more marked in the veins in the lymphatic tissues that it will be more fully described in connection with them.

Both the superficial and deep lymphatic vessels were dilated. They contained a finely granular coagulated material and very few cells. (Plate XIX., Fig. 1.) Their nuclei showed no change. Where the tissue was most altered, immediately beneath the membrane, the lymphatics could not be recognized with certainty, and it is possible that some of the hyaline vessels in the tissue may have been lymphatics. All observers have particularly called attention to a general

cellular infiltration of the tissue below and in the vicinity of the membrane. Under normal conditions there are great numbers of lymphoid cells in the mucous membrane of the throat, not only in the lymphoid tissue itself, but as a more diffuse infiltration. This general infiltration was in some cases markedly increased, in others not. The cells were almost exclusively lymphoid and plasma cells. Polymorphonuclear leucocytes were found as a rule only in connection with necrotic tissue, either in the necrotic tissue or in the tissue around it.

Marked changes were found in the mucous glands of the tissue. These varied from congestion with slight degeneration to complete necrosis. The slightest form of degeneration consisted in swelling and œdema of the cells. The lumen of the alveolus of the gland was occluded by the projection of the swollen and vacuolated cells. Brightly stained granules were often contained in the vacuoles. The vacuoles were most marked in the portion of the cell bordering the lumen. Hyaline globules similar to those found in the epithelium of the kidney were found in the single cells, and in some cases the entire mass of cells was converted into hyaline, in which nuclear fragments were found. Not infrequently the cells contained small round masses similar in appearance to certain of the inclusions in carcinoma cells. In the most marked degeneration entire alveoli were converted into granular masses containing nuclear detritus. Polynuclear leucocytes in various stages of degeneration were found in the tissue. The interstitial tissue of the glands was variously affected. In the slightest cases the tissue was œdematous with more or less cellular infiltration. In some cases there was extensive hæmorrhage in the gland and extending into the surrounding tissue. This degeneration of the glands was most marked in those near the surface. It extended, however, into the deeper portions and was more marked in the glands than in the surrounding tissue. This glandular degeneration seems to us to account for the very small amount of mucin which is found in connection with the membrane. Orth thinks that the reason why the membrane is so easily removed from the trachea is that it is elevated by the mucous secretion coming

from the glands beneath. We have never seen any evidence of this. The glands are so degenerated as to seem incapable of secretion.

In most of the cases there were evident alterations in the striated muscles of the pharynx. They were most marked in the muscle nearest the membrane and became progressively less further down. There was general œdema; the muscle bundles and the individual fibres were separated from one another. In many cases there was hæmorrhage, fibrin, and infiltration with leucocytes.

The first change which took place in the muscle fibre was the disappearance of the fibrillæ; the fibre became converted into a swollen, homogeneous, refractive mass. This change seemed most often to begin in the centre of the fibre. Cross-sections often showed fibres with a comparatively homogeneous centre surrounded by intact fibrillæ. In the swollen fibres there appeared to be a system of small vacuoles giving to the cross-section the appearance of a very fine reticulum. In the more altered fibres this was lost and the homogeneous material in some cases showed fine fracture lines radiating from the centre, or it was broken up into a number of small masses. In the most altered fibres the nuclei either had disappeared or were fragmented. Occasionally degenerated nuclei in all stages of direct division were found. Where the fibres were most altered and broken down they often contained numbers of leucocytes. Varying degrees of hyaline degeneration were found in the vessels.

Distinct ulceration involving a greater or less degree of tissue was found in 12 cases. The ulceration involved the tonsils 5 times, larynx 3, trachea 2, pharynx 1, epiglottis 1. All of these were severe cases and all of them were intubed. In the tonsils the ulcers were produced by extensive necrosis extending from the membrane into the tissue. They were foul and ragged; the necrosis extended into the tissue from the sides of the ulcer. Those in the pharynx and epiglottis were of the same character as in the tonsils, though not so extensive. Those in the air passages were clearly due to

the influence of the intubation tube. Those in the trachea were less marked.

One case was in a child who died on the sixteenth day of the disease, and who was intubed on admission into the hospital one week after the disease appeared. In the trachea, which contained only shreds of membrane, there were several small clean-cut ulcers extending down to the cartilage. On the sides there was a small amount of necrotic tissue which contained large numbers of cocci both in chains and in the diplococcus form. They extended some distance beyond the necrosis and were found both in and between the infiltrating pus cells. The necrotic tissue contained fragmented nuclei of pus cells, and in the adjoining tissue there were both pus cells and evidences of repair. An earlier stage of ulceration was shown in the trachea of a second case which died on the third day and which also was intubed. In this case there was extensive membrane in the trachea with large numbers of diphtheria bacilli and cocci on the surface and within the membrane. In one place in the section the membrane was absent. There was a sharply circumscribed necrosis at this point, 3 mm. in width, and extending to the cartilage. On the surface there were some masses of diphtheria bacilli and but few other organisms. In the interior the necrotic tissue was filled with masses of cocci so numerous that the whole tissue stained blue with the bacteria stain. The organisms extended for some distance into the tissue beyond the necrosis. The necrotic tissue showed but little evidence of purulent infiltration and there were but few pus cells in the adjoining tissue. The ulceration was evidently due to the casting off of the necrotic tissue. The necrosis was due to the pressure of the laryngeal tube.

In the earlier cases in which there was a definite membrane the diphtheria bacilli were found almost without exception in the histological preparations. In the later cases they generally were missed, although in some instances they were present in large numbers. They were found chiefly in clumps of varying size, on the surface of the membrane. This was particularly the case in the trachea, but was not

so obvious in the tonsils. The clumps of bacilli varied in size from small groups in which all the bacilli could be counted to large masses of the micro-organisms filling the entire field of an immersion. In the vicinity of the large masses very small groups of bacilli were found. Even when growing on the surface the bacilli were in the necrotic tissue and fibrin and not in free masses. In á few specimens groups were found deep down in the membrane, but these groups usually did not stain so brightly as those on the surface. They were often found on the surface in what could be recognized as degenerated epithelial cells, filling them up, and small groups were found corresponding in size and shape to such cells. In three cases in which the hyaline membrane with thick reticulum was very evident the bacilli were found growing on the surface in this membrane, forming with a low power a blue mass having the form of the reticulum. With higher power the single bacilli could be recognized in the reticulum, in some cases filling this up, or single ones were seen on the surface. Occasionally they were found scattered in considerable numbers in the depths of the membrane enclosed in polynuclear leucocytes. In but one case of extensive membrane formation in the pharynx were they found below the surface, and here they were enclosed within polynuclear leucocytes.

In no case were the bacilli found in connection with the epithelial degenerations, which probably should be regarded as the initial lesions in the membrane formation. This was very evident in the œsophagus, where apparently the very earliest lesions were found. In one section, which showed only superficial desquamation of the epithelium with vacuolation and direct nuclear proliferation, close examination failed to show a single bacillus, while numbers of them were found in an adjoining piece of membrane.

In many cases where the bacilli were most numerous they were growing on the membrane in pure culture; no other organisms seemed to be mixed with them. In no case were other organisms found mixed with the bacilli in the single clumps. As a general rule, where the bacilli were most

prominent the other organisms were least evident. Of the other organisms, cocci were the most numerous. In one section of the epiglottis small groups of very large brightly staining cocci similar in appearance to the large cocci so often found in throat cultures were found. Cocci in diplococcus form often were found enclosed in pus cells. Streptococci were more common in the tonsils. In one case in which there were extensive necroses extending from the crypts into the tissue, large masses of streptococci were found in the necrotic tissue. Occasionally the necrotic masses on the surface were filled with masses of cocci forming a dark rim around the edges. The membrane and necrotic masses on the surface were in two cases found to be invaded by a leptothrix, forming a dense mass of closely woven long threads parallel to one another.

It was interesting to see that the membrane and the necrotic tissue in connection with it could be invaded by fungi. In a section of the epiglottis which contained membrane with bacilli, there was an area in which the membrane was broken down into a mass of detritus. In this the mycelium of a fungus was found with the threads growing perpendicular to the surface. The growth extended down to the tissue beneath, but did not invade it. A similar condition was found in another case on the surface of the tonsil, and here the threads of the mycelium extended into the tissue and were surrounded by cells. That such a growth of a fungus can extend deeply into the tissue was shown in a section of the tonsil in one case. In the tonsil there was a slight formation of membrane on the surface containing diphtheria bacilli and cocci. Deeper down in the tissue and close to the crypt were a number of giant cells arranged around filaments of the mycelium of a fungus. The filaments stained imperfectly and probably were degenerated.

In only one case was there distinct membrane formation on the skin. The superficial epithelial erosions in the vicinity of the nares and the lips are generally covered by a thin scab and not by a definite membrane, although diphtheria bacilli were found in them on culture. The only case that was in-

vestigated histologically was one of membrane of the ear following diphtheritic otitis media with perforation of the drum; the infection of the ear took place from the discharge running down over it.

B. C. H., '97 371. Child two years old.

Posterior third of tongue is covered with a dirty greenish-gray membrane which extends out over the tonsils, both of which show losses of substance and are covered by dirty gray necrotic material. The membrane extends backwards over the pharynx, epiglottis, and into the larynx to a point just below the vocal cords. The membrane is extremely dirty and foul smelling, and can be removed with slight force, leaving a granular surface beneath. Trachea and bronchi normal.

Stomach. — At the junction of the œsophagus and stomach there are 3 small losses of substance covered with a thin grayish membrane. These areas are about the size of half a pea. Around them the mucous membrane is hyperæmic and covered with mucus.

Nose. — The membrane extends from the pharynx up into the posterior nares, which are filled with thick, firm, greenish, foul-smelling membrane which can be easily removed.

The left antrum of Highmore contains a grayish-white fluid, and from its walls small pieces of false membrane can be stripped off. Right antrum shows a similar condition.

Right external ear. — The entire lower and posterior portions of the ear are reddened and covered irregularly with a thin whitish false membrane. Behind the ear is a fissure 1.5 cm. long, covered with membrane of same character. For an area of 2 to 3 cm., all around the ear, the skin is reddened, and shows a slight serous exudate and desquamation of the epithelium. The external meatus contains a small amount of cloudy fluid. The middle ear and mastoid cells are filled with a dirty greenish-yellow purulent fluid, of extremely foul odor. The membrana tympani is ruptured. Cultures from membrane on external ear show diphtheria bacilli and the staphylococcus aureus; from right middle ear diphtheria bacilli, the streptococcus, and the pneumococcus.

Microscopical examination of the ear showed on the surface a mass composed of blood and dried exudation, and beneath this a fibrinous reticulum enclosing pus cells. In places this mass lay upon the epithelium, which was comparatively intact, although the horny cells were swollen and separated. In other places the epithelium was entirely removed, or only the lower layers were preserved. In many of these places there was the same hyaline degeneration of cells

and fibrin formation between them which has been described in the œsophagus. The inflammation was essentially hæmorrhagic. (Plate XVIII., Fig. 1.) The blood vessels were distended, there was hæmorrhage around them, and the entire tissue contained great numbers of blood corpuscles. Blood corpuscles were found in the membrane on the surface, and in the epithelium. Pus cells were present in comparatively small numbers. There was extensive fibrinous exudation in the tissue beneath, which was continuous with the membrane on the surface. This particularly involved all the epidermic appendages, and extended into the hair follicles and into the glands. The sebaceous glands were often filled with a mass of reticular fibrin, and the cells were nearly all necrotic with fragmented nuclei. In the deeper tissue there was a fine fibrinous exudation, œdema, and degeneration of the muscle fibres. There were numerous cocci on the surface, and in the necrotic tissue small masses of diphtheria bacilli which stained very imperfectly.

We have taken from the clinical records the following excerpts relating to other skin lesions:

Subcutaneous ecchymoses occurred in 2 cases. In 1, a child aged four and one-half years, they appeared on the fourth day and were quite generally distributed; in the other, aged six years, they were limited to the lower extremities.

Erythema multiforme appeared on the third day in a case aged fifteen years.

A vesicular eruption with slightly blood-stained fluid appeared in a child four years old. It was distributed over all parts of the body. The vesicles first appeared on the fourth day and increased in number up to the seventh day.

We have found in the literature the following references to diphtheria of external parts:

Prescott found diphtheria bacilli in the vesicles produced by a poultice applied to enlarged lymph nodes of the neck. Cultures from the throat and nose were negative. Cases of diphtheritic conjunctivitis have been reported by Babes, Elschig, Kalisko, Paltauf, Escherich, and Wright. Neisser

reports a case in which diphtheria bacilli were found in inflammatory tissue around the anus. Dr. Abner Post has also found a diphtheritic inflammation of the skin around the anus with diphtheria bacilli in the cultures, in a case in which no bacilli were present in the throat and nose. (Case not previously reported.) Wright reported a case of diphtheritic conjunctivitis due to diphtheria bacilli; 7 cases of ulcers and abrasions of various parts of the body in which the bacilli were found; and also 1 case of fistula in ano. Park reported 2 cases of wound of a finger in which diphtheria bacilli were found; McCollom 2 cases of diphtheria of penis; Brunner 1 case in which diphtheria bacilli were found in a phlegmon of the scrotum, and 3 cases in which the bacilli were found in various inflammatory processes of the fingers; Flexner and Pease 2 cases of primary diphtheria of the lips and gums. There are quite a number of reports of diphtheria of the female genitalia. Maultain, Nisot, Longyear, Stahl, Bumm, report cases of diphtheria of the uterus developing in the puerperal period; Williams and Müller cases of diphtheria of vagina and external genitalia.

Summary.

We have never found the diphtheria bacilli growing in the living tissue, or in connection with those degenerative lesions in the epithelium which can be regarded as the primary lesions of the disease. They were found in the necrotic tissue and in the exudation, usually only in the latter. In a very few cases the bacilli were found enclosed in pus and in necrotic epithelial cells. They were nearly always found in clumps and masses. The masses found deep down in the membrane probably do not represent a downward growth in this, but have been covered up by a further formation of membrane on the surface. The diphtheria bacillus shows in its growth an affinity for solid structures, and is found rather on the reticulum than in the spaces between. It seems most probable to us that the beginning of the lesions is due to the toxic action of bacilli possibly growing in the fluids of the mouth

or throat. When necrosis is once produced the necrotic tissue forms a suitable culture medium. Usually other organisms, particularly the pyogenic cocci, are found associated with it, though not intimately. The membrane and necrotic tissue may also be invaded by fungi.

The membrane formation is due to a combination of processes. It seems probable that the first step in its production is degeneration and necrosis of the epithelium, often preceded by active proliferation of the nuclei of the cells by direct division. The cells may either break up into detritus, with fragmentation of the nuclei, or they may become changed into refractive hyaline masses. An inflammatory exudation rich in fibrin factors comes from the tissue below, and fibrin is formed when this comes in contact with the necrotic epithelium. The fibrin in part is formed into a reticulum around exudation cells and degenerated epithelium, in part it combines with the hyaline degenerated cells to form a hyaline membrane. It is probable that a hyaline membrane may be formed without the exudation; in this case the network of the membrane represents the edges of the cells, and the spaces the former nuclei. The hyaline membrane is most often formed on those surfaces which are covered with epithelium having several layers of cells. It may be formed by a hyaline degeneration of exudation cells; in this case the spaces in the meshwork are smaller. It is probable that the fibrinous membrane is formed both on the surfaces and in the tissue. The fibrin is first formed around cells which afterwards disappear. In the trachea the fibrinous membrane often has a definite structure. The membrane may disintegrate and be broken up into a mass of detritus (the process commences on the surface), or it may be cast off as a whole by being elevated by an exudation beneath. Very thick masses of membrane may be formed by the constant addition of fibrinous exudation. The membrane is never formed primarily on an intact epithelial surface, but it may extend over it. Nothing is to be gained by making an anatomical distinction between a croupous and a diphtheritic membrane. There is nothing specific in the membrane formation in diphtheria.

We have found typical hyaline and fibrinous membranes in cysts of the ovary in the formation of which bacteria played no part.

The membrane formation is accompanied by changes in the tissue beneath, which represent a combination of degeneration and exudation. The connective tissue and blood vessels undergo a hyaline fibrinoid degeneration very similar to the degeneration of the epithelium. Necrosis may extend deeply into the tissue, but there is little tendency to deep ulceration or abscess formation. The degeneration in the mucous glands of the tissue is so pronounced as to be almost specific. Marked degeneration of the epithelium of the glands may be found without any change in the surrounding tissue. The changes in the blood vessels, though so pronounced in diphtheria, are not specific. We have frequently found changes in all respects similar in the walls of abscesses and ulcers. The extent of the necrosis in the primary lesions is greater than is found in the action of any other bacteria.

HEART.

The changes produced in the heart in diphtheria have received more attention than have any of the other visceral lesions. Most of these investigations were undertaken with the view of finding in pathological conditions in the heart an explanation of the clinical evidences of impaired cardiac action. The earlier investigators regarded the presence of clots (there was no distinction made between these and thrombi) as a sufficient explanation of the clinical conditions. Apart from the work of Mosler, who described degenerative conditions in the heart muscle in diphtheria, the first careful anatomical investigation of the heart in diphtheria was by Hayem. He described changes in the muscular tissue consisting of granular and fatty degeneration, and of changes in the vessels and in the interstitial tissue. He was undoubtedly the first to describe the acute interstitial myocarditis. He says the muscular fibres atrophy, there is an increase in the connective tissue, and new elements appear between the

fibres. He particularly describes large granular cells of irregular round or oval form which lie between the fibres, and have one and sometimes two nuclei with evident nucleoli. There were also smaller cells analogous to leucocytes. He supposed that new muscular fibres were formed from the large cells. Shortly before the work of Hayem, Desnos and Huchard investigated the heart in cases of smallpox, but their work did not add to our knowledge of the pathological anatomy. Rosenbach described granular and waxy degeneration of the muscular fibres and cellular infiltration of the interstitial tissue. There was proliferation of the nuclei of the muscular fibres following the degeneration, and large cells were produced which took the place of the muscular fibres. The interstitial infiltration was most marked beneath the pericardium, the degeneration beneath the endocardium. Birch-Hirschfeld found acute interstitial myocarditis in two cases of diphtheria in which death took place suddenly. Leyden found fatty degeneration of the muscular fibres, increase of their nuclei, and cellular infiltration around the blood vessels. In two of the three cases he investigated there were areas of acute interstitial myocarditis, and he regards this as the essential pathological condition and the cause of the heart paralysis. The interstitial change was accompanied by degeneration of the fibres, but was not dependent upon it. In one case he examined the vagus nerve and found it normal. Unruh describes myocarditis in localized areas and fatty changes in the cardiac muscle. He does not think the heart failure is due to changes in the nerves, because it is an early symptom and the definite paralyses appear later. He asks why the nerves of the heart should be affected so early and the other nerves later. The dilatation of the heart also shows that the cause is due to changes in the muscle. Martin described in both typhoid fever and diphtheria acute endarteritis in the coronary arteries, and regarded the degeneration of the myocardium as secondary to this lesion. Huguenin found granular and hyaline degeneration of the muscle fibres, increase of connective tissue, much increase of the nuclei, and small hæmorrhages. He speaks of parenchy-

matous and interstitial myocarditis, and of proliferating endarteritis. He found the pneumogastric nerve and medulla normal. Oertel found degeneration and foci of interstitial infiltration. There was a general increase both in the size and number of the nuclei of the muscle fibres. The nuclei often were several times their normal length and were irregular in outline. Appearances indicating direct division were seen, but this was regarded as indicating degeneration. The greatest change found by Oertel in one of the three cases examined was immediately beneath the endocardium adjacent to the coronary arteries. The enlargement of the nuclei of the muscular fibres had previously been described by Ehrlich in a case of pernicious anæmia, and was regarded by him as a degenerative condition; he believed that the nuclei enlarged to take the place of the diminished muscular fibres. Schemm describes fatty and granular degeneration of the heart muscle fibres, with swelling and increase of the nuclei, and a slight hyaline degeneration and atrophy. The connective tissue is often rich in cells, and in one case he found blood extravasations. Savigne found the muscular fibres variously altered and embryonic infiltration of the interstitial tissue with round and lymphoid cells. He thinks the interstitial change does not necessarily lead to increase of the connective tissue. Rabot and Philippe describe granular degeneration of the muscular fibres of the heart, with a slight increase in the size of the nuclei, and with small areas of inflammatory infiltration. They found no changes either in the peripheral nerves or in the central nervous system, and conclude that the essential process in the heart is an interstitial myocarditis. By far the most important article on the condition of the heart in diphtheria is that by Romberg. He studied sections made from a number of different places in the heart in eight cases of diphtheria and found great variation in the extent of the lesions. A section cut from one part of the heart may be normal, while one from another part may show extensive lesions. There were small foci of leucocytic infiltration around the smaller coronary arteries, while the larger were intact. Degeneration of the muscle

fibres was the most marked lesion. The fibres most degenerated had no nuclei. He also describes a peculiar vacuole formation in the centre of the fibre. Krehl had previously described this condition and regarded the vacuoles as due to fat.[1] He found a marked change in the nuclei of the muscular fibres consisting of hypertrophy with an accompanying vesicular condition which he regarded as degeneration and not indicating nuclear proliferation. The inner and outer portions of the myocardium were most subject to degeneration. Interstitial changes were found in all cases. They were in foci and were more common beneath the pericardium. The interstitial change consisted of cellular infiltration around the vessels and between the fibres. Most of the interstitial cells were leucocytes, but among them were large cells similar to those described by Hayem. There was no connection between the degeneration of the muscle and the interstitial infiltration. He thinks the large cells may be myoplastic, but he has never seen striation in them. The interstitial foci may heal, suppurate, or lead to areas of fibrous myocarditis. There was pericarditis in 5 of the 8 cases and endocarditis in 3. Arnheim examined the heart in 8 cases and found degeneration in 3. Hesse examined the heart in 29 cases and found but little in the macroscopic examination save dilatation of the apices of the ventricles in prolonged cases. In one case of 28 days' duration both ventricles were dilated and hypertrophied. The parenchymatous changes were not marked under 3 days and were more evident in the right than the left side. In 25 of the 29 cases there was some interstitial myocarditis, and in 4 it was pronounced. It was noticeable in the first week of the disease, but was more marked in the third and fourth. The left ventricle was most often the seat of the interstitial change. The cells in the interstitial tissue were leucocytes, and their presence was due to changes in the vessels produced by the toxin in consequence of which they become more penetrable. He concludes that the sudden death in diphtheria is due to heart

[1] It is possible that the condition of vacuolation described by Romberg did not refer to the actual fat vacuoles, but to the disappearance of the contractile elements in the centre of the fibre, a degenerative condition often met with.

failure brought about by the action of toxins on the heart. Preisz in one case of death from heart failure found that the muscular fibres of the heart had lost their striations and were granular, while the nerve cells stained by Nissl's method showed no change. Vincent in a case of sudden death due to diphtheria found no change in the muscle save loss of striation of the muscular fibres. There was some increase in the nuclei of the sarcolemma, and the connective tissue cells were increased about the blood vessels. The vessels of the heart were dilated, but there was no cellular infiltration or hæmorrhage, and no changes in the nerve cells. The myelin sheaths of the nerve fibres in the pneumogastric nerve were thickened in places, but there was no marked degeneration. The sympathetic nerve was normal, but in the lower cervical sympathetic ganglion some of the cells showed granular degeneration. In the cardiac plexus he found marked changes. There was intense parenchymatous degeneration and absence of the axis cylinders. The capillaries were dilated and the nerve cells were granular, vacuolated, and in some there was loss of the nucleus and nucleolus. Schamschin found in addition to the degeneration of the muscular fibres, which was more pronounced in the papillary muscles, fatty degeneration of the walls of the small blood vessels and of the cells contained in them. The cells in the interstitial tissue he regarded as emigrated leucocytes. Papkow examined the hearts of children from one and a half to nine years old who had died of diphtheria from the third to the fourth day, without treatment by antitoxin. In all cases there was extensive fragmentation of the muscle, with white and red blood corpuscles between the fragments. The cause of the fragmentation was the swelling and destruction of the cement substance. He thinks this is an early change and he ascribes it to the cardiac weakness which is often seen as early as the third day. The waxy degeneration and interstitial changes belong to a later period of the disease. Scagliosi found chiefly degeneration of the muscle affecting groups of fibres. He did not find that interstitial processes play any decided part in the alterations. There is fatty de-

generation of the small vessels, in consequence of which the toxin passes through more rapidly. Hallwachs investigated the myocarditis of diphtheria in 14 cases. There was great degeneration and often complete destruction of the muscle fibres; the nuclei persisted longest. Interstitial small cell infiltration was found from the fourth day on and was most extensive in the third and fourth weeks. There was no alteration in the vessels. The ganglia were normal and only slight parenchymatous changes were found in the nerves. Growth of the connective tissue was observed as a secondary change. The changes in the heart produced experimentally by the inoculation of the diphtheria bacilli or their toxins have also been studied. Welch and Flexner described fatty degeneration and necrosis of the muscle fibres, and later Flexner described swelling and deeper staining of the nuclei with final disappearance. No proliferation and no interstitial changes were found. Comba found in animals essentially the same changes as those described, namely, degeneration of the muscle fibres with increase in the interstitial tissue, and regards these changes as independent of each other. Mollard and Regand made a careful study of the degeneration produced experimentally. The appearance of granulation in the muscle they think is due to a displacement or breaking up of the fibrillæ. It is frequently seen in longitudinal section of the fibre, while invisible on cross section. They have also observed the disappearance of the transverse striation with preservation of the longitudinal, or the transverse striation may be exaggerated. A frequent condition is atrophy of the sarcous elements, with increase in the protoplasm around the nucleus. The apparent vacuolation of the fibres is due to an alteration of the contractile substance, which becomes homogeneous. Vascular lesions consisting of cellular infiltration of the adventitia with degeneration of the media and intima were constantly found. There was no increase in the connective tissue cells; the cells found in the interstitial tissue were leucocytes. In another publication by the same authors chronic changes produced by the administration of very small doses of the toxin are described. In two rabbits that

were treated in this way for five months, the consistency of the myocardium was increased and white patches found in it. These proved to be areas of fibrous myocarditis which followed the acute degeneration.

In addition to routine examination of fresh sections at the autopsy to determine fatty degeneration a more complete examination was made in 60 cases. The same methods of hardening and staining were used as in the case of the other tissues. The examinations of the heart are incomplete in that the condition of the cardiac ganglia and nerves was not investigated, nor was a sufficient number of pieces from different parts of the heart examined. As a rule pieces were taken for examination from the interventricular septum and from the wall of the left ventricle near the aorta.

Fatty degeneration of the muscular fibres varying in extent and degree was found in 36 of the 60 cases. The presence of fat was determined in most cases by fresh examination at the autopsy. In thin sections of tissues hardened in Zenker's fluid it is easy to determine any considerable degree of this degeneration (Plate XXI., Fig. 1) by the large vacuoles left in the fibres after the fat is dissolved out, but the minor degrees will escape observation. It is probable that the number of cases given is below the actual number, for fresh examinations were made in only 40 of the 60 cases, and it might have been missed in the examination of the hardened sections. Of the 40 cases in which fresh examinations were made it was present in 29. In all there were fresh examinations made in 67 cases, this including the 40 cases in which hardened sections were examined as well, and in 46 of the 67 cases fat was found. The extent of the degeneration varied greatly. In some cases it was denoted only by the fine longitudinal rows of dots in the muscular fibres, in others there seemed to be but little of the substance of the fibre remaining. The fatty degeneration was in some cases the only change recognizable in the muscular fibres, but it was constantly found accompanying the more advanced forms of degeneration leading to necrosis and complete destruction of

the fibres. In the least marked cases it was diffuse; only single scattered fibres were affected. Cases were found, however, in which there were areas of marked degeneration, and between these areas occurred single degenerated fibres. It was always more marked in the vicinity of the endocardium than elsewhere. There was but little relation between the duration of the disease and fatty degeneration; it was found in cases of short and of long duration. It was generally the only lesion of the myocardium in the cases of great severity which died shortly after entering the hospital.

Segmentation of the myocardium, separation of the fibres along the line of juncture, without other serious lesion, was not found in a single case. There were numerous cases of fragmentation and rupture of the muscle fibres in the degenerated areas, and this condition was sometimes accompanied by slight degree of segmentation. It seemed to us that this was probably due to the good preservation of the tissue and the care exercised in making the sections. In the routine examinations of the myocardium made at the City Hospital we have been surprised at the infrequency of this lesion, which, according to the observations of some authors, should be regarded as one of the most common lesions of the heart.

In 13 cases very much more extensive degeneration leading to complete destruction of the muscle fibres was met with. (Plate XXI., Fig. 4.) This was always accompanied by fatty degeneration, and in some cases seemed to be preceded by it. This degeneration affected all parts of the muscular fibre, the contractile elements, the protoplasm, and the nucleus. In some cases the disappearance of the contractile elements was the most obvious lesion. In preparations stained with iron hæmatoxylin, which brings out sharply the markings of the muscle fibres, cross-sections showed numerous fibres which were generally swollen, and in which the markings had disappeared to a greater or less extent. In the least marked cases the degeneration took place in the centre of the cell. Fibres were frequently found in which there was but a small margin which was normal. In some cases the sarcous elements seemed to have disappeared, and their place was taken

by granular material; in others the rods were swollen and fused together. Many of the fibres contained large rather irregular vacuoles which could be distinguished from the fat vacuoles by their large size and irregularity of shape. A further form of degeneration consisted in the complete destruction of the fibrillæ with the formation of large irregular hyaline masses, which stained with hæmatoxylin. Cross-sections showed entire fibres converted into a hyaline mass, which often showed fine lines of fracture radiating from the centre. Longitudinal section of fibres which were least degenerated showed increase in the protoplasm around the nucleus. The protoplasm was coarsely granular, and contained hyaline. In the least marked cases only single scattered fibres were degenerated, and surrounded by fibres which were unchanged. On longitudinal section, the degenerated muscle cell frequently adjoined a normal cell which showed striation. In one case almost every fibre in a section from the interventricular septum was affected; but the degeneration was not extreme, and affected only the centre of each fibre. Where the degeneration was extreme, it was both general and focal; areas were found in which almost every fibre was destroyed. In one case it was estimated that at least one-third of the total substance of the heart was destroyed. There was a definite relation between this intense degeneration and the duration of the disease. It was found only in the later stages. The average duration of the 13 cases was 15 days. The degeneration was present in slight degree in 1 case of 6 days' duration, and was best marked in 2 cases, 1 of 20 and 1 of 13 days' duration. It was also extensive in 1 case of 42 days' duration. The degeneration was always more intense on the endocardial side than elsewhere, and in 1 case was limited to the fibres of the papillary muscles. Various changes in the nuclei were almost universally found accompanying the degeneration of the fibre. The most common condition observed in the nucleus was swelling and increased vacuolation. The degenerated nucleus was vesicular, and the edge often remarkably irregular. Not infrequently two or even a series of such nuclei were found together. This evi-

dent increase in the nuclei was due to direct division, nuclear figures never being found. The constriction of the nucleus, and the changes in the chromatin indicative of direct division, were often seen. In addition to these changes consisting of vesicular swelling and direct division, the changes described by Romberg were frequently observed, particularly in the least altered fibres of degenerated areas. The nuclei stained intensely and homogeneously, and were often enormously enlarged, so that they were several times the size of the normal. No evidence of either direct or indirect division was seen in these degenerated nuclei.

In several of the earlier cases there was well marked œdema of the tissue. Not only were the septa between the muscle masses wider, but the single fibres were often separated from one another. In the case in which this was best marked there was an increase in the weight of the heart which was probably due to the œdema.

Interstitial lesions consisting of cellular infiltration (Plate XXII., Fig. 1) of the interstitial tissue with or without an actual increase in the tissue were found in 18 of the 60 cases. We have not included in our series those cases of degeneration in which polynuclear leucocytes were found in and between the degenerated fibres. Acute interstitial myocarditis is focal, although in addition to the well marked foci there may be some general increase in the cells in the interstitial tissue. It may or may not be accompanied by degeneration. Two forms may be distinguished, and it is uncertain whether or not they can pass into one another. In one case small areas are found, often in the midst of unaltered muscular fibres, in which the interstitial tissue both in the septa and between the single fibres is dilated and infiltrated with cells. Polynuclear leucocytes are but rarely found among these cells. Nearly all observers have called attention to the large size and peculiar character of these cells. The most of them are plasma cells of the same character as those found in the interstitial tissue of the kidneys and other organs. Among them are lymphoid cells which are so often found in connection with them. The number of cells varies,

but they are rarely found in the compact masses in which they are seen in the kidneys. The foci are usually small and not sharply circumscribed; the cells extend from the focus into the surrounding tissue. Among the plasma and lymphoid cells larger cells with an epithelioid nucleus are sometimes found. Occasionally eosinophile cells are found in the foci, and in one case they were numerous. These cells had but a single nucleus and were similar to those found in the bone marrow. The number of these foci varies, but they are always more numerous close beneath the endocardium than elsewhere. In one case the interstitial change was confined to the papillary muscles. Cells similar to those in the interstitial tissue were found in the vessels in the foci. This form of interstitial myocarditis must be considered a rather rare heart complication in diphtheria. It is usually accompanied by degenerative changes in the muscle, but does not seem to be dependent on this, as the degeneration is not more marked in the interstitial foci than elsewhere. This form of interstitial myocarditis was found in but 6 cases. The average duration of the disease in these 6 cases was 10 days.

The other form of interstitial myocarditis was accompanied by and seemed clearly secondary to degeneration. The interstitial tissue, particularly in the septa, was dilated and infiltrated with large cells of an epithelioid character. There were a few lymphoid and plasma cells among them, but the epithelioid type predominated. In addition to the cellular infiltration there was in some cases considerable formation of connective tissue. This was particularly marked in one case of 42 days' duration. The average duration of the 14 cases was 17 days.

Changes in the vessels of the heart were not marked. In one case there was a recent thrombus in a branch of the coronary artery. In several cases the very rare condition of general capillary injection was found; death had evidently taken place in diastole and without further contraction after death. We do not remember of ever having seen this condition of general capillary injection of the heart in any other

case. The capillaries were very numerous, very small, and there was very little connective tissue about them. In the cases of marked degeneration accompanied by interstitial changes there was proliferation of the endothelium of the small veins and sinuses. The endocardium in two cases showed the same condition. There was some cellular infiltration in the vicinity of the veins, but this condition was not marked. No lesions were found in the arteries which could be attributed to the acute infection. In one case of thrombosis in an adult there was advanced endarteritis which probably had nothing to do with the acute infection.

Heart thrombi were found in 8 of the 60 cases. The thrombi varied in size and situation. They varied considerably in character. In two cases there were very few white corpuscles present; the mass of the thrombi was composed of blood platelets with separating masses of fibrin. (Plate XXI., Fig. 2.) The connective tissue stain of Mallory is admirably adapted to the demonstration of the blood platelets. One case was peculiar from the large number and variety of the cells included in the thrombus. These were chiefly large mononuclear leucocytes, and among them there were numbers of plasma cells and large and small lymphocytes. The endothelial lining of the endocardium was always absent beneath the thrombi, and there was cellular infiltration extending into the adjacent myocardium. In one case of thrombosis of the auricle there was evident necrosis of the endocardium, and the necrotic tissue was infiltrated with polynuclear leucocytes, many of which were fragmented. Although this was the only case in which it was possible to demonstrate the connection between the thrombi and necrosis of the endocardium it seemed probable that the thrombus formation in all cases may have depended upon this and that the primary area of necrosis was not included in the sections. No bacteria were found in the thrombi on microscopic examination, although careful search was made for them. There seemed some relation between the thrombi and the interstitial changes. In 7 of the 8 cases there was not only cellular infiltration of the tissue in the vicinity of the thrombus, but the heart elsewhere

was the seat of an interstitial myocarditis. Thrombi usually occurred in the cases of longer duration. The average duration of the 8 cases was 16 days. The most recent case was one of 6 days, and the longest one of 42 days.

In but three cases was there hæmorrhage into the myocardium, exclusive of the numerous cases in which small foci of hæmorrhage were found in both the peri- and endocardium. In two of the cases the hæmorrhagic foci were small and not numerous, and in one they were extensive. The hæmorrhages were not accompanied by extensive degeneration or by interstitial changes. The three cases in which they occurred were all of them of short duration.

In three cases there was pericarditis. In two of these the condition was acute, in one of long duration. In one of the acute cases the relation of the fibrinous exudation to the lining cells of the pericardium was beautifully shown. The exudation was on the surface of the endothelium, which was preserved and formed a line of proliferating cells. Here and there were small foci in which fibrin was found below the surface as well. In the more chronic case the fibrin had in great part disappeared or was converted into hyaline masses which were partly on the surface, partly enclosed by granulation tissue. The granulation tissue contained large numbers of plasma and lymphoid cells, among which were numerous large connective tissue forming cells. On the surface there was a line of these large cells. In this case the endothelial lining had almost entirely disappeared, and was represented only by the cells lining large cavities in the granulation tissue.

Summary.

Degeneration of the myocardium is one of the most common conditions found in diphtheria. The simplest form of this is fatty degeneration, which is found in the majority of all cases. This varies in extent, at times affecting the myocardium generally, at times occurring in foci. It may appear only in the form of fine granules at the junction of the cross and longitudinal striations, or in large globules which involve

the greater part of the substance of the muscle cell. The fatty degeneration accompanies and seems to precede the more advanced forms of degeneration which lead to the complete destruction of the muscle. In this there is destruction of the sarcous elements, which become swollen, broken up, and converted into hyaline masses. In other cases large vacuoles are formed in the cell, which differ in size and in their irregularity of shape from the fat vacuoles. Fragmentation and fracture of the degenerated muscle cells is often found, but the segmentation or separation of the cells along the line of junction does not take place, or is very limited in extent. Simple fatty degeneration is found in the severe cases of short duration, the more extensive degenerations in the more prolonged cases. The degenerations may be so extensive as to account fully for the impairment of the heart action. No bacteria are found in connection with the degeneration, but like most of the lesions of the disease it is due to the influences of the toxic substances in the blood.

Acute interstitial lesions of two sorts are found. In one there are focal collections of plasma and lymphoid cells in the tissue, which may be accompanied by degeneration of the myocardium, but are not dependent upon it. This condition is analagous to acute interstitial nephritis. In the other condition the interstitial change consists of a proliferation of the cells of the tissue and is secondary to the degeneration of the muscle. It is probable that this may lead to extensive formation of connective tissue and some of the cases of fibrous myocarditis may be due to this.

Thrombosis is not an uncommon condition and is due to primary necrosis of the endocardium. Lesions of the vessels of the heart play but little part; the only lesion of interest is proliferation of the intima, the same lesion which is frequently found in the vessels in other organs.

LUNGS.

In the course of our investigations of the lungs we have found it necessary clearly to define certain anatomical features. The simplest conception of the lung is that of a race-

mose gland; the bronchi represent the excretory ducts, and the lining epithelium of the alveoli the secreting epithelium of the gland. Each lung is divided into lobes by deep constrictions extending nearly to the hilum. The lobes are subdivided into the lobules, and each lobule into a number of small areas which, carrying out the analogy with the gland, we propose to call acini.[1] The acinus is composed of the terminal bronchus and the various air spaces connected with it. The acinus corresponds to the lobule of the lung as described by Miller.

On a section made through the interior of the lung the lobules cannot be distinctly made out. If the pleural surface of the lung of an adult be examined, a network of dark lines usually can be seen, which are due to carbon pigment in the tissue, surrounding the lymphatic plexus of the pleura. These lines more or less clearly mark out the lobules of the lung and they always correspond to the interlobular septa, although they may enclose several lobules. If a section is made perpendicular to the pleura, particularly in an œdematous lung, small bands of connective tissue can be seen extending from the pleura between the lobules. Usually the lobule does not receive a complete investment with connective tissue. From the larger masses of connective tissue small septa are given off which penetrate within the lobule and to a slight extent separate the acini. (Plate XXX., Fig. 1.) The lobules vary in size, and according to Laquesse and D'Hardeviller may each contain from 50 to 100 acini. On the pleura they have a more or less triangular shape; the base corresponds to the pleura, and the bronchus and artery enter at the apex. In the interior of the lung they are naturally of irregular shape. The lobules and their relations are well shown in corrosion specimens of lungs which are incompletely injected from the bronchi, so that only some of the lobules are filled with the injection mass. The bronchus and artery after entering the lobule divide rapidly but not

[1] In describing this ultimate area of the lung as an acinus we have followed Orth. In the admirable article on the pathological anatomy of the lung contained in his textbook he says, "Man nennt einen solchen Abschnitt des Lungenparenchyms, der aus je einem Endbronchus hervorgeht einen Acinus."

dichotomously. The artery accompanies the bronchus throughout. The veins always run in the interlobular septa and in the small masses of connective tissue which imperfectly separate the acini.

According to the description of Miller the terminal lobule which we call acinus is formed in the following manner: The bronchus after a final division terminates in the bronchial passage (bronchiole) from which single alveoli are given off, and which has a greater diameter than the bronchus. (Plate XXVIII., Fig. 2; Plate XXVII., Fig. 5.) The bronchial passage after a constriction terminates in several dilatations called atria (Plate XXVII., Fig. 4), from which are given off a number of large air sacs (infundibula), and from these the air cells (alveoli) arise by partitions springing from the walls. There are constrictions at the beginning of the bronchial passage, at the atria, and at the air sacs. The artery extends along the bronchial passage, and its last divisions can be recognized in the walls of the atria. The atria can always be easily distinguished from the other spaces in the lung by the presence of a small amount of muscular tissue. Muscular tissue is usually not found in the wall of the bronchial passage. The epithelium of the bronchus becomes low columnar in the bronchial passage and then passes into the extremely thin epithelium lining the air spaces. In the normal lung it is extremely difficult to demonstrate the epithelium lining the alveoli, and to distinguish the nuclei of the epithelial from the nuclei of the vessels. In pathological conditions it so readily becomes swollen and proliferates that it is often very conspicuous even with a low power. The ends of the projecting partitions, both those of the atria and those in the air sacs separating the alveoli, are sometimes covered with a cap consisting of several layers of epithelial cells.

The lymphatics are usually distended and are easily demonstrated by means of the hardening and staining employed. We distinguish two sets in relation to the lobule, one central, always accompanying the artery, the other peripheral, ramifying in the interlobular and interacinar tissue. The central lymphatics pass to the hilum of the lung, the periph-

eral lymphatics into the lymphatic plexus of the pleura. This is certainly the case with regard to lymphatics in the lung adjacent to the pleura, but we are not able to say positively that it holds for the lymphatics everywhere. We have never found any communications between the central and the peripheral lymphatics of the lobule. There are no distinct valves in the central periarterial lymphatics; in the peripheral they are very numerous and their position shows that the direction of lymph flow is towards the pleura. The large lymph vessels receive numerous smaller ones. A very effective valve is placed at the entrance of the small vessel into the large, due to the extension of the walls of the small vessel a considerable distance into the larger. The peripheral lymphatics accompany the veins, though they have not the same definite relations with these as have the central lymphatics with the arteries.

There is but a small amount of lymphoid tissue in the lung. In the walls of the bronchi, and to a less extent in the walls of the arteries and veins, there is considerable infiltration with lymphoid cells. In various places definite collections of lymphoid cells forming microscopic lymph nodules are found. These are always in close relation to lymphatic vessels; the mass of cells often projects into the vessel and is separated from its lumen by only a single layer of endothelium. Such small lymph nodules in the interior of the lung are more nearly related to the arteries than to the bronchi and veins. They are also not infrequently seen beneath the pleura. The lymphoid cells may extend from them for a considerable distance in the walls of the partitions. We have never found any such collections of lymphoid cell in the wall of the acini.

The macroscopical appearance of the lungs presented considerable uniformity. As the cases were mostly in children, there were rarely fibrous adhesions between the pleural surfaces. The lungs were usually voluminous, and contracted but little on opening the pleura. In most cases there was considerable injection of the vessels, and in some this was extreme. The most constant lesions were small areas of solidification which varied considerably in size. In many

cases they were sharply limited to lobules, in others they were much smaller, and in some they involved a number of lobules. The character of the solidification varied. In some cases the foci were so sharply circumscribed as to resemble tuberculous areas, but generally they were more diffuse and faded gradually into the surrounding tissue. They were usually of a reddish color, and the tissue around them was deeply injected, but in some cases they were grayish-red or even gray. Even when the solidification affected considerable areas it was not homogeneous; there were centres slightly elevated which were firmer than the other tissue. It was evident that these large areas were formed by the confluence of adjoining small areas. Such areas of bronchopneumonia were found in 131 of the 220 cases examined, or in 60 per cent. Of the 131, the areas were discrete in 76 and confluent in 55. In the majority of cases the posterior portion of the lung was affected and especially the lower lobes. This was particularly true of the confluent form. The occurrence of the discrete or of the confluent form does not appear to bear any relation to the variety of micro-organisms present, nor does the presence of membrane in the bronchi appear to influence the extent of the solidification. There is, however, a very definite relation between the presence of membrane in the lower respiratory passages and the occurrence of bronchopneumonia. Thus of 100 cases with membrane in one or more of the lower respiratory passages (epiglottis, larynx, trachea, or bronchi), bronchopneumonia was present in 72, or 72 per cent., while in the remaining 120 cases it was present only in 59, or 48 per cent. Of still more interest is the fact that of 76 cases which were intubed (in 7 also tracheotomy performed) all but 16, or 80 per cent., had bronchopneumonia. The cases of bronchopneumonia may further be divided into four groups:

I. Twenty-seven cases in which only one lobe of one lung was involved. Of these, in 13 the left lung was affected, in 14 the right. The areas were in the upper lobe in 7 cases, in the middle in 4, and in the lower in 16. In 8 cases they were confluent; in 19 discrete.

II. Twenty-one cases in which two or more lobes of one lung were involved. The left lung was affected in 8, the right in 13. All the lobes of the right lung were affected in 8 cases, the upper and lower in 5. In 13 cases the areas were discrete, in 5 confluent, and in 3 both discrete and confluent. These figures show that the right lung is more likely to be affected than the left.

III. Twenty-six cases in which one or more lobes of both lungs were involved. The lower lobes of both lungs were affected in 8 cases; the foci were discrete. All the lobes of the right lung with one lobe of the left lung were affected in 7 cases; the foci were discrete in 2, confluent in 3, and in 2 both discrete and confluent. Of the remaining 9 cases one or two lobes of each lung were involved; the foci were discrete in 9, confluent in 1, and in 4 both discrete and confluent. This shows further that when the affection involves both lungs it is more extensive in the right than in the left.

IV. Fifty-seven cases in which all the lobes of both lungs were affected. The foci were discrete, affecting mainly the posterior portion of both lungs in 30 cases, confluent in 12, and both discrete and confluent in 15.

In two cases, both associated with abscess, organizing pneumonia was found. In no case was there a definite lobar pneumonia, although in some of the most marked confluent cases but little of the lower lobes contained any air. On section the areas were usually smooth, though in some cases, particularly in adults, the cut surface was fully as granular as in lobar pneumonia.

The bronchi were usually affected. The mucous membrane of the large bronchi was reddened and covered with exudation, and usually small drops of pus could be forced from the small bronchi on pressing the cut surface of the lung. In 43 cases there was a fibrinous exudation in the bronchi, forming in the larger bronchi a distinct membrane, and completely filling the smaller. The membrane was similar to that in the trachea.

The tissue in the vicinity of the foci of solidification was generally œdematous, but there was but little general œdema

of the lung comparable to that so commonly found in adults. The œdema was in distinct relation to the inflammation; it was not the general œdema due to disturbances of the circulation.

Where the areas of bronchopneumonia adjoined the pleura the pleural surface was usually slightly cloudy and in some cases there was an evident fibrinous exudation confined to the small areas. In 18 cases there was pleurisy with fibrinous exudation, in 1 sero-fibrinous exudation, in 7 empyæma, in 1 pyopneumothorax, and in 1 hæmorrhage into the pleural cavity. A very common lesion of the pleura consisted of the presence of small ecchymoses, irregular in shape, and from 1 to 10 mm. in diameter. They were irregularly distributed over the surface, but were most numerous over the lower and posterior surfaces of the lung.

The lungs were examined microscopically in 133 cases. Those cases especially were selected for microscopic examination in which the tissue was best preserved and in which the lesions seemed to be most important. There was a close general agreement between the character of the lesions as determined by the naked eye and the results of the microscopic examination. In several cases in which no bronchopneumonia appeared macroscopically the microscope showed very small areas limited to an acinus or part of one.

From the examination of so many cases of bronchopneumonia, representing as they did lesions in every stage, it is possible to form a very definite idea of the mode of origin and extension of the process. What we have regarded as the earliest lesions were found in those cases which presented little or no change to the naked eye. As a rule there was considerable uniformity in the extent of the lesions shown in the sections from the same case.

The process begins in the atria (Plate XXVII., Fig. 3), with congestion of the vessels, cellular infiltration of the walls, and exudation into the lumen. As a rule the terminal bronchus is involved with the atrium (Plate XXVIII., Fig. 2; Plate XXVII., Fig. 5), but in several cases the atria alone were affected. No cases were seen in which exudation was found

in the terminal bronchi without affection of the atrium. From the atrium the exudation extends to the air sacs and alveoli connected with them. In some cases all the air sacs were affected, in others only a few. The exudation either fills the sacs or clings to the walls, leaving in the centre a round or oval space with sharp cut edges, evidently due to the presence of air. In a number of instances the solidification of the tissue was limited to single acini (Plate XXVIII., Fig. 1), while the adjoining acini were free from exudation. It would be possible to use the term "acinous pneumonia" to distinguish this condition. The larger areas are due to a similar process affecting a number of acini. The infection of these may have been simultaneous or have extended from one to the other. We are inclined to believe that there is little, if any, lateral extension from one acinus to another through the intervening walls. We have repeatedly seen cases in which all the air spaces of an acinus were filled with exudation while the spaces of adjoining acini were free. Moreover, when adjacent acini were affected, the character of the exudation in the different acini often varied. The large foci of solidification do not show the homogeneous character which would come from a lateral extension of the process. The general arrangement is that of a centre with complete solidification, and at the periphery a very irregular outline formed of single affected acini. Occasionally in these acini the process is limited to the atria, but generally it is more advanced. When the process extends it is by way of the bronchus; successive acini are infected when the bronchial infection reaches the terminal bronchi supplying them. From a single acinus in any part of a lobule, all the acini of the lobule can become affected. It seems to us that this better explains the frequently sharply lobular character of bronchopneumonia than the supposition that it is due to lateral extension. It is very striking to see how sharply the process is often limited to the lobule. (Plate XXX., Fig. 1.) On one side of the thin connective tissue imperfectly separating the lobules we may see complete solidification of a large area and on the other normal or slightly emphysematous tissue.

In cases of marked bronchitis, especially of the larger bronchi, there was exudation in the alveoli adjoining the walls of the bronchi; the affection evidently extended laterally through the bronchial wall, but this mode of infection of the lung is relatively unimportant because no considerable area of tissue is affected.

The character of the exudation varied in the different cases. It was generally of the same character in the different foci of the same case, but it often varied in the different foci and even in a single focus. In several cases the tissue around the larger bronchi contained a fibrinous exudation (Plate XXVIII., Fig. 4), while in other parts the exudation was cellular. Sometimes a single acinus had a fibrinous exudation. The most numerous cells in all cases and in some the only ones are the polynuclear leucocytes which are easily recognized by the irregular shape and intense stain of the nucleus, the granules in the protoplasm, and the definite cell membrane. They are found in the exudation, in the walls of the air sacs and alveoli, in the capillaries, and often in the act of migration. The nuclei and cells are generally well preserved, but in some cases there was extensive fragmentation of the nuclei. They frequently contained bacteria; the pneumococcus particularly was often found within them. Next to the polynuclear leucocytes the most numerous cells are those which in their general characters are similar to the so-called transitional leucocytes of the blood. These cells are generally larger than the polynuclear leucocytes, though they vary considerably in size. The nucleus is single, in shape round, oval, or curved; the nuclear membrane is distinct, and fine chromatin granules are contained within the nucleus. Nuclei are occasionally found which are nearly as irregular in shape as the nuclei of the polynuclear leucocytes. The protoplasm is not at all or only faintly granular and has not a sharp outline. The number of these cells varied greatly in the different cases, forming in some the most numerous or almost the exclusive cells of the exudation, while in others but few were found. They are phagocytic for other cells to a limited extent; polynuclear leucocytes,

lymphoid and plasma cells, or nuclear detritus sometimes are found enclosed in them. Bacteria of any sort are rarely seen within them. These cells are similar to some of the emigrated cells found in the rabbit's cornea after inflammation.[1] In the cases where they were numerous in the exudation they were also found in the septa and in the blood vessels, but they were never seen in the act of migration as were the polynuclear leucocytes. Pratt has described similar cells in acute croupous pneumonia, and in some of his cases they were the only cells in the exudation. The great irregularity in their numbers was striking and could not be explained by the duration of the process or the variety of the organisms causing it. Although it is possible to find certain cells which, judging from the character of the nucleus alone, it is difficult to distinguish from the polynuclear leucocytes, they certainly are not converted into these in the exudation. It is much more difficult to distinguish certain of them from the cells which are formed by proliferation of the lining epithelium. The cells in the exudation which we regard as formed from the epithelium vary greatly in size, but are generally larger than the exudation cells. They have a round or oval vesicular nucleus, and clear or finely granular protoplasm, which often shows a peculiar condensation around the edge. They are very similar to the large cells found in tuberculous bronchopneumonia. Their numbers varied greatly; in some cases they formed the majority of the cells enclosed in the exudation. In many cases there was marked proliferation of the lining epithelium with numerous nuclear figures, and the

[1] Councilman has described these cells under the name of nongranular leucocytes. They appear in the inflamed area of the cornea after the polymorphonuclear emigration has subsided. They are the same cells which are found in the sinuses of the lymph nodes and in other situations, and are probably found in greater numbers in the various lesions of typhoid fever (Mallory) than in other processes. It seems to us that they are of endothelial origin, formed from the endothelium of the blood and lymph vessels. They are generally described by the writers on the blood as mononuclear or transitional cells. We do not believe that they ever undergo a further metamorphosis resulting in the formation of the polynuclear leucocyte. Cells of a very similar character may be derived from the epithelium of the peritoneum, pericardium, and pleura, and from the alveoli of the lung. We shall refer to these cells hereafter as mononuclear leucocytes.

cells in the spaces were similar to those still attached to the walls. The proliferation of the epithelium seemed to take place in two ways. In some cases the cells were swollen, increased in number, retained their flat shape, and adhered to one another, forming a ring around the alveolus. This epithelial ring was often separated from the wall. In other cases the epithelium was swollen, and the cells took the shape of low columnar epithelium. In places a large number of these cells were found adhering one to another and to the wall, while in other places the wall would be bare of them. They were often found in large numbers in the spaces without any evidence of proliferation around the outside. Not only were these cells in many cases very large, but they sometimes formed definite giant cells resembling the giant cells of tuberculosis. Such giant cells were either attached to the wall or free. These cells differ from most cells derived from epithelium in their marked phagocytic properties. The various other cells found in the exudation, particularly the lymphoid cells, were frequently enclosed within them, and they also frequently enclosed small pigment granules. The proliferation of epithelium varied in different parts of the lung. It was always more marked in the vicinity of connective tissue, as around the larger bronchi, beneath the pleura, and along the interlobular septa. From these places it extended a variable distance. In some cases it affected the alveoli everywhere. In these cases it was combined with proliferation of the interstitial tissue. (Plate XXIX., Fig. 1.) Lymphoid and plasma cells, especially the former, were found in the exudation. When this was the case there was infiltration of the interstitial tissue with these cells. Both the epithelial cells and lymphoid cells were found in the greatest number in the more advanced cases. A few red blood corpuscles were also universally present, and in some cases the exudation was practically composed of them. In one case there were perfectly definite foci of hæmorrhage without admixture of other cells and having the same relation to the tissue as the foci of pneumonia. In other cases a part of the exudation was hæmorrhagic, and this was surrounded by cellular or fibrinous exudation, both sharply

separated. The red corpuscles were more frequently associated with the fibrinous exudation, though in some cases not a trace of fibrin was found in the hæmorrhagic foci. In several of the cases there was a peculiar form of exudation which frequently accompanies tuberculosis. In these cases there were large areas in which all the spaces were filled with a mass which under a low power appeared perfectly smooth and hyaline. Under an immersion a fine, even granulation could be distinguished in it. It closely filled some of the cavities and had slightly shrunken from the walls of others, leaving small crescent-shaped clear spaces. In the interior of the mass small clear circles were occasionally seen. It usually contained numbers of red blood corpuscles aggregated into small masses and occasionally leucocytes. Such an exudation differs from the ordinary serous exudation which is found in œdema. This is granular and does not so completely fill the spaces. It is probable that this exudation is serous, but the serum has undergone some change in passing through the vessels or afterwards. It is most often found in combination with hæmorrhagic exudation, rarely with the fibrinous or purulent.

The amount of fibrin in the exudation varied. In some cases it was so abundant and so evenly distributed that the microscopic picture was that of a typical croupous pneumonia. In other cases but a small amount was present. As we have said, it was always more abundant in the vicinity of the larger bronchi (Plate XXVIII., Fig. 4), and was occasionally limited to this situation. When present in very small amount it often formed a distinct rim around the alveolar wall as has been described by Ribbert. We were never able, however, to find any indication of its formation in connection with cast-off and necrotic lining epithelium. The character of the fibrin varied, forming in some cases a very fine reticulum; in others the fibres were coarse and irregular in size. In several cases the fibres were greatly swollen and fused together, forming irregular hyaline masses which no longer gave the typical staining reactions for fibrin. Fibrin often in the

form of single filaments was also found in the alveolar walls both in the capillaries and outside of them.

In most cases the bronchi at a distance from the areas of pneumonia showed evidences of inflammation, but they were frequently intact. In other cases bronchitis was so pronounced as to form the most prominent feature in the process. In the slightest degree of inflammation the epithelial lining was intact (Plate XXX., Fig. 3) and there was a slight amount of cellular exudation composed of polynuclear leucocytes in the lumen. The same cells were found in the walls and in and between the epithelial cells. In a few cases there was exudation in the bronchi without any evidence of inflammation of the walls; the exudation evidently came into the bronchus from some other focus, or it may have been forced into it from the handling of the tissue while fresh. In the more severe forms of bronchitis there was a large amount of exudation in the lumen, the epithelium was infiltrated with cells and partially stripped from the wall, the blood vessels of the wall were deeply injected, and the tissue was swollen and densely infiltrated with cells. (Plate XXIX., Fig. 2.) The epithelial cells often adhered to one another, forming convoluted masses lying in the exudation. The exfoliation of the epithelium was due to the accumulation of exudation beneath it. In some cases a small amount of granular coagulated material, often showing the same small circles which are found within the tubules of the kidney, was found beneath it; in others a large mass of hæmorrhagic or purulent exudation. The exudation within the bronchi was composed chiefly of polynuclear leucocytes; in some cases it was distinctly hæmorrhagic. The same nongranular leucocytes which were found in the alveoli were also present, and occasionally the large cells regarded as derived from the lining epithelium of the alveoli. In all cases where the inflammation was severe there was intense cellular infiltration of the wall. The most numerous of the infiltrating cells were the lymphoid and plasma cells. These cells were both scattered diffusely in the tissue and collected in groups. The connective tissue cells of the wall were swollen and proliferating as shown by the presence

of numerous nuclear figures. Nuclear figures were also abundant in the plasma cells. The cellular infiltration almost invariably extended from the bronchus to a considerable distance into the surrounding lung tissue. (Plate XXX., Figs. 2 and 3.) The walls of the adjoining air spaces were thickened, infiltrated with the same cells, and the epithelium swollen and proliferating. In some cases this was accompanied with exudation. This extension of an inflammatory process from the wall of a bronchus into the adjoining lung tissue is very different from the ordinary bronchopneumonia. In this latter process the infecting material, whatever its character, is carried into the terminal bronchi and atria, and lateral extension plays little or no part in the process. The lateral extension is seen only along the larger bronchi in which there is intense inflammation, and the character of the exudation may be totally different from that in the lung elsewhere. The bronchi seem often to form the centre of a large area of pneumonia, but further sections will show the relation of this pneumonia with terminal bronchi which have come from some other point of the large trunk which is affected or from neighboring bronchi. We have repeatedly found cases in which there was extensive bronchopneumonia without any evidence of bronchitis in the larger vessels; the foci were distinctly terminal. We are aware that the prevalent idea is that the exudation is due chiefly to a lateral extension from the bronchus, but we think this idea has been due to the fact that the cases examined have not been sufficiently numerous or early enough, and the method of examination by serial sections has not been generally employed.

The cases of bronchitis with distinct membrane formation due to an extension of the diphtheritic process from the trachea into the bronchi deserve especial mention. In 43 of the cases membrane was found in the bronchi, generally in those of larger calibre. In a few cases it was found in all the smaller bronchi as well. No trace of epithelium was found in the affected bronchi. The membrane was fibrinous in character and seated on the membrana propria. There was no hyaline or fibrinoid degeneration of the tissue similar to

that seen beneath the membrane in the trachea. A large number of leucocytes with a few red corpuscles were found in and on the membrane. In the smaller bronchi the membrane took the form of a fibrino-purulent exudation.

Atelectasis varying in extent and somewhat in character was almost universally present. When most marked it was constantly associated with extensive bronchitis. It was usually much more distinctly lobular than the areas of bronchopneumonia. Large areas were frequently present involving a number of lobules, and even here limited to these. We never found areas of atelectasis limited to acini, a fact which goes to prove the absence of bronchitis in the terminal bronchi without extension to the air spaces. A varying amount of atelectasis irregularly distributed and generally of slight degree was often found in the lobule in combination with the pneumonia. It was most marked in the lung immediately beneath the pleura. In the atelectatic lung there was never complete solidification. Portions cut out never sank in water, and on microscopic examination, though there was usually some exudation, it never filled the spaces. In most cases the epithelium lining the aveoli was swollen and proliferating. The spaces contained granular material, large cells probably derived from the epithelium, leucocytes, and red blood corpuscles. The walls of the air sacs were folded in, often almost filling the cavities. The pleura over the atelectatic areas was thickened and œdematous, as were also the connective tissue septa in the vicinity. In some cases the vessels were deeply injected.

Emphysema was constantly found adjoining the areas of atelectasis and to a less extent in connection with the areas of pneumonia. It was never confined to definite areas of the lung, as was the atelectasis and bronchopneumonia. It was very common to find the air spaces adjoining the areas of solidification dilated. When large areas of the lung were solidified or atelectatic the remainder of the lung was emphysematous, and the emphysema was more marked in the vicinity of the solidified portions. In one case there was rupture of the emphysematous lung beneath the pleura, giving

rise to the formation of small blebs, but no general interstitial emphysema was found.

In the œdematous lung between the numerous foci of pneumonia, particularly in the posterior borders, there were granular material, evidently coagulated albumen, and a few cells. As we have said, the general œdema so common in adults and probably due to disturbances in the circulation was never found. The œdema we found was inflammatory in character.

In 14 of the cases there was necrosis, often combined with definite abscess formation. Abscesses were noted at autopsy in 11 cases. The abscesses were more common in the cases of longer duration, although they were found in 2 cases in which death occurred on the third day, and in 1 on the fourth. The cases of long duration were in the fifty-third and forty-ninth days of the disease. The average duration of the 14 cases in which they occurred was 17 days. The necrosis and abscess formation was due to infection through the bronchi. The foci seemed in some cases to begin as terminal foci similar to the foci of pneumonia in other cases, though extension through the walls of the bronchi could not be excluded. In some cases there were sharply circumscribed areas of necrosis, involving but a few of the air spaces of an acinus. In the same cases there was found necrosis of the bronchial wall and of the adjacent air spaces. There was little or no inflammatory reaction around the necrotic tissue, and both the air spaces and walls were so filled with masses of diphtheria bacilli as to appear under a very low power as brightly stained areas. In other cases the tissue was partially broken down and necrotic, and filled with degenerated pus cells and red blood corpuscles. In one of these cases, in the midst of the necrotic material, there were small islands of tissue, generally around the larger vessels, which were well preserved and infiltrated with pus cells. In other cases the abscesses were of a more chronic character. Nothing of the lung structure could be recognized in the interior and there was extensive purulent or fibrinous exudation in the surrounding tissue with infiltration of the interstitial

tissue with leucocytes and lymphoid and plasma cells. Such infiltration often extended a long distance into the tissue around the abscess. About some of the abscesses there was an extraordinary absence of inflammatory reaction. At the edge of the abscess the necrotic tissue adjoined tissue with but little exudation and cellular infiltration of the walls. In one case small areas of necrosis were formed immediately beneath the pleura.

The interstitial tissue of the lungs is so generally affected that it deserves especial mention. We have already alluded to the cellular infiltration of the walls of the air sacs in connection with the exudation into the cavities and to the lateral extension of the peri-bronchial infiltration. In some of the cases of abscess there was not only marked infiltration of all the connective tissue in the vicinity of the abscess, but it affected distant parts of the lung having no connection with abscess formation. In some cases this was so marked that it seemed that the abscess had formed in tissue which was already the seat of an interstitial process. There were in addition acute interstitial processes in the lungs, which seemed to be of the same nature as the acute interstitial nephritis. We never found this process alone, but always accompanied by bronchopneumonia or bronchitis. In these cases all the interstitial tissue was thickened and infiltrated with cells. The most intense infiltration was seen along the small veins and in the small fibrous septa. It also involved the connective tissue of the pleura and the peri-bronchial tissue, and might or might not be accompanied by exudation in the spaces. From all these places it extended into the walls of the air spaces, becoming less intense as it extended. The infiltrating cells were almost exclusively lymphoid and plasma cells; only occasionally were polynuclear leucocytes found among them. The large plasma cells stained intensely with methylene blue and gave a striking appearance to the section. The same cells as those in the tissue were often found in large numbers in the small veins and capillaries. This condition was found more frequently when diphtheria bacilli were present in large numbers and were the principal infect-

ing agents, but it was also found in equal intensity in cases in which the infection was due to streptococci and pneumococci. In none of the cases were bacteria found in immediate connection with the interstitial processes. Nuclear figures were found both in the cells within the vessels and in those in the tissue. There was often marked œdema of the connective tissue septa, and in some cases a great deal of fibrin was found in it, even in cases where the adjoining air spaces showed no fibrin. The œdematous tissue contained numbers of lymphoid and plasma cells, and large cells similar to the cells of supposed epithelial origin in the alveoli, lying loosely in the tissue. The stellate cells of the connective tissue were swollen and occasionally contained nuclear figures.

In a very large number of cases, both in those in which death occurred very early and in those in which it occurred late in the disease, peculiar bodies were found in the capillaries, giving the impression of masses forced from a larger into a smaller tube. (Plate XXIX., Fig. 5.) The bodies were often bifurcated at one end, and the bifurcation extended into the junction of two capillaries as a riding embolus. It was at first supposed that these bodies were composed of hyaline fibrin and represented the hyaline thrombi so often described in the capillaries of the lung. They stained brilliantly with the nuclear stains, but did not give the reaction for fibrin. In some cases a small amount of granular protoplasm was found in connection with them, and their evident nuclear character was shown by strands and granules of chromatin. Every transition was seen from such structures of evident cellular character to homogeneous masses which took the nuclear stain. They were not confined to the areas of bronchopneumonia, but were uniformly scattered through the tissue. The only cells of a similar character are certain of the cells of the bone marrow, and we have considered these cells in the capillaries to be marrow cells which were brought to the lung as emboli and forced into vessels of a smaller lumen than their diameter. No such cells were found in the sections of the larger vessels of the lung, though they were

found in the vessels of the marrow. No hyaline thrombi were found in the capillaries, and it seems possible that some of the hyaline thrombi which have been described may have been these large marrow cells. Pratt has described similar cells in the capillaries in cases of acute lobar pneumonia. In no case were they numerous and they were not found in all cases. Possibly the cells only occasionally find their way into the blood, and they may remain a considerable time in the capillaries and undergo necrosis, so that the nucleus loses its characteristic appearance and stains homogeneously. In several cases numbers of the large eosinophile cells derived from the marrow were found in the vessels.

Thrombi were occasionally found in the larger vessels, both arteries and veins. They were in some cases mural, in others totally occluding. In quite a number of cases small collections of leucocytes with fibrin between and around them were found lying loosely in the lumen. In two cases acute phlebitis was found. In both instances the veins adjoined large areas of bronchopneumonia. In one case there were collections of polynuclear leucocytes beneath the endothelial lining and infiltrating the wall. In the other case the condition was similar to that described in acute pneumococcus meningitis. The endothelium of the vessel was elevated, often forming festoons, and beneath this were collected large cells of an epithelioid character. Many of them resembled closely the large cells described in the exudation. Only an occasional polynuclear leucocyte was found among them.

Chronic interstitial processes, evidently connected with healing and consisting of thickening of the walls of the alveoli, and of organization of the exudation within them, were found in several of the more chronic cases, and were particularly marked in one. This was a child three years old, who died on the one hundred and eighth day of the disease. The child had entered the hospital with scarlet fever and diphtheria. They were followed by whooping cough, and infection of both middle ears and mastoids, necessitating operation. Two months before death there was clinical evidence of pneumonia, followed by resolution and a fresh attack two

weeks before death. At the autopsy there were areas of solidification of the right lung; the solidified areas were very firm and dry. On microscopic examination there was great thickening of the walls of the air spaces, due partly to a general increase in the tissue of the wall, and partly to a formation of connective tissue just beneath the epithelium. The epithelium was in part converted into low cylindrical epithelium similar to that in the terminal bronchi, in part it was simply swollen. The exudation was fibrinous, with the fibrillæ swollen and indistinct. The masses of fibrin were in many cases completely or partially covered by a layer of epithelial cells. The formation of connective tissue inside the cavities took place in two ways: in one by a growth of a polypoid mass of connective tissue from the wall retaining the covering epithelium over it, in the other by the penetration of the fibrinous exudation by connective tissue forming cells, leading to a definite organization of the exudation. In one section a long process of organizing tissue was followed from an atrium where it was attached, through the whole extent of the acinus. Polypoid masses of connective tissue, which possibly represented the last stages of organization, were frequently found in the small bronchi, and the formation seemed often to proceed from these and the atria, extending into the air spaces. One well-marked case was found in a man thirty years old, who died on the second day after entering the hospital. It was evident in this case that the lung affection was an old one, while the diphtheria was a secondary infection. In this case the growth of polypoid masses of the connective tissue into the small bronchi and atria was well marked.

The lymphatics were affected in a large number of cases, and were easily demonstrable. In all cases of œdema of the interlobular tissue the lymphatics in it were enormously dilated and contained some granular material. They were more generally dilated here than around the arteries. In many cases they contained large numbers of cells and in some they were filled with fibrin. The cells within these dilated lymphatics attracted particular attention from their character. There were few red corpuscles among them and

comparatively few polynuclear leucocytes even when these were abundant in the exudation around the lymphatics. The principal cells were lymphoid and plasma cells and large cells eminently phagocytic and in all respects similar to the large cells in the exudation with the air sacs. They varied like these in size, had abundant homogeneous protoplasm, and a round or oval vesicular nucleus. The origin of these cells was not clear. It seemed improbable that they had entered the lymphatics from the air spaces; on the other hand, in the majority of cases no proliferation was seen in the endothelial lining. In one case in which there was great proliferation of both the interstitial tissue and the lining epithelium, several dilated lymphatics were found in the interlobular tissue near the pleura containing numbers of these cells. (Plate XXIX., Fig. 4.) The endothelial cells were so swollen and increased in number that the section of the vessel was similar to an air space surrounded by proliferating epithelium. In this case certainly the large cells in the lumen were due to proliferation of the lining cells, and it seems possible that in the other cases the cells may have originated in this way and extended to some other point in the vessel where this proliferation was not taking place. These large cells were rarely found in any numbers in the periarterial lymphatics.

The lymphoid tissue of the lung seemed to be little if any increased. Most of the autopsies were on young children, and in these there is more of such tissue than in adults. In one section a small lymph nodule was found near the hilum of the lung containing a necrotic centre similar to those in the lymph nodes.

In 18 cases there was a fibrinous exudation extending over the entire pleural surfaces. In addition to this there were frequently small areas over the bronchopneumonic foci where the pleura was either slightly cloudy or covered with a thin exudation. So many sections were examined and tissue was generally so well preserved that the relations of the exudation with the epithelial lining of the pleura and the tissue could be easily seen. It was interesting to find how various these relations could be. The exudation was chiefly

fibrinous with a varying admixture of red blood corpuscles and polynuclear leucocytes in the different cases. In some cases the exudation was on the surface and the epithelium could be distinctly made out beneath it; in other cases the epithelium had disappeared. In several cases the exudation was beneath the epithelium either in the meshes of the connective tissue or immediately beneath the epithelium, which it had elevated. The character of the epithelium was always changed. The cells were large, the protoplasm abundant, granular, and somewhat colored with the staining reagent, the nuclei large and rich in chromatin. Nuclear figures were numerous. The connective tissue was simply infiltrated with fibrin. The hyaline fibrinoid metamorphosis of the connective tissue so often seen in connection with the diphtheritic membrane was never found. In several cases very peculiar relations of the fibrin and epithelium were seen. In one case in particular the surface of the fibrin was almost totally covered with proliferating epithelium, and in the fibrin itself numerous spaces were found lined by similar cells. This condition was evidently due to a growth of the epithelium into the spaces of the fibrin, or to folding in of the irregular surface. A similar condition was found in the fibrinous exudation in one of the cases of pericarditis. In another case there was a thin layer of fibrin over the epithelium and above this a similar complete row of epithelium, then fibrin, and occasionally a shred of connective tissue. It seemed in this case that a part of the parietal pleura had been stripped off, and in this the exudation was beneath the epithelium, while on the surface of the lung it was over it.

Older cases were found representing all stages of organization. In one case the pleura was thickened, and elevated in folds which were covered by swollen epithelium similar to columnar epithelium, and without a trace of exudation. In all cases in which the pleura was affected there was marked proliferation of the epithelial cells of the adjoining air spaces.

In the microscopic examination of the lung sections the presence of bacilli and their relation to the lesions was noted. The examination was made on sections stained in the routine

manner with methylene blue and eosin. Although the bacteria stain extremely well by this method, some of the sections studied were old and faded, and it is possible that the bacteria were not visible, or overlooked in a considerable number of cases. More attention was paid to their relation with the lesions than to their mere presence. Cultures had been made in 97 of the 133 cases examined, and on comparing the results of cultures with the microscopic examination there was considerable discrepancy. This was most marked in the case of the pneumococci, which were often found on microscopic examination in such large numbers that they were considered the prime infectious agents, and yet they were not found in the cultures. The pneumococcus is one of the difficult organisms to cultivate, and in a mixture of other organisms it may be completely overshadowed, or its growth prevented by such rapidly growing organisms as the streptococci or diphtheria bacilli even when these are present in such small numbers as not to be recognized on microscopic examination of the tissue. We must recognize the fact that it is extremely difficult, if not impossible, to obtain absolutely accurate results where cultures are made at autopsies as a matter of routine. The results of cultures taken are as a whole valuable and fairly accurate, but in any single case certain organisms, and possibly the most important, may be overlooked. The pneumococcus was found 59 times in the sections and 11 times in the cultures made from the same cases. Other organisms, such as the diphtheria bacillus and the streptococcus, were found more frequently in cultures than in the sections; diphtheria bacillus in culture 60 times, in sections 38 times; the streptococcus in cultures 53 times, in sections 29 times. In the great majority of cases only one variety of micro-organism was found in the sections, and this in such numbers and in such relation to the lesions that it was considered as the infectious agent. Large bacilli which were occasionally found in the bronchi or in the air sacs, but without any apparent relation to the lesions, were assumed to be saprophytes and were not considered.

The diphtheria bacillus was found (Plate XXX., Figs. 2 and

4; Plate XXIX., Fig. 5) alone in 18 cases, in connection with the streptococcus in 6 cases, with the pneumococcus in 9, and with the streptococcus and the pneumococcus in 5 cases. The micro-organisms were usually present in very large numbers. The records frequently mention "large masses" or "enormous numbers." When only a few were found they were usually confined to the bronchi, while in the lung elsewhere streptococci or pneumococci were found. The diphtheria bacilli were found in connection with all the inflammatory lesions of the lung. They were frequently the only bacteria found in definite foci of bronchopneumonia. In these cases they were in the air spaces and generally in enormous numbers. (Plate XXIX., Fig. 5.)

The character of the exudation caused by them varied. Usually little or no fibrin was found, and it was frequently purulent and hæmorrhagic. The bacilli were both free and enclosed in pus cells. The cells enclosing them seemed to be exclusively polynuclear leucocytes. In some cases, owing to the number of bacilli in the cell, the nucleus could not be distinguished with sufficient accuracy to determine the character of the cell, but they were never found with certainty in the mononuclear leucocytes or in the larger cells of epithelial origin. The diphtheria bacilli were the only micro-organisms in four cases of abscess of the lung. They were found in enormous numbers in the necrotic tissue of the abscess and in the wall. In two of the abscesses there was but little reaction in the surrounding tissue. They were also found in equally great numbers in areas of necrotic tissue which had not yet broken down to form abscesses. In one of these cases there were large masses of bacilli marking out the air spaces, of which all the cells in the walls were necrotic. (Plate XXIX., Fig. 5.) In one case they were found in large masses in air spaces filled with serous exudation and had produced neither suppuration nor necrosis. It could not be assumed that such an enormous growth of the bacilli could be post mortem, for as a rule the autopsies were made but a short time after death, and a similar growth was not found in other situations as in the pharynx. They were found in the membrane of the

bronchi, chiefly in small masses on or near the surface, but in many cases the membrane contained few or none, while they were in large numbers in the air spaces. The bacilli were generally well preserved and stained brilliantly. In some cases branched forms and long degenerated forms were seen. There was no marked difference in the character of the lesions when the streptococcus or the pneumococcus accompanied the diphtheria bacilli.

In four of the cases of abscess formation streptococci were found in such numbers and relations that they were regarded as the causative agents. In one case the abscesses seemed to be produced by the streptococci, while diphtheria bacilli were found elsewhere in large masses. No definite character of lesions was found in the streptococcus cases. The lesions varied from abscess formation to pneumonia with fibrinous, purulent, or hæmorrhagic exudation. The exudation produced by the streptococcus was more commonly fibrinous than that produced by any other organism, not excepting the pneumococcus. In one of the cases of acute pleurisy with fibrinous exudation they were found in great numbers in the pleural exudation and in the dilated pleura and interlobular lymphatics.

Pneumococci were associated with abscess formation and regarded as the cause of this in one case. They were regarded as by far the most frequent cause of bronchopneumonia. They were found either free in the exudation or enclosed in polynuclear leucocytes. They were frequently absent in the older parts of a focus and present in great numbers where the lesions appeared to be more recent, and where the exudation was principally serous. This we have also found to be the case in acute lobar pneumonia. We have found the pneumococcus associated with every form of exudation which we have described, but somewhat less frequently with fibrinous exudation than the streptococcus.

Staphylococci were extremely rare in the sections, though so commonly found in the cultures. We are not able to associate them with any of the lesions, and we think they

play little or no part in the production of the lung lesions of diphtheria.

The histological examination points clearly to the fact that infection takes place through the bronchi. Flexner and Anderson found that when small quantities of diphtheria bacilli were injected into the trachea, typical foci of bronchopneumonia developed. In this experimental form also they found the first lesions in the atrium. Boassohn thinks that the infection generally takes place by the bronchi, but may also take place by means of the blood and lymph. He supposes that when the mouth becomes dry the micro-organisms may be lifted from the dry surface and carried with the air into the lung. Katzenstein thinks that the infection usually takes place by the bronchi, but that infection by the blood is most probable in the small foci in the lower lobes. Mya in an elaborate article on the subject concludes that there are two factors, one mechanical and the other biochemical. One of the most fundamental causes, according to him, lies in the affection of the lymphatics and the disturbance of the lymph circulation. There may also be disturbances of the blood circulation, all of which produce conditions favorable to the action of micro-organisms. We have not been able to find these favorable conditions, and have called attention to the absence of circulatory œdema. We do not believe that the infection is embolic to any extent at least. The lesions are different from the embolic pneumonias. We have only found in one case evidences of the embolic action of the diphtheria bacilli; the few which enter the circulation and are found in cultures from internal organs are certainly not the cause of the lesions found in these organs.

Summary.

There is no organ in the body in which lesions accompanying diphtheritic infection are so generally found or so serious as in the lung. In very many cases they are so extensive that death may be considered as due rather to the condition of the lungs than to the throat affection. We have frequently found extensive lesions on microscopic examination even

when the lungs presented little or no change to the naked eye. It seems probable that the frequency of these lesions may be due to the fact that most or all of our cases were treated with antitoxin, and that those in which the lung complications were not present, or at least not severe, recovered. This should always be taken into consideration in the results of antitoxin treatment. Antitoxin cannot influence the pneumococcus or streptococcus infection.

The most common lesion is bronchopneumonia. The term implies both the manner in which infection takes place and the relation of the foci to the bronchi. The process begins as an infection of the atria and from here extends. It may be limited to single acini, to lobules, or to groups of lobules. There is but little lateral extension of the infection through the walls of the alveoli or the bronchi into the surrounding air spaces. Acute inflammation of the larger bronchi usually accompanies the bronchopneumonia, but is not constant. Atelectasis varying in extent from one to several lobules, or even confined to a few air spaces, is very commonly present. The same is true of emphysema. True acute lobar pneumonia was never found. The cases resembling this were found on closer examination to be cases of extensive confluent bronchopneumonia. General œdema of the lung comparable to the circulatory œdema of adults was never found, although inflammatory œdema was common. The character of the exudation varies greatly. It may be fibrinous, hæmorrhagic, serous, or almost entirely cellular. In a few cases a hyaline exudation similar to that found in tuberculosis was present. The cells in the exudation are partly leucocytes, partly cells derived from proliferation of the lining epithelium. Lymphoid and plasma cells also are found in the exudation. Cellular infiltration of the interstitial tissue and productive changes in it are common, both in connection with the acute exudative lesions and apart from them. In some cases organization of the exudation and connective tissue formation within the air spaces was found. Proliferation of the lining epithelium of the air spaces is frequent, and is always more pronounced in the vicinity of the pleura and the connective

tissue septa. It is possible that this is to be explained by the concentration in the lymphatics of substances causing proliferation. Necrosis in some cases leading to abscess is not an uncommon feature.

Large objects considered to be marrow cells which in many cases had undergone degeneration are frequently found in the capillaries, and it is possible that these have been frequently mistaken for hyaline thrombi. Single strands of fibrin are sometimes found in the capillaries and interstitial tissue, but never definite capillary thrombi. Thrombi are occasionally found in the larger vessels. Dilatation of the lymphatics is very common. They may contain coagulated albumen, fibrin, or cells. They are often found packed with lymphoid and plasma cells, and large cells similar to the large cells in the air spaces.

Nothing has shown so well how little the character of a pathological process is influenced by the character of the micro-organism as has the examination of these lungs. Pneumococci, streptococci, and diphtheria bacilli have been found in connection with serous, purulent, fibrinous, and hæmorrhagic exudations, necrosis, and abscess formation. Contrary to the results obtained from cultures, the pneumococcus must be considered the principal agent in producing the lung infection. The diphtheria bacilli are frequently found and may be the cause of bronchitis with membrane formation, of purulent exudation, of bronchopneumonia, necrosis, and abscess. They are often found in the lung in much greater numbers than in any other situation, and there may be but little change in the tissue around them.

We have not attempted to review the literature of the lung lesions in diphtheria. It relates chiefly to the frequency of lung affections in diphtheria and their bacteriology. The literature of the bacteriology of the lung has already been considered.

SPLEEN.

Bizzozero found acute enlargement of the spleen in several of the 24 cases he investigated. In the splenic pulp he found congestion with some hæmorrhage, but the main

changes were in the Malpighian bodies, in which there were small foci of necrosis. The lymph nodules contained very large phagocytic cells which enclosed degenerated lymphoid cells and frequently red blood corpuscles. Oertel found the spleen enlarged, the pulp increased, the entire organ soft and frequently hæmorrhagic. There was marked cellular infiltration due to emigration of leucocytes from the vessels of the pulp and to proliferation of the pulp cells. He found the lymph nodules often filled with cells of an epithelial character, which enclosed degenerated cells. Müller in general confirmed the description of Oertel and described in addition a fatty degeneration of the cells; small drops of fat were contained both in the cells of the lymph nodules and in the sinuses. In the centre of the lymph nodule there were often large cells of an epithelioid character. There were regressive changes in the cells of the lymph nodules leading to the formation of nuclear detritus which was often taken up by the large cells. He speaks of these as germinal necrobiotic foci. Such foci were never seen in the pulp, but there was necrosis of single cells. Katzenstein found necrosis in the Malpighian bodies and fibrin around the foci. Ziegler describes necrosis of the lymphoid cells of the lymph nodules, while the reticulum takes the form of a network of swollen cells. Ribbert says the large cells are similar to swollen endothelium. In a recent article Waschkewitch reports that he examined the spleen in a large number of diseases to ascertain the frequency of the large cells in the lymph nodules. He regards them as formed from leucocytes which have wandered into the tissue, and claims that he has seen transition forms. Babes in experimental lesions found hyperplasia of the lymphoid tissue, congestion of the vessels of the pulp, with degeneration of the leucocytes contained in them. Flexner found lesions in the lymph nodules very similar to those in the lymph nodes, but the nuclear fragments were not so frequently enclosed in phagocytic cells as was the case in the lymph nodes. In the pulp there was hyperplasia of the reticular and vascular endothelia with nuclear destruction of the cells both within and without the vessels.

There was very little change in the spleen on macroscopic examination; it was generally firm, and the capsule was smooth, but not distended; as a rule, however, the lymph nodules were distinctly visible on section, and sometimes they were very prominent. There was considerable variation in the size of the organ, but this was within the normal variation.

The spleen was examined microscopically in one hundred and eighty-one cases selected at random, or according to the state of preservation of the tissue. The same methods of preservation and of examination were used as in the other tissues. The cases examined were from the second to the one hundred and eighth day of the disease, and from ten months to sixty years of age. Most of them were from cases under four years of age, and under ten days' duration of disease. There was considerable uniformity in the size of the lymph nodules. In several cases, however, they were much larger than usual, and in two cases, one a child of four and the other an adult of twenty, they were so small as scarcely to be distinguishable. It is probable that such variation in size comes within the limits of the normal. There was but little variation dependent upon age. In one case of sixty-four years they were of the average size of those in the children. There was considerable variation in the size and character of the cells composing the lymph nodules. In most cases they were of the ordinary lymphoid variety. In other cases the nuclei were larger and more vesicular. Cells similar to the cells in the germ centres of the tonsils surrounded by brightly stained lymphoid cells were rarely found. Among the lymphoid cells of the lymph nodule, cells of the same general character, but with a comparatively large amount of blue stained granular protoplasm, were frequently found. These cells are similar to the large lymphoid cells described in the lymph nodes. A few nuclear figures were also invariably found in the lymph nodules, and the number varied much in the different cases. Plasma cells were rarely present, and then only in the periphery of the lymph nodule.

The most obvious change in the lymph nodules con-

sisted of the formation of small areas composed of epithelioid cells, of hyaline formation, and of a variable amount of nuclear detritus. To a certain extent the character of the change in the lymph nodules is dependent upon the duration of the disease, seeming to show a certain sequence in the process. The epithelioid formation was usually found in the early cases, the hyaline formation in those of later date, rarely before the fifteenth day. Such areas were found in 91 of the 181 cases examined. The epithelioid cells were similar in size and in their general character to the large epithelioid cells of the tubercle. They were large, the nuclei vesicular, round, oval, or irregular in contour, and the protoplasm finely granular. In the smallest and apparently youngest foci the single cells could easily be distinguished and were often separated by small intervals. These epithelioid cells could be easily distinguished from the lymphoid cells, even from the larger varieties of these, and no changes in the lymphoid cells which could be supposed to precede the formation of epithelioid cells could be made out. The focus may be composed of epithelioid cells alone or there may be small numbers of lymphoid cells between them. At the edge single epithelioid cells could be distinguished among the lymphoid cells. It seemed to us that here just as in the areas in the lymph nodes the epithelioid cells were formed from proliferation of the cells of the reticulum. The areas formed of distinct and separate epithelioid cells were found in but a small number of cases. Usually the centre and the greater part of the focus was formed of hyalin which stained faintly with eosin; the epithelioid cells were on the outside. In the hyaline centre there were nuclei similar to those of the epithelioid cells, but more or less shrivelled and distorted. In some cases this hyalin formed a solid mass; in others there was a sort of reticulum with spaces either empty or containing lymphoid cells. There seemed little doubt that the greater part of the hyaline was formed by degeneration of the epithelioid cells. There was also a formation of hyalin in the walls of the capillaries, and the vessels in the foci were closed both by this and the proliferation of the cells of

their walls. Single capillaries with thick hyaline walls and still containing red blood corpuscles were found both in the interior and on the edge of the areas. The hyalin stained more brightly with eosin and dark with iron hæmatoxylin, but not so dark as fibrin. These areas varied greatly in size; in some cases they could be seen in the section with the naked eye, in others they formed but a very small point in the lymph nodule. They were distinctly round or oval when cut in all directions and did not extend along the course of the lymph nodules. The same thing was true of them in the lymph nodes.

In the majority of cases there was considerable nuclear detritus in these areas. The nuclear detritus was chiefly found in the periphery of the area and was contained in the epithelioid cells. All or nearly all of the nuclear detritus came from lymphoid cells, and every degree of degeneration leading to complete destruction could be found in lymphoid cells enclosed in the epithelioid cells. In a few cases the degeneration was so marked that the structure of the area could not be made out; all the cells within it had apparently contributed to the formation of the detritus. Polynuclear leucocytes took no part in the process, did not contribute to the formation of detritus, and were not found even when the necrosis was far advanced. There was a very close similarity between the appearance of these areas in the spleen and young miliary tubercles, just as was the case in the nodules in the lymph nodes. The mode of formation is the same and the epithelioid cells play the same important part. The giant cell formation and the caseation of the tubercle is absent.

In addition to the degeneration of the lymphoid cells in the lymph nodules in connection with the formation of these distinct foci there was a more diffuse form of degeneration which affected the lymphoid cells in the pulp as well as in the lymph nodules. Sometimes almost all the cells in a lymph nodule would be affected. In this form of degeneration the chromatin of the nucleus did not break up into fragments, but became arranged in irregular clumps which often

closely resembled on a small scale the nuclei of the polynuclear leucocytes.

Fibrin was found in the lymph nodules in 29 cases. It was chiefly in the periphery and showed as a few strands among the hyaline cells. There was but little formation of fibrin elsewhere in the tissue. Single capillaries contained it, and it was found to some extent in the sinuses of the pulp. There was no relation between its presence and cell degeneration. None was found in the nodules which were principally composed of nuclear detritus; and in the case in which it was most abundant it formed a network between seemingly intact nuclei. In this case the fibrin was marked by peculiar morphological and staining characteristics. It formed a network of broad smooth filaments with small nodular projections along them; some of the filaments were so large as to suggest hyaline capillaries. Globular masses and granules of the same hyaline appearance were also found in a few of the veins. It stained feebly with eosin; with plain hæmatoxylin it stained intensely, much more so than the nuclei of the cells, and with iron hæmatoxylin it gave a feebler color than ordinary fibrin. Fibrin of a similar character and in great abundance was once found in the kidney in a case of scarlet fever. In one case there was a peculiar arrangement of the fibrin around the lymph nodules.

In 17 of the 181 cases there was well marked degeneration of the arteries in the lymph nodules. This was found both in the lymph nodules in which focal lesions were present and in those without them, so that there seemed to be no relation between the formation and degeneration of the nodules and disease of the arteries. The degeneration was confined to the arteries in the lymph nodules. The larger arteries and those which sometimes accompany the veins in the trabeculæ were free from it. In the least marked cases only small masses of hyalin were found beneath the intima; in other cases the entire wall of the vessel was hyaline, and the hyalin extended from the vessel into the tissue. A number of degenerated nuclei were found in the hyalin, but it did not seem to be formed by degeneration of tissue, but, like amyloid,

represented an infiltration of the tissue. In nearly all cases the lumen of the affected vessel was narrowed and in some it was almost obliterated. The hyalin stained brightly with eosin and slightly with hæmatoxylin. This condition was found at every age and was generally most pronounced in the more acute cases. The earliest case in which it was found was one which the history gave as of only 2 days' duration, and the most prolonged case was one of 32 days. It was found in the case sixty-four years of age, and the character of the change did not differ from that in the youngest case.

Changes in the veins similar in their general character to those described by Pearce in scarlet fever were found in twelve cases. This change consists in an accumulation of lymphoid and plasma cells, chiefly the latter, in the intima beneath the endothelium. In some cases the cell accumulation was more marked, in certain places producing nodular projections into the lumen; in others the cells were more homogeneously distributed. It varied in degree from a few cells beneath the endothelium to large masses almost occluding the lumen. The cells seemed to extend beneath the endothelium of the veins from the pulp, and the accumulations were most marked where the small veins of the pulp emptied into the veins of the trabeculæ.

Changes in the pulp of the spleen were not so obvious as those in the lymph nodules. There was considerable variation in the degree of hyperæmia, and in several cases there were hæmorrhages. In one case of 32 days' duration there was a good deal of pigment in the tissue, evidently the remains of old hæmorrhages. The most marked change in the pulp consisted in variation in the number and character of the cells enclosed in it. In the normal spleen there are considerable numbers of lymphoid cells outside of the lymph nodules, and in some of the diphtheria cases the number of these was greatly increased. The large lymphoid cells with numerous nuclear figures similar to those described in the lymph nodes were also found. The chief difference as compared with the normal spleen was the large number of plasma

cells in the diphtheria cases. The normal spleen contains very few of these. They were present in all cases, and in 24 enormous numbers of them were found. They were distributed both generally throughout the pulp and in masses. The masses were so large and in some cases so circumscribed that with a low power it was difficult to distinguish them from the lymph nodules. The masses were generally grouped around the small veins of the pulp. Where the cells were fewer in number and more uniformly distributed they appeared to be enclosed in the reticulum of the pulp, and in some cases numbers of them were found in the sinuses. These plasma cells varied considerably in size, and numerous nuclear figures were found in them. All of the cases in which plasma cells in large numbers were found died at a late period of the disease; none of the cases was earlier than 6 days, and the average was of 25 days' duration.

It was difficult to determine the extent of the changes in the cells lining the blood sinuses. In comparatively normal conditions the character of these cells varied greatly, depending chiefly upon the varying degree of dilatation of the sinuses. In a well-preserved specimen of a hyperæmic spleen the cells lining the sinuses, though more numerous, did not differ in character from the endothelium of other vessels. In a contracted spleen the cells were closely packed together, their nuclei had their long axes at right angles to the axis of the lumen, and the sinus closely resembled a section of a gland. In some of the diphtheria cases there seemed undoubtedly to be proliferation of these cells. In one case not only were the sinuses lined with these cells, but masses of them projected into the lumen. Single cells undoubtedly coming from this source were also found free in the lumen. Against the view of hyperplasia was the complete absence of nuclear figures. Where the cells were most numerous the nuclei were pale and distorted, and suggested the nuclei of cells which were dividing directly, but the single cells in the lumen were too normal in appearance to have originated in such a way. In a few cases nuclear figures

were found in the cells lying free within the sinuses. There was usually no change in the reticulum of the pulp. There was no evidence of hyperplasia in the endothelium of either the arteries or the veins. No bacteria were found in the sections.

Summary.

Lesions of the spleen play but a slight part in the pathological anatomy of diphtheria. The spleen macroscopically does not differ from the normal, except that the lymph nodules usually are more prominent. The most obvious lesion microscopically consists of the formation of foci of epithelioid cells in the lymph nodules, which are of the same character and formed in the same way as those in the lymph nodes. The epithelioid cells are phagocytic, and the nuclear detritus found in these foci comes chiefly from the lymphoid cells which are enclosed in the phagocytic cells. The hyaline degeneration of the vessels is interesting in showing at what an early age this condition can occur. The arteries of the spleen seem to be more liable to this degeneration than the arteries of any other organs in the body. The routine examination of spleens from all sorts of cases shows its great frequency. The presence of large numbers of plasma cells in the organ in the later stages of the disease shows that the spleen may play an important part in their formation. Bacteria were absent and the changes found are not due to their presence in the organ.

ALIMENTARY CANAL.

Smirnow in 1888 reported 6 cases of diphtheria of the stomach with membrane formation, and investigated the mode of formation of the membrane. There is no doubt from the associated lesions of the pharynx that the cases were all true diphtheria. In 3 of the cases the membrane was formed by an inflammatory fibrinous exudation. In the other 3 he described hyaline degeneration of the glandular and surface epithelium, and regarded the membrane as formed of the hyaline material derived from cells. Cronemeyer in his analysis of 459 cases of diphtheria gives 29 cases of diphtheria of

the stomach, but he says nothing of the character of the lesions. He also gives a great number of pathological conditions of the stomach which were associated with the disease, but which were not immediately dependent upon it.

In 5 of our cases a definite diphtheritic membrane was found in the stomach. The extent and distribution of this membrane varied in different cases. In one case almost the entire surface of the mucous membrane beginning at the cardiac orifice was covered with a thick ragged grayish-brown membrane, which was thicker over the rugæ and easily removed, leaving a red granular surface beneath. In the other cases the formation of the membrane was not so extensive and was limited to lines on the surface of the rugæ. The mucous membrane elsewhere was very hyperæmic, and there were small scattered hæmorrhagic points. Microscopical examination showed the membrane to be fibrinous; in no place was there any of the dense hyaline membrane which was so often found in the pharynx. The membrane was always attached to a surface deprived of epithelium, and the fibrin rarely extended to any depth into the tissue below. In several cases it extended from its place of origin a considerable distance over the surface on all sides. The section in one case showed a small mass of membrane, which had a small base of attachment and which projected like a mushroom over the surrounding surface. (Plate XVIII., Fig. 2.) The under surface of the membrane for a short distance was covered by epithelium. It appeared from this that the exudation had first lifted the epithelium over it, and then becoming more extensive had broken through at one place and spread over the surface as a viscid mass turning back the epithelium. In the membrane the filaments of the fibrin seemed to radiate from the stalk of attachment.

Sections of the more extensive membrane showed this to consist of fibrin which had extended over the surface. In one case beneath the membrane there was a loss of substance involving perhaps one-half the length of the glands, with considerable hæmorrhage both beneath and in the mem-

brane. Another section from the same stomach showed several shallow erosions extending nearly to the muscularis mucosa, but without any membrane formation over them.

In addition to the fibrin the membrane contained a small amount of nuclear detritus and red blood corpuscles. The mucous membrane of the stomach both below the membrane and at a distance from it showed numerous alterations. The most striking lesion was the abundant hæmorrhagic exudation. Even in places where there was no membrane and the covering epithelium was intact there was generally extensive hæmorrhage beneath the surface. (Plate XIX., Fig. 2.) Numerous red blood corpuscles were found also deeper down between the glands, and the vessels were generally dilated. The glands in some places were separated by considerable intervals, and in the interstitial tissue were numerous lymphoid and plasma cells and red blood corpuscles. In other places in the mucous membrane there were foci of infiltration with polynuclear leucocytes. Next to the hæmorrhage the most striking alteration was in the glands. In these every degree of degeneration was found. All of the specimens of the stomach examined were from autopsies made only a few hours after death and the tissues were in perfect condition. So remarkable was the preservation of the histological details of the tissue that it seemed unlikely that the stomach contained any fluid capable of causing maceration after death. The epithelium was so perfectly preserved on the surface and in the glands that all changes found were assumed to be pathological. The surface epithelium was everywhere free from degenerative lesion, and there was but slight degeneration of the cylindrical epithelium lining the ducts of the glands. In one specimen there was evident desquamation of the epithelial cells of the peptic glands. The peptic cells lay in the lumen of the gland not only low down, but in the upper part. Their nuclei were in part well preserved, in part they were degenerated. The change was not general and was more evident in some parts of the section than in others. Some of the glands were filled with a mass of cast-off and degenerated cells, both peptic and simple cells.

In some cases the tissue beneath the membrane was necrotic and hæmorrhagic, and the glands as such could not be recognized. Apart from the changes in the glands in the immediate vicinity of the diphtheritic membrane, striking changes in the glands were found in the deeper portions of the mucous membrane. These changes were not more marked in sections containing membrane than in those in which no membrane was present. The slightest changes consisted of swelling of the cells, with an increase of granulation and hyaline degeneration. The nucleus was in part preserved, and in part broken up into detritus. Cells which had wholly undergone hyaline degeneration often lay in the lumen, and where the most extensive degeneration and necrosis were found, numbers of pus cells were contained in the lumen generally showing the same nuclear degeneration. The degenerated cell never showed any tendency to direct nuclear proliferation which was such a prominent feature in the epithelium of the œsophagus, and the covering epithelium elsewhere. None of these changes were focal; a gland showing marked degeneration was often found in the midst of glands completely normal. Sometimes there were areas in which the degenerated glands seemed somewhat more abundant, but nothing approaching a focal lesion was found. It is greatly to be regretted that no sections were examined from a stomach in which no lesions were found. Various bacteria were found in the membrane, but there were very few diphtheria bacilli. In only two sections were the characteristic small groups of these found on the surface. The cultures from the stomach in these cases gave abundant diphtheria bacilli.

The intestinal canal in general showed but few changes macroscopically. It varied considerably in thickness, due chiefly to different degrees of dilatation, but in some cases it seemed undoubtedly to be atrophic. The most marked change consisted in swelling of the lymphoid tissue. The Peyer's patches in some cases were so swollen that they resembled those in an early stage of typhoid fever. The swelling was rarely homogeneous, but the single lymph

nodules, or groups of them, could be distinguished forming round or elongated elevations with pits or furrows between them. The solitary lymph nodules in both small and large intestine were prominent. Considerable care must always be exercised in estimating changes in the lymphoid apparatus in the intestine of the child, for the lymphoid tissue is relatively so much more developed in the child than in the adult. There seems to be some hyperplasia of this in all of the infectious diseases of children, but it is more marked in diphtheria. The duodenum in one case showed a membrane on the surface similar in its macroscopic aspects to the membrane which was found in the stomach of the same case. Microscopically there was superficial necrosis, and on this, and not extending over the adjacent surface, a mass composed of pus cells, nuclear detritus, necrotic epithelium, and mucus. There was no fibrin. In the tissue beneath the membrane there was slight hæmorrhage. In another place there was an erosion which extended nearly to the muscularis mucosa, and which was evidently due to the separation of such a mass. It is remarkable that although fibrin was so abundant in the membrane in the stomach, none was formed in the duodenum.

Exclusive of the stomach the alimentary canal was examined in 60 cases. Usually the examination was confined to the lymphoid tissue and the mucous membrane in the immediate vicinity of it, but in several cases sections were made from a number of places in both small and large intestine. The changes found in the intestinal lymph nodules were of the same character as those found in the lymph nodes, but in general they were not so marked. In the cases of most evident hyperplasia the lymphoid cells extended to the surface, and formed a diffuse infiltration in the tissue below and adjoining. In many cases the so-called germinal centres of the lymph nodules were prominent; in others they were not found. Focal lesions, such as those described in the lymph nodes and spleen, were found in 20 of the cases. The same description which has been given of them in these organs applies to the intestine. The swelling and proliferation of the vascular endothelium was very evident; the nuclei pro-

jected into the lumina of the vessels, causing them to simulate glands. The endothelial cells frequently contained lymphoid cells. In the mucous membrane elsewhere no lesions were found. These lesions in the intestine agree with the description given by other authors. Bizzozero found in the solitary lymph nodules and Peyer's patches changes similar to those in the lymph nodules of the spleen and in the mesenteric lymph nodes. The swelling was due to the infiltration of the internodular tissue with lymphoid cells. Oertel found no changes in the epithelium, but necrotic foci were found in the lymph nodules. The changes found experimentally are more marked. Welch and Flexner found in addition to necrotic centres in the lymph nodules a general diffuse necrosis affecting the epithelial cells of the glands. Courmont, Dogan, and Paviot, who injected dogs with the toxin, found hyperæmia and degeneration in Peyer's patches. They think that the intestinal lesions are produced by the elimination of the toxin by the intestine. In addition to these examinations the appendix was examined in 15 cases. The same lesions were found in the lymphoid tissue of this as in the intestine. In two cases an interesting condition not connected with diphtheria was found in the appendix. In one, a child of five years, the appendix in one place was occluded by a mass of mucus, cast-off epithelium, and detritus in which chains of streptococci were found. In the other, a child of ten months, there was a foreign body surrounded by a mass composed of degenerated epithelium, mucus, and bacteria. The bacteria were chiefly the ordinary intestinal bacteria, but in places a few elongated diplococci resembling pneumococci were found. The exact character of the foreign body could not be determined, but it was evidently the remains of a small round parasite, probably an oxyuris vermicularis.

Summary.

The lesions of the small and large intestine in diphtheria in man are relatively unimportant. They consist of hyperplasia of the lymphoid apparatus and the same other changes found in the lymph nodules elsewhere. The slight extent

of the lesions does not indicate the action of toxins absorbed from the alimentary canal; they are probably due to the action of toxins from the blood current. There is nothing in the character of the lesions to indicate the elimination of the toxins by the alimentary canal.

LIVER.

The liver in diphtheria has not been investigated with the same care as the other organs, and until recent years some of the most important lesions have been overlooked. The most constant lesion found in the liver by Oertel consisted of small hæmorrhages beneath the peritoneum and in the more superficial part of the parenchyma. He also found a leucocytic infiltration of the subperitoneal and periportal connective tissue, which though varying in extent was never wholly absent. The leucocytes frequently extended from these places into the lobule, separating the columns of liver cells. The lesions in the liver cells were relatively unimportant and consisted of fatty degeneration in the vicinity of the foci of leucocytic infiltration. Katzenstein found cloudy swelling and fatty degeneration of the liver cells, leucocytic infiltration in the periportal connective tissue, and in some cases a tendency to destruction of the nuclei, which stained faintly. In a few cases he found hyaline degeneration of the walls of the capillaries in some parts of the portal spaces and in the peripheries of the lobules. The blood in the capillaries of the liver contained large numbers of leucocytes. Gaston in his treatise on the changes in the liver produced by various infections described in a very general way the changes found in diphtheria, namely, congestion of the vessels, fatty degeneration of the liver cells especially in the centre of the lobules, and infiltration of the portal spaces with embryonic cells. There is embryonic infiltration around the veins, arteries, and bile ducts, and in the latter a catarrhal condition. Macroscopically the liver is enlarged, congested, and contains the "plaques infectieuses" which Hanot described as characteristic of the liver of acute infectious diseases. The plate which Gaston gives shows a

congested liver with nutmeg markings. Barbacci has described the lesions in the liver more fully. He found an abundance of leucocytes in the vessels. The capillaries in places were so greatly dilated that the tissue simulated cavernous tissue, the rows of liver cells between them were reduced to thin masses, and in places they completely atrophied. In the capillaries there were large blocks of stained material which resulted from the breaking down of the blood.[1] The endothelium of the capillaries was often swollen to a considerable degree, and hyaline degeneration of the walls was met with. The liver cells were granular, swollen, and œdematous, and often the cell columns more or less disarranged (*dislocation de la travée hepatique Hanot*). Various degenerative conditions but no actual necroses were found. The lesions in the periportal connective tissue were almost constant and consisted of small cell infiltration which often extended beyond the bounds of the connective tissue and invaded the lobule.

The liver lesions in experimental diphtheria have been much more carefully studied. Babes has given an interesting account of the lesions in the liver, which in several respects agrees with what we have found in man. He found the liver cells swollen, pale, coarsely granular, and in places filled with fat. The lobules occasionally contained small inflammatory foci, and in the vicinity of these the liver cells were more or less separated from their connections. Between the liver cells and in the interior of the capillaries there were mono- and multinucleated leucocytes. The endothelium of the vessels was often greatly swollen and proliferating. The cells coming from this proliferation were large, often exceeding the liver cells in size. They were round or oval, sharply circumscribed, the protoplasm homogeneous, and the nuclei large and irregular. These cells together with leucocytes and granular masses often filled the capillaries. He also speaks of finding groups of pale homogeneous yellow-

[1] This condition described by Barbacci is an artefact due to imperfect preservation of the blood. The tissue of the liver is so dense that hardening agents will only penetrate when very small pieces of tissue are immersed in them. Even then it is advisable to take the sections for microscopic work from near the surface.

ish liver cells without nuclei separated from their connection with one another. Between these there were masses of multinucleated leucocytes, and nuclear fragments derived from the swollen endothelium. The most thorough study of the lesions in the liver produced experimentally is that by Welch and Flexner. The chief changes described by these authors were necrosis of liver cells, affecting usually definite groups, although single necrotic cells were occasionally found. Among the necrotic cells were polynuclear leucocytes which came from the capillaries. The capillaries in and in the vicinity of the necrotic foci contained large numbers of leucocytes, and often swollen and desquamated endothelial cells. Baldassari paid particular attention to the changes in the nuclei. He found the changes most marked in those cases in which the infection took a longer course. The liver cells showed cloudy swelling, fatty degeneration, and necrosis; the necrotic cells formed foci chiefly in the vicinity of the central vein. In places the necrosis was so advanced that the structure disappeared, and in the area there was only cell detritus composed of albuminous granules, altered nuclei, and emigrated leucocytes. The most characteristic changes in the nuclei consisted of fragmentation of the chromatin network; the chromatin masses separated from their connection and formed a circle around the nuclear membrane. The whole chromatin network might break down, and the nucleus become diminished in size and stain intensely. In other cases the nucleus contained no chromatin network, and appeared as a vesicle. Sometimes the nuclear membrane broke up and particles of the chromatin appeared in the cytoplasm. In the most severe cases not only was there no chromatin, but the nucleolus was not visible. He quotes the work of Trambus to the effect that the nucleolus is more resistant than the chromatin; and where it has disappeared this denotes a more intense action of the injurious substance. The only other agents which he found to produce results comparable to those in the diphtheria were arsenic and phosphorus.

The recognition and the interpretation of the lesions in

the liver presented great difficulties. This was not due to the complexity of the structure, but to the closeness of the texture; so many different elements, which, especially in a degenerated condition, may closely resemble one another, are so close together. The ordinary paraffin sections proved totally inadequate, and it was only after securing, by means of the Blake-Minot microtome, sections 2 μ in thickness, and by the application of special means of staining that it was possible to explain some of the conditions met with. The tissue was hardened in the usual way in Zenker's fluid, and only those cases were examined in which the preservation was good. The stain found most useful was the connective tissue stain of Mallory. The especial advantage of this was that it differentiated clearly the walls of the capillaries, and showed the structure of the cytoplasm much better than any other that we used. The presence of necrotic foci could most easily be distinguished under a low power in sections stained with methylene blue and eosin, or hæmatoxylin and eosin, because the eosin stains the necrotic cells intensely. The liver was examined in 180 cases, these embracing cases of all ages and of all stages of duration of the disease. The character and extent of the lesions varied greatly, and did not seem to depend, to any degree at least, upon the duration of the disease. In a general way, however, certain lesions were more marked in the more acute cases, and others in those of longer duration. The liver did not present any characteristic macroscopic appearance. Generally it was slightly swollen, somewhat tense, and congested. In some cases the congestion was marked and a considerable amount of blood flowed from the cut surface. Frequently the congestion was irregular; there were pale, slightly yellowish foci from one to several cm. in diameter in the dark red tissue. In some cases the liver was pale and cloudy; this was due chiefly to the extent of the fatty degeneration. There was nothing in the macroscopic appearance to distinguish the liver in diphtheria from the liver in any of the other acute infectious diseases.

On microscopic examination the most constant lesion was

swelling of the cells with increased granulation. This affected all portions of the lobule, but was rather more marked in the centre. In specimens stained with the triple (connective tissue) stain the cell boundaries were sharply outlined, due to the staining of the bile capillaries, which are refractive and take a distinct brownish-red color. The normal cell is indistinctly granular, and there is a fine reticulum to be made out extending throughout the cell protoplasm. In what we regard as the slightest form of degeneration the reticulum is more evident and actual spaces in the cells can be seen. (Plate XXIII., Fig. 2; Plate XXII., Fig. 2.) These spaces probably are due to increase in the intracellular fluid. They are totally different from the distinctly round and sharp-cut outlines of the cavities due to fatty degeneration of the cell, remaining after the fat has been dissolved out. In places the capillaries are compressed by the swollen cells, in others they are wider than normal. With this œdematous condition of the cells there is often combined a change in the granulation. The granules become more prominent and vary in size and in staining. The reticulum of the cytoplasm becomes less evident or invisible. In place of the fine, even granulation of the normal cell, coarse granules of irregular size appear, some of them staining a deep brown in the triple stain. In some of the swollen cells this granulation is extremely evident, owing to the disappearance of the intracellular network. In certain of the sections stained with methylene blue there are granules in the protoplasm which take the blue stain with varying degrees of intensity. Some of these are of regular size and often arranged in pairs or short series resembling micrococci or short bacilli. In most cases the stained material is of irregular size and stains indistinctly. Similar stained masses were found in the specimens stained with hæmatoxylin, but they were not so evident. In two of the cases, both of them acute, granules of varying size staining more distinctly than the other granules in the cell were found enclosed in definite vacuoles. They were very similar to the inclusions found in the epithelial cells of the kidney in one of the cases, and also similar to some of the inclusions found in

carcinoma cells. A definite hyaline degeneration of the protoplasm resulting in the formation of hyaline globules was found in but one case and in but a few cells in this. The hyaline droplets stained blue in the triple stain just as did the hyalin in the kidney epithelium. This form of degeneration is certainly rarer in the liver than in other glandular organs. This degeneration of the protoplasm in most cases takes place without any change in the nucleus. An apparently normal nucleus was often found in cells in which there were marked changes in the protoplasm. In several cases a peculiar change in the nucleus was found which has been described by several authors (Barbacci, Katzenstein, Baldassari). In this condition the nucleus becomes greatly enlarged and vesicular. The chromatin disappears entirely from the interior of the nucleus and becomes arranged around the periphery, making the nuclear membrane more conspicuous. The nucleus then appears as a large, conspicuous vacuole in the cell, and within it, usually at one side, clinging to the nuclear membrane, is a very small unstained vesicle which we have regarded as the altered nucleolus. This form of degeneration of the nucleus of the liver cell is comparatively rare and it is not confined to diphtheria. We have found a great number of nuclei so altered in the liver from a case of leucæmia. The vesicular nucleus is not always round, but may be bent or folded on itself in a variety of ways.

It was very difficult to judge of the presence and degree of fatty degeneration. A varying number of fat vacuoles were found in the cells. Some of these were large, others very small. The large fat vacuoles were more commonly found in cells in the periphery of the lobule, and the smaller were more evenly distributed. In some cases almost all the cells were filled with very small fat vacuoles. There was no relation between the amount of fat present and other degenerative conditions of the cells, and a similar distribution of fat may be found in the livers of children dying from other diseases.

The most extensive degeneration consisted of an actual necrosis of the liver cells. The necrosis was always more

marked in the vicinity of the hepatic veins than elsewhere. The necrosis was never diffuse affecting scattered cells, but was always found in groups of cells. (Plate XXIII., Fig. 1.) Two distinct forms of necrosis could be distinguished. In one, the more common form, it affected the cells around the central vein. From this it extended a variable distance towards the periphery. In the specimens stained with methylene blue and eosin the necrotic foci could be easily distinguished even with a low power by the more intense staining of the necrotic cells with eosin. In the triple stain they stained darker than the other cells. Apparently various stages of the necrosis could be distinguished. The totally necrotic cells were homogeneous, hyaline, and refractive. They were small and had lost their typical shape and their connection with one another, appearing as irregular masses lying loosely in contact. (Plate XXIII., Fig. 3.) There was no appearance of the nucleus in these cells, and no nuclear detritus. Where the necrosis was not so far advanced the cells were larger, contained more granules, and the nucleus could be distinguished, though it had undergone various changes. In some cases the nucleus seemed simply to disappear; in others the chromatin became swollen, forming a homogeneous mass which in some cells stained intensely. The chromatin seemed to undergo the same hyaline degeneration as the protoplasm and never broke up into fragments. In most cases this central necrosis occupied the entire centre of the lobule; in others it appeared only at a small point, the remaining cells being unaltered, and from this extended a short distance towards the periphery. The very considerable space separating the rows of liver cells in these foci was very striking. Barbacci has called attention to this and regarded the degeneration of the cells as due to pressure exerted by the dilated capillaries which filled the space between them. Examination with low power of specimens stained with methylene blue and eosin seems to show this, but high power examination of very thin specimens stained with the triple stain shows a very different condition. This stain brings out sharply the capillary wall and shows that the altered liver

cells lie in a wide space between the capillaries. (Plate XXIII., Fig. 3; Plate XXII., Fig. 3.) On either side between the degenerated liver cells and the capillary walls there is a space which is filled with granular debris apparently resulting from the destruction of the cells and from the coagulation of the exudation. The granular material is very irregular in size and most of it is colored by the orange stain in the mixture. When the liver cells are entirely separated from their connection they lie as a loose mass in the space among the granular debris. Clear orange-stained vesicles similar to those so commonly found in the tubules of the kidney were occasionally found in the space lying among the debris. (Plate XXII., Fig. 4.) The capillaries instead of being dilated are actually compressed and in places totally obliterated. They contain a variable number of red corpuscles which are also sometimes found in the intercapillary spaces with the other material. In most cases the necrosis is confined to the centres of scattered lobules; in others almost all the lobules in the section are affected. One remarkable fact about these central necroses was the rarity with which they were invaded by other cells. In most cases the spaces were entirely occupied by the necrotic cells, granular debris, and an occasional red corpuscle. In other cases a very few polynuclear leucocytes which generally showed some nuclear degeneration were found, and occasionally an endothelial cell. Nor did the capillaries either in the necrotic foci or surrounding this contain an unusual number of leucocytes. We have regarded the formation of this space around the capillaries as due in part to exudation and in part to the shrinkage of the cells forcing the intracellular fluid from them. The main element, however, in producing the condition must be exudation through the capillary walls. It is not a process secondary to the necrosis, for it was found in places where there was no necrosis, though it was more marked in the central necrotic foci than elsewhere.

The disseminated foci of necrosis were not so common as the central necroses, and in a number of ways differed from them. They were found in but 7 of the 180 cases, while the

central necroses were found in 22. The two processes were but rarely found associated together. The disseminated foci varied in size from those containing but few cells to those forming a considerable part of the lobule. (Plate XXIII., Fig. 1.) They were much more difficult of interpretation than the others, owing to the greater number of cellular elements contained in them. The necrotic liver cells presented about the same appearance as the necrotic cells in the central necroses. Like these they were more or less broken down and separated from their connection with one another, and lay in spaces between the capillaries, though the spaces were not so large. Among the necrotic cells in the spaces there were almost invariably numerous other cells. These were in part polynuclear leucocytes, with the nucleus in some cases well preserved, in others fragmented. These lay between and in some cases within the necrotic cells. Among them were other cells, with large irregular vesicular nuclei, which were similar to the cells, evidently of endothelial origin, which were found within the capillaries. In some foci all these cells could be distinguished as such; in others they were so degenerated that only fragments of cells and nuclear detritus appeared. The capillaries were difficult to make out. They contained very few red corpuscles, a variable number of leucocytes and endothelial cells, and almost invariably some fibrin. The capillary walls were frequently thickened and hyaline. The obstruction of the capillaries was due only in part to the œdema, but chiefly to the cells and fibrin. In one case small foci were found which could almost be regarded as minute abscesses. In these foci the capillaries were filled with polynuclear leucocytes, and such numbers of them were found in and among the necrotic cells that the details of the lesion were obscured. In no case did either of these forms of necrosis seem to be entirely due to an injurious agent affecting the liver cells primarily.

These circumscribed necroses met with in the liver have attracted much attention and their pathogenesis has been obscure. A very diffuse form of necrosis apparently not connected with bacteria was described by Councilman in

yellow fever. The necrotic cells were invaded by leucocytes. Subsequently Councilman and Lafleur described necrosis of the central cells of the lobules in amœbic dysentery, and regarded it as due to the action of toxines absorbed from the alimentary canal. Reed regarded the nodules found in the liver in typhoid fever and generally described as typhoid lymphomata as due to primary necrosis of groups of liver cells with subsequent invasion by polynuclear leucocytes. Mallory subsequently showed that these foci were due to capillary occlusion, and that the cells found in the capillaries and among the necrotic liver cells were chiefly or entirely endothelial in origin. Barker described necrotic foci in the liver in malaria. There were numerous thrombosed capillaries in the necrotic foci, and Barker was inclined to regard the necrosis as secondary to the capillary thrombosis.

Flexner, who has given the most complete description of the necroses in the liver produced in experimental diphtheria, regards the necroses as due to injury of the wall of the vessel at some point allowing transudation to take place more freely. He supposes that the injury is produced at some period of greater concentration of the toxin and at a point where the circulation is slowed or at a standstill. He very properly rejects the theory that the necrotic cells represent cells of less resistance which succumb to the action of the toxin. It seems possible that such a theory might explain the very diffuse necroses in yellow fever, but it is impossible to apply it to groups of cells. Although Flexner rejects the theory of less resistance the theory he advances is almost as hypothetical. It is impossible to compare the necroses met with in the human liver in diphtheria with those produced experimentally. The livers both of rabbits and of guinea-pigs are much more susceptible to necrosis than the human liver, and necroses are found in them in a great number of infections. The most common of the necroses in man, that around the central vein, is rarely found in these animals; the necroses in them take the disseminated form. We are inclined to regard both forms of necroses, both that around the central vein and the form in disseminated nodules, as due

to capillary obstruction plus the action of the toxic substance. The main factor in the production of the central necrosis is capillary occlusion due to the pressure exerted by the exudation. Occlusion of the capillaries by thrombi also plays some part. Though exudation is more marked in the central necrotic area it is not confined there. The fact that the necrosis takes place in the centre and not in the periphery may be due to the fact that the circulation in the periphery may be maintained by the capillaries in the periphery discharging into those of adjacent lobules. The disseminated necroses are almost certainly due to capillary obstruction brought about by fibrin (Plate XXII., Fig. 4), by endothelial cells (Plate XXIII., Fig. 4), and by leucocytes, either singly or combined. In one case necroses were found which were very similar to those found in typhoid fever. There is nothing characteristic about these diphtheria necroses. They are found in the same form and in almost as great numbers in other infectious diseases. They sometimes very closely resemble miliary tubercles. In the most acute form of miliary tuberculosis of the liver there is necrosis of the liver cells and accumulation of endothelial cells in the capillaries, but the formation of the latter is due chiefly to the tubercle bacilli enclosed in them.

Apart from the lesions in the capillaries which we have described in connection with the necroses there are few other changes in these vessels. The walls of the capillaries are often swollen and hyaline in the necrotic foci, and occasionally a slight degree of this change is found elsewhere, but we have never found any extensive hyaline degeneration such as Barbacci has described.

In the examination of the liver our attention was early attracted by the number and character of the cells in the vessels. It has seemed to us that in the normal liver there are few leucocytes in the capillaries, fewer than in the capillaries of other organs. Almost all observers have described increased number of leucocytes in the capillaries and veins of the liver in diphtheria. It is true that the number of cells is increased in almost all cases and in some greatly so.

Comparatively few of these are polynuclear leucocytes, except in the vessels within and in the vicinity of the foci of necrosis. The most numerous cells found are the varieties and derivatives of the lymphoid cells, the small and large lymphoid cells, and the plasma cells. We have never found this accumulation comparable to that met with in the vessels of the medulla of the kidney. The next most numerous cells are large cells derived from proliferation of the endothelium of the vessels. These are found both attached to the wall and free in the lumen. They have a vesicular, often distorted nucleus and pale homogeneous protoplasm. The cells vary greatly in size. Some of them are so large that they extend along the capillary a distance of the diameter of 4 or 5 liver cells; others are no larger than the ordinary leucocyte. These cells have marked phagocytic properties and they often contain cell inclusions. The included cells are chiefly lymphoid cells and red blood corpuscles. Polynuclear leucocytes are rarely found within them. The nuclei of the included lymphoid cells are often fragmented and the cell contains the peculiar nuclear detritus to which these cells give rise. The protoplasm of the endothelial cells is often degenerated, contains numerous vacuoles, and an occasionally hyaline droplet. We have never found any bone marrow cells in the liver capillaries. Particular attention was directed to the search for parenchymatous emboli of liver cells. These were never found in the examination of the lung and other organs, and it would seem as though the central necroses with disruption of the liver cells should have given rise to them. In the larger vessels single liver cells and adherent masses of these were frequently found. They were found, however, fully as often in the portal as in the hepatic veins, and in our microscopic examinations of the liver in all sorts of diseases they were often found. We have regarded these cells, particularly the masses of them, as artefacts; in the cutting of the fresh tissue the liver cells must often be forced by the knife into the larger blood vessels. Similar conditions are often found in the kidneys, where single epithelial cells or adherent masses are contained in the large

veins. Cells which could be recognized as liver cells were never found in the capillaries; but we do not think it would be possible to distinguish a degenerated liver cell in a capillary from a degenerated endothelial cell.

Hæmorrhage was rare, and was found in a marked degree in but two cases. In the central necroses single red corpuscles were often found in the pericapillary spaces. In the two cases in which the hæmorrhage was marked there was considerable congestion, particularly in foci, and in some of these the red corpuscles were closely packed in the pericapillary spaces, and between the liver cells. No rupture of the capillary walls could be made out in these places, the hæmorrhage having probably taken place by diapedesis.

There was often a marked degree of cellular infiltration around the portal spaces, and these were increased in size. The cellular infiltration was more marked in the chronic than in the acute cases. The infiltrating cells were chiefly lymphoid and plasma. In a few cases the cellular infiltration extended from the portal spaces into the lobule, and in some cases was undoubtedly accompanied by connective tissue formation.

No diphtheria bacilli were found in the liver on histological examination, and in but one case were emboli of micrococci found, and in this case there were no lesions in the liver cells around them.

Summary.

The lesions produced in the liver in diphtheria are not characteristic, and do not differ from those found in other acute infectious diseases. They are due to the effect of soluble toxic substances, and not to the presence of diphtheria bacilli. The most common lesions are a general degeneration of the liver cells, and necroses which are chiefly found in the centres of the lobules. It is probable that the disturbance of the circulation without the injury produced by the toxin would be insufficient to produce necrosis. Slight hyaline degeneration of the capillary walls is occasionally found, and the capillaries constantly contain an increased number of cells, which are partly produced by proliferation

of the endothelium, and partly brought to the liver by the circulation. The lesions in the human liver differ from the lesions produced experimentally in guinea-pigs and rabbits by the diphtheria bacilli or toxin chiefly in the greater frequency of the central situation of the necroses.

KIDNEYS.

The literature on the anatomical changes in the kidneys in diphtheria is not extensive. The article of Brault is the first which is devoted exclusively to the renal lesions produced in diphtheria. He found the kidneys hyperæmic, the vessels of the glomeruli dilated, and blood and epithelium in the capsular spaces. The chief change consisted in degeneration of the epithelium of the convoluted tubules, and this was more marked in diphtheria than in other infectious disease. The endothelium of the vessels was often swollen and projected into the lumina. Fürbringer, who examined the kidneys in 10 cases, found intense parenchymatous degeneration of the epithelium of the labyrinth with desquamation, no changes in the glomeruli, and in a few cases an interstitial cellular infiltration. Fischl found interstitial cellular infiltration around the vessels, swelling and degeneration of the epithelium of the glomeruli, and hyaline masses in the capsular spaces. Tschiglow investigated 17 cases and found degeneration of the convoluted tubules in all and lesions of the glomeruli in six. Oertel devotes considerable attention to the lesions in the kidneys and gives a very good description of the interstitial changes. Hæmorrhages were constantly found beneath the capsule and but rarely in the parenchyma. Foci of cellular infiltration consisting of large and small round cells were frequently found beneath the capsule, around the vessels and glomeruli, between the tubules in the upper and deeper layers of the cortex, and around the small arteries of the pyramids. The cells in the foci seemed to be only in small part formed by proliferation of the connective tissue cells. The changes in the glomeruli consisted of hæmorrhage, exudation into the capsular space, and degeneration of

the capillaries. He describes as a peculiar form of degeneration the appearance of a striated border on the cells in the convoluted tubules. He believed that this condition, regarded by Lorentz as normal, was due to degeneration and partial destruction of the protoplasm laying bare the rod-shaped structures which Heidenhain had described in the epithelial cells. Kuck in an article on albuminuria in diphtheria says that in spite of the albuminuria the changes found at autopsy are chiefly negative. Bernard and Felenthal found extensive lesions in the convoluted tubules consisting of granular and hyaline degeneration. Casts, generally hyaline, were found in all cases. Hæmorrhages were commonly found. Changes in the glomeruli were not common, but in several cases the capsular epithelium was swollen and granular. In all of the 24 cases investigated foci of cellular infiltration were found in the interstitial tissue. Reiche found in all cases examined degeneration of the epithelium, in a few cases lesions of the glomeruli. In a number of cases there was inflammatory proliferation of the connective tissue, and in three cases interstitial round cell infiltration in the pyramids. Katzenstein found degenerative changes the most common lesion, and interstitial changes only in the most severe cases. Flexner in the experimental lesions of diphtheria found hyaline thrombi frequently in the vessels of the glomeruli, and degeneration and necrosis in the tubules. Councilman[1] found interstitial changes in the kidneys in 24 out of 103 cases of pure diphtheria, and in 5 out of 23 cases of mixed infection of diphtheria with scarlet fever.

The kidneys were examined microscopically in 171 cases. Only those cases were excluded from microscopical examination in which the tissue was imperfectly preserved. The usual method of hardening in Zenker's fluid and cutting the sections in paraffin was followed. The Blake-Minot microtome was found extremely useful in preparing very thin sections for examination with high power. As a matter of routine the sections were stained in methylene blue and eosin,

[1] This material is also included in the present article.

in hæmatoxylin and eosin, and in plain hæmatoxylin. In studying the degenerations the connective tissue stain of Mallory gave excellent results.

In a number of cases serial sections were made in order to find in just what part of the course of a tubule certain changes occurred. In this study of serial sections we were greatly aided by photography. The ages of the cases ran from two months to thirty years; the general average was three and three-fourths years. In the examination of so large a number of cases of the kidneys of children there were certain anatomical points brought prominently to our notice. It is known that the glomerulus of the newly-born child differs widely from the glomerulus of the adult. The difference is shown in the small size, the simpler structure, and the very evident covering epithelium in the glomerulus of the child's kidney. This type of glomerulus is gradually lost. There is very little difference in structure between the glomeruli in a child of two months and the newly born. The adult type is not reached before four years, and there seems to be a gradual increase in size of the glomerulus up to ten or twelve years. This gradual growth of the glomerulus is so well marked that under seven years it is possible to tell the age with considerable accuracy from the examination of the kidneys. Not all the glomeruli in the child's kidney show the same stage of development. Glomeruli corresponding perfectly to the embryonic type consisting of a few vascular loops covered with high epithelium were found up to seven years of age. Their number varies greatly in different cases. They are almost always present up to two years and after this they may or may not be present. They are confined almost exclusively to the tissue just beneath the capsule, but they may be found elsewhere. None of the cases enables us to say whether these embryonic glomeruli were more numerous adjoining losses of substance, nor was it possible to say what part they played in the pathological conditions of the glomeruli, for they were not present in any of the cases marked by glomerular lesions. No attempt was made to trace the relation of these embryonic glomeruli to the tubules.

From the microscopic examination it was found possible to divide the kidneys examined into five groups: 1. Those in which degeneration of the epithelium was the chief or the only lesion. (Plate XXIV.) 2. Those in which acute interstitial changes, consisting of cell accumulations in the vessels and interstitial tissue, were present. (Plate XXV., Figs. 2 and 3.) 3. Those in which the chief lesions were found in the glomeruli. (Plate XXVI.) 4. Those in which hæmorrhage into the tubules was present. 5. Those in which chronic interstitial lesions were present as shown by atrophied glomeruli and increase in the connective tissue.

1. *Degenerative changes.* — There is a geat deal of difficulty in the determination of slight degenerative lesions in the kidney. The epithelium, particularly of the convoluted tubules, changes rapidly after death. Differences in mode of hardening and staining lead to differences in the appearance of the tissue. Even extensive desquamation of the epithelium may be found as the result of post-mortem change. The normal epithelium is very granular and differences in the degree of granulation and in the size of the cells are difficult to determine. It is often more easy to determine slight degrees of degeneration from the general aspect of the tissue under a low power than by a more detailed examination under high powers. The convoluted tubes are easily distinguished from the other tubes by their course and the character of the epithelium. The upper portion of the ascending loop of Henle has epithelium similar to the distal convoluted tube. We shall speak throughout of the convoluted tube which passes from the glomerulus as the proximal convoluted tube, and the convoluted portion which is the continuation of the ascending loop of Henle as the distal convoluted tube. There is considerable uniformity between the structure of the epithelium in these two portions of the tubule. In both the epithelium is granular. The granules are distinct, they vary somewhat in size and in intensity of staining. They appear to be enclosed in a meshwork; at least a more or less indefinite reticulum can be distinguished in the cases of degeneration in which the contents of the cells

have been in great measure lost. There is nothing corresponding to the rod-like structures described by Heidenhain. Toward the bases of the cells there is some tendency for granules to arrange themselves in rows perpendicular to the base. The rows of granules somewhat simulate the appearance of rods. The cells terminate towards the lumen by a ciliated border.

The cilia are relatively short compared with cilia in other situations, but are perfectly distinct, and in good preparations the separate cilia can be distinguished. (Plate XXIV., Fig. 2.) They are not easily lost, and they are present in places even when there is a considerable degree of degeneration. In sections stained with Mallory's connective tissue stain they are darker than the cell protoplasm. Often when the cilia cannot be distinguished the border of the cell has a rather indefinite darkish color due to the adhesion of the separate rods. (Plate XXIV., Fig. 1.) These cilia spring from a sharp border of the cell in which there is a row of small granules which stain in the same way as the eosinophile granules, and which can be distinguished by their bright color and situation from the other granules in the protoplasm. The cilia apparently terminate in this granular border, but we were not able to make out with certainty any connection between the cilia and the granules. In some cases it seemed possible to follow the cilia into the cell protoplasm beneath the granules, but this was probably due to imperfections in the sections. Certain conditions in the tubules will make the cilia more apparent. They are most easily seen when the lumen is large. They are found in normal kidneys, and in all possible pathological conditions, but fresh tissues are necessary for their demonstration. It is not possible to make out any of the fine structures of the kidney epithelium when the autopsy is more than a few hours after death, unless the body has been kept at freezing temperature. The cilia are found only in the ascending loop of Henle, and in the convoluted tubules. In the latter they are much more evident in the distal than in the proximal tubule. The difference is so marked that we were at first inclined to consider them absent

in the proximal tube, but we have in a few cases undoubtedly found them in this situation.

In a number of cases the tubules of the cortex contained a number of vesicles. They varied in size, and when few were present they were round; when numerous they were pressed closely together, and their edges formed a reticulum. They were either empty, or contained a few granules which were generally larger and less brightly stained than the granules in the protoplasm. The envelope of the vesicle was usually thin and smooth, but occasionally granules were adherent to it. The vesicles were not found except in the cortex of the kidney, in the convoluted tubules, and in the ascending loop of Henle. The envelope of the vesicles and the granules contained in or adherent to it stain with eosin and with fuchsin; with the connective tissue stain of Mallory they take a decided yellow color due to orange G. We are not able to say anything about the character and origin of these vesicles. They are usually very well marked in the kidneys from cases of acute infectious diseases; they may be present along with evidences of degeneration, or in kidneys apparently normal. In this large series of cases presenting every form and degree of degeneration the condition was not common; but in the kidney obtained from a young woman (who committed suicide by stabbing) and used as a normal type for comparison, these vesicles were extremely well marked. In other normal kidneys they were not present. These vesicles have been considered as drops of secretion coming from the cells, as evidences of cell degeneration (in this case the vesicles are supposed to represent sections of the ends of the swollen vesicular cells), and as formed from the coagulation of albumen. None of these explanations seem to us sufficient. Were they actually drops of secretion, they should be seen as well in the cells as in the lumina of the tubules; they were not present in the cases in which the epithelium was swollen and vesicular, and we have never found the coagulation of an albuminous exudation in any situation to give such an appearance. That it is not peculiar to the kidney is shown by our finding a similar appearance in other situations, as in the

bronchi behind the epithelium, which was raised from the surface, and in similar relation to the gastric and other epithelia.

Degenerative changes varying in character and extent were found in 112 of the 171 cases examined. Macroscopically these kidneys differed but little from the normal. The degree of congestion varied; in some cases the kidneys were slightly swollen, the cut surface more opaque, and the markings obscure. A considerable degree of degeneration may be found in a kidney which presents a perfectly normal appearance to the naked eye. According to the degree of degeneration the cases were divided into those with slight degeneration, 26 cases; those with a medium degree, 38 cases; those with a marked degree, 37 cases; and those with an extreme degree, 9 cases. The most extreme degree was found in those cases of severe type which died shortly after their entry into hospital. The average duration of the 9 cases was four and one-half days, and of all the cases of degeneration seven and one-half days. Fatty degeneration as determined by frozen sections was usually only slight in degree. It was found, however, in 44 out of 58 cases which were examined for it. The slightest form of degeneration shown in the hardened sections consisted of swelling and irregularity of form of the cells with an increase of the granular contents. The granules were often larger or smaller than normal and the increased size of the cells seemed to be due more to increased size of the granules than to an increase in their number. (Plate XXIV., Fig 1.) In places the part of the cell adjoining the lumen was swollen, pale, and contained very few granules. The outlines of the altered cells in many cases were sharp and the ciliated border perfectly preserved. (Plate XXIV., Fig. 2.) In other places the cells were ruptured and their granules escaped into the lumina of the tubules. The granules were often found in tubules in which there was no rupture of the cells. They may have escaped from the cells without any rupture, or may have come from some other point in the course of the tubules. Not only single granules but adherent masses of them represent-

ing entire fragments of cells were found. In places tubules could be found entirely filled with a mass of granules and cell fragments. The process of cell destruction was often very apparent in tubules in which the cells were represented by only a small mass of granular material around the nucleus, and in places no trace of the cells could be made out. With this change in the cells, consisting of simple destruction, there was often combined a more advanced form of degeneration consisting of a change in the character of the cell contents. Among the granules certain ones could be distinguished by their larger size, and less degree of refraction. These larger granules stained in some cases as the other granules of the cells, or were somewhat paler. As they increased in size they gradually assumed with the Mallory connective tissue stain a deep blue color, similar to that of the connective tissue. Only single scattered blue globules were found in the cell, or the entire cell was filled with them. (Plate XXV., Fig. 1.) They varied in size from those no larger than the cell granules to large masses twice the size of the nucleus. Finally the cells ruptured and the hyaline globules filled the lumen of the tubule. Some degree of this hyaline degeneration was found in almost all the cases, even in those in which the lesions were very slight. In some cases it was most marked and some degree of it was found in almost all the proximal convoluted tubes. It was most evident in the degeneration which occurs in connection with the glomerular affections. It was much more evident in the proximal than in the distal convoluted tubules and in that portion of the tubule nearest the glomerulus. In one case in which serial sections were cut it was possible to trace the hyaline degeneration to the beginning of the tubule, and in this case the glomeruli were not affected. The nuclei in many cases were unaltered even when a high degree of degeneration was present. (Plate XXIV., Fig. 1.) But in some cases they also showed pathological conditions consisting of swelling and loss of chromatin, or the whole nucleus was converted into a faintly staining homogeneous mass somewhat resembling a hyaline globule. In several cases the cells

were greatly swollen, filling entirely the lumina of the tubules. In these swollen cells there was a more or less definite reticulum enclosing scattered granules of various sizes. (Plate XXIV., Figs. 3 and 4.) Extreme degrees of degeneration could be present without any formation of hyalin in the cells.

In one case a form of degeneration was found which we have never seen before. In this case, along with a general high degree of degeneration, vacuoles were found in the cells containing round, generally granular masses. These masses varied somewhat in size, and they were usually found in the peripheral part of the cell. The nuclei, though often degenerated, were generally present in the cells containing the enclosures. It was impossible for us to determine the exact nature of these enclosed masses; they certainly did not seem to be enclosed cells, for they varied too much in size and contained no chromatin fragments. They appeared rather to be masses of protoplasm separated from the remainder of the cell. In one place there was a double inclusion: a small mass lying in a vacuole itself contained a vacuole and a small included body. The included bodies were only found in the cells of the convoluted tubules and the ascending loop of Henle. The case was that of a child five years old who died on the seventh day of the disease.

The degree of degeneration varied not only in the different tubules, but in different parts of the same tubule. This was particularly true of the hyaline degeneration. Desquamation of epithelium was not marked. Occasionally the tubules of the pyramids contained single epithelial cells and adherent masses of them, but usually the cells seemed to go to pieces gradually rather than to be lost as a whole. Casts were practically always present. They were most numerous in the cases with marked hyaline degeneration of the epithelium, and the hyaline material of the casts stained in the same way as the hyaline globules in the protoplasm. The actual formation of the cast from such hyaline material could be often followed. Masses of granules from the cells were also found in the tubules, often mingled with the hyalin. There is but little doubt that both the granular and hyaline casts

which are found in the urine in these cases are formed from degeneration and destruction of cells. It is also true that this is not the only source of the cast, for in some of the cases of glomerulo-nephritis the tubules contained a considerable amount of fibrin.

The most constant change found in the glomeruli consisted of a small amount of granular coagulum between the tuft and the wall. In cases of marked hyaline degeneration of the tubules, this change extended to the epithelium of the capsules and the cells were swollen and contained hyaline droplets. The degeneration was rarely associated with any cellular exudation. In one case of mixed infection of diphtheria and measles large numbers of polynuclear leucocytes were found in the tubules and in the vessels. In this case both diphtheria bacilli and staphylococci were found in cultures made from the kidneys.

There are records of the examination of the urine in 40 of the cases of simple degeneration. So many of the cases were in very young children who were brought into the hospital in a moribund condition that the systematic examination of the urine was a matter of great difficulty. Albumen was present in 33 of the 40 cases. As a rule the examination was made in the cases of longer duration. While there was some general agreement between the presence of albumen and the degree of degeneration, there were some exceptions to this; in one case no albumen was found where marked degeneration existed, and in another a large trace was found with very slight degeneration. In two of the cases there is a note of complete suppression for twenty-four hours. In the few microscopic examinations of the urine which were made there were granular and hyaline casts.

The mixed infections were less common in the cases which showed degenerative lesions than in the cases with more severe lesions. In the degenerative cases mixed infections were more frequent according to the severity of the lesion. In the 26 slight cases there was no scarlet fever and but 1 case of measles; in the remaining 84 cases there were 11 of scarlet fever and 5 of measles. There seemed to be no

relation between the character of the degeneration and general infection with various bacteria. In the 110 cases a general infection with the diphtheria bacillus was found 20 times, with the streptococcus 29 times, and with the staphylococcus aureus 4 times; with the pneumococcus 3 times. In 9 cases in which the degeneration was most extreme there was a general infection in but 1 case and that with the streptococcus. Bacteria were found in the cultures from the kidney in 61 cases. In this group of cases also there was no relation between the extent and character of the lesions and the presence or the character of the bacteria.

2. *Acute interstitial changes.* — In 43 of the cases acute interstitial nephritis was present. (Plate XXV., Figs. 2 and 3.) We have included under this head all of the cases in which the interstitial tissue of the kidney was infiltrated with cells of the plasma variety. In the most marked cases of this lesion the kidneys were greatly enlarged. In one case of combined diphtheria and measles in a child of two years the combined weight of the kidneys was 480 gms., and in two other cases, one a child of five years, the other a child of two and one-half years, the kidneys weighed respectively 250 and 225 gms. This extreme enlargement, which may be more than four times the normal, is rare; the kidneys usually are little if at all enlarged. In the cases of great enlargement the capsule is distended, thin, and often separates spontaneously on section; the fœtal markings are less distinct and often obliterated, and the surface is pale, of a grayish opaque color, mottled, with irregular, more hyperæmic areas. The stellate veins of the surface are enlarged, and punctiform hæmorrhages are often found in their vicinity. On section the normal markings are obliterated and the contrast between pyramids and cortex is less distinct. The increased size is chiefly due to the swelling of the cortex. In the less marked cases there are opaque areas often in lines corresponding to the course of the tubules and due to the interstitial infiltration. In the most marked case, in which the two kidneys weighed 480 gms., the interstitial infiltration was so intense that the tubules were masked by it. (Plate XXVI., Fig. 3.) It

was general in all parts of the kidney, but was more intense in foci; groups of tubules were often found with but little infiltration between them. Most of the cells in the interstitial tissue are plasma cells with typical nucleus and protoplasm. In the most extreme case there were numerous polynuclear leucocytes among them and some of the tubules were filled with them. In this case there were also numerous large phagocytic cells which often contained plasma cells, lymphoid cells, or polynuclear leucocytes lying in vacuoles. These phagocytic cells were rarely seen in any of the other cases. Lymphoid cells were numerous, and also cells which seemed to represent a transition between these and plasma cells. The focal character of the infiltration was well marked. The foci were most numerous at the base of the cortex adjoining the pyramids, just beneath the capsule, and around the glomeruli. In some cases the foci were confined to the pyramids. Polynuclear leucocytes may or may not be present. They were found both in the tubules and in the interstitial tissue, and there seemed to be some relation between them and the degree of degeneration of the epithelium. The degeneration of the epithelium varied in the different cases and in different foci in the same kidney. In some places there was little or no degeneration, and a marked degree of interstitial infiltration was often found between tubules which presented a perfectly normal appearance. In other cases the tubules in the interior of the interstitial foci showed a marked degree of degeneration and in some cases actual necrosis.

The infiltrating cells were usually confined to the interstitial tissue. Occasionally a few cells similar to them were found in the tubules themselves, especially where these were degenerated. Nuclear figures were found in variable numbers in the cells in the interstitial tissue. In no case were they wholly absent. These changes in the interstitial tissue are always accompanied by changes in the vessels. The infiltrating cells are found in the vessels as well as in the tissue, and they may be so crowded together that it is difficult to distinguish the vessels. Most of the cells in the vessels have the same character and the same peculiarity of staining as

the cells outside. Nuclear figures were found in these cells, but in no such numbers as in the cells outside the vessels. Very few polynuclear leucocytes were found in the vessels along with these cells. The numbers of cells in the vessels were not always proportionate to the degree of interstitial change. Sections in which the vessels were blocked with cells might show but slight interstitial change, and occasionally interstitial foci are found where but few cells could be made out in the vessels.

Particular attention was paid to the vessels in the examination of all the sections. Cell accumulations were found in the vessels in a large number of cases in which degeneration was the only lesion. The cells were found in greater numbers in the small veins in the upper part of the pyramids than elsewhere. In certain cases they were so numerous that the vessels were apparently blocked by them. Such cell collections were occasionally seen in the stellate veins of the cortex and elsewhere, but in most cases they were confined to the veins of the pyramids.

Most of the cells in the vessels had the same general character as those in the interstitial tissue. Others resembled closely the large granular cells of the bone marrow, and in a number of cases, representing all forms of lesions, the large cells of the marrow were found in the capillaries of the glomeruli, but they were never so numerous as in the capillaries of the lungs. In some cases only lymphoid cells were found in the vessels. Polynuclear leucocytes were extremely rare among them. In some cases a few might be found, but in most cases it was possible to examine all the vessels in the pyramids without finding any. The presence of the cells in the interstitial tissue does not seem to be in any degree dependent upon the degeneration of the epithelium. The most advanced epithelial degeneration was found in cases in which no cells were present, and as we have said marked interstitial changes were found without degeneration. The degeneration found in foci of intense infiltration seems to depend on this infiltration, and be due to malnutrition produced by the blocking of the vessels.

In all of the interstitial cases the duration of the illness was more prolonged than in cases of simple degeneration. The average duration of all cases was 21½ days. Omitting three cases in which the duration was 53, 136, and 42 days respectively, and in all of which the interstitial lesions were slight, the average duration of the 40 cases was 16 days. The age varied curiously with the degree of the lesions. In 19 cases in which the lesions were of slight extent the average age was two and one-sixth years; in 11 cases of medium intensity seven and one-half years; and in the remaining cases, in which lesions were extensive, eleven and one-half years. There was some relation between the lesions and the degree and duration of the affection; the lighter cases were of shorter duration, but this relation was not so marked as was the relation between the age and intensity. This shows that the interstitial process takes some time for its development and the younger cases do not live sufficiently long for the process to reach its maximum. There are some striking exceptions to this statement; in the two most extensive cases the ages were two and two and one-half years. Complications with other diseases play a more important role than in the degenerations. Scarlet fever was found in 13 cases, measles in 5, being three times more common than in the degenerations. Various other complications, such as bronchopneumonia, otitis media, etc., were but slightly more common than in the degenerations. Tuberculosis was present in 10 of the 43 cases of interstitial nephritis, and in 15 of the 112 cases of degeneration. General infection with diphtheria bacilli or streptococci was slightly more frequent than in the degenerations, and they were frequently found in the cultures from the kidney. In 15 cases the urine was tested for albumen, and in 1 case the sediment was examined microscopically. Albumen was present in 14 cases. In the one case in which the sediment was examined numerous leucocytes were found in it. In this case the interstitial infiltration was most extensive, and it is possible that the cells found in the urine may have been of the same character as those in the interstitial tissue.

3. *Glomerular changes.* — Glomerulo-nephritis was found in 11 cases. We have considered under this head all those cases in which lesions in the glomeruli were so marked as to constitute the most important lesions in the tissue. Lesions in the glomeruli play but little part in the cases of simple degeneration or of acute interstitial changes. In most of the cases of degeneration it was not possible to make out the condition of the epithelium covering the vascular tufts. In one case the epithelium of the capsule was swollen and filled with hyalin for a short distance adjoining the exit of the tubule, and an occasional swollen capsular cell was found attached to the tufts. There was usually a small amount of granular material, evidently coagulated albumen, in the capsular space. The glomeruli took no part in the acute interstitial cases. The interstitial infiltration was usually prominent around the glomerulus, but there were no cell accumulations between the capillaries or in the capsular space. Even in those cases in which the vessels elsewhere in the kidney contained large numbers of cells, the vessels of the glomeruli were generally entirely free or contained but a few scattered ones. In a number of cases large marrow cells similar to those so frequently found in the capillaries of the lung were found in the vessels of the glomeruli. In one case in which acute interstitial lesions were found along with well marked glomerular lesions a few of the cells in the glomerular vessels were similar to those in the interstitial tissue.

The changes in the glomeruli were more easily studied in the kidneys of children than of adults, owing to the greater simplicity of the glomerular structure. Important assistance was rendered by the connective stain of Mallory, which enabled us to distinguish the walls of the vessels much more clearly than by any other method. The walls of the vessels composing the glomerulus are thicker and more homogeneous than vessels of a similar size elsewhere; they stain a bright blue color and resemble the membrana propria around the tubules.

In nine of the cases the changes in the glomeruli were of the same general character, varying only in intensity and chron-

icity. From the study of the glomeruli in these cases, and of the different glomeruli in the same case, it was possible to obtain a fair idea of the character and progress of the lesions. In most cases there was very little difference in the degree of involvement of the different glomeruli in the same kidney. The first evidence of change in the glomeruli is an increase in the number of cells. (Plate XXVI., Figs. 1 and 2.) Some of the cells in the capillaries appear to be free, but others are apparently seated on the wall and project into the lumina. Red blood corpuscles may be found within the vessels, and the changes may be so slight as easily to be overlooked. From this condition the process increases in intensity by continued formation of cells. The glomerulus becomes converted into a confused mass in which it is difficult to distinguish the single capillaries. (Plate XXVI., Fig. 3.) These become entirely occluded by the increased cell formation and thickening of the wall. All the vessels of the glomerulus may be affected, but in most cases single dilated vessels containing red blood corpuscles may be found. At this period the lobulation of the glomerulus begins to be very evident and some of the lobules are converted into homogeneous hyaline masses containing numerous small irregular nuclei. In the hyaline mass the vessels may be represented by small, irregular, empty spaces. In a further degree of the process they may be entirely occluded, and the entire glomerulus represented by a hyaline lobulated mass. There is usually some enlargement of the entire glomerulus, and small masses of it may project for some distance into the tubule passing from it. The occlusion of the vessels and the formation of hyalin is produced both by hyaline thickening of the wall and hyaline degeneration of the cells. The character of the cells within the capillaries can be made out only in the least advanced cases. In cases uncomplicated by necrosis the cells were almost entirely of an epithelioid type and were derived by proliferation of the vascular endothelium, as was shown by the presence of nuclear figures. (Plate XXVI., Fig. 2.) Polynuclear leucocytes were very rare and an occasional lymphoid cell was found. With these changes in the vas-

cular type there was a varying degree of involvement of the covering epithelium. In some of the cases this was not evident at all. In others the epithelial cells were enlarged, increased in number, and covered some of the lobules as a cap; occasionally a large number of these cells was found in the capsular space. We have never found it possible to make two types of these glomerular lesions. The vascular changes may be accompanied by a varying degree of proliferation of the covering epithelium, but the latter is not found alone. In two cases the lesions had a different character. One of these was complicated by erysipelas and in the other the diphtheria was secondary to epidemic cerebro-spinal meningitis. In these two cases, particularly in the latter, there was extensive necrosis of the glomeruli with hæmorrhage into the capsular spaces. In the case secondary to the meningitis the glomeruli were in many cases surrounded by masses of hyaline material in which both fibrin and red blood corpuscles were included. (Plate XXVI., Fig. 5.) This hyaline material passed for a considerable distance into the tubule which led from the glomerulus, and the entire proximal tubule was in some cases filled with fibrin. In the necrotic tissue of the glomerulus there were numerous polynuclear leucocytes.

The average age in the cases of glomerulo-nephritis, excluding an adult of forty-five, was greater than in either the degenerative or interstitial cases. The average duration of the disease was also greater. That this affection can take place at an early age is shown by one case of one and one-half years. The shortest duration of the disease was four days in two cases. In one of these the diphtheria was secondary to cerebro-spinal meningitis and the acute character of the changes in the glomeruli corresponded perfectly with this history. The other was in an adult of forty-five years. The glomerular lesions were of a chonic type and were probably to be referred to an acute antecedent attack of endocarditis. Four of the cases were complicated with scarlet fever, one with measles, and one with both scarlet fever and measles. In two of the cases there was a general

infection with the diphtheria bacillus, in four general infection with the streptococcus. In cultures from the kidney the diphtheria bacillus was found in two cases, the streptococcus in four, the staphylococcus aureus in one, and the pneumococcus in one.

4. *Hæmorrhage.* — Slight hæmorrhages were found in the kidneys in three cases, but the hæmorrhagic type of nephritis in but one. In this case the tubules over large areas as well as the interstitial tissue contained great numbers of red blood corpuscles. No hæmorrhage was found in the glomeruli. The case was a child two years old who died on the third day from severe uncomplicated diphtheria. In the other cases which were of the glomerular type, in one, blood corpuscles were found in the capsular space and in the proximal tubules. In the other the blood evidently came from interstitial hæmorrhages in the pyramids. In the cortex occasionally entire series of distal convoluted tubules were filled with blood which had either backed up into them from the collecting tubules or had come from the ascending branch of Henle's loop. The hæmorrhage rendered it easily possible to follow the tubules in serial sections, and in one instance the hæmorrhage was traced into the collecting tubule; the loops of Henle were free. We have been much surprised at the rarity of hæmorrhages in these cases. Almost all the writers on the lesions in the kidneys in diphtheria refer to hæmorrhages, and by some they have been regarded as the chief lesion. Cases of hæmorrhagic nephritis in diphtheria have also been described clinically, although Baginsky calls attention to the infrequency of red blood corpuscles in the urine.

5. *Chronic changes.* — There were four cases in which there were well marked chronic lesions consisting of atrophy of tubules and increase in connective tissue. In two in which the duration of the disease in one was three and in the other two days, the interstitial change was well marked and evidently had nothing to do with the diphtheria. In one case, a child one year old, dying on the third day of the disease, there was a circumscribed focus of atrophy with connective

tissue formation just beneath the capsule, a condition which certainly should be referred to some antecedent condition. In the other case, a child two and a half years of age, dying on the twentieth day of the disease, there was slight acute degeneration of the epithelium and numerous small foci of cellular infiltration, increase in connective tissue, and atrophy. In these foci there was almost invariably an atrophied glomerulus and the focus probably represented the area of tubules belonging to it, but this relation could not be made out with certainty, nor could it be determined whether the lesion belonged to the diphtheria or antedated it.

No bacteria were found in the kidneys on microscopic examination.

Summary.

Lesions of the kidney varying from simple degeneration to the more serious conditions of acute nephritis are found in all fatal cases of diphtheria. Some of the lesions are somewhat more common in the mixed infections of diphtheria combined with scarlet fever than in pure diphtheria. The more severe forms of degeneration are found in those cases of diphtheria of great intensity which die shortly after the onset. The interstitial and glomerular lesions are more common in older children and in cases of longer duration of the disease, though these conditions usually are combined. There is no type of lesion peculiar to diphtheria. The lesions in the kidneys are not due to the presence of bacteria in the blood, but to the action of injurious substances in solution in the blood.

LYMPH NODES.

Lesions in the lymph nodes must be considered as among the most constant changes produced in diphtheria. The character of these lesions was first studied by Bizzozero. He described the necroses in the lymph nodules of the spleen and found very similar changes in the lymph nodes. The swelling of the nodes he attributed to an increase in the lymphoid cells. Oertel devotes a great deal of attention to the changes in the lymph nodes. He found the most marked

changes in those lymph nodes which were contiguous to the seat of primary lesion. The cervical and sub-maxillary nodes were swollen and there were small hæmorrhages in the connective tissue capsule. Sections showed an intense infiltration with cells, so that the distinction between the lymphoid tissue and the sinuses was obscured. With a low power small pale foci were observed chiefly in the peripheral nodules. These foci were formed of degenerated cells which were often included in large cells. He found in the nodes a large number of cells of various sorts, many of them much larger than the lymphoid cells, and some processes of direct and indirect cell division were observed. He gives a very good description of the character of the nuclear detritus which results from the necrosis of the lymphoid cells. He found similar changes, though less marked, in the more remote lymph nodes. Bullock and Schmorl found only inflammatory changes in the nodes in the lighter cases of diphtheria. In the more severe cases the nodes were enlarged and of firm consistency. In the peri-nodular tissue there was hæmorrhage, and yellowish streaks were frequently seen which represented lymphatics filled with fibrin. In the least altered nodes there was simply cell hyperplasia which might be so considerable that the sinuses could not be distinguished from the lymphoid tissue. In the more severe cases the necrotic foci described by Oertel were found in the lymph nodules. These writers described particularly the formation of fibrin in connection with the necrosis. In the later stages, according to them, the fibrin may disappear or be converted into hyalin. The perinodular hæmorrhages were most marked in the cervical nodes of children on whom tracheotomy had been performed. The cervical nodes were most affected, the bronchial only when there was bronchitis. They found bacilli in the nodes in 11 out of 14 cases and think the lesions may be due to their presence. The most recent work of Barbacci adds but little. He found nuclear fragmentation in the lymph nodules and numerous karyokinetic figures indicating cell division. In the remainder of the tissue there was œdema, hyperæmia, and frequently hæmorrhage. The vas-

cular endothelium was swollen and many of the cells desquamated. The vessels were often plugged with fibrin, and fibrin was found in the sinuses and parenchyma. The experimental lesions in the lymph nodes have been most carefully described by Flexner. He finds lesions both in the nuclei and in the protoplasm of the cells, which may be diffuse, affecting all parts of the node, or occur in definite foci. These lesions are seen both in lymphoid cells and in large swollen cells, phagocytic in character, great numbers of which are found in the nodes. Most of the changes in the nuclei precede degeneration, but proliferation takes place actively, both by direct and indirect division. The degenerative changes are more marked in the cortex of the node. Nearly all of the nuclear detritus is contained in cells which may be of colossal size. He thinks the large phagocytic cells are probably derived from the cells of the germinal centres. Bezancon and Labbe compare the action of the diphtheria bacilli on the lymph nodes with that produced by the injection of the toxin. They find an active inflammation produced in the adjacent nodes by the injection of the bacilli. There is no necrosis, but an abundant infiltration of the tissue with polynuclear leucocytes. Bacilli are found in the interior of phagocytic cells shortly before the death of the animal. After the injection of the toxins the inflammatory reaction is absent and early necrosis of the cells takes place.

The nodes most affected are those connected with the seat of the primary lesions, the tonsils, and the cervical nodes. Next in the frequency and extent of the lesions are the bronchial, the intestinal, and the mesenteric nodes. The distant lymph nodes, such as the inguinal and axillary nodes, are but slightly if at all affected. Macroscopically the affected nodes are enlarged, soft, and hyperæmic; in some cases there is extensive hæmorrhage in and around the node, and in rare cases suppuration occurs.

The lymph nodes were examined in 109 cases; this number includes cases of all ages and duration of disease.

Usually the examination was confined to those nodes which were manifestly affected, though in a few cases all the principal nodes of the body were examined. The tissue was hardened in Zenker, cut in paraffin, and stained with hæmatoxylin, methylene blue and eosin, and Mallory's connective tissue stain. The latter stain was most serviceable in demonstrating the reticulum of the tissue.

The most common condition found on microscopic examination was a sharp separation between the lymphoid tissue and the sinuses, due to dilatation of the latter. (Plate XX., Fig. 1.) The enlargement of the node was not due to hyperplasia of the lymphoid cells, though there was some evidence of this in most cases. The lymph nodules themselves were little if at all enlarged, and when they were enlarged this was due chiefly to the separation of the cells by œdema. The dilatation of the sinuses was more marked in the peripheral sinus than elsewhere. (Plate XX., Fig. 4.) The dilated sinuses were in some cases closely packed with cells; in others they contained but few cells and a variable amount of granular coagulum. The cells in the sinuses varied greatly in character. Polynuclear leucocytes were present to some degree in all cases and in some the sinuses were packed with them. This was particularly the case in one of the bronchial nodes examined. The leucocytes were in most cases well preserved; in others there was degeneration with the formation of nuclear detritus. A variable number of lymphoid cells were present, and in one case the sinuses contained almost as many as the lymph nodules. Even in this instance there was not much hyperplasia; there was, however, a general œdema of the tissue, and the enclosing reticulum of the lymphoid tissue was dilated, giving free entrance to the cells of the lymphoid tissue into the sinuses. The separation between the lymphoid tissue and the sinuses was very evident, particularly in the specimens stained with the connective tissue stain. It shows a reticulum throughout the node, which is connected with the capsule. The sinuses are crossed by fibres of reticulum which are connected with the fine reticulum of the lymphoid tissue. Each lymph nodule is sur-

rounded by a condensation of reticulum which forms an imperfect capsule around it in which there are numerous spaces connecting the interior of the nodule with the sinus. The reticulum of the nodule is more abundant in the periphery; in the centre it may be entirely absent. The separation of the spaces in the reticulum by œdema will render it much more easy for the cells of the nodules to pass into the sinuses.

In addition to the lymphoid cells and polynuclear leucocytes it is possible to distinguish three other varieties of cells in the sinuses. The most striking of these are cells of apparently the same character as the mononuclear leucocytes. (Page 225, and foot-note.) They were present in all cases and in some were so abundant that the dilated sinuses were crowded with them. They were either diffusely scattered in the sinuses or collected into masses. The same description of them which has been given in the lungs and elsewhere applies here. They are of the same size or a little larger than the polynuclear leucocytes. The protoplasm stains sharply with eosin and contains no distinct granules. The periphery is more irregular than that of the polynuclear leucocyte, and the definite membrane of the latter is absent. The nucleus is vesicular and may be round, oval, or almost as much curved as the nucleus of the polynuclear leucocyte. No transitions were seen between these cells and the polynuclear leucocytes, nor was there any relation between them in the respective numbers present. These cells were apparently formed in the lymph node. The efferent lymphatics often contained considerable numbers of them, and in the few cases in which the afferent lymphatics could be made out they were not present in these. Certainly no transitions could be seen between these and the lymphoid cells. In some of the cases of general œdema of the node a few non-granular cells were found within the lymph nodules, but they were not generally present. It seems to us most probable that they are derived from proliferation of the endothelial cells lining the sinuses. In one case particularly, in which there was great dilatation of the sinuses, there was evident

proliferation of the endothelium of the sinus and nuclear figures were found in the cells. In a normal node it is difficult to demonstrate this endothelium which lines the sinus and invests the intersecting fibres, but it was perfectly evident in the œdematous nodes. In the case referred to, groups of two or three nuclei were found in the endothelium, and in a few places cells of the same character as those contained in the sinuses adhered to the fibres. We could not make out the relation of these endothelial cells within the lymph nodules to the reticulum; there was only an occasional nucleus here of the same character as those lining the sinus. Another possible source of these cells is from proliferation of the endothelium of the small blood vessels. This was most marked in some cases both in the vessels in the sinuses and in the thin-walled vessels of the lymph nodules. The nuclei are large, project into the lumen, and often have their long axes perpendicular to the axis of the vessel. Cross-sections of these small veins often resemble glands. In one instance several of these cells were found overlying one another and almost occluding the small vein. Cells similar to those within the vessel were found on the outside.

Cells distinguished by their phagocytic properties were also numerous in the sinuses. These cells presented considerable variation in size, but all seemed to be of the same character. Some were not larger than the cells they enclosed; others were very large and enclosed as many as twelve other cells. Their outlines were irregular, the protoplasm indistinctly granular. The nucleus was large, generally oval, and vesicular. It always stained less distinctly than the nuclei of the enclosed cells and in some cases was difficult to distinguish. The cells enclosed in the phagocytic cells always lay in vacuoles. In rare cases two or more cells were enclosed in the same vacuole. The enclosed cells were in some cases well preserved, so that their character could be distinguished; in others they had undergone degeneration, and the nuclei had given rise to nuclear detritus. The principal cells enclosed in the phagocytic cells were either lymphoid or plasma cells. Polynuclear leucocytes were occa-

sionally found in them. The most common cell found in the sinuses, the nongranular cell, or endothelial cell, was never found enclosed in the phagocytic cells. It seems to us that the phagocytic cells are of the same character as the nongranular cells. Every transition can be seen between the large phagocytic cells and cells which are evidently nongranular leucocytes. Both nucleus and protoplasm have the same characteristics of staining as the nongranular cells. Phagocytic cells occasionally were found attached to the reticulum within the sinus.

The sinuses also contained a variable number of large cells having some similarity to the cells of the germ centres of the lymph nodules, but very much larger than these. They are found both in the sinuses and in the nodules, and in some cases are in such number as to form the principal cell in the node. They vary in size and are often double or three times the size of a red blood corpuscle. The outline is irregular and the protoplasm granular. The granules are not regularly round, vary greatly in size, are often apparently joined in small clumps; they stain brightly with methylene blue. The granules appear to be loosely enclosed in the cytoplasm; they project from the edge of the cell, and numbers of granules of the same character as those enclosed in the cells may be found free in the vicinity. We were not able to make out whether these were extruded from the cells or whether they were due to breaking up of the cell protoplasm in the manipulation of cutting, etc. The nucleus is relatively large for the size of the cell, stains very brightly, and is somewhat vesicular in character. The chromatin is arranged in granules around the periphery of the nucleus and in two or three large masses in the centre which are connected by chromatin filaments. Nuclear figures are often found in these cells. When they are present the cell protoplasm is more granular; the granules are larger and stain more brightly. These cells more nearly approach the lymphoid cells in some of their characteristics than any others, and from their presence in both the lymph nodules and sinuses they seem to be derived from these. On division they

give rise to cells of a similar character. These cells are perfectly distinct from the plasma cells, numbers of which are often present both in the sinuses and in the lymphoid tissue. In lymph nodes which are much affected they are often found in the capsule and in the surrounding tissue.

A few eosinophile cells are always found, and in some cases considerable numbers of them. There are two distinct forms of these, one with a nucleus very similar to that of the polynuclear leucocyte, and the other with a nucleus similar to that of the plasma cell. The latter were found in one case in considerable numbers among the plasma cells in the capsule of the node, and seemed to be formed from these. In some of these cells there was an accumulation of eosinophile granules around or on one side of the nucleus, the remainder of the protoplasm being unchanged. In other cases the granules filled the entire cell.

In nearly all the nodes there was congestion and the blood vessels were evident. In several there was hæmorrhage involving a part of or the entire node. The hæmorrhage often extended into the surrounding tissue. In the slightest cases only a few red corpuscles were found in the sinuses among the other cells, and in the most marked cases both sinuses and nodules were packed with them. In the extreme cases there was a general necrosis of the tissue combined with the hæmorrhage. These extensive hæmorrhages were, almost without exception, found in cases of great severity in which death took place early in the disease. The longest duration was eleven days, and the average of ten cases was four days. The cervical nodes were almost the only ones so affected. There was no especial feature in the bacteriology of these cases.

In addition to the extensive necrosis of tissue combined with hæmorrhage, more or less circumscribed necrosis, combined with leucocytic infiltration, was found in a number of cases. This necrosis did not differ from necrosis found in other situations. (Plate XIX., Fig. 4.) The necrotic area contained comparatively little nuclear detritus except that which was derived from the infiltrating polynuclear leucocytes.

These foci were exclusively found in the periphery of the node adjoining the peripheral sinus. In one case great numbers of streptococci were found in the necrotic tissue, and in one case staphylococci. In but three cases of the entire number was there a definite suppuration. In a number of cases there was a diffuse necrosis extending thoughout the entire node, and affecting scattered cells both in the lymph nodules and in the sinuses. It was more marked in the periphery of the node than in the centre, and was shown by scattered nuclear fragments. In no case was it very extensive.

Fibrin was found in variable amount in connection with the hæmorrhages and circumscribed necroses. In several cases the dilated sinuses contained a great deal of fibrin.

The lesions of the nodes which have been described have nothing characteristic about them. They may be found in the nodes in a great number of pathological processes. The most interesting and in some respects the most characteristic lesion of the disease, and the one which was found in the greatest number of cases, consisted in the formation of discrete foci due to cell proliferation combined with necrosis. (Plate XIX., Fig. 3; Plate XX., Fig. 1.) These foci generally have been considered as formed by a simple necrosis of the tissue due to the action of toxic substances. In the large number of cases at our disposal every stage of the process could be followed; we were also aided by the very thin sections which were cut on the Blake-Minot microtome. These foci were formed exclusively in the lymph nodules and were more numerous and larger in the periphery of the node than in the centre. We shall give the structure and mode of formation of these foci, as we have learned it from the study of a great number of cases, and omit the description of single cases. The first step consists in the appearance of a group of cells among the lymphoid cells. These cells have a faintly stained vesicular nucleus and a large amount of pale, faintly granular protoplasm which stains with eosin. The cell outlines are faint and irregular. The cells usually are fused together into a mass in which the pale vesicular nuclei

are embedded. (Plate XX., Fig. 2.) Single cells of this sort are occasionally found in the periphery not joined with the main mass. (Plate XX., Fig. 3.) Even when the cells are joined in a mass, round spaces are occasionally found, giving to it a more or less reticular structure. At this stage there is often a striking similarity to the structure of a small miliary tubercle without giant cells. The size varies greatly, but generally is about that of a small miliary tubercle. With a low power the foci are very evident, standing out sharply from the surrounding lymphoid tissue. They are rendered much more evident by the close packing of the lymphoid cells around them. The smallest and apparently the youngest foci are often formed of these large cells alone. In other cases a variable number of lymphoid cells are found among them. The large cells are phagocytic, and in the larger nodules almost invariably contain enclosed within them lymphoid cells which show every stage of nuclear degeneration. In some cases the lymphoid cells are enclosed in definite vacuoles in the larger cells, but in most cases they are so degenerated that only the fragments of the nuclei are found. The nuclear detritus coming from the lymphoid cells is different from that derived from other cells, particularly from polynuclear leucocytes. The first stage in the degeneration is shown in the accumulation of chromatin in a thick mass around the periphery of the nucleus. Sometimes it forms a regular circle, or it may accumulate at two or three points. It then divides sometimes into two masses or into a number of small fragments which in nearly all cases are distinctly round and show a darkly stained periphery and a clear centre. In some cases the dark stained masses are distinctly crescentic in form. Even when the nucleus breaks up into exceedingly small fragments not larger than cocci this same peculiarity of staining is found. The nuclear detritus derived from other cells is always more irregular in form. The number of cells included in the large phagocytic cells and the amount of nuclear detritus varies greatly. It is always more abundant at the periphery of the nodule, which is often surrounded by a dark line formed of nuclear detritus. The degeneration

often extends beyond the foci, so that a number of large cells are nearly always found among the lymphoid cells and the same process of phagocytosis takes place in them. It is only in very young foci that the process, as we have described it, can be followed. It becomes complicated by the degeneration which the entire focus, including the phagocytic cells, undergoes. These cells lose their distinctness, the nucleus swells, becomes more vesicular, appearing only as a faint outline, and finally degenerates and itself gives rise to nuclear detritus. At this stage we can recognize in the focus a more or less irregular central area in which there is considerable nuclear detritus, and this is surrounded by a dense zone of nuclear detritus. This formation of discrete foci may be the only change in the node or it may be combined with the various processes described. There may be a greater or less amount of diffuse necrosis in the surrounding lymphoid tissue, but this is totally different from the phagocytosis with degeneration which takes place in the nodule. The process may be further complicated by hæmorrhage and fibrin formation. Hæmorrhage into a focus may take place at the beginning of its formation, and red blood corpuscles may be found among the other cells or enclosed in the phagocytes. Fibrin formation may accompany the hæmorrhage, but is more frequently seen without it. The fibrin may be limited to small areas or the whole focus may be filled with it. It is always more abundant in the periphery than in the centre. From the combination of hæmorrhage and fibrin formation the entire focus may be converted into a hard compact mass which is more resistant to disintegrating processes than the surrounding tissue. This was very evident in the tonsils in the cases in which ulceration and softening extended into the lymphoid tissue from the crypts; the foci formed round masses lying loosely in the tissue. Polynuclear leucocytes take little or no part in the formation of these foci. They are but rarely found among the other cells. Even when there is extensive necrosis the necrotic tissue seems to exert but little attraction for them.

We have already alluded to the resemblance between these

foci and tubercles; the foci, like the tubercles, contain no vessels. We are unable to state with certainty how the large cells are formed. They are certainly not formed from any variety of the lymphoid cells or from polynuclear leucocytes. The only cells in the lymph nodules from which they could arise would seem to us to be the cells covering the reticulum. It is, however, possible that the cells lining the lymphatics or even the capillary cells may take some part in the formation. In several cases there was evident proliferation of the cells of the vessels, and in one case a focus seemed to be formed around a vessel. The occlusion of the vessels was probably due to proliferation of the endothelium with subsequent degeneration of the cells. There is no continuous formation of large cells. Nuclear figures were searched for in them, but never found. In some cases there seemed to be direct division of the nuclei, but this did not lead to the formation of new cells.

Tonsils.

The lesions in the lymphoid tissue of the tonsils differ somewhat from the lesions in the other lymphoid tissue. They are constantly found and in most cases are much more marked.

The lymphoid tissue of the tonsils differs from that of the lymph nodes in the large size of the lymph nodules and the great development of the so-called germ centres in them. These are circumscribed masses of cells which differ considerably in character from the lymphoid cells around them. The nucleus is larger than that of the lymphoid cells, often double the size; it is paler and contains fewer granules. It is usually round or oval in outline and may be slightly curved. The protoplasm is more abundant than in the lymphoid cells, ragged in outline, and stains with methylene blue. The cells have much similarity to the large cells of lymphoid character which we have described in the sinuses and lymph nodules of the lymph nodes. Nuclear figures are very abundant in them, and the name "germ centre" has been given to them by Fleming from the supposition that the new

formation of lymphoid cells takes place chiefly or exclusively from these cells. These germ centres do not form a constant constituent of the lymph node. They are invariably present in the tonsils and in the lymph nodes of the intestinal canal in children. They may be found in the bronchial lymph nodes and are generally absent elsewhere. They are always larger and more numerous in children than in adults. We have never been able to satisfy ourselves that the new formation of lymphoid cells takes place exclusively from proliferation of the cells composing the germ centres, or that there is a constant relation between the presence of germ centres and proliferation of lymphoid cells. In the tonsils the lymphoid cells are closely packed around the germ centres, especially on the side nearest the crypts, where the compact mass of cells has a crescentic shape. In all the tonsils examined there was never the sharp separation between the lymph sinuses and the lymph nodules which was so often seen in the other lymphoid tissue, and usually the lymph nodules could be recognized only by the pale germ centres. Generally the tissue was formed of a mass of cells, principally small lymphoid cells, a variable number of plasma cells, and large lymphoid cells. We very rarely found the large mononuclear leucocytes with oval nuclei which were so abundant in the sinuses of the lymph nodes. The lymphoid and plasma cells were not confined to the tissue of the tonsil, but often extended as a diffuse infiltration far into the surrounding tissue. Phagocytic cells were occasionally seen, but they were never so abundant as in the sinuses of the nodes. The foci composed of phagocytic epithelioid cells were found both among the lymphoid cells and in the germ centres. Both a diffuse necrosis affecting single cells and necrosis and ulceration extending into the tonsils from the crypt were frequently found. In several cases there had been membrane formation secondary to the ulceration, and a fibrinous membrane formed directly in the lymphoid tissue; in these cases the reticulum was apparently converted into hyaline fibrin. In a number of cases there was extensive hæmorrhage accompanied by fibrin and necrosis. Fibrinous exudation without hæmor-

rhage was also frequently found. Micro-organisms were rarely found in the tissue on microscopic examination; the most frequent organism was the streptococcus, which was found in four cases.

Summary.

The lymph nodes are affected in nearly all cases of diphtheria. The lesions are most marked in the nodes which are nearest to the primary lesions and rarely extend to the distant nodes. The lesions are most marked in cases of great intensity in which death takes place early. Two sorts of lesions may be recognized:

1st. The ordinary lesions which may follow an injury of almost any sort and which consist in congestion, hæmorrhage, and diffuse and circumscribed necrosis. Numerous cells, not ordinarily found in the tissue, appear in combination with these processes. These new cells are derived in part from the lymphoid cells and in part from proliferation of the endothelial cells of the sinuses and reticulum. There is little or no increase in the number of lymphoid cells. The swelling of the nodes is due chiefly to congestion, hæmorrhage, and dilatation of the sinuses.

2d. Lesions which are distinctive of diphtheria, but which may be found in other infectious diseases of children. These lesions consist of the formation of foci which are very similar in appearance to miliary tubercles. In the formation of these foci there is a combination of proliferation, phagocytosis, and degeneration. Proliferation, most probably of the endothelial cells of the recticulum and possibly of the vessels, gives rise to the formation of large cells resembling the epithelioid cells of the tubercle. These cells devour the lymphoid cells and from these the nuclear detritus is chiefly derived. Afterwards the large cells themselves undergo necrosis and their nuclei give rise to nuclear detritus. Caseation is never produced, nor are giant cells formed in connection with the nodules. In all these changes in the lymph nodes bacteria play but little part directly. We have never found the diphtheria bacilli in the nodes and only rarely the pyo-

genic cocci; the latter are always in combination with necrosis and hæmorrhage. The lesions are due to the absorption of the toxic products of the diphtheria bacilli and other organisms. These toxic products are brought to the node by the lymphatics, and all the lesions are most pronounced in the vicinity of the afferent lymphatics.

THYMUS.

We have not been able to find any references to the examination of the human thymus in diphtheria. In his study of experimental lesions Flexner found the same lesions in the thymus as in the lymphatic tissue elsewhere. He calls attention to the frequency with which the degenerated cells were found in the neighborhood of the Hassel bodies.

We have examined the thymus in 20 cases, the ages extending from seven months to five years, and the duration of the disease from two to sixteen days; most of them were under six days. For the sake of comparison we have examined the thymus of a child ten days old which died of inanition, and of a child ten months old which died of dysentery. The thymus of the latter showed conditions very similar to those which we have found in diphtheria. There was a very marked difference in the size of the glands in the different cases, and this was not dependent on the age. A small and atrophic gland was found in a child fifteen months old and a large well-developed gland in a child of five years. The thymus has some resemblance in its structure to the lymph node. It is composed chiefly of lymphoid cells which lie in large masses separated by bands of loose connective tissue containing numerous cells. There is no division of the lymphoid tissue into lymph nodules and sinuses. There are numerous blood and lymphatic vessels which are contained both in the lymphoid tissue and in the connective tissue septa. The lymphoid cells are of both the small and the large variety, and among them there are numerous large cells with vesicular nuclei. No so-called germ centres were found in the lymphoid tissue. Lying generally in the middle of the lymphoid tissue are large cells

of a distinctly pavement epithelial type frequently arranged in concentric masses. They stain intensely with eosin and the nuclei are faint and indistinct. There are numerous eosinophile cells in their vicinity. In the thymus of the child of ten days no degenerative conditions were found in the tissue; in that of the ten-months' child degenerated lymphoid cells were found in the large cells and there was some diffuse degeneration.

The principal change found in the diphtheria cases was degeneration of the lymphoid cells. The nuclei showed the peculiar forms of detritus seen in these cells. The degeneration was most marked in the vicinity of the Hassel bodies, and the degenerated cells were most frequently included in the large cells with vesicular nuclei. The degeneration was much more diffuse than in the lymph nodes, and the definite nodules of epithelioid and degenerated lymphoid cells were not found. In addition to this there was diffuse degeneration of the lymphoid cells forming small masses of nuclear detritus scattered through the tissue. Brightly staining eosinophile cells were very numerous in all cases, and more numerous than in the cases used for comparison. They were single and scattered through the tissue, or in masses chiefly in the vicinity of the Hassel bodies. The eosinophile cells are large and uninuclear. Nuclear figures were frequently found in them. The eosinophile cells were never included in other cells, nor did they contain inclusions. Very few polynuclear leucocytes were found in the tissue. A few eosinophile granules were also found in large cells apparently belonging to the connective tissue which were found in the connective tissue septa. The lymphatics were frequently dilated and in one case they contained great numbers of cells similar to those found in the sinuses of the lymph nodes. Hyaline degeneration of the walls of the vessels was found, and in one case, a child seven months old, who died on the seventh day of the disease, thrombi composed of polynuclear leucocytes, lymphoid cells, and a small amount of fibrin were found in a number of the small veins. No bacteria were found in the sections from any of the cases.

NERVOUS SYSTEM.

The study of the lesions of the nervous system in our cases of diphtheria has been made by Drs. J. J. Thomas and H. S. Steensland. The work on the ganglion cells has not yet been completed, that on the nerves has already for the most part been published, so that only a summary of the results obtained is included here.

In all 28 cases were examined; they were selected either on account of cardiac symptoms, paralyses, or severity of the disease. Various nerves were examined by Marchi's method: the olfactory once; the optic chiasm twice; the third cranial nerve once; the fourth twice; the fifth twice; the sixth, seventh, eighth, and ninth each once; the pneumogastric 28 times; the twelfth nerve twice; the phrenic twice; the splanchnic once; the ulnar once; the obturator once; the anterior crural three times; the sciatic twice. In addition Marchi's method was used for the cortex cerebri five times, the cerebellum twice, the pons three times, the medulla four times, the spinal cord seven times, the Gasserian ganglion once. In many cases the nerves from both sides of the body were examined, but no differences in the results obtained were observed.

All of the nerves in the 28 cases showed various degrees of fatty degeneration, from slight to extreme. The degeneration seems almost invariably to begin in the myelin sheath. Clearly to demonstrate this it is necessary to stain the axis cylinders in the Marchi preparations by means of a rather strong mixture of acid fuchsin and picric acid. In sections stained in this way the axis cylinders often are found pushed to one side, so that the drops of fat lying in the middle of the nerve fibre and apparently within the axis cylinder are clearly shown to have originated in the myelin sheath.

As a rule the change in the myelin which causes it to stain with osmic acid in the Marchi method begins at some point close to the axis cylinder and gradually spreads around and along it. The myelin breaks up into granules, droplets, and very irregular bizarre figures of which the peripheries

usually are more refractive than the centres and often doubly contoured. As a rule the centres of the masses stain more deeply than the peripheries, but sometimes small black globules appear with pale centres.

The change in the axis cylinder seems to consist chiefly of swelling which is often irregular, so that the axis cylinder presents a beaded appearance. As it swells it stains very faintly, so that it is often difficult and sometimes impossible to make it out. When the myelin sheaths have undergone marked fatty degeneration, the axis cylinders usually cannot be distinguished. Whether they have simply swelled up and disappeared, or have undergone fatty degeneration, is difficult to determine; but in no axis cylinder which could be positively demonstrated was there any evidence of fatty degeneration.

Examination of the cerebrum five times, cerebellum twice, pons three times, medulla four times, and cord seven times, showed everywhere a slight to marked diffuse fatty degeneration of the white substance. The same change was present in the anterior and posterior nerve roots.

The results of the investigation of the nervous system may be summed up as follows: There occurs in certain cases of diphtheria a slight to marked diffuse fatty degeneration of the nerve fibres of the central nervous system and of its peripheral extensions.

SKELETAL MUSCLES.

In one case in which the nerve fibres of the central nervous system and of the peripheral nerves showed marked fatty degeneration, the muscles of the tongue, of the ulnar side of the forearm, the sartorius muscle, and the biceps of the thigh were examined by Marchi's method. All showed a marked degree of fatty degeneration. About one muscle fibre in four seemed affected. The fat drops were small and usually very evenly distributed throughout the whole of the fibres affected. The heart muscle in this case also showed marked fatty degeneration. In a second case where fatty degeneration of the heart and of the nervous system was

marked, the muscles of the tongue, the diaphragm, and the tibialis anticus all showed a similar degenerative process. In places three fibres out of four were studded with fat drops. It seems probable that in all cases where fatty degeneration of the heart and of the nervous system has occurred, a similar change will be found in the skeletal muscles.

BONE MARROW.

We have been able to find but two references to the condition of the bone marrow in diphtheria, and both of these are in reference to lesions produced experimentally. Trambusti found increased granulation and proliferation of cells produced by small doses of toxin. According to him, large doses seemed to exert a paralytic action on the cells. He is inclined to think that these changes in the marrow are concerned with the production of antitoxic substances. Roger and Josue found that proliferation of the marrow cells was produced by both the toxin and antitoxin. The toxin affects the large and medium cells, the antitoxin the small. The changes produced by the toxin appear earlier than those produced by the antitoxin.

The bone marrow was examined in 48 cases. No selection was made in these cases as to the duration or character of the disease. The marrow in all cases was taken from the middle of the femur; the bone was laid bare and the upper surface chiselled off, exposing the marrow. In a few cases the tissue was hardened in formalin or in corrosive, but generally only Zenker's fluid was used. After hardening, the marrow was decalcified in 5 per cent. nitric acid for 24 hours. The sections were cut in paraffin and stained in the usual way. The marrow was perfectly preserved and the cell granules stained clearly.

In all cases the marrow was hyperplastic. (Plate XXVII., Fig. 1.) Three of the cases were in adults, the remainder in children. The hyperplasia was less marked in the adults than in the children. In the adult cases the marrow was reddish with areas of yellow fat. In the children there was

considerable difference in the character of the marrow. In most cases it was red, of firm consistency, and could be removed in solid pieces; in some cases it was more grayish and softer. Microscopic examination showed the same difference in the degree of hyperplasia. In some of the sections the marrow appeared as an almost solid cellular mass with only a few scattered fat spaces. In others the fat was more abundant, and the cell masses formed a reticular structure between the fat spaces.

It was impossible to procure normal marrow of children of different ages for comparison. The cases selected for comparison were a child ten months old which died of colitis after an illness of ten days, a child which died ten days after delivery, and a fœtus of eight months. Comparison with all these cases showed a very evident hyperplasia in the diphtheria cases. In all three of the non-diphtheria cases the marrow was cellular, but neither in the abundance of cells nor in their character was there much similarity with the diphtheria cases. In one of the diphtheria cases the condition of hyperplasia was but slightly marked. This was from a child six years old which died of heart paralysis in the forty-eighth day of the disease. The marrow of this case was very similar to the marrow of the eight-months' fœtus.

All of the cases presented marked differences with regard to the character and the relative numbers of the different cells in the marrow. The most prominent cells and those which were always present in large numbers were large cells which varied in size; the average size was about five times that of a lymphocyte. (Plate XXVII., Fig 2.) The nucleus was somewhat vesicular, the periphery stained sharply, and the chromatin was in granules which were in the interior of the nucleus and attached to the periphery. The chromatin granules were connected by threads. The protoplasm varied in amount, but was generally considerable relative to the nucleus; it was finely granular; the granules in some cases stained slightly with blue, in others they took a reddish tinge from the eosin. The slight eosin stain was more marked in the vicinity of the nucleus than elsewhere. These cells

were always present. They were found in small numbers in the cases selected for comparison; in the diphtheria cases the numbers of them varied, in some cases forming the great majority of all the cells present. Active proliferation of these cells was taking place and nuclear figures in great abundance were found. These cells cannot be distinguished from plasma cells, and like the plasma cells they are never phagocytic.

A variable number of lymphoid cells was always present. (Plate XXVII., Fig. 1.) In the comparison cases the lymphoid cells were relatively more abundant than in the diphtheria cases. In the diphtheria cases they were generally diffusely scattered among the other cells, but occasionally compact masses of them were found. It was never possible to show in these masses a reticulum or a similarity of structure to that of the lymph node. In one case there was a circumscribed area of necrosis in the midst of the collection of lymphoid cells. (Plate XXI., Fig. 3.) It did not extend to the adjacent marrow cells.

The number of eosinophile cells in the marrow varied greatly. They were very numerous in seven cases in which the average duration of the disease was six days. Eosinophile cells were certainly less numerous in the cases of longer duration and in the cases of greater age. There was a general agreement between longer duration and greater age in all the cases in which the marrow was examined. In the cases used for comparison there was a good deal of variation in the number of eosinophile cells, and they were most abundant in the marrow of the eight-months' fœtus. The eosinophile cells presented the same variety in character and in numbers as the other cells. They were found both in groups and irregularly scattered among the other cells. In the cases in which they were most abundant areas were found almost composed of them. Many of the eosinophile cells in size and in the character of the nucleus were similar to the cells first described. Apparently transition forms between these cells which resemble plasma cells, and which should probably be considered as the most typical cells of the marrow, and eosinophiles were found. Single oxyphilic granules

appeared in the blue staining protoplasm and increased in number until they filled the cell.[1] The eosin granules varied considerably in size, and in several instances cells were found which contained large round granules similar to those found in the eosinophile cells of the horse's blood. These large eosinophile cells were in the minority. Most of them were smaller, no larger than the eosinophile cells of the blood. They usually contained a single small nucleus similar to that of the lymphoid cell; in other cases two nuclei were found, or the nucleus was curved or even as irregular as the nucleus of the polynuclear cell. In the cases in which the eosinophile cells were most abundant, numerous eosinophile granules were found scattered in the tissue. This condition is probably an artefact resulting from the breaking up of the cells in cutting the sections. Nuclear figures were found in small numbers in the eosinophile cells. They were most numerous in the larger cells.

Polynuclear leucocytes were found in very small numbers. They were never in groups, but irregularly distributed among the other cells. A few cells of a definite endothelial character similar to those described in the other tissues were found. These cells here also showed their phagocytic character, and both polynuclear leucocytes and lymphoid cells, principally the latter, were found enclosed in them.

There was considerable variation in the number of large myeloplaques in the different cases. There was considerable variety among them and it was not certain if they represented different forms of the same cell. The most abundant were large cells with finely granular protoplasm which stained slightly with methylene blue. Occasionally definite blue granules were found in the protoplasm, or one part of the cell stained more distinctly than another. There were often a number of round, oval, and vesicular nuclei in these cells. In some cases, instead of a number of separate nuclei, a large irregular nuclear mass was found, which often presented the appearance of a central mass with knob-like projections ex-

[1] Howard has recently advanced the view that in various organs eosinophilic cells are formed from plasma cells.

tending from it. The periphery of the nuclear mass often stained intensely, or large threads of chromatin resembling fibrin passed through it. Often the cell may be almost filled with an extremely irregular nucleus showing a large vesicular mass at the periphery. Another variety of these myeloplaques consists of cells somewhat smaller than these just described, with a large amount of structureless chromatin in the cell. The mass of chromatin stains homogeneously and intensely. There is still a third variety of cells which is smaller than either of the others, and which contains a solid, structureless, intensely staining nucleus.

Cells similar to those described in the marrow were found in the veins in nearly all cases. In three cases the large myeloplaques were found in the veins enclosed in a mass of red blood corpuscles, so that their presence there could not have been due to an artefact. These were evidently the cells which we have described in the capillaries of the lung and in the vessels of the glomeruli.

In nearly all cases a variable number of nucleated red corpuscles were found in the marrow. They were easily recognized by the intensely stained structureless nucleus and by the outside rim of the corpuscle.

Very little connective tissue was found in the marrow and that was along the arteries. The veins are numerous and their walls have almost a capillary structure. Red blood corpuscles were found outside the vessels among the other cells, but there was in no case any extensive hæmorrhage.

It is difficult to find what is the relation of the condition of the marrow to the other features of the disease. It is certain that all the varieties of cells in the marrow are continually entering into the blood; the way of entrance is given by the thin walls of the veins and their close relation to the marrow cells. Cells in all respects similar to those in the marrow are found in the vessels there and in the vessels in other organs. It seems probable to us that the cells found in the interstitial tissue of various organs are derived from the marrow, but this is hardly their exclusive source. It is possible that the ordinary marrow cell is the same as the plasma cell, and

that the slight differences in size and staining may be due to the decalcifying process. Our knowledge of the structure of the marrow at different ages is very incomplete. It was not possible to obtain this knowledge from our autopsies, as they were all cases of infectious disease. The condition of the marrow which we have described is not confined to diphtheria. We have found the same changes in diphtheria, scarlet fever, measles, and other infections.

PANCREAS, ADRENALS, THYROID GLAND, SALIVARY GLANDS, TESTICLES, AND PITUITARY BODY.

These glands showed no macroscopic changes. We have examined them microscopically in a large number of cases with negative results. In one section a superficial necrosis with purulent infiltration was found in a submaxillary gland due to an extension of the infectious inflammation from the throat. It is remarkable that no lesions were found in the adrenal glands, for congestion, hæmorrhage, and foci of necrosis in these are the most common lesions in the disease produced experimentally, either when the bacilli are inoculated or the toxins injected (Welch and Flexner, and J. H. Wright).

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PLATE XV.

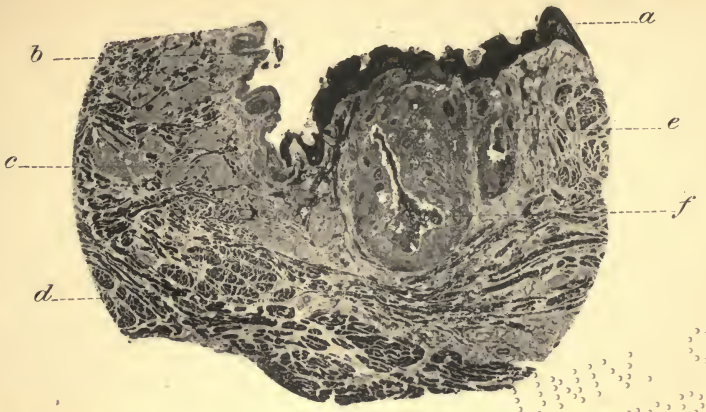
Plate XV.

Figure 1. — Section through edge of tonsil. A dense membrane extends over a part of the surface. The large crypt in the tonsil is filled with cast-off epithelium and exudation. "a," membrane on surface denuded of epithelium. "b," adjacent unaltered mucous membrane. "c," mucous glands. "d," muscle. "e," tonsil. "f," interior of crypt.

Figure 2. — Section through tonsil showing crypts communicating with the surface. There are only a few shreds of membrane on the surface. On one side there is extensive fibrinous exudation within the crypts, with hæmorrhage and necrosis of the adjoining tonsillar tissue. "a," small mass of membrane on surface. "b," crypts filled with fibrinous exudation.

Figure 3. — Section through recently formed hyaline membrane on surface of pharynx. In the interstices of the membrane there are a few leucocytes.

Figure 4. — Older and denser hyaline membrane from pharynx, showing small spaces in the reticulum. Figures 3 and 4 are stained with iron hæmatoxylin.



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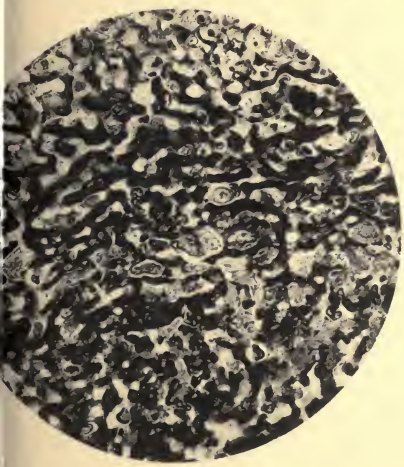

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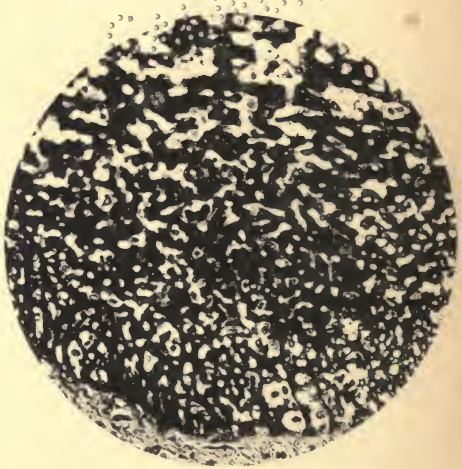

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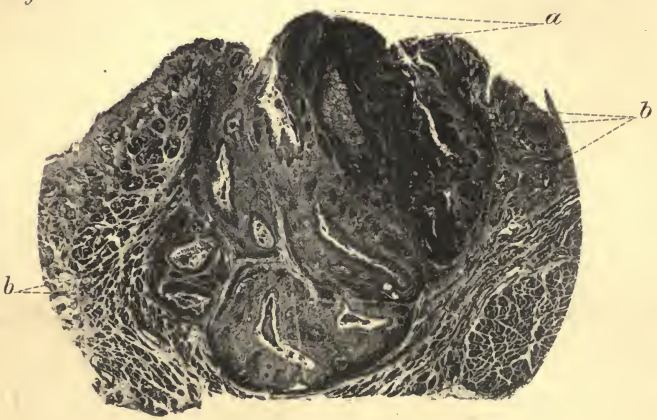

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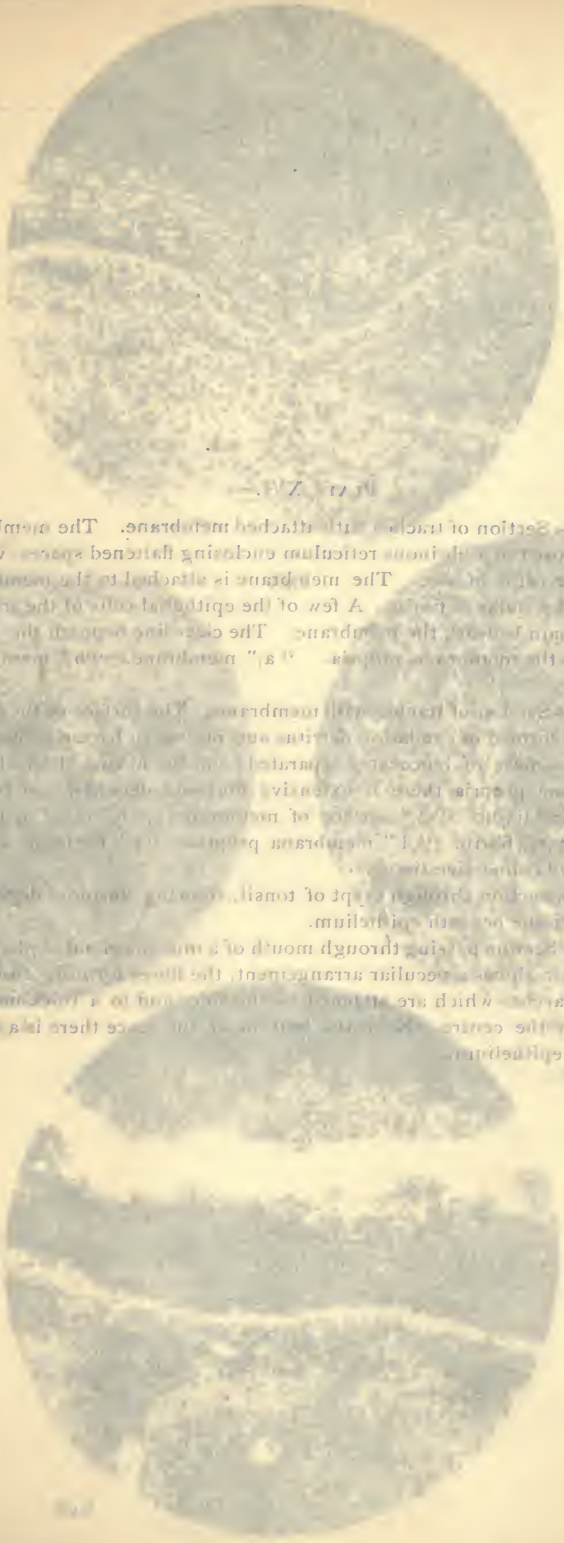


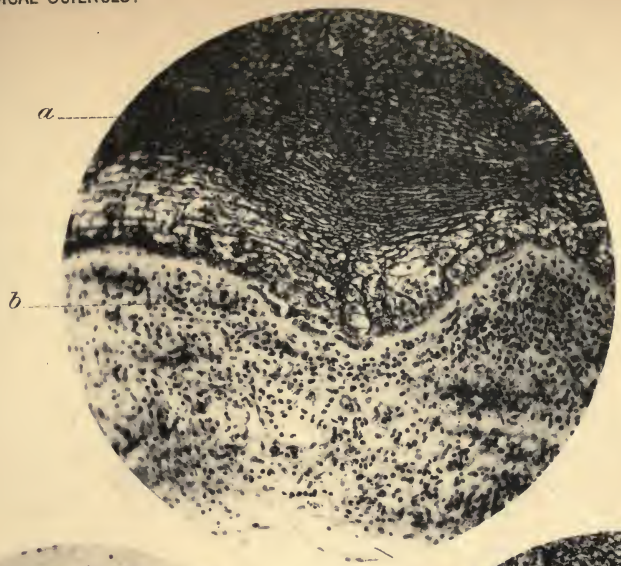
Plate XVI.

Figure 1. — Section of trachea with attached membrane. The membrane is composed of a fibrinous reticulum enclosing flattened spaces, which vary but little in size. The membrane is attached to the membrana propria by stalks of fibrin. A few of the epithelial cells of the trachea still remain beneath the membrane. The clear line beneath the membrane is the membrana propria. "a," membrane. "b," membrana propria.

Figure 2. — Section of trachea with membrane. The surface of the membrane is formed of exudation detritus and masses of bacteria; beneath this is a mass of leucocytes separated from the fibrin. Beneath the membrana propria there is extensive fibrinoid degeneration of the connective tissue. "a," surface of membrane. "b," layer of leucocytes. "c," fibrin. "d," membrana propria. "e," fibrinoid degeneration of connective tissue.

Figure 3. — Section through crypt of tonsil, showing fibrinoid degeneration of tissue beneath epithelium.

Figure 4. — Section passing through mouth of a mucous gland of pharynx. The fibrin shows a peculiar arrangement, the fibres forming two systems of arches which are attached to the sides and to a thick mass of fibrin in the centre. Near the bottom of the space there is a small mass of epithelium.



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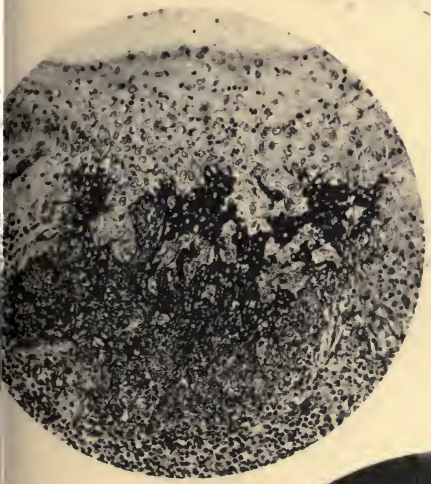

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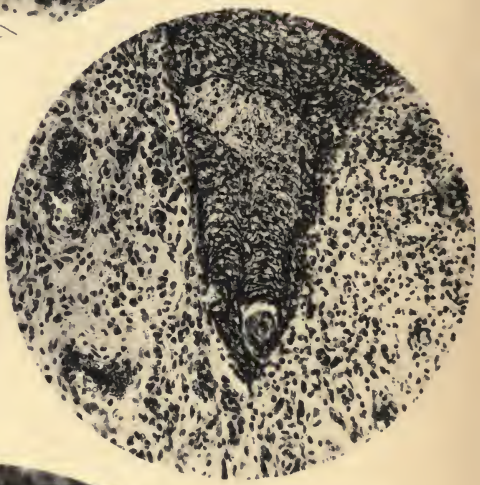

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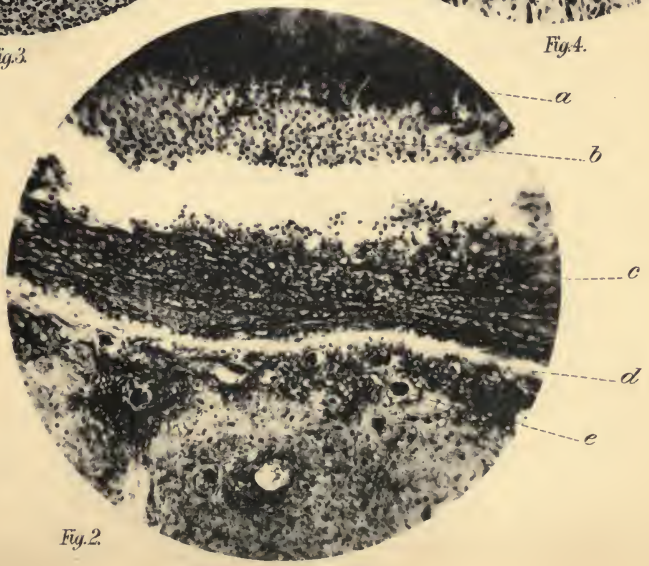

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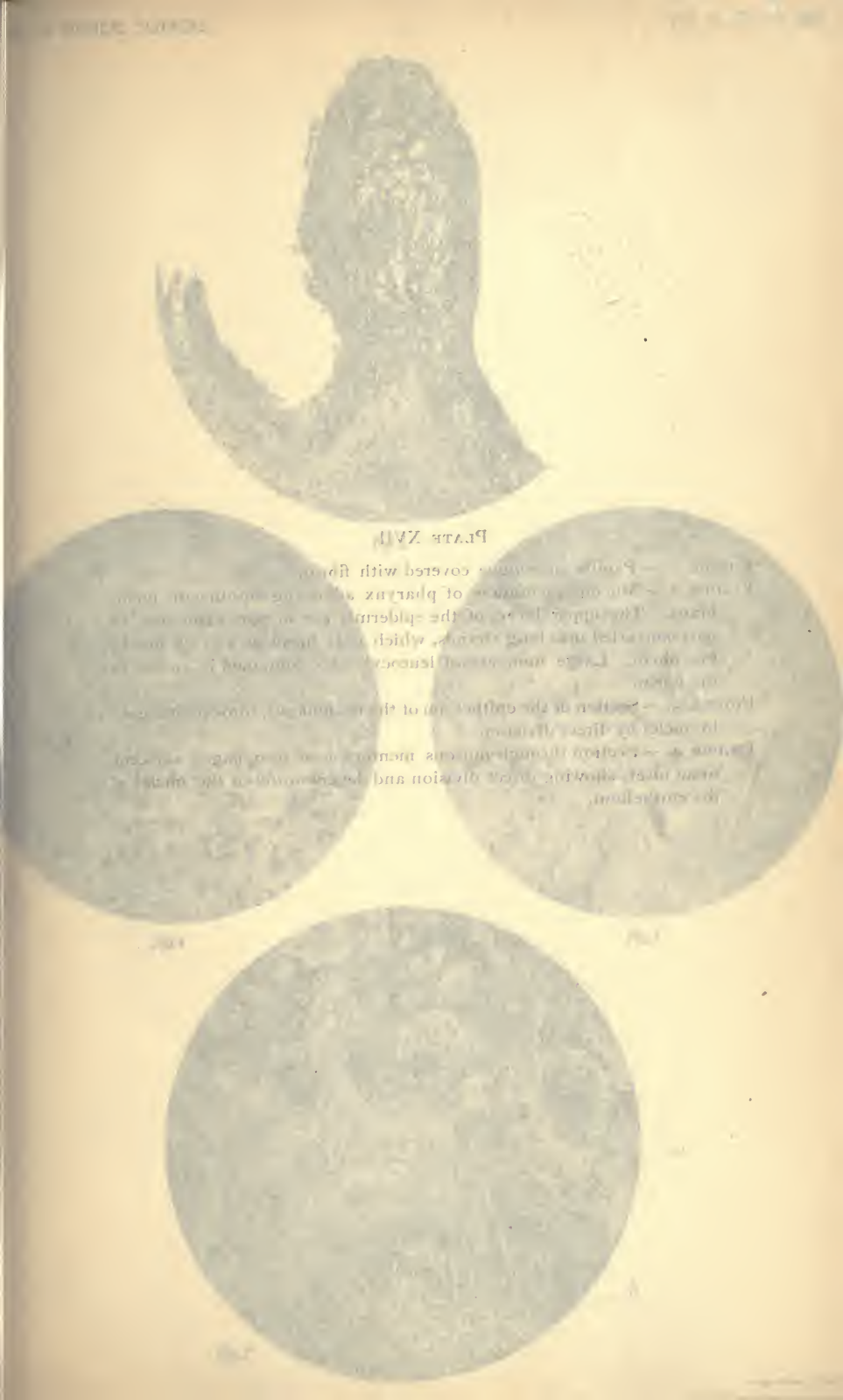

Plate XVII.

Figure 1. — Papilla of tongue covered with fibrin.

Figure 2. — Mucous membrane of pharynx adjoining diphtheritic membrane. The upper layers of the epidermis are in part exfoliated, in part converted into long strands, which pass upwards and are lost in the fibrin. Large numbers of leucocytes are contained in spaces in the fibrin.

Figure 3. — Section of the epithelium of the œsophagus, showing increase in nuclei by direct division.

Figure 4. — Section through mucous membrane of œsophagus adjacent to an ulcer, showing direct division and degeneration of the nuclei of the epithelium.

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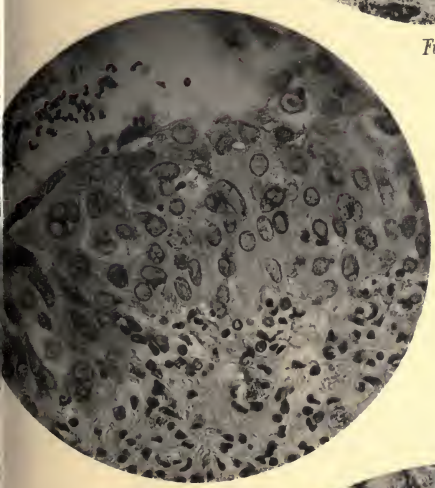

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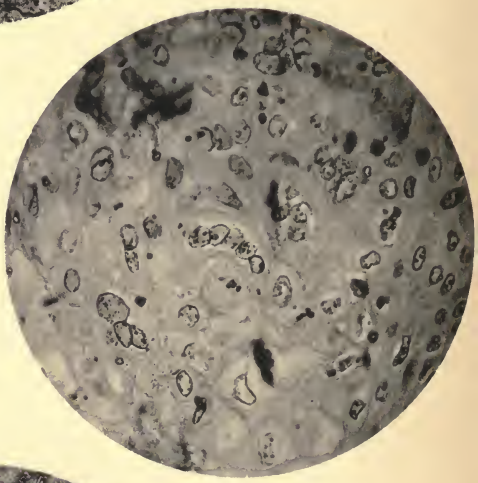

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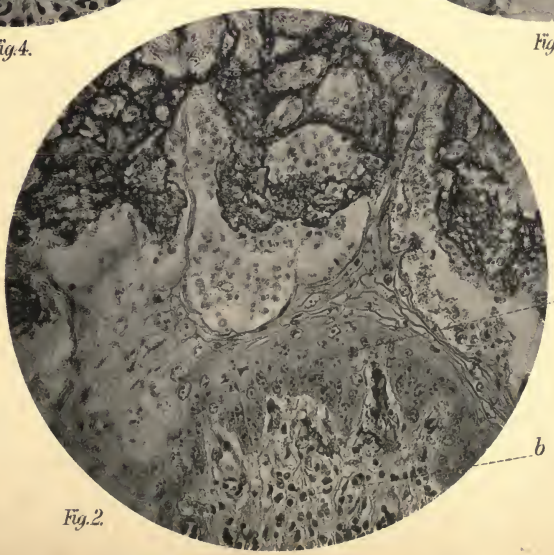

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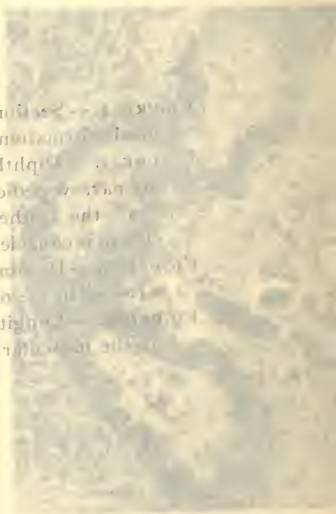

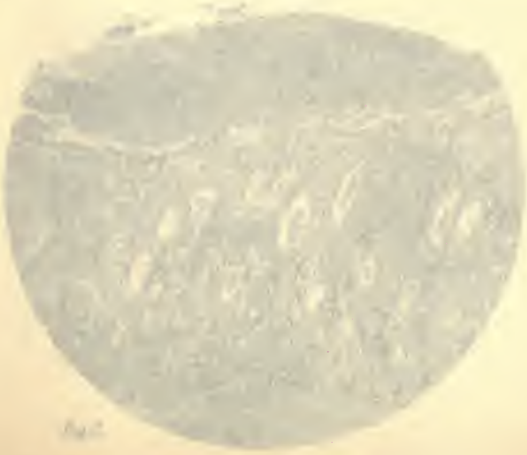

Plate XVIII.

Figure 1. — Section through skin of ear, showing necrotic epithelium with fibrin formation.

Figure 2. — Diphtheria of stomach. The fibrinous exudation is attached by narrow pedicle, and spreads on either side over the surface. At "a" the epithelium is turned back and attached to the membrane. There is considerable hæmorrhage in the mucous membrane.

Figure 3. — Hyaline fibrinoid degeneration of the muscular coat of arteries in the mucous membrane of pharynx.

Figure 4. — Longitudinal section of artery, with slight hyaline formation in the muscular coat.

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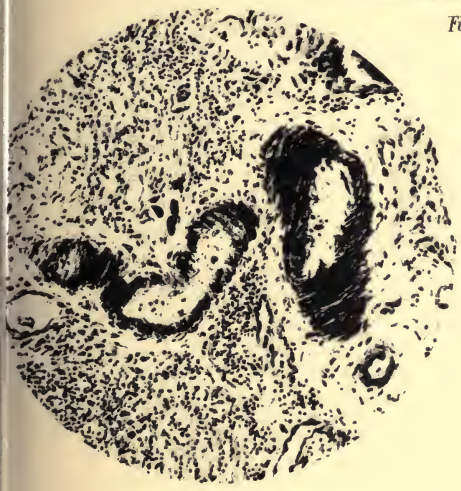

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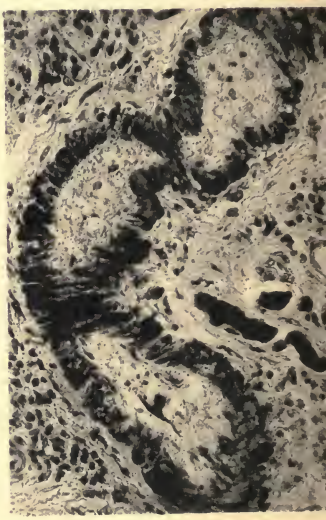

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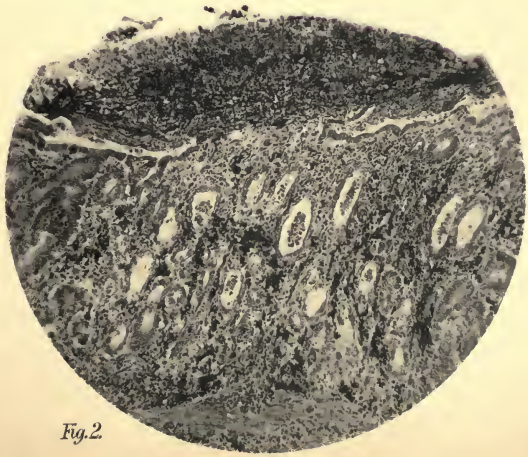

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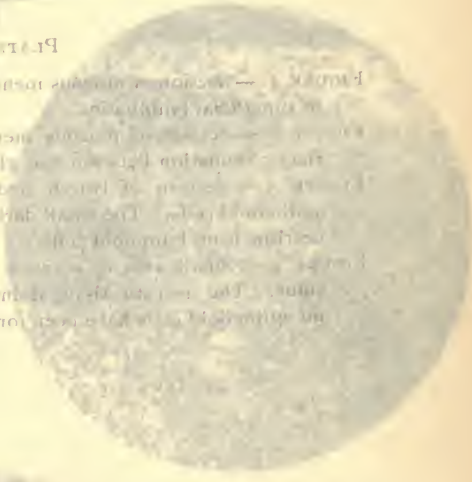


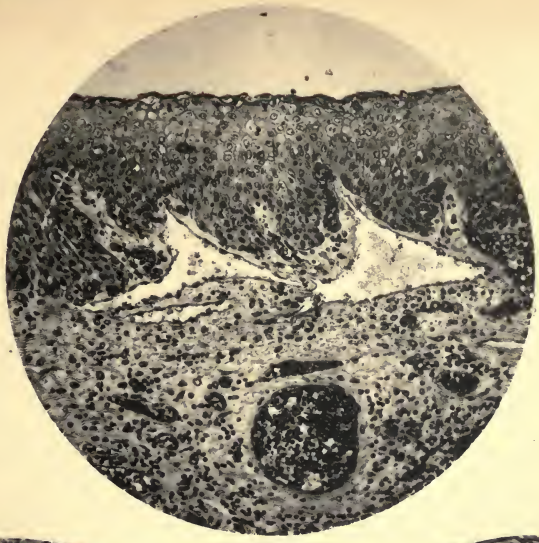
Plate XIX.

Figure 1. — Section of mucous membrane of pharynx, showing dilatation of superficial lymphatics.

Figure 2. — Section of mucous membrane of stomach, showing hæmorrhagic exudation between the glands near the surface.

Figure 3. — Section of lymph node containing circumscribed mass of epithelioid cells. The small dark-points in the area represent nuclear detritus from lymphoid cells.

Figure 4. — Small area of necrosis in lymph node near the peripheral sinus. The necrotic tissue is invaded by polynuclear leucocytes and no epithelioid cells have been formed.



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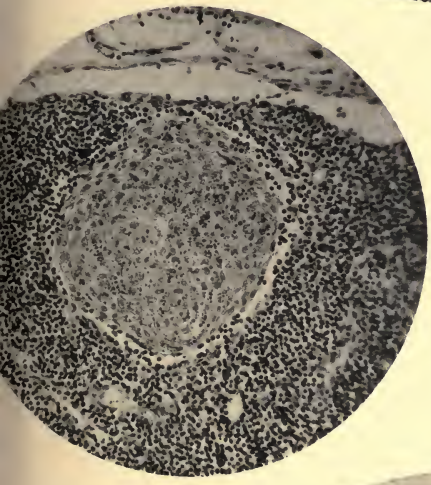

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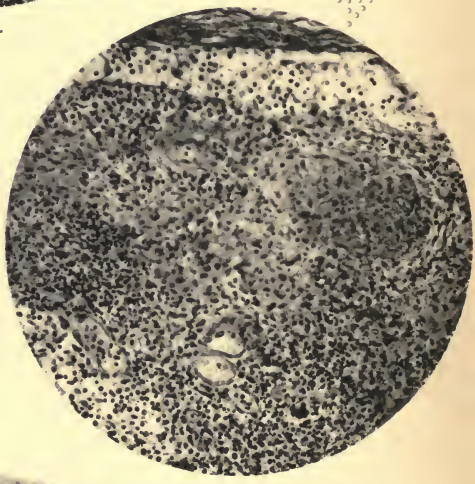

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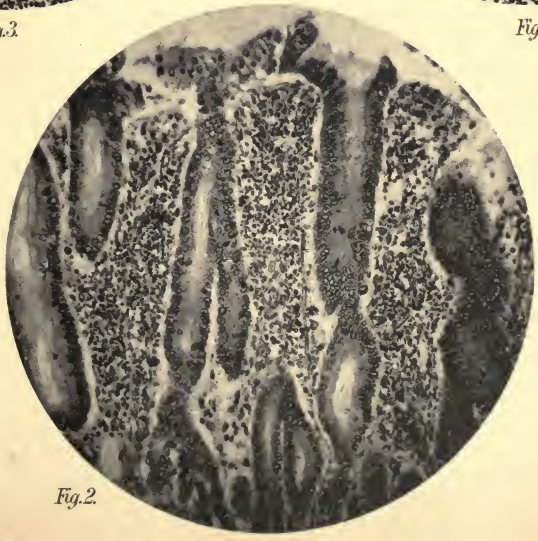

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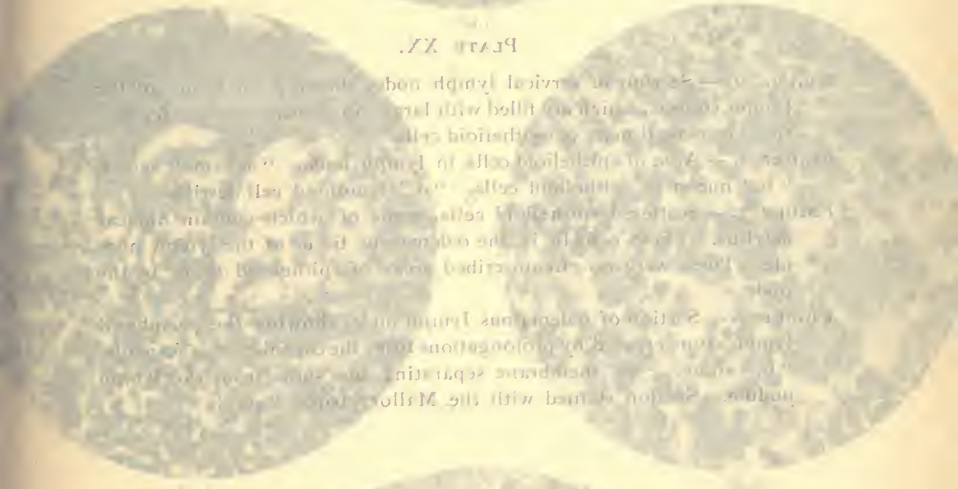


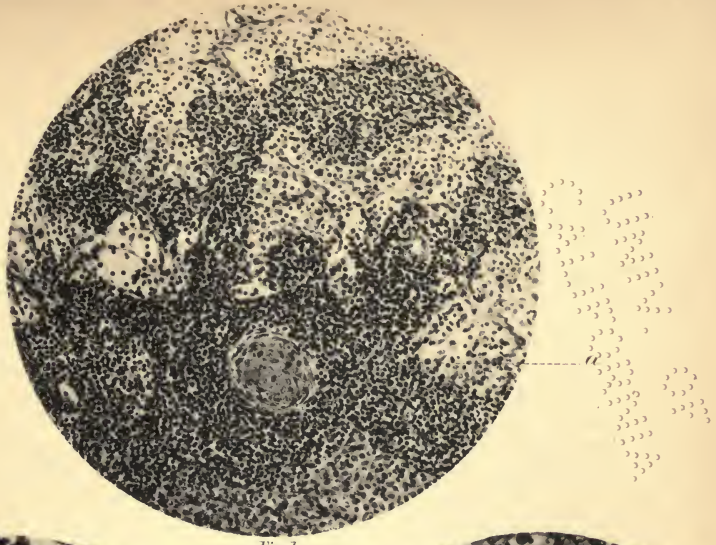
Plate XX.

Figure 1. — Section of cervical lymph node, showing dilatation of the lymph sinuses, which are filled with large mononuclear cells. At "a" there is a small mass of epithelioid cells.

Figure 2. — Area of epithelioid cells in lymph node. "a," small vessel. "b," nuclei of epithelioid cells. "d," lymphoid cell detritus.

Figure 3. — Scattered epithelioid cells, some of which contain nuclear detritus. These cells lie in the œdematous tissue of the lymph nodule. There were no circumscribed areas of epithelioid tissue in the node.

Figure 4. — Section of œdematous lymph node, showing the peripheral lymph sinus crossed by prolongations from the capsule. "a," capsule. "b," sinus. "c," membrane separating the sinus from the lymph nodule. Section stained with the Mallory triple stain.



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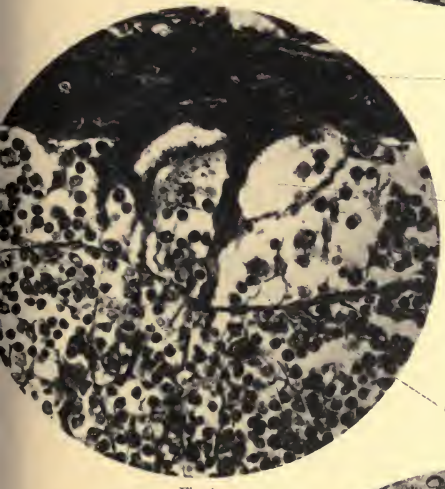

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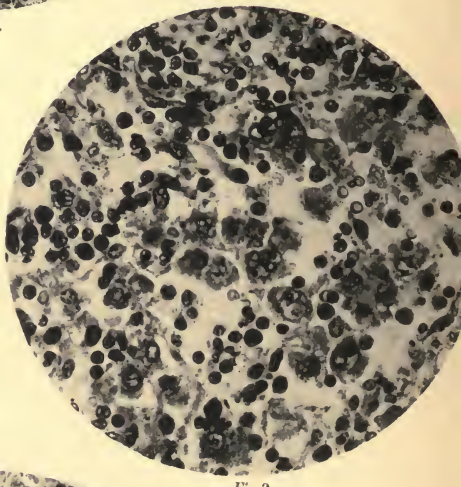

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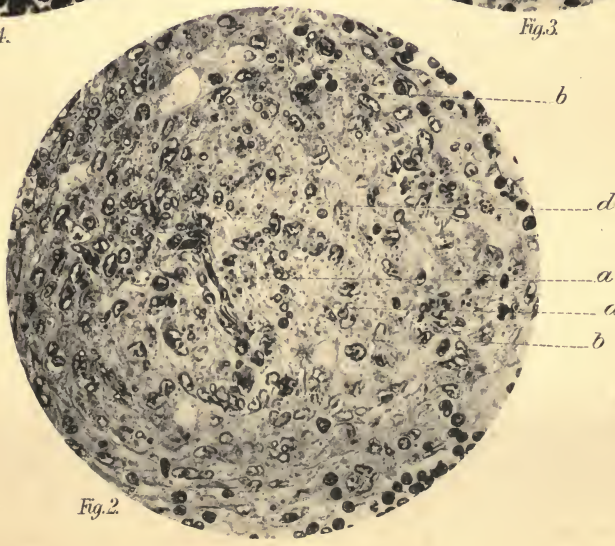

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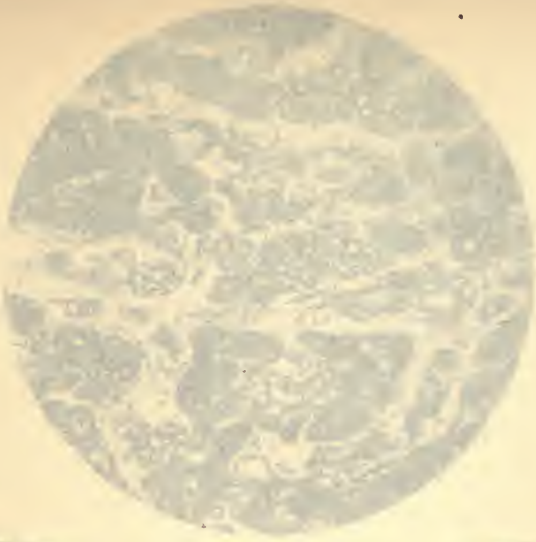


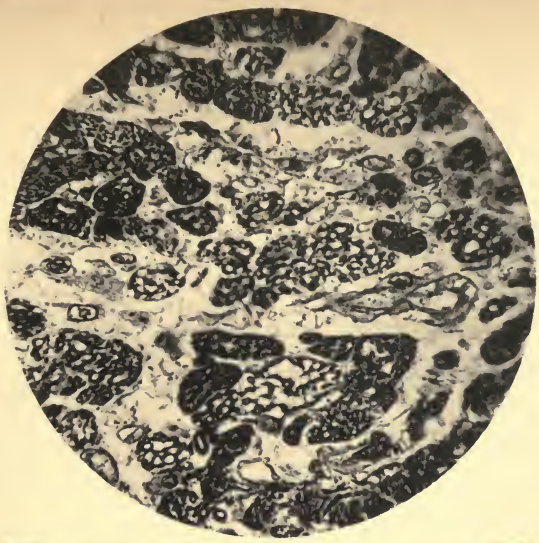
Plate XXI.

Figure 1. — Section of myocardium, showing fatty degeneration and separation of the fibres.

Figure 2. — Recent blood plate thrombus in heart.

Figure 3. — Bone marrow, very rich in lymphoid cells, and containing a small area of necrosis and hæmorrhage.

Figure 4. — Myocardium, showing separation and degeneration of muscular fibres.



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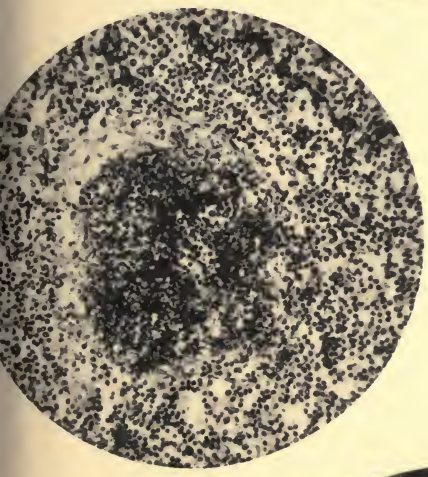

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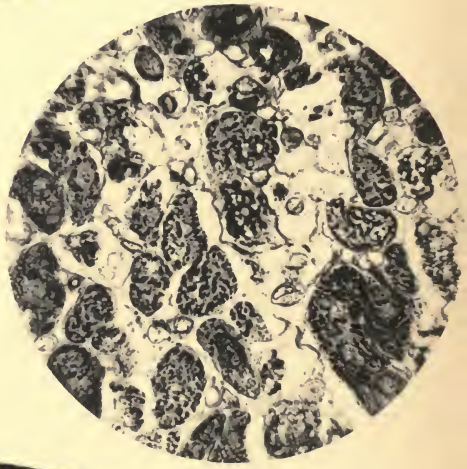

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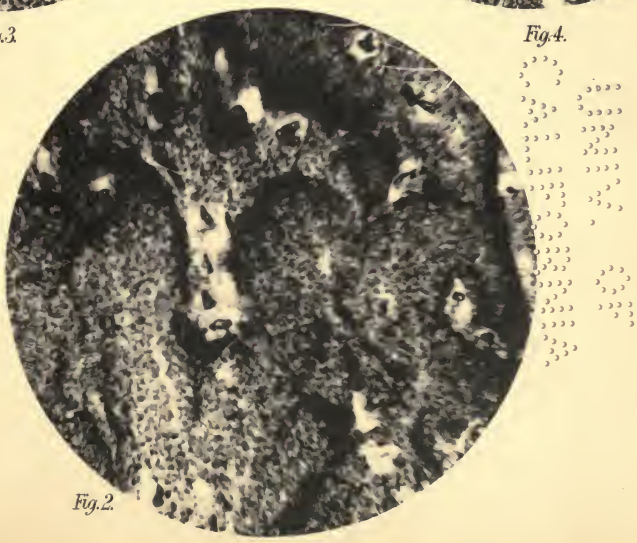


Fig. 2.

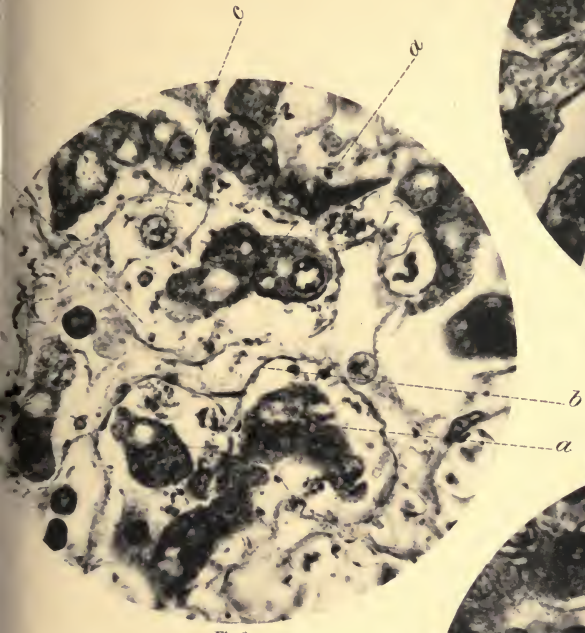
Plate XXII.

Figure 1. — Section of myocardium, showing acute interstitial myocarditis.

Figure 2. — Section of liver, showing slight degeneration. The liver cells are swollen and contain large pale granules.

Figure 3. — Section of liver through an area of central necrosis. The liver cells are broken up, separated from their connections, and lie in large spaces. "a," liver cells. "b," walls of capillaries. "c," endothelial cell in capillary.

Figure 4. — Section of liver through central necrosis, showing capillaries between necrotic liver cells occluded by thrombi of fibrin.



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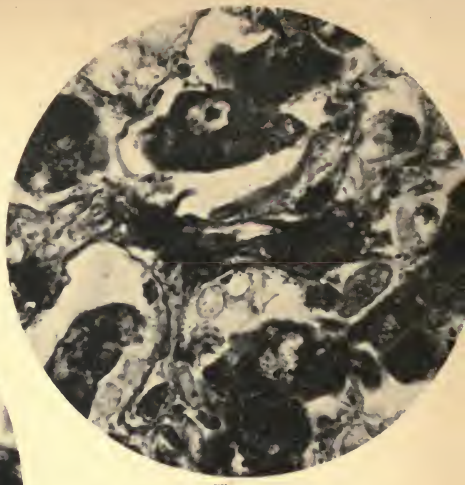

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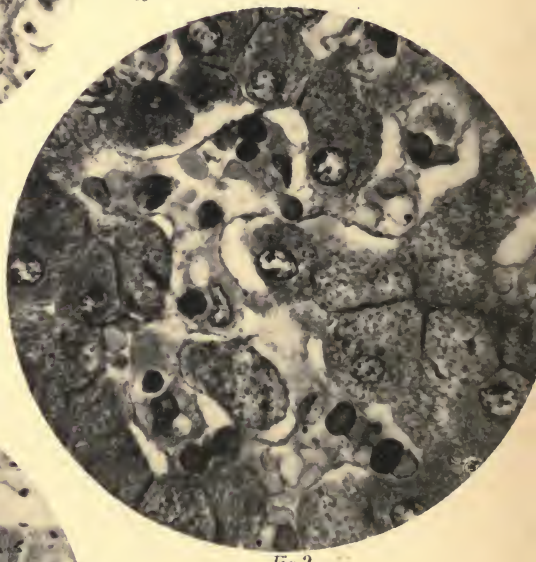

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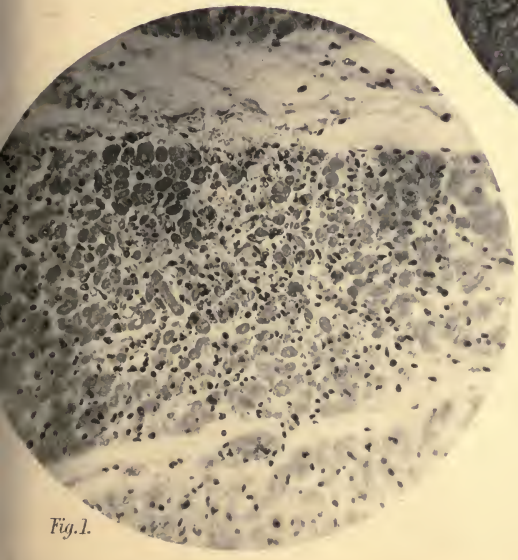

Fig. 1.

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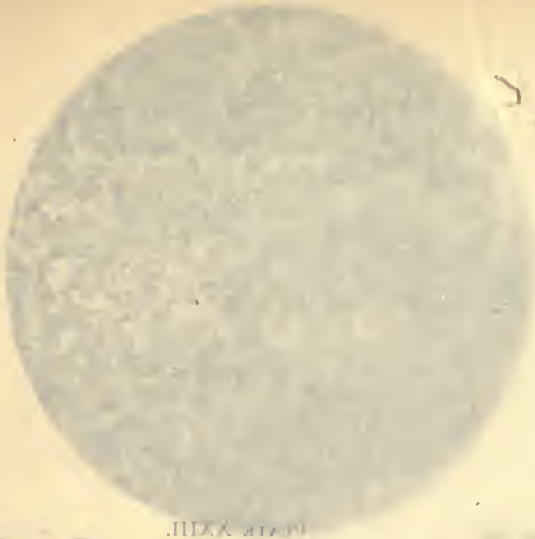


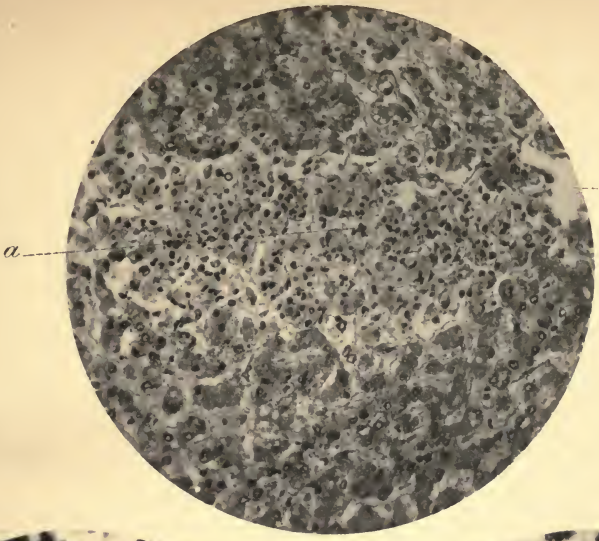
Plate XXIII.

Figure 1. — Focal necrosis of liver adjoining central vein of lobule. The small dark nuclei of the necrotic area represent polynuclear leucocytes which have invaded the necrotic liver cells. "a," focus of necrosis. "b," central vein.

Figure 2. — Degeneration of liver cells not so marked as in Fig. 2, Plate XXII. "a," endothelial cell. "b," endothelial cell enclosing a polynuclear leucocyte.

Figure 3. — Degenerated liver cells from an area of central necrosis. There is a wide space between the degenerated liver cells and the capillary walls. The endothelial cells of the capillaries are swollen and the vessels and spaces around the liver cells contain granular débris.

Figure 4. — From the same section as Fig. 3. The liver cells broken up into fragments. There are numbers of endothelial cells in the capillaries.



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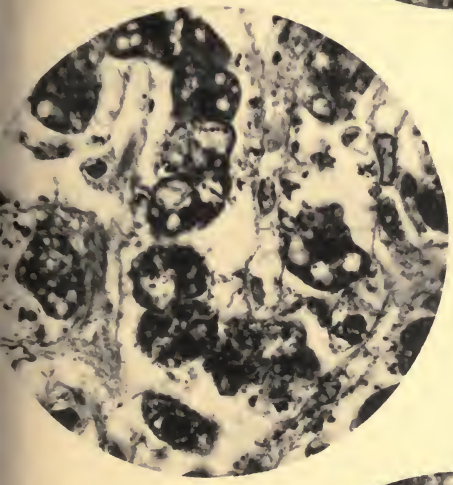

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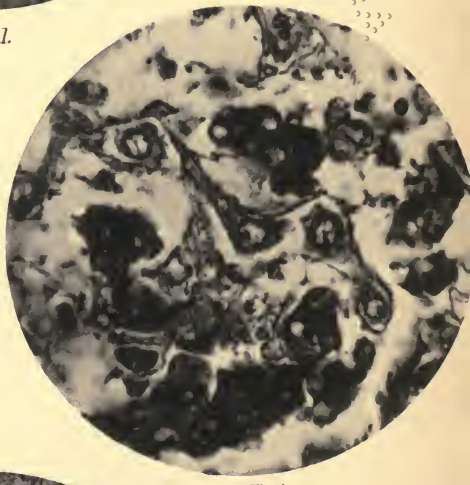

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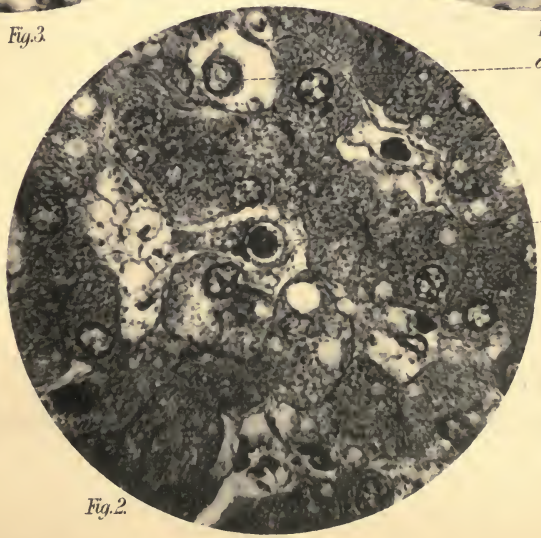

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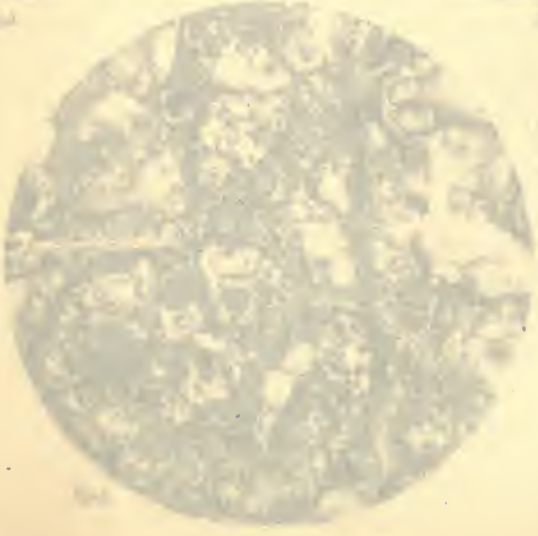


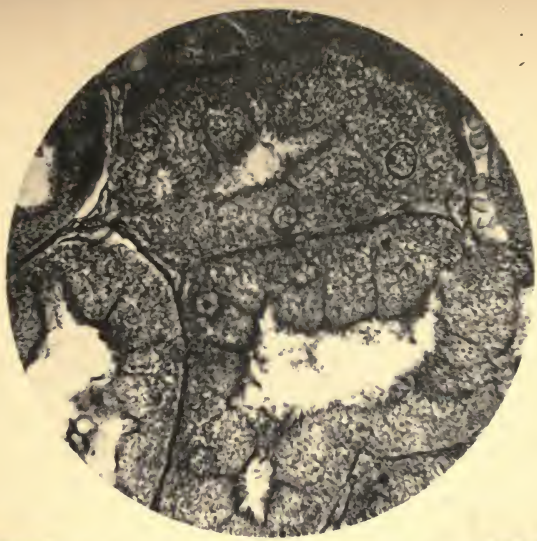
Plate XXIV.

Figure 1. — Convoluted tubules of kidney, showing cloudy swelling. The cells are greatly swollen and the granules increased in size and number. The ciliated borders of the cells are irregular.

Figure 2. — Longitudinal section of ascending loop of Henle. The ciliated border and the granules at the base of the ciliæ are well shown. The cells are swollen, their texture much looser than normal, and the lumen contains granules probably derived from the cells.

Figure 3. — Sections of convoluted tubules. The cells more granular and so swollen as to occlude the lumen.

Figure 4. — Greatly degenerated convoluted tubule. The cells are greatly swollen; the granules, many of which are distinctly hyaline, lie in spaces in the cells. The lumen is completely occluded.



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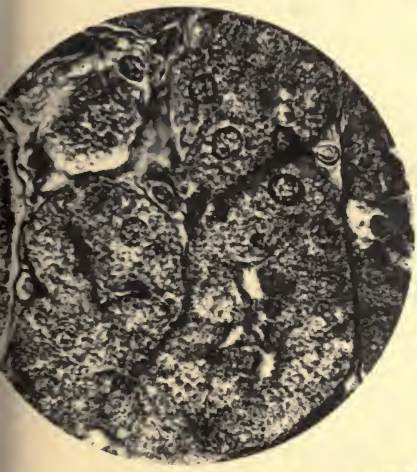

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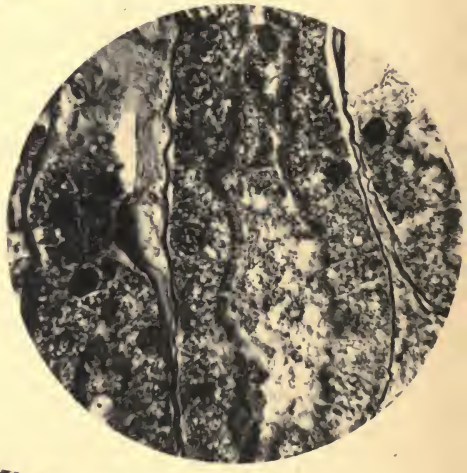

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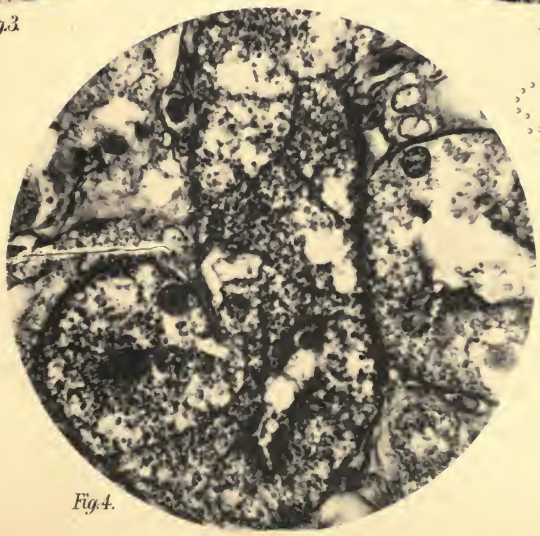


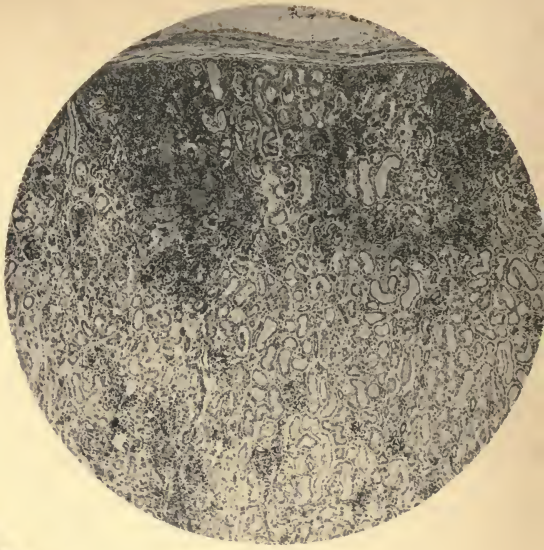
Fig. 4.

Plate XXV.

Figure 1. — Hyaline degeneration of proximal convoluted tubule. The cells contain large numbers of round hyaline droplets.

Figure 2. — Acute interstitial nephritis, circumscribed foci of interstitial infiltration with plasma cells chiefly beneath the capsule.

Figure 3. — Intense acute interstitial nephritis. The kidneys in this case were greatly enlarged. The dark color of the section is due to the great numbers of cells in the interstitial tissue.



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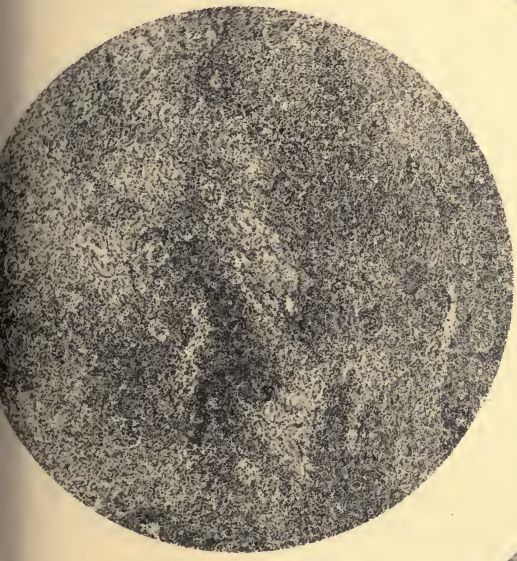

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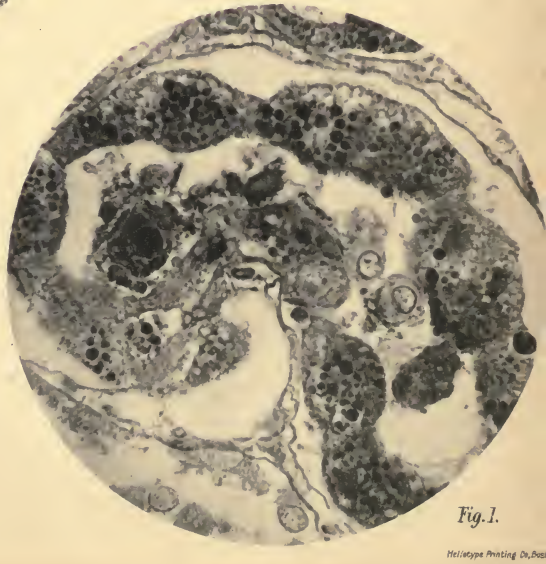

Fig. 1.

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Plate XXVI.

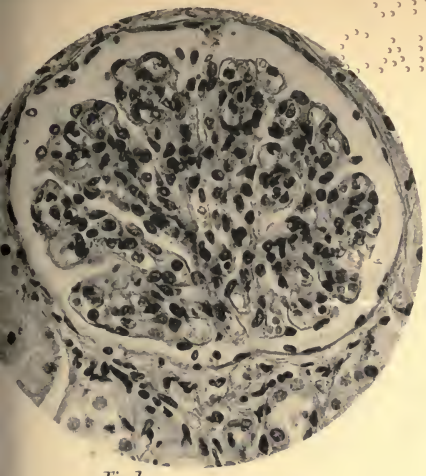
Figure 1. — Acute intracapillary glomerulo-nephritis. The glomerulus is enlarged, the lobulation more evident than normal, and the capillaries contain few blood corpuscles and an increased number of cells.

Figure 2. — Early stage of acute intracapillary glomerulo-nephritis. There is slight increase in the capillary cells. "a," nuclear figure in cells within the capillaries.

Figure 3. — Glomerulus from an advanced case of glomerulo-nephritis. The glomerulus is lobulated and contains great numbers of cells. There is also a great increase of cells in the capsular space.

Figure 4. — Acute glomerulo-nephritis with exudation. The capillaries are bare of epithelium, and in places are necrotic. There is abundant hæmorrhagic and fibrinous exudation in the capsular space, and extending from this into the tubule.

Figure 5. — Acute glomerulo-nephritis. In the capsular space a dense mass composed of red blood corpuscles and hyaline fibrin. The vascular tuft necrotic.



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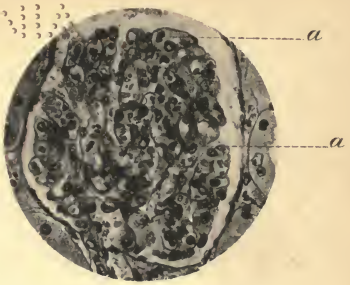

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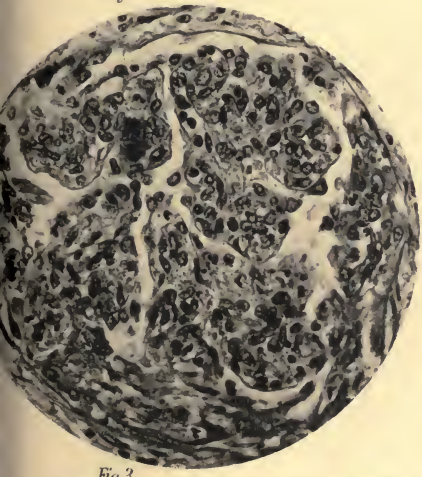

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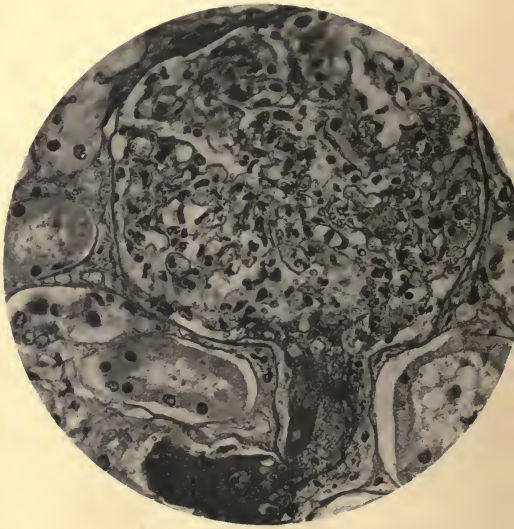

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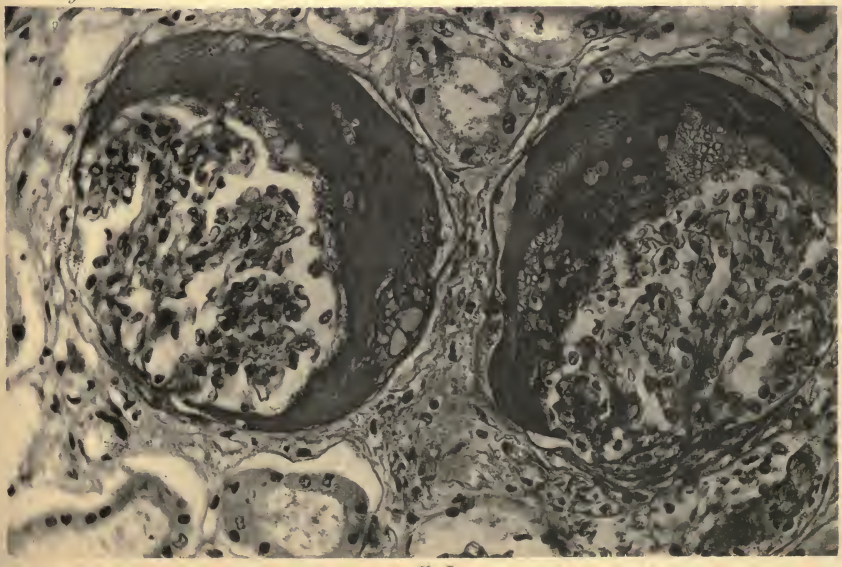


Plate XXVII.

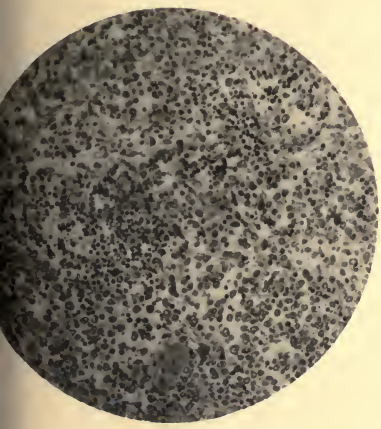
Figure 1. — Bone marrow, showing the relative numbers of marrow and lymphoid cells. The small dark nuclei belong to lymphoid cells.

Figure 2. — A part of same marrow highly magnified, showing the marrow cells.

Figure 3. — Section of lung, showing 5 atria with cellular infiltration about them. No exudation in the other air spaces. "a," atrium.

Figure 4. — Primary infection about atrium. "a," atrium. "b," air sac. "c," alveolus.

Figure 5. — Primary infection of terminal bronchus and atria. "d," bronchus. "a," atrium. "e," artery accompanying bronchus.



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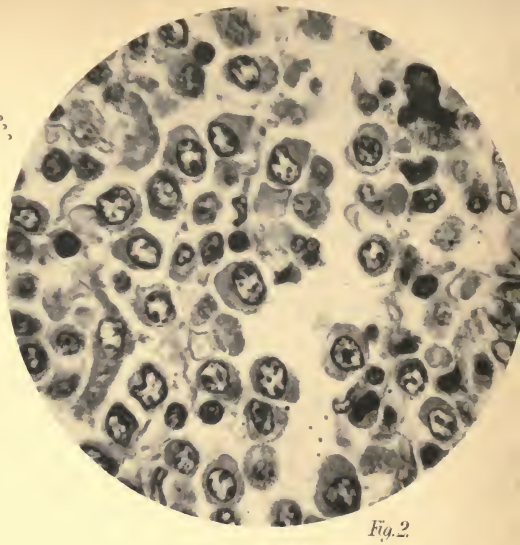

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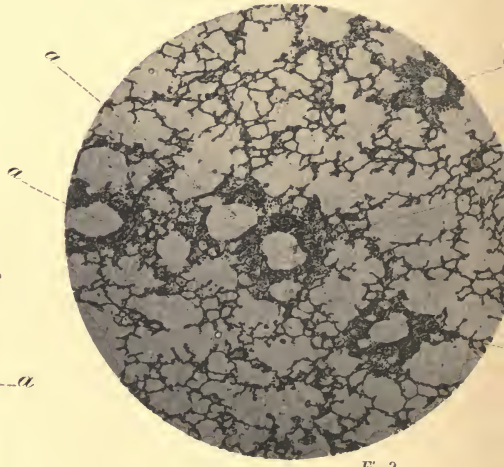

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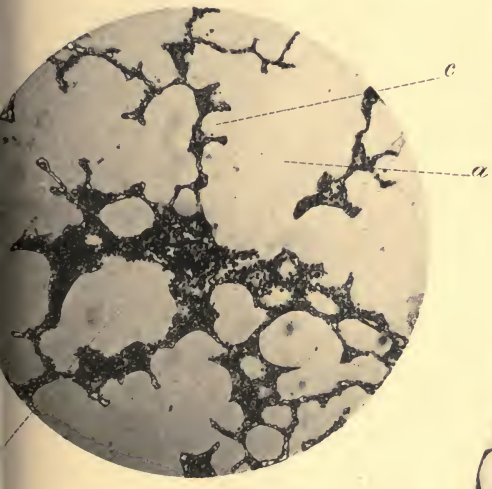

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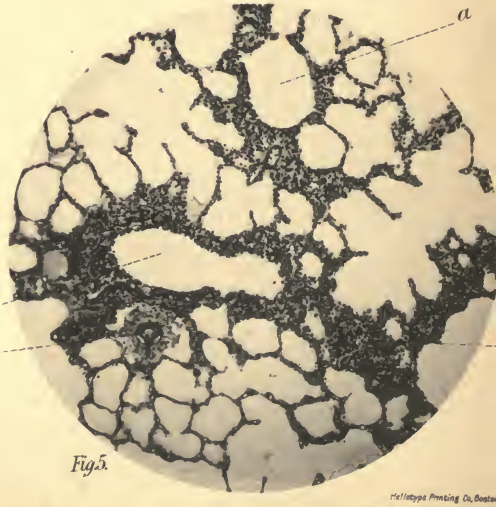

Fig. 5.

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Plate XXVIII.

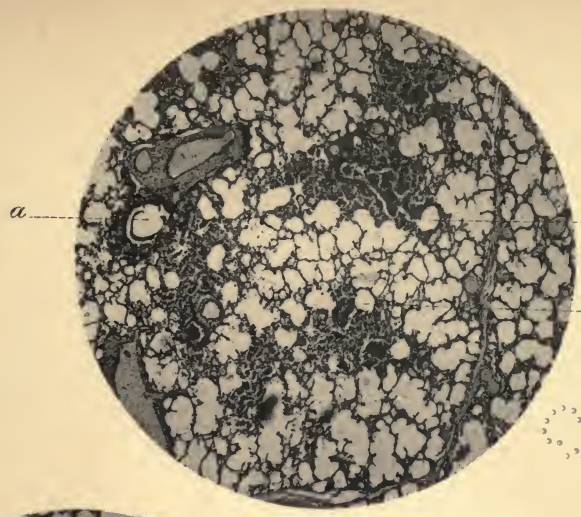
Figure 1. — Section of lung, showing several small foci of exudation affecting terminal bronchi and atria. "a" "a" "a," terminal bronchi.

Figure 2. — Longitudinal section of terminal bronchus and bronchial passage, showing gradual downward extension of the exudation.

Figure 3. — Section of lung, showing infection of two terminal bronchi and the adjoining lung tissue. "a," bronchus just above bifurcation. "b" "b," terminal bronchi.

Figure 4. — Section through large area of complete consolidation. The opening in the centre represents a bronchus. There is fibrinous exudation in the surrounding air spaces, shown by the dark masses within them. In the lung elsewhere the exudation is cellular. "a," artery accompanying bronchus with masses of fibrin in the lymphatics around it.

Figure 5. — Section of lung with serous and hæmorrhagic exudation in the air spaces. "a," bone marrow cell in capillary.



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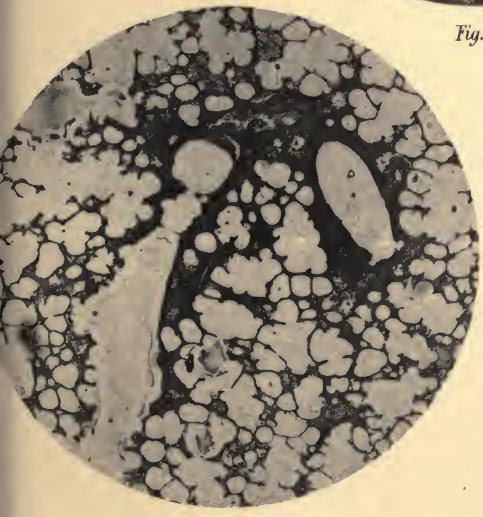

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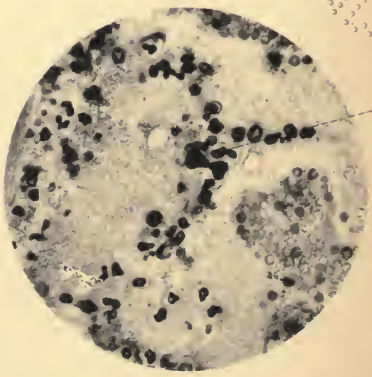

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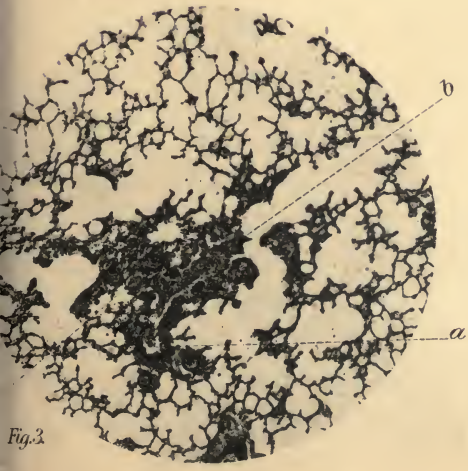

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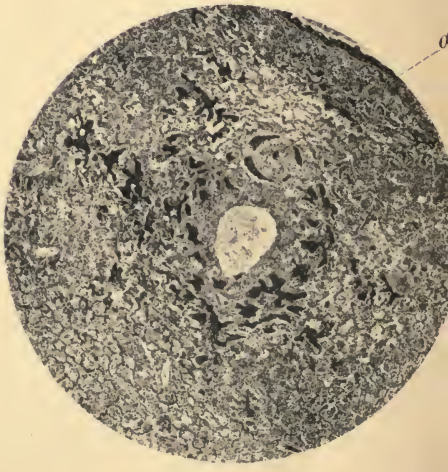

Fig. 4.

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Plate XXIX.

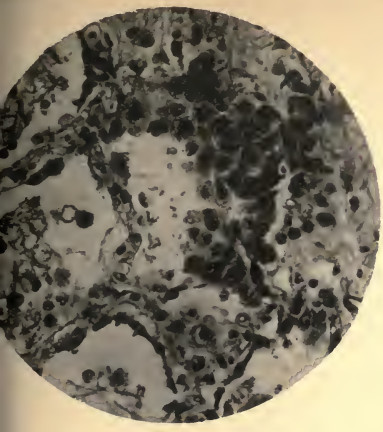
Figure 1. — Section of the lung from a case of interstitial pneumonia, showing great swelling and proliferation of the lining epithelium.

Figure 2. — Section of bronchus, showing hyperæmia of the wall, desquamation of epithelium, and a large exudation between the wall and the desquamated epithelium.

Figure 3. — Sub-pleural lymphatic with mass of newly formed connective tissue within it.

Figure 4. — Sub-pleural lymphatic filled with large endothelial cells and polynuclear leucocytes.

Figure 5. — Large masses of diphtheria bacilli completely filling the air spaces of the lung. The walls of the air spaces are represented by the clear spaces.



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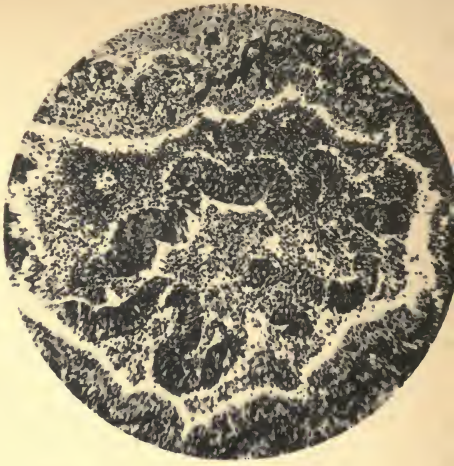

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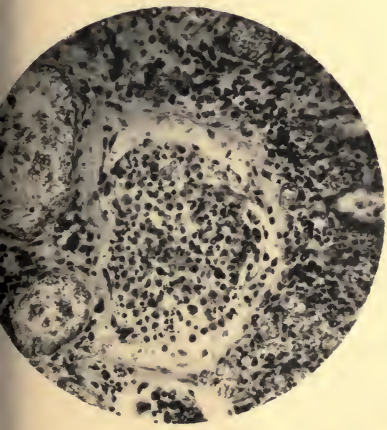

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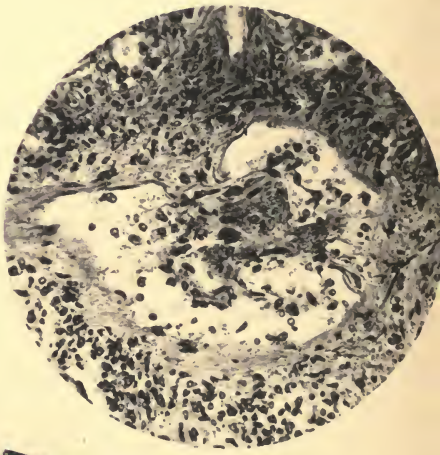

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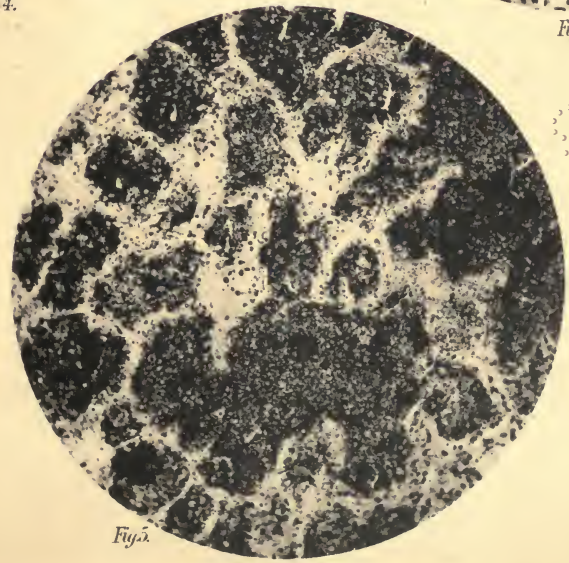

Fig. 5.

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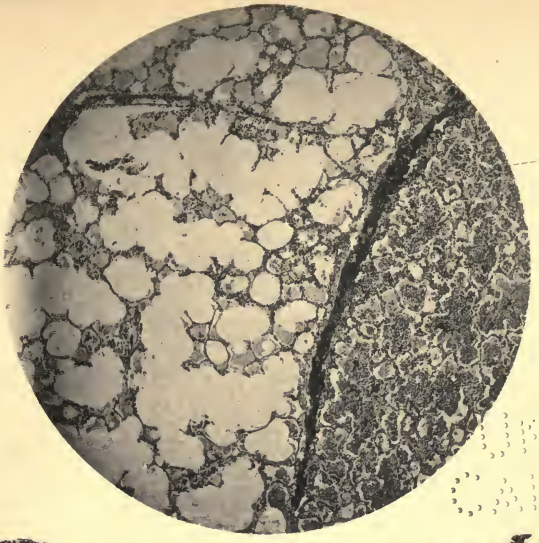
Plate XXX.

Figure 1. — A lobule of the lung completely solidified, with very slight exudation in the adjoining lobule. The interlobular septum contains fibrin. "a," lymph spaces in interlobular septum filled with fibrin.

Figure 2. — Small bronchus containing exudation, in the middle of which is a large mass of diphtheria bacilli.

Figure 3. — Small bronchus with exudation within it and cellular infiltration of the walls.

Figure 4. — Small bifurcated bronchus in the interior of area of pneumonia. The dark areas in the bronchi are composed of solid masses of diphtheria bacilli. The exudation in the lung is purulent.



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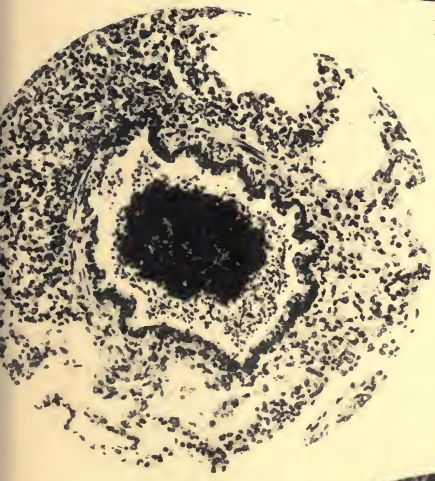

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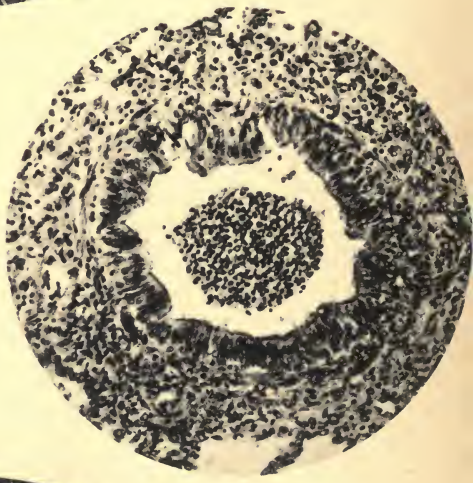

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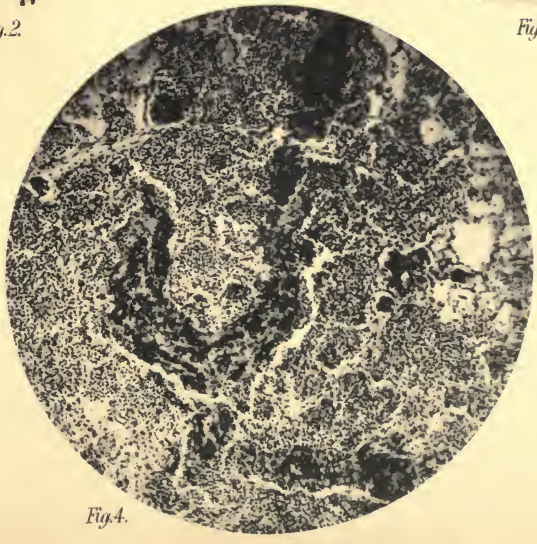

Fig. 4.

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