THE AMERICAN JOURNAL OF PATHOLOGY

VOLUME VIII MARCH, 1932 NUMBER 2

# INTRANUCLEAR AND CYTOPLASMIC INCLUSIONS ("PROTOZOAN-LIKE BODIES") IN THE SALIVARY GLANDS AND OTHER ORGANS OF INFANTS *

SIDNEY FARBER, M.D., AND S. BURT WOLBACH, M.D.

*(From the Department of Pathology, Harvard Medical School, and the Pathology Laboratory of the Children's Hospital, Boston, Mass.)*

A routine study of the salivary glands in a fairly large series of postmortem examinations on infants has revealed a hitherto unsuspected large number showing intranuclear and cytoplasmic inclusions in the duct epithelium, often in intimate association with foci of lymphocytic infiltration. In two infants inclusion bodies were found in cells in epithelial-lined spaces in various organs of the body. These findings are included in this report.

## LITERATURE

Ribbert [1] in 1881 first noted large "protozoan-like" cells in the kidney of a luetic stillborn infant. In 1904 he published this observation, together with a description of similar structures in the parotid glands of two non-luetic infants. The large cells occurred within ducts, singly or in groups. He was preceded in publication by Jesionek and Kiolemenoglou,[2] who noted the large cells in the lungs, kidneys and liver of an 8 month luetic fetus. The large cells averaged from 20 to 30 microns in diameter and were usually oval in outline with a well defined, though not sharply stained, cuticular zone having the appearance of a capsule. The nuclei were large and eccentrically placed. Each contained a "central nuclear body" surrounded by two well defined zones, an inner dark and an outer clear zone. In the clear zone deeply staining granules averaging

* Received for publication December 10, 1931.

1 micron in diameter were found. The cell body was spongy and the pole near the nucleus was filled with granules. The nucleus appeared to be separated from the cell body by a membrane. The large cells were most numerous in the interstitial tissues of the kidney, in association with areas of congenital luetic inflammation.

Löwenstein,[3] working in Ribbert's laboratory in 1907, found inclusions in both parotid glands in four of thirty infants. He described without recognition the cytoplasmic, as well as the nuclear inclusions. Additional instances were reported in 1910 by Pisanò,[4] who found inclusions in the kidneys, liver and lung, and Mouchet,[5] who noted inclusions in the bile ducts. Pettavel[6] in 1911 studied the thyroid of a 10 day old prematurely born infant, and described peculiar degenerative changes in the epithelial cells. Although he did not recognize the inclusions, the illustrations in his paper leave no doubt that he was dealing with the same type of inclusion bodies. This marked the first finding of the inclusions in the thyroid gland. In 1910, and again in 1914 Smith and Weidman[7, 8] described similar findings and concluded that they were dealing with protozoa. They gave the name *Endameba mortinatalium* to the structures. Jackson[9] in 1920 called attention to cells which she called protozoan parasites, in the ducts of salivary glands of guinea pigs. These were apparently identical with those noted in infants. Goodpasture and Talbot[10] in the following year reported the finding of similar structures in the lungs, liver and kidneys of a 2 months' old infant. The salivary glands were not examined. On the basis of their study of this case, and of salivary glands of guinea pigs, they concluded that they were dealing with a new kind of abnormal cytomorphosis, to which they gave the name *cytomegalia*. They stated definitely that the structures were not protozoa and they described not only the intranuclear inclusions, but the cytoplasmic inclusions as well.

In the following year de Lange[11] reported the inclusions in the kidney, and Müller[12] described a similar finding in the kidneys of three infants. VonGlahn and Pappenheimer[13] found the inclusions in the intestines, liver and lungs of a 36 year old man, for the first time in an adult. Walz[14] in 1926 observed the inclusions in the pancreas, as well as in the kidneys, liver, lungs and thyroid of a newborn infant. In a discussion of Walz's paper von Albertini mentioned a similar unreported observation. The last case report was by Wagner,[15] who noted the inclusions in the lungs, kidneys, liver,

pancreas, thyroid, epididymis and sublingual gland of a 2 weeks' premature infant, in whom no evidence of congenital lues could be found. He also found the inclusions in the parotid glands of four of a small series of infants.

An excellent review of the cases mentioned above, and a discussion of the various explanations advanced are given by VonGlahn and Pappenheimer,[13] so that a more complete review need not be given here. The cases are summarized in Table I, which is a combination of the tables of VonGlahn and Pappenheimer,[13] and Walz,[14] with corrections and additions. It will be noted that the distribution of the inclusions in the various organs of the reported instances is as follows:

| | |
|---|---|
| Kidneys | 11 cases |
| Parotids | 10 |
| Lungs | 8 |
| Liver | 8 |
| Pancreas | 2 |
| Thyroid | 3 |
| Intestine | 1 |
| Sublingual gland | 1 |
| Epididymis | 1 |

Goodpasture and Talbot [10] first called attention to the similarity of these bodies to a structural variation in the intranuclear body described by Tyzzer [16] in cutaneous lesions in varicella. Although the protozoa theory was kept alive in Germany until 1930 (Wagner [15]) a new significance was given these findings in 1921, when Lipschütz [17] reported that similar structures are constantly associated with the lesions of the herpes virus in man and rabbits. Later, due to the work of Cole and Kuttner [18, 19] and to a number of intensive studies which have appeared from the laboratories of Goodpasture [20, 21] and Cowdry [22, 23] and their associates, a mass of data has accumulated to show that a definite relation does exist between inclusion bodies and certain types of filtrable virus disease (variola, vaccinia, sheep-pox, fowl-pox, molluscum contagiosum, herpes, submaxillary virus disease of guinea pigs, and so on). Goodpasture [20] believes that such intranuclear inclusions indicate an intranuclear localization of the infective substance in filtrable virus disease. The controversial theories and data are admirably expressed by Goodpasture [20] in a recent review of the subject of inclusion bodies in relation to the etiology of virus diseases.

TABLE I

*Reported Cases with Inclusion Bodies*

| No. | Year | Author | Age | Location of Inclusions | | | | | | | | | Pathological diagnosis | Interpretation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Kidney | Parotid | Lung | Liver | Pancreas | Thyroid | Intestine | Sublingual gland | Epididymis | | |
| 1 | 1904 | Jesionek and Kiolemenoglou | Stillborn | × | .. | × | × | .. | .. | .. | .. | .. | Congenital lues | Gregarines (R. Hertwig) |
| 2 | 1904 | Ribbert | Stillborn | × | .. | .. | .. | .. | .. | .. | .. | .. | Congenital lues | Amebae or sporozoa (Ehlers-Rhumbler) |
| 3 | | | 1 yr. | .. | × | .. | .. | .. | .. | .. | .. | .. | No lues | |
| 4 | | | 3 mo. | .. | × | .. | .. | .. | .. | .. | .. | .. | No lues | |
| 5 | 1907 | Löwenstein | 2 mo. | .. | × | .. | .. | .. | .. | .. | .. | .. | .... | Coccidia (Ludwig) |
| 6 | | | 3 mo. | .. | × | .. | .. | .. | .. | .. | .. | .. | .... | |
| 7 | | | 10 mo. | .. | × | .. | .. | .. | .. | .. | .. | .. | .... | |
| 8 | | | 3 mo. | .. | × | .. | .. | .. | .. | .. | .. | .. | .... | |
| 9 | 1910 | Mouchet | 8 days | .. | .. | .. | × | .. | .. | .. | .. | .. | Congenital lues | Sporozoa |
| 10 | 1910 | Pisanò | Stillborn | × | .. | × | × | .. | .. | .. | .. | .. | Congenital lues | Embryonic epithelial cells |
| 11 | 1910 | Smith and Weidman | Stillborn | × | .. | × | × | .. | .. | .. | .. | .. | Focal nephritis | Endameba mortinatalium |
| 12 | 1911 | Pettavel | 10 days | .. | .. | .. | .. | .. | × | .. | .. | .. | Purpura | Peculiar epithelial degeneration |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 13 | 1914 | Smith and Weidman | 2 mo. | .. | .. | × | .. | .. | .. | .. | .. | .. | Pneumonia | Endameba mortinatalium |
| 14 | | Goodpasture and Talbot | 6 wks. | × | .. | × | × | .. | .. | .. | .. | .. | Edema, cough and loss of appetite | Abnormal cytomorphosis "cytomegalia" |
| 15 | 1922 | de Lange | 8 days | × | .. | .. | .. | .. | .. | .. | .. | .. | Congenital lues? | Cellular degeneration |
| 16 | 1922 | Müller | 8 wks. | × | .. | .. | .. | .. | .. | .. | .. | .. | Hydrocephalus, nephritis | Degeneration |
| 17 | | | Stillborn | × | .. | .. | .. | .. | .. | .. | .. | .. | | |
| 18 | | | 2 mo. | × | .. | .. | .. | .. | .. | .. | .. | .. | Lues | |
| 19 | 1925 | VonGlahn and Pappenheimer | 36 yrs. | .. | .. | × | × | .. | .. | × | .. | .. | Abscess of liver, ulcerative colitis, pneumonia | Filtrable virus Inclusion bodies |
| 20 | 1926 | Walz | 20 min. | × | .. | × | × | × | × | .. | .. | .. | Prematurity, asphyxia | Protozoa |
| 21 | 1930 | Wagner | 2 wks. | × | .. | × | × | × | × | .. | × | × | Prematurity | Undecided |
| 22 | | | up to 2 yrs. of age | .. | × | .. | .. | .. | .. | .. | .. | .. | | |
| 23 | | | | .. | × | .. | .. | .. | .. | .. | .. | .. | | |
| 24 | | | | .. | × | .. | .. | .. | .. | .. | .. | .. | | |
| 25 | | | | .. | × | .. | .. | .. | .. | .. | .. | .. | | |
| Total No. cases | | | | 11 | 10 | 8 | 8 | 2 | 3 | 1 | 1 | 1 | | |

× = present

Pearson [24] in a recent study called particular attention to the cytoplasmic inclusions. In a study of guinea pig salivary glands he found these inclusions to be spherical or oval in shape, and varying in size from a fraction of a micron up to 6 to 8 microns. They do not contain fat or lipoid in demonstrable amounts. Pearson had the opportunity of studying two cases from our group reported here, and found the guinea pig cytoplasmic inclusions indistinguishable from "certain cytoplasmic inclusions of rare occurrence in the human submaxillary glands." We have examined the salivary glands of a small number of normal guinea pigs and have noted on several occasions inclusions apparently identical with those found in our series of infant submaxillary glands. The guinea pig salivary gland inclusions were often accompanied by marked lymphoid infiltration.

In a discussion to a preliminary report of this study [25] Dr. Oskar Klotz of Toronto mentioned that inclusions similar to those described here were found by Dr. J. Thompson in the submaxillary glands in 14 per cent of a series of rats 2 months' old. These rats had been subjected to experiments on vitamin D over a short period. On the same occasion, Dr. E. V. Cowdry of St. Louis stated that Dr. G. H. Scott had found no inclusions in one hundred newborn infants and fetuses collected in St. Louis, Minneapolis and the Middle West.

## Discussion of Present Series

The submaxillary glands, and often the parotid glands, were removed in a consecutive series of autopsies on infants to determine the incidence of inclusion bodies in the salivary glands of infants, and to study the clinical and general pathological features of the cases in which these inclusions occurred. A portion of each gland removed was put immediately into sterile glycerine for further experimental work, and the remainder fixed in Regaud's fluid. Routine stains were made with hematoxylin and eosin; Giemsa and eosin-methyline blue were also employed. A study of the preparations showed the inclusions in twenty-two or 12 per cent of the 183 cases studied. In addition, two cases in which the submaxillary inclusions were noted on a previous occasion, and two others in which inclusions were found in various body organs were studied with this series, making a total of twenty-six cases available for clinical and general pathological analysis. It might be well to stress

the fact that in none of these cases was attention called to the submaxillary or parotid glands during life.

The clinical and pathological records of the twenty-six patients can be summarized as follows:

*Age:* Twenty-one instances ranged from 2 days to 1 year of age; the remaining five from 13 months to 17 months.

*Sex:* There were fifteen males and eleven females.

*Season:* The cases were scattered throughout the period of a year, with no definite seasonal preponderance.

*Past History:* In twenty-five of the twenty-six infants, the past history was essentially negative. There was no history of mumps or of infection in the general region of the salivary glands in any of the cases. The group includes both breast and artificially fed infants. Only one of the group had a history of contagious disease. This patient had measles, followed four months later by fatal miliary tuberculosis at 17 months' of age.

*Present Illness:* Vomiting and diarrhea marked the onset of illness in four cases. These were regarded as acute nutritional disturbances. In three instances the fatal illness had a sudden onset and a brief course, with death occurring in five to twenty hours. One of these had *Streptococcus hemolyticus* septicemia, one acute fulminating meningococcus meningitis, and the third died five hours after an operation for the repair of a large umbilical hernia.

There were symptoms referable to the central nervous system in several cases of meningitis due to various microörganisms, but there were no cases with unexplained manifestations of central nervous system disturbances. The remainder of the group had signs and symptoms referable to acute inflammation somewhere in the body, most often in association with the upper respiratory tract.

*Clinical Course:* The clinical course was variable and was usually characteristic of the particular disease. The duration of the fatal illness varied from several weeks to several hours.

*Temperature:* The temperature was usually high, varying in most cases from 101° to 104° F, the highest temperature occurring terminally in the instances of tuberculous meningitis.

*Cause of Death:* An adequate cause of death was found in every case. Five died of acute miliary tuberculosis, one having in addition a *Streptococcus hemolyticus* septicemia. Three could be grouped under the term "acute nutritional disturbance" ending with terminal infections. Bronchopneumonia and otitis media were the main features in three instances. There were two cases of pneumococcus septicemia, and two (not of the present series) of keratomalacia. Congenital lues occurred in but two patients. The other causes of death occurred singly (Tables II and III).

This summary indicates that there are no findings which would justify the grouping of these cases into a single, or even a homogeneous, clinical or pathological class. The outstanding features common to most of the group are hyperpyrexia and acute infection somewhere in the body. The occurrence of such heterogenous con-

TABLE II

*Present Series with Inclusions in Submaxillary Glands*

| No. | Case No. | Age | Sex | Pathological diagnoses |
|---|---|---|---|---|
| 1 | A-29-245 | 10 mo. | Male | Miliary tuberculosis, Strep. hem. septicemia |
| 2 | A-29-246 | 11 mo. | Female | Idiopathic hypertrophy of heart, terminal pneumonia |
| 3 | A-30-1 | 8 mo. | Male | Congenital lues, Strep. hem. septicemia |
| 4 | A-30-8 | 12 mo. | Female | Miliary tuberculosis, tuberculous meningitis, osteomyelitis |
| 5 | A-30-39 | 7 mo. | Male | Pneumococcus septicemia, pneumonia, otitis media |
| 6 | A-30-52 | 8 mo. | Male | Strep. hem. septicemia |
| 7 | A-30-69 | 17 mo. | Male | Miliary tuberculosis |
| 8 | A-30-72 | 5 mo. | Female | Pneumonia, enteritis |
| 9 | A-30-78 | 17 mo. | Female | Pneumonia, otitis media |
| 10 | A-30-79 | 15 mo. | Female | Umbilical hernia, pneumonia |
| 11 | A-30-80 | 17 mo. | Female | Miliary tuberculosis, pneumonia |
| 12 | A-30-84 | 3 mo. | Male | Pneumonia, otitis media |
| 13 | A-30-98 | 11 mo. | Female | Meningococcus meningitis |
| 14 | A-30-99 | 7½ mo. | Female | Strep. hem. septicemia, pneumonia |
| 15 | A-30-107 | 3 mo. | Female | Pneumonia, otitis media |
| 16 | A-30-110 | 8 mo. | Male | Pneumonia, otitis media |
| 17 | A-30-111 | 7 mo. | Female | Meningococcus meningitis |
| 18 | A-30-117 | 13 mo. | Male | Miliary tuberculosis |
| 19 | A-30-181 | 2½ mo. | Male | Pneumonia, otitis media |
| 20 | A-30-192 | 6 mo. | Male | Pneumonia, otitis media |
| 21 | A-30-242 | 8 mo. | Male | Chronic bronchopneumonia |
| 22 | A-31-13 | 3½ mo. | Male | Congenital lues, pneumococcus septicemia |
| 23 | A-1009 | 5 mo. | Male | Keratomalacia |
| 24 | A-24-48 | 4½ mo. | Male | Keratomalacia |

TABLE III

*Present Series with Inclusions in Viscera*

| No. | Case No. | Age | Sex | Pathological diagnoses |
|---|---|---|---|---|
| 1 | A-30-159 | 20 days | Female | Hemorrhagic diathesis, inclusions in lungs, kidneys, liver, pancreas and thyroid |
| 2 | A-31-110 | 2 days | Male | Erythroblastosis, inclusions in kidneys, lungs, pancreas and liver |

ditions in even so small a series can serve to halt, for a time at least, any speculation as to the association of the inclusion bodies with any single disease.

The fact that 80 per cent of the cases occurred in individuals under 1 year of age, that is, during a period when known diseases associated with a filtrable virus are rare, is of more than passing

interest. The series is naturally too small to permit any conclusions in regard to sex or seasonal incidence. The past history was essentially negative, except in one instance where measles occurred four months before death. Local factors are ruled out by the absence of a history of mumps or of any apparent lesion of the salivary glands during life. The clinical signs and symptoms were all satisfactorily explained by the clinical course and the postmortem findings. Of particular interest is the fact that there were no unexplained central nervous system disturbances. Congenital lues, with which many of the early reported cases were associated, was found but twice in this series. A listing of the cases by diseases and causes of death would show, in general, an approximate cross-section picture of the entire series from which this group was selected.

Gordon [26, 27] in 1913, and again in 1914 reported the association of pyrexia, collapse, diarrhea and vomiting, with symptoms of meningeal irritation followed by death in from twenty-four hours to twelve days in a group of twelve children, who at autopsy showed no adequate cause for the signs and symptoms. In the salivary glands of these patients Gordon found areas of interstitial inflammation consisting mainly of lymphocytes. His descriptions and illustrations resemble very much similar areas of infiltration which were found in the vicinity of the inclusions in our material. However, Gordon states definitely that the ducts were clear, and he makes no mention of either intranuclear or cytoplasmic inclusions. He examined the salivary glands of thirty other individuals, varying from infancy to old age, and found two of that group which showed areas of lymphocytic infiltration similar to those found in his main group. These were both adults who died of peritonitis. There are no points of similarity between Gordon's group and the present series, except clinically the hyperpyrexia, and pathologically the areas of lymphocytic infiltration in the salivary glands.

## Description of Microscopic Findings

In the series of submaxillary glands studied, the number of cells containing inclusion bodies varied from large collections scattered over many fields to single cells which were found only after a long search. Often inclusions were present in one gland only. When two blocks were taken from the same gland the inclusions were some-

times absent in one. Where the inclusions were numerous the ducts were often dilated, and areas of lymphoid infiltration (Fig. 1) were usually present in the immediate vicinity of the inclusion-laden ducts and acini, replacing areas of gland parenchyma. Such areas of infiltration are similar to those described by Gordon and were the most prominent accompanying pathological processes. In a few of the "negative" gland preparations areas of acute inflammation consisting of collections of polymorphonuclear leucocytes were noted, but inclusions were lacking. Where the inclusions were rare lymphocytic infiltration was usually absent, and there was no demonstrable associated pathological process. The large cells were found always in acini and ducts of the submaxillary glands, and their relationship to the lining epithelial cells appeared definite.

In the viscera the cells were always in epithelial-lined spaces — in the tubules of the kidney, the bile ducts of the liver, the acini and ducts of the pancreas, the acini of the thyroid, and the alveoli and bronchioles of the lung. They were never found free in the interstitial tissues, blood vessels, or in association with cells of other than epithelial type. This is in contrast to the observations of several of the earlier authors. No distinctive pathological process was found in these organs, the large cells often being found in otherwise normal appearing areas. In one kidney tubule there were large cells, so numerous and large in size that the lumen of the tubule appeared almost obliterated. The greatest number of large cells found in the organs of the body were in the kidney, lung and liver. Relatively few large cells were found in the pancreas and thyroid. None were noted in the intestine (VonGlahn and Pappenheimer). The epididymis was unfortunately not examined, so the observation of Wagner could not be verified.

The cells varied greatly in size, most authors mentioning a variation of from 10 to 35 microns, with an average size of 25 microns. Most often the large cells could be recognized under low powers, after some training. The shape of the cells varied from round or oval to elongated or markedly irregular outlines. Rare multinucleated cells containing inclusions were found. A sharp nuclear membrane divided the nucleus from the cytoplasm. Within the nuclear membrane was a large inclusion body which varied considerably in size, shape and staining intensity. Usually the intranuclear inclusion appeared as an ovoid or elongated, dense, homogeneous

acidophilic body. Often the body stained more deeply in the central portion and shaded off slightly to a paler portion at the periphery. The outline of the body was usually not sharp. In some instances delicate honeycombing to coarse vacuolization could be observed within the inclusion body. No finer structures could be recognized. Surrounding this body, and between it and the nuclear membrane, there was usually a clear zone which varied in size with the outline of the nuclear inclusion body. Occasionally the clear zone was entirely obliterated by the encroachment of a vacuolated, swollen, nuclear inclusion body. In the clear zone there were usually one or two, sometimes three or four small, round to oval or spherical, dense, basophilic, granular masses, which in some cases had apparently fused to form irregularly shaped, densely staining clumps. In rare instances, in the cells of comparatively small size, no definite nuclear body was found. In the clear zone of such nuclei twenty to thirty small, densely staining masses of chromatin material were scattered, sometimes distributed in almost concentric arrangement, and at other times gathered in groups adjacent to the nuclear membrane. This we regard as an early stage in the formation of the inclusions. One perplexing feature in our study of the inclusion bodies was the failure to find small forms which could with confidence be interpreted as stages in formation. If the inclusions were present at all they were strikingly alike and within a constant narrow range of size and detail.

The cytoplasm of the cells with inclusions was basophilic in staining reaction, and usually contained a few to large numbers of dense, basophilic, oval to spherical granules which varied greatly in size. Often these cytoplasmic inclusions appeared almost round in shape, and were arranged in curved rows, conforming to the shape of the cytoplasm. The cytoplasmic inclusions were present in almost all of the large cells in the submaxillary glands, and in most of the large cells in the organs of the body. Often, when they were apparently lacking, better stained sections would bring the cytoplasmic inclusions out more clearly. The cytoplasmic inclusions do not represent mucus droplets, as might be at first suspected. Microchemical studies were carried out by Pearson,[24] who found that specific tests for mucin yielded rather inconclusive results. Furthermore, we have repeatedly observed cytoplasmic inclusions in epithelial cells lining structures where mucus-secreting cells normally do not occur.

## Summary and Conclusions

In the submaxillary glands removed in a series of 183 postmortem examinations on infants, large cells containing intranuclear and cytoplasmic inclusion bodies ("protozoan-like bodies") were found in twenty-two cases (12 per cent). In addition, two older cases with inclusions in the parotid and submaxillary glands, and two instances in which inclusions were found in epithelial-lined spaces of the liver, lungs, kidneys, pancreas and thyroid are reported, making a total of twenty-six new cases to be added to the twenty-five already in the literature. All the patients in this series were less than 17 months of age, the majority being under 1 year. These inclusions are apparently identical with those found in the submaxillary glands of guinea pigs, and are generally similar to inclusions which are found in diseases due to filtrable viruses. Clinical and pathological studies of the series reported reveal no association with any distinctive feature or group of symptoms or disease changes. The frequency of the inclusions in our postmortem series suggests geographical factors affecting this occurrence and leads naturally to the suspicion of the existence of a disease in infants of filtrable virus etiology. However, if that be true, there are no distinctive clinical or pathological features which would permit its recognition on the wards or in the pathology laboratory. The clinical and pathological findings in the "positive" instances resemble, in general, the findings in the entire group studied.

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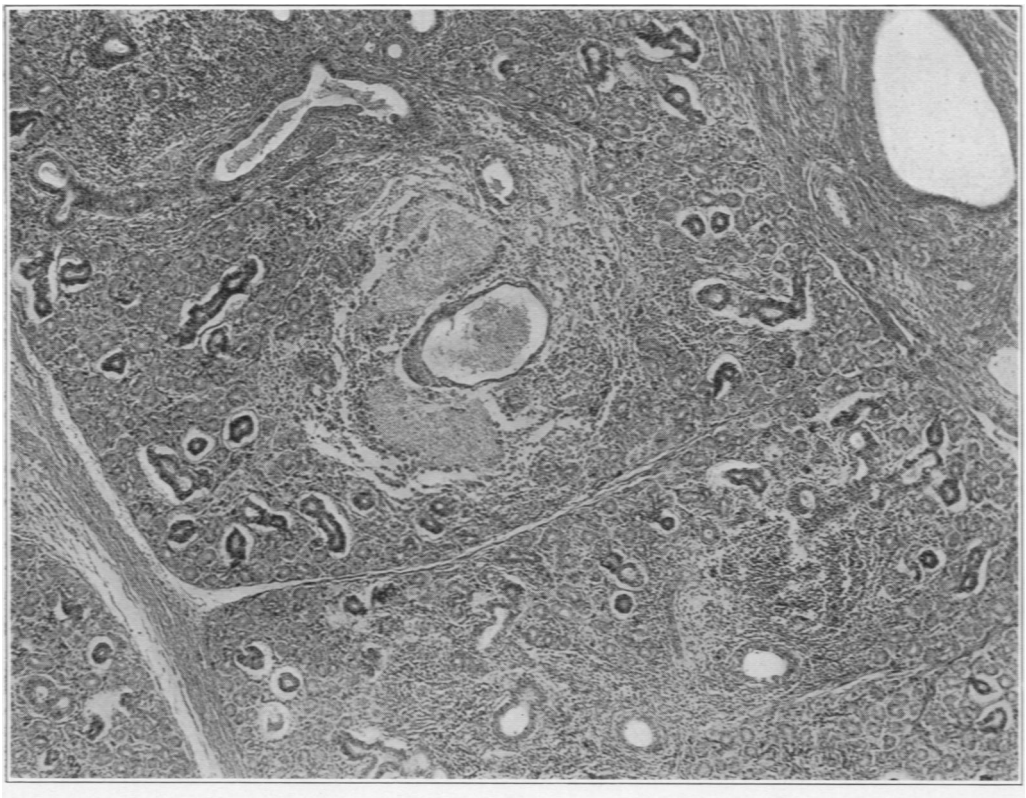
## DESCRIPTION OF PLATES

### PLATE 22

FIG. 1. Photomicrograph of submaxillary gland. Note areas of lymphoid infiltration. Hematoxylin and eosin. Low power.

FIG. 2. Photomicrograph of submaxillary gland showing large cells with inclusions lining the duct. Hematoxylin and eosin. × 550.



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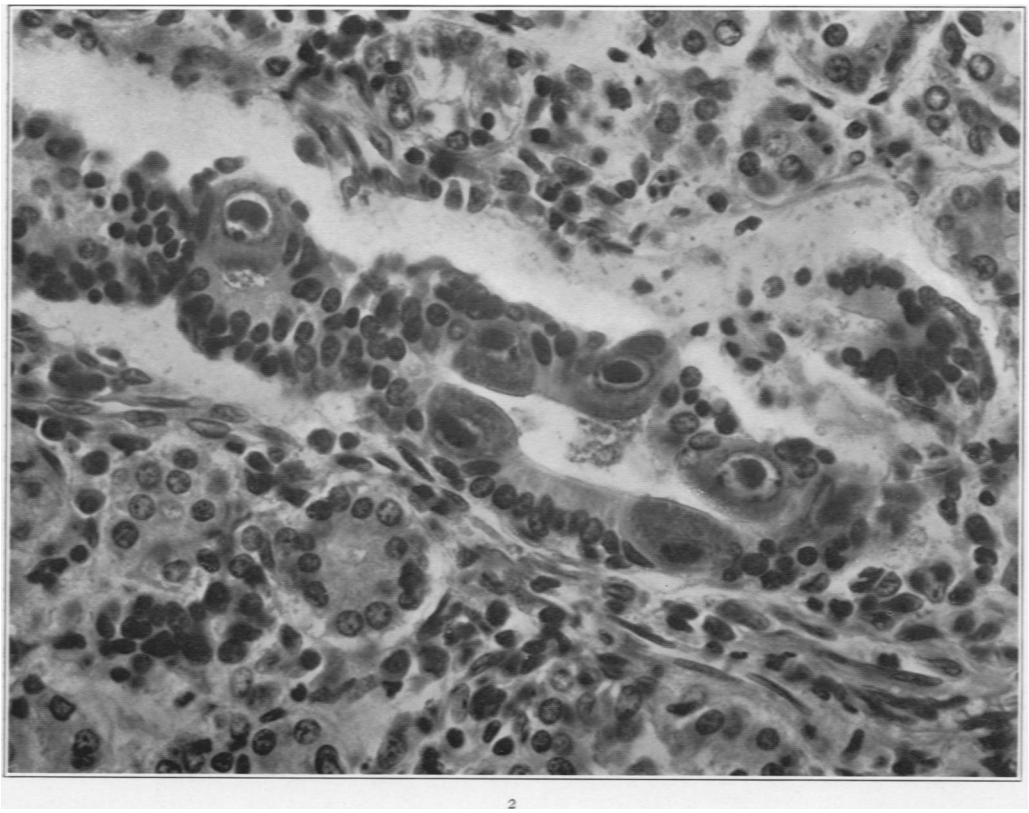


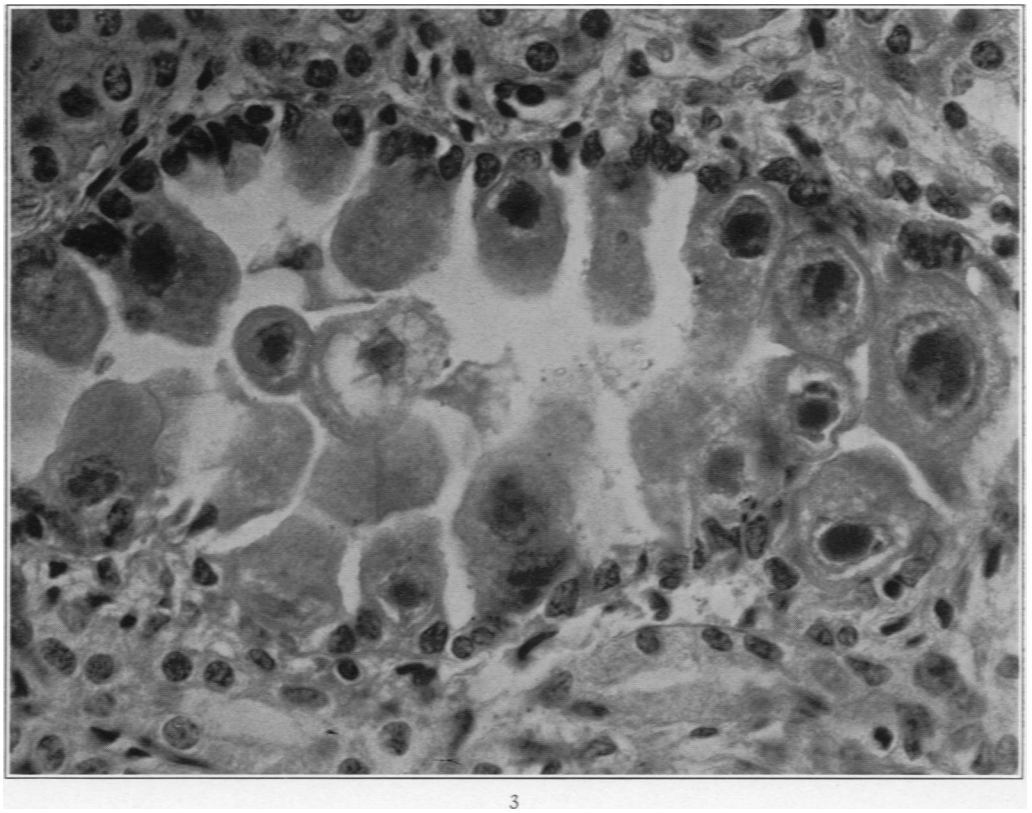
2

Farber and Wolbach Intranuclear and Cytoplasmic Inclusions

## PLATE 23

FIG. 3. Photomicrograph of kidney showing large inclusion-laden cells lining the kidney tubule. Note the swollen cytoplasm and vacuolated appearance of some of the cells. Hematoxylin and eosin. × 750.

FIG. 4. Photomicrograph of submaxillary gland showing a large cell in the duct lining. Note intranuclear inclusion, pale area at periphery, clear zone, small masses in clear zone, nuclear membrane and large inclusion bodies in cytoplasm. Hematoxylin and eosin. × 2300.



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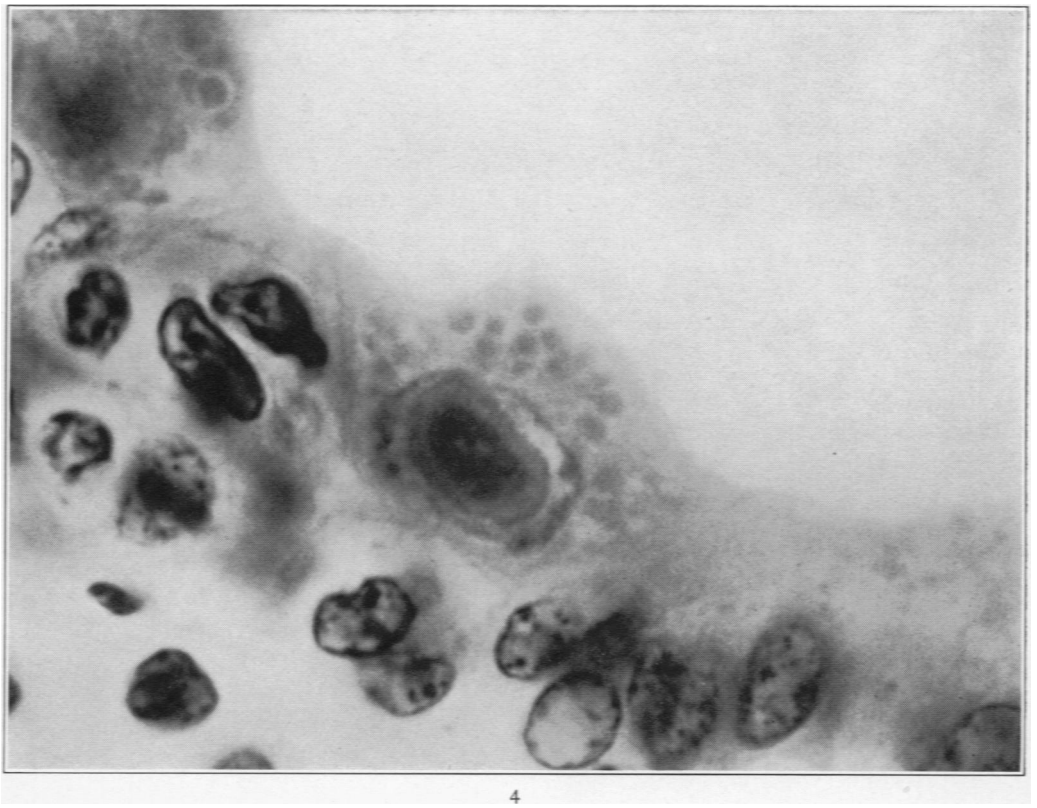

4

Farber and Wolbach Intranuclear and Cytoplasmic Inclusions