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## SOME GENERAL ASPECTS OF PATHOLOGICAL CONDITIONS CAUSED BY FILTERABLE VIRUSES *

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In a previous paper an attempt was made to summarize and to correlate in a general way knowledge concerning filterable viruses. At that time, facts and hypotheses regarding the nature and characteristics of the agents themselves were primarily considered. During the discussion, however, it was shown that in the majority of virus diseases a close relationship exists between the etiological agent and cells of the host. In view of this intimate type of parasitism, it seems desirable at the present time to examine carefully and, if possible, to correlate information regarding the reaction of host cells to viruses. Moreover, a knowledge of the pathological conditions produced by viruses is essential to the study of this group of etiological agents, because their existence cannot be determined, nor can their identification be established in any manner other than by the evidences of their activity exhibited in some host.

In spite of the fact that many viruses appear incapable of multiplying in the absence of suitable living host cells, it is not definitely known whether their reproduction occurs intra- or extracellularly. Nevertheless, these agents have a profound influence upon cells and produce within them remarkable changes. This influence most likely accounts for the fact that in lesions produced by many viruses the intracellular changes are sufficiently characteristic to be spoken of as inclusion bodies. In this respect a number of virus diseases differ from those caused by ordinary bacteria.

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The inclusions have attracted the attention of many workers whose ideas concerning their nature have led to numerous discussions. It is undoubtedly true that these bodies are interesting and play an important rôle in experimental and diagnostic work, yet there are other pathological phenomena that are just as interesting as, and perhaps more important than the inclusions themselves, inasmuch as a better knowledge of them may lead to a clearer understanding of the nature of the action of viruses on cells and consequently to an explanation of why certain diseases exhibit significant inclusions while others do not. In view of the fact, however, that inclusion bodies are thought of immediately when one mentions the pathology of virus diseases, a summary of the knowledge concerning these structures will be given first and then some of the other interesting features of the pathological conditions induced by viruses will be discussed.

## Inclusion Bodies

Inclusion bodies have been seen in cells of plants, insects, fish, birds, and mammals affected by virus diseases. In some of the diseases the bodies are intranuclear, *e. g.*, in varicella and in polyhedral diseases of caterpillars; in others they are found in the cytoplasm, *e. g.*, in vaccinia and in mosaic diseases of some plants; in still others they occur both in the nucleus and in the cytoplasm, *e. g.*, in smallpox and in paravaccinia. Many of the inclusions described, however, cannot be accepted as specific or characteristic and it is these that detract from the significance of the ones well established and accepted by numerous critical observers. In Table I are listed the majority of diseases in which inclusions of one kind or another have been described. The diseases are grouped according to the location of the inclusions in affected cells.

In spite of the chaos suggested by Table I, no worker familiar with the microscopic pathology of virus diseases doubts the importance and significance of Guarnieri bodies in vaccinia, Negri bodies in rabies, Bollinger bodies in fowl-pox, polyhedral bodies in certain diseases of insects, and the nuclear inclusions seen in varicella, herpes, and several other virus diseases. Since some of the diseases in the table exhibit inclusions of significance while others do not, I have made a selection of the pathological conditions in which the inclusions appear sufficiently characteristic to be of importance. The

TABLE I

*A List of the Majority of Diseases in which Intracellular Inclusions have been Described. The Diseases are Grouped According to the Location of the Described Inclusions within Affected Cells.*

| | |
|---|---|
| A. CYTOPLASM | Mosaic disease of certain plants |
| | Sheep-pox |
| | Contagious epithelioma (fowl-pox) |
| | Molluscum contagiosum |
| | Lymphocystic disease of fish |
| | Rabies |
| | Distemper of dogs |
| | Fowl plague |
| | Lethargic encephalitis |
| | Trachoma and inclusion blenorrhea |
| | Hog cholera |
| | South African horse sickness |
| | Rickettsia diseases |
| | Measles |
| | Scarlet fever |
| | Cancer (malignant growths) |
| | Kurloff bodies (guinea pigs) |
| | Todd bodies (frogs) |
| | Grahamella (moles) |
| | Bartonella bacilliformis (verruga peruviana and Oroya fever) |
| | Bartonella muris (splenectomized rats) |
| | Protozoan-like bodies in white blood cells of fowls in Palestine and Nigeria |
| B. NUCLEUS | Polyhedral disease of certain caterpillars |
| | Foot-and-mouth disease |
| | Vesicular stomatitis |
| | Borna disease |
| | Virus III infection of rabbits |
| | Herpes zoster |
| | Salivary gland disease of guinea pigs |
| | Epithelioma of fish |
| | Carp-pox |
| | Warts of *Discoglossus pictus* (frog) |
| | Warts |
| | Condyloma acuminatum |
| | Psoriasis |
| | Protozoan-like bodies observed in human visceral lesions of unknown etiology |
| C. CYTOPLASM AND NUCLEUS | Smallpox (and alastrim) |
| | Cow-pox (vaccinia) |
| | Paravaccinia |
| | Chicken-pox |
| | Infectious myxomatosis of rabbits |
| | Symptomatic herpes |

selected diseases have been placed in Table II and grouped according to the location of the significant inclusions within affected cells. It is not unlikely that other diseases will be added to the table, and that some now included may in the future be omitted. In Plates 22 and 23 the significant inclusions of the diseases listed in Table II are graphically portrayed.

## Nature of Inclusions

Various ideas are held concerning the origin and nature of inclusion bodies, and, in a general way, they may be divided into three groups. By some investigators they are considered merely as products of degeneration, but by others they are believed to be the virus itself, while by yet others they are thought of as virus surrounded by a mantle of altered cellular material.

*Inclusions as Virus Itself:* The idea that inclusions represent the virus itself is not absolutely irrational, inasmuch as bacteria and protozoa are frequently found within cells. Moreover, some protozoa are obligate parasites and multiply only in the cytoplasm or only in the nucleus of suitable host cells, while others reproduce both in the cytoplasm and in the nucleus of such cells. In fact, observations concerning coccidia, malarial parasites, and the more recently described organism of Wright and Craighead have in the main been responsible for the idea that inclusions are parasites.

*Inclusions as Virus Surrounded by Altered Cellular Material:* Upon the discovery that the etiological agents of the diseases under discussion pass through earthenware filters, a group of workers immediately realized that inclusion bodies probably do not represent virus alone, inasmuch as many inclusions (2–15 microns in diameter) are sufficiently large to render such a possibility unlikely. To adapt theories to facts, von Prowazek then described his hypothesis concerning the nature and development of viruses and their relation to inclusions. According to this worker, extracellular forms of a virus, "elementary bodies," are from 0.25 to 1.0 micron in diameter and are able to pass through filters. Upon entering a cell the "elementary bodies" become "initial bodies" which immediately begin to reproduce by division, thus forming a colony of parasites within its host. The cell then reacts to the presence of these minute organisms around which a mantle of altered cellular material is thrown. In this manner von Prowazek's *Chlamydozoa*, mantled

TABLE II

*A List of the Filterable Virus Diseases in which Intracellular Changes are Sufficiently Characteristic to be of Significance. The Diseases are Grouped According to the Location of the Significant Changes within the Cells.*

| | | |
|---|---|---|
| A. CYTOPLASM | Mosaic disease of certain plants | |
| | Sheep-pox | |
| | Cow-pox (vaccinia) | |
| | Contagious epithelioma (fowl-pox) | |
| | Molluscum contagiosum | |
| | Rabies | |
| | Lymphocystic disease of fish (no reports on filtration) | |
| | Infectious myxomatosis of rabbits | |
| B. NUCLEUS | Polyhedral disease of certain caterpillars | Inclusions are acidophilic |
| | Symptomatic herpes | Inclusions are acidophilic |
| | Herpes zoster (No reports on filtration.) | Inclusions are acidophilic |
| | Chicken-pox (No reports on filtration.) | Inclusions are acidophilic |
| | Virus III infection of rabbits | Inclusions are acidophilic |
| | Salivary gland disease of guinea pigs | Inclusions are acidophilic |
| | Borna disease | Inclusions are acidophilic |
| C. CYTOPLASM AND NUCLEUS | Smallpox (and alastrim) | |
| | Paravaccinia (no reports on filtration) | |

Rickettsia diseases are not included in the table because the evidence is in favor of the idea that there is a distinct difference between rickettsiae and the inclusions discussed in this paper.

After further study, carp-pox, epithelioma of fish, and warts of *Discoglossus pictus* (frog) may be placed in Group B in view of the inclusions (probably acidophilic) described in nuclei of affected cells.

Evidence is increasing in favor of the idea that the nuclei of cells affected by warts and condyloma acuminatum show certain characteristic changes — basophilic masses or "chromophane" masses of Lipschütz.

Trachoma and inclusion blenorrhea are omitted from the table awaiting further observations concerning the nature and significance of the cytoplasmic inclusions observed in affected cells.

After further study some of the diseases in the table may be removed or new ones may be added.

animals or inclusion bodies, are formed. The host cell finally ruptures freeing the parasites which again become "elementary bodies." In general, von Prowazek's ideas are in accord with those of Lipschütz, who suggests for the small bodies without mantles the name *Strongyloplasmen*, rounded bits of protoplasm. The ideas of these men are plausible enough, yet in most instances it is difficult either to prove or to disprove conclusively whether they correctly portray the actual facts concerning viruses.

*Inclusions as Products of Cellular Degeneration:* At present, numerous investigators believe that inclusions do not consist of virus and that at least a major portion of the bodies comprises products of cellular degeneration. These workers frankly admit, however, that in most cases, it is very difficult to establish the fact that the virus is not enveloped by the products of cellular reaction. In one instance only has it been possible to show that active virus is not structurally related to the inclusions characteristic of the disease in which they occur. This was accomplished by Glaser, who found that polyhedral bodies observed in virus diseases of caterpillars can be separated from active incitant and when freed from it are incapable of producing disease in normal larvae.

Although many workers consider inclusions as products of cellular degeneration, there is no unanimity of opinion regarding the manner in which they arise and the cellular constituents they comprise. The nuclear inclusions seen in several diseases, *e. g.*, varicella, herpes, and Virus III infection of rabbits, resemble each other so closely that a differentiation of the diseases one from another by means of the appearance of the inclusions alone is impossible. More specificity, however, is observed concerning cytoplasmic inclusions, inasmuch as no two virus diseases exhibit absolutely identical changes in the cytoplasm of affected cells. The marked degree of specificity displayed by these inclusions is believed by Cowdry and others to be due to the fact that the cytoplasm, by virtue of its composition and position in the cell, may respond more readily and more characteristically to different kinds of stimuli arising either intra- or extracellularly. In spite of the tremendous variations exhibited by inclusions of different diseases, the constancy of their size, form, staining reactions, location in cells, and components such as proteins, fats, and lipoids, in any one disease under similar conditions is very striking. This constancy, however, is by no means dependent upon a

homogeneity of the inclusions, for the majority of them comprise several kinds of constituents. A complete review of the ideas concerning the origin and structure of characteristic inclusions is not possible at the present time. Nevertheless, a few opinions will be cited for the purpose of emphasizing the radical manner in which views of competent workers differ.

*Vaccine Bodies:** Guarnieri (1892) believed vaccine bodies to be protozoa, and, since he thought of them as possessing a peculiar power of devouring the cytoplasm of cells, thus creating a hole within which they lie, gave them the name *Cytoryctes vacciniae.* Although Hückel (1898) considered Guarnieri bodies specific for vaccinia, he believed that they are not the virus itself, but arise entirely within the cytoplasm of affected cells. According to him, under the stimulus of the virus, a portion of the cytoplasm undergoing colloid degeneration near the nucleus becomes cyanophilic (blue-staining). Later the erythrophilic (red-staining) cytoplasm in the immediate neighborhood of the blue mass undergoes hyaline degeneration and separates from the rest of the cell. The two masses, the blue in the center surrounded by the red, are situated within a "hole" in the cytoplasm and constitute a vaccine body. Ewing (1904–05) believes that Guarnieri bodies are altered portions of the cytoreticulum into which nuclear material has diffused. According to Cowdry (1922) these bodies are the result of a stimulation of cells by vaccine virus leading to an increase of a substance present in small amounts in normal cells.

*Molluscum Bodies:* Molluscum corpuscles were first described in 1841 by Paterson, who thought of them as parasites. In 1892, Macallum (Plate 24, Fig. 5) stated that molluscum bodies are merely migrated plasmosomes or modified chromatin arising as a result of hyperplasia and hyperchromatosis. According to him, one might classify the disease as a neoplasm. Lipschütz (1911) believes that three abnormal substances are found in the cytoplasm of cells affected by molluscum virus; migrated nuclear substance, products of a keratin-like degeneration, and a mass of virus, elementary bodies or *Strongyloplasma hominis* (Plate 22, Fig. 24). In 1918, Sanfelice, using Mann's stain in the study of molluscum bodies, described the following steps in their formation. Normal cells swell. Nucleoli re-

* Weigert, 1874, first described and portrayed inclusions in cells affected by smallpox virus. (Plate 23, Fig. 8.)

tain the red instead of the blue stain and migrate into the cytoplasm where they again stain blue. In the cytoplasm the nucleoli become vacuolated and granular, and, as they enlarge, assume the appearance of typical molluscum bodies filled with fine red-staining granules. More recently, 1927, Goodpasture expressed his ideas concerning molluscum bodies in the following manner: "The bodies are not derived from extruded nucleoli, nor from any formed cytoplasmic constituent. . . . The minute bodies develop about, and later within, cytoplasmic vacuoles which may be regarded as the cellular response to the presence of a living foreign body . . . elementary bodies of Lipschütz. . . ."

*Bollinger Bodies.** Bollinger, in 1873, described in tissues affected by fowl-pox or epithelioma contagiosum a hyperplastic condition of epithelial cells, many of which were greatly swollen, 25 microns in diameter, and contained near their nuclei large bodies with fat-like appearances. These bodies were considered by Bollinger to be parasites. Michaelis (1904) also found evidences of proliferation and swelling of cells in this disease. The inclusions, according to him, are made up of albuminous and fatty substances. Although he was unable to determine whether the disease is parasitic or not, he was, nevertheless, of the opinion that the inclusions themselves do not represent parasites. Borrel (1904), using Loeffler's flagella stain in the study of material from the lesions of fowl-pox, found myriads of minute coccoid bodies about each of which appeared some kind of capsule. Burnet (1906) thought that the small bodies described by Borrel represent the incitant of the disease and are closely associated with the specific inclusions. Ludford and Findlay (1926) state that the inclusions of fowl-pox appear only in epidermal cells, an occurrence which is probably related to the process of keratinization. They state further (1) that the earliest indication of the activity of the virus on cells is the formation in their cytoplasm of small vacuoles, to the periphery of which minute granules adhere, (2) that mitosis† is usually seen in cells containing such vacuoles, (3) that

* Rivolta, 1869, was probably the first investigator to describe inclusions in fowl-pox.

† In Fig. 7, Plate 24, mitosis is taking place, and, although Ludford and Findlay say nothing regarding the matter, one gets the impression from the picture that the virus body has divided also and that a daughter body will go with each daughter cell. This phenomenon has attracted practically no attention in virus diseases of animals, yet it is a well-known fact (Kunkel and others) that inclusions in mosaic diseases of

the vacuoles increase in size, and coincidentally with the enlargement become enclosed by a lipoidal lining and exhibit a granular appearance internally, (4) that many cells become hypertrophied and at an early stage in the disease show a complete reversal of the Golgi apparatus, and finally (5) that the inclusions are not the virus itself. (See Plate 24, Figs. 6–9.)

*Negri Bodies:* In nerve cells injured by the virus of rabies Negri (1903) discovered certain inclusions which he regarded as protozoa. Levaditi and his coworkers (1926) still believe in the parasitic nature of Negri bodies and propose that they be named *Glugea lyssae.* According to Acton and Harvey, however, these structures are not parasitic, but arise as a result of an interaction between the cytoplasm of cells and particles of nuclear matter which have been extruded through catabolic changes induced by the action of the virus. In Goodpasture's opinion (1925), Negri bodies represent the results of a slow necrobiosis of nerve cells and originate in a degenerative change in mitochondria producing vacuoles with small bodies within them, "about which through a partial disintegration of neurofibrillar material a capsule is formed."

*Nuclear Inclusions:* Ideas of the nature and origin of acidophilic nuclear inclusions have also led to numerous discussions. Loewenthal believes that they are parasites. Lipschütz, Goodpasture, and others are of the opinion that the bodies, although not necessarily consisting entirely of virus, are in some manner intimately associated with it. Luger and Lauda, however, contend that these nuclear changes are due to oxychromatic degeneration (Plate 22, Figs. 8–15) and have no genetic affinity with the virus.

Sufficient examples have been cited to show that able investigators frequently disagree radically in their views concerning the inclusions of each virus disease. Furthermore, from what has been said it is obvious that the intracellular structures described in various morbid conditions may not be of a similar character. Therefore, in discussing intracellular pathology, one should be careful not to make general statements based on observations limited to one virus

certain plants frequently divide when the host cells do and that a daughter inclusion body goes with each daughter cell. This phenomenon is interesting, but it does not necessarily imply that the inclusion is an autonomous parasite, inasmuch as the Golgi apparatus and at times mitochondria (Cowdry) divide during cell division, and a portion of each structure goes with each daughter cell.

TABLE III

*A List Indicating Hypotheses Concerning the Nature and Origin of Inclusions Observed in Cells Affected by Viruses*

A. CYTOPLASMIC INCLUSIONS

1. Bacteria.
2. Fungi.
3. Protozoa.
4. Products of cellular degeneration or cellular reaction to the viruses. According to Lipschütz and others, the etiological agents are visible; they are called strongyloplasms, initial bodies, or elementary bodies. According to Prowazek and others, inclusion bodies consist of viruses surrounded by products of cellular reaction; they are called chlamydozoa (mantled animals).
5. Products of cellular degeneration; agent unseen or not identified; no proof of genetic relation between inclusion and virus.
   (*a*) Engulfed or phagocyted cells undergoing degeneration.
   (*b*) Nucleoli or necrotic nuclear derivatives extruded into the cytoplasm.
   (*c*) Extruded nuclear material mixed with cytoplasmic elements.
   (*d*) Central body or archoplasmic structures undergoing degeneration.
   (*e*) Degeneration of cytoplasm and cytoplasmic structures.
   (*f*) Degeneration of daughter nuclei in cells in which amitotic division of the nuclei occurs.
   (*g*) Results of secretory activity of affected cells.
   (*h*) Inclusions consist of substances normally present in small amounts in the cytoplasm. Under the influence of viruses, however, these substances are greatly increased.

B. NUCLEAR INCLUSIONS

1. Protozoa.
2. Similar to No. 4 under Cytoplasmic Inclusions.
3. Nucleoli undergoing degeneration.
4. Results of nuclear degeneration (oxychromatic degeneration). Inclusions are not genetically related to the viruses.
5. Similar to (*h*) under No. 5 (Cytoplasmic Inclusions) except that the changes occur in the nucleus instead of in the cytoplasm.

disease. For convenience, a summary of the ideas regarding the mode of origin and the nature of inclusions is given in Table III.

## CHANGES PRODUCED IN INCLUSIONS BY EXPERIMENTAL PROCEDURES

The relation of smallpox to vaccinia furnishes an interesting topic for discussion. In most respects these diseases behave differently: one is highly contagious, the other is spread only by direct inoculation; in one, generalized lesions regularly occur, in the other, this

happens only rarely; in cells affected by smallpox, inclusions are seen in the nucleus as well as in the cytoplasm, in cells injured by vaccinia, significant inclusions are found only in the cytoplasm. Smallpox virus, however, passed through several calves, becomes vaccine virus. Furthermore, it remains vaccine virus, even though it be returned to human beings. Thus, smallpox virus passed from man to lower animals, excepting monkeys, is so altered that apparently a different disease is caused by its action. Not only is the character of the disease altered but the intracellular pathology is also changed. Observations of a similar nature have been made in regard to rabies. When "street virus" is passed through a large number of rabbits a "fixed virus" is obtained which no longer produces typical inclusions but causes atypical Negri, lyssa, or passage bodies. These facts are extremely interesting, and certainly, so far as smallpox and vaccinia are concerned, no one has been able to determine just what occurs when smallpox virus becomes vaccine virus. Nor is it known why the intracellular pathology under these conditions is also altered.

## Inclusions in Malignant Growths

Paterson saw molluscum bodies in 1841, Bollinger described inclusions in contagious epithelioma in 1873, and Guarnieri observed vaccine bodies in 1892. In spite of these facts, the chief interest in inclusion bodies during the latter part of the nineteenth and the first part of the twentieth centuries centered around peculiar intracellular structures observed in cells of neoplasms. Some of this interest may have been due to the fact that many workers considered molluscum contagiosum and epithelioma contagiosum as tumors. Aside from that, however, great interest was evidenced regarding the so-called cancer inclusions described by Plimmer, Feinberg, von Leyden, Russell, Schüller, Thoma, Darier, and others.

Practically all inclusions described in tumor cells have been situated in the cytoplasm. Many of them have been portrayed as having definite and characteristic structures, *e. g.*, Plimmer bodies. Hypotheses regarding the nature of cancer inclusions are numerous, and strange to say, with a few exceptions, are similar to the theories in Table III concerning cytoplasmic inclusions in virus diseases. Interest in these structures in cancer resulted in little or no progress in the recognition of the cause of newgrowths. Furthermore, the

irregularity of their occurrence, and the difficulty encountered in finding them, rendered these bodies of little value as a diagnostic aid. Consequently, cancer inclusions are rarely mentioned at the present time.

Concurrently with a decreasing interest in cancer bodies and a better understanding of the nature of such diseases as contagious epithelioma and molluscum contagiosum the inclusions in virus diseases received an increasing amount of attention. The regularity with which characteristic structures are found in cells affected by certain morbid conditions render them of value in experimental and diagnostic work, *e. g.*, in rabies and in smallpox. Jackson and Goodpasture's descriptions of nuclear changes observed in duct cells of guinea pigs' salivary glands induced Cole and Kuttner to search for a virus. Their investigations resulted in the discovery of a new filterable virus which injected into susceptible pigs produces nuclear changes identical with those described by Jackson and Goodpasture. Moreover, all work with polyhedral diseases of caterpillars is controlled by the presence or the absence in blood cells of characteristic nuclear changes. Consequently, it is unlikely that the inclusions in virus diseases will cease to be of interest as quickly as did those of tumors. It is true that the nature of the intracellular bodies has not been definitely determined. Nevertheless, in spite of the ignorance concerning their nature, inclusions have held and will continue to hold an important position in the study of this group of diseases.

Many attempts to produce significant inclusions by artificial means have been unsuccessful. It is interesting, however, to note that, when intracellular changes resembling inclusions of virus diseases have been experimentally induced, they have followed the use of such agents as arsenic, tetanus toxin, and diphtheria toxin. Some of the experimentally induced changes closely resemble those seen in virus diseases, yet they are not identical. Therefore, under properly controlled conditions, the presence of inclusions, accepted as significant, will undoubtedly in the majority of instances be indicative of the presence of a virus in the immediate vicinity.

## Pathological Changes Other than Inclusion Bodies

In the foregoing section of the paper, facts and conjectures regarding inclusion bodies have been discussed. While these intracellular structures play an important rôle in the study of virus diseases, they, nevertheless, constitute a minor part of the reaction in the host to the infectious agents. Furthermore, if no inclusions are found in cells affected by certain disease processes, or if the intracellular changes described have not been generally accepted as significant, one is not warranted in concluding that the morbid conditions are not caused by viruses. This statement is emphasized by the fact that significant inclusions have not been described in measles, poliomyelitis, and fowl plague, diseases generally believed to be caused by filterable viruses. Therefore, one is justified in raising the question as to whether inclusions constitute the only characteristic response of cells to viruses. Moreover, one would like to know whether, in addition to specific or characteristic responses, there are also reactions similar to those induced by substances of bacterial or other origin.

### Inflammation

Although the majority of pathologists interested in virus diseases have devoted most of their energy to the study of inclusions, there is a group of workers who either ignore the existence of such structures or believe that they are of no significance, and contend that the pathology of certain virus diseases is not essentially different from that observed in inflammatory processes produced by ordinary bacteria. Furthermore, as one reads the reports of work recorded in the literature, one is impressed by the fact that many investigators assume that inflammation caused by bacteria is thoroughly understood. Of course, such is not the case, inasmuch as it is not known whether certain responses of the host are due to the direct action of bacteria and their products, whether they are dependent upon the presence of substances derived from host cells that have been injured or killed by bacterial activity, or whether they are caused by the action of an injurious agent formed or liberated when infectious organisms (antigen) unite with their specific antibody.

The fact that inflammation occurs in many virus diseases cannot be denied, and, despite the acute nature of some of the diseases, if

secondary infections do not intervene, the inflammatory process is usually characterized by an infiltration of mononuclear cells. The question whether the inflammation is a primary or secondary phenomenon, however, has in certain instances led to lengthy discussions. Weigert (1874) looked upon the primary changes caused by the virus of smallpox as non-inflammatory and considered them to be necrobiotic or diphtheroid in nature. According to him, when the primary degenerative changes in the epidermis have reached a certain stage in their development, the inflammatory reaction appears as a secondary phenomenon and consists of exudation of fluid into the area of degenerated cells, of proliferation of epidermal cells with giant-cell formation around the necrotic tissue, and of infiltration of various kinds of leucocytes. Auspitz, Unna, Renaut, Ledingham, and others have regarded the variolous changes in the skin from the beginning as merely the expression of an acute inflammatory process. Furthermore, Unna and Ledingham have raised the question whether the virus of smallpox must necessarily cause necrosis of epidermal cells and whether the necrobiosis frequently observed is only accidental or secondary to an inflammatory reaction which begins in the corium. According to this view, the degenerative changes in epidermal cells and the formation of pocks result from pressure caused by the accumulation of exudate just beneath the epidermis.

In a number of diseases, particularly those involving the skin, it is difficult to determine precisely the location and the character of the primary injury or to follow accurately the development of a lesion. This difficulty is experienced because of the complex nature of the skin and the rapidity with which the lesions of such diseases as measles, smallpox, and varicella develop. If the inciting agent is borne into the skin by the blood, it is highly probable that the initial injury is in or around small blood vessels just beneath the epidermis, provided the cells in these tissues are susceptible to the virus.

So far as the discussion in the present paper is concerned, it is not so important to determine the point of the primary lesion caused by the virus as it is to ascertain the nature of the injury. Frequently conditions are unfavorable for such investigations. In some diseases, however, and under certain conditions in others, information concerning this question may be obtained. For instance, in variolous or vaccinal lesions of a rabbit's cornea definite and characteristic

changes are observed in the epithelial cells before any evidence of inflammation in the form of cellular or other exudate is seen. The lesions of molluscum contagiosum occur within the epidermis, and according to Benda,* Unna,* and Goodpasture (1927) little or no inflammatory reaction is observed in the corium. Furthermore, if inflammation occurs accidentally through secondary infection or as the result of treatment, the lesions heal promptly (Henderson, 1841). Goodpasture (1925) working under experimental conditions, found that the first evidences of injury caused by rabic virus are observed "within ganglion cells, not in the surrounding tissue," and that "these cells may undergo complete necrosis without cellular or other exudate about them." He also found that Negri bodies frequently "occur in great numbers within the ganglion cells entirely in the absence of evidences of inflammation in the form of cellular or other exudation." Finally, the pathological picture presented by mosaic disease in plants is one of necrosis and hyperplasia, and that observed in bacteriophagy is unlike the morbid processes usually associated with inflammatory diseases.

## Degeneration and Proliferation

If inflammation, as it appears to be, is a secondary phenomenon in many virus diseases, what, then, are the primary changes produced in cells by these active agents? In all probability, they are either degenerative or proliferative in character. In fact, both types of changes are usually seen, and it is difficult at times to determine definitely whether degeneration precedes proliferation or whether they occur in the reverse order.

In certain diseases, particularly the ones producing vesicles in the skin, the degenerative changes have attracted most attention and the majority of workers consider that they precede evidences of proliferation. Opinions as to the type of degeneration, however, are numerous and many names have been used in its description, *e. g.*, coagulation necrosis, reticulating colliquation, and diphtheroid, fibrinoid, colloid, hyaline, parenchymatous, ballooning, or reticulating degeneration. Be that as it may, the type of degeneration in certain virus diseases is somewhat different from that ordinarily observed, inasmuch as the "reticulum" in the vesicles is formed by the

* Cited by White and Robey.

remains of swollen degenerated cells that have lost their nuclei and from which the major portion of the cytoplasm has disappeared (Plate 26, Figs. 1–8).

To investigate the relation of degeneration to proliferation in tissues infected with vaccine virus or smallpox virus, one should observe the phenomena as they occur in the cornea of rabbits. Within a short time after the cornea is inoculated, 3 to 6 hours, changes are seen in the immediate vicinity of the point infected; the epithelial cells are larger and stain less intensely than usual, mitotic figures and amitotic giant cells begin to appear. Within 6 to 24 hours, vaccine bodies are frequently found in affected cells. Small, yet macroscopic nodules are observed on the surface of the cornea 24 to 48 hours after inoculation. Examination of these nodules reveals, in addition to a hypertrophy of individual cells, a definite increase in the number of cells as compared with the findings in control areas. At this time, 48 hours after inoculation, evidences of degeneration and inflammation appear. Guarnieri, in 1892, von Wasielewski, in 1901, and Paul, in 1916, graphically recorded many of the changes just described (Plate 25, Figs. 1–4). Moreover, von Wasielewski stated that the first influence of vaccine virus is to produce increased nutrition and enlargement of cells. Therefore, as far as vaccinal and variolous infections in cornea of rabbits are concerned, one seems justified in concluding that the pathological changes occur in the following order: (1) stimulation and proliferation, (2) degeneration, (3) inflammation.

At this point it is interesting to note that in sheep-pox, a disease similar to vaccinia or cow-pox, Bosc and others have described remarkable proliferative changes in the skin, lungs, and other organs of the body. The proliferation in the lungs (Plate 25, Fig. 5) is evidenced by minute translucent nodules, "sheep-pox adenomas," which represent alveoli completely filled with peculiar, pale-staining cells with vesicular nuclei. Bosc believed the cytoplasmic inclusions (Plate 22, Fig. 22) observed in sheep-pox to be parasites, and, in view of the fact that hypertrophy and hyperplasia of cells are quite evident in infected tissues, he proposed for the inciting organism the name *bryocyte*, an agent causing cells to proliferate.

Mosaic disease in certain plants, frequently spoken of in Germany as "Pockenkrankheit," resembles in many respects the vesicular eruptions observed in animals. This similarity is particularly notice-

able when fruits are attacked (Plate 27, Figs. 1–8). The pathological picture presented by mosaic is said to be characterized by necrosis and hyperplasia occurring in the order mentioned. In view of the fact, however, that mosaic inclusion bodies are found in living cells, some of which are undergoing division, and in the light of what is known concerning other virus diseases, it is possible that further studies concerning the relation of necrosis to hyperplasia in mosaic conditions may reveal some interesting facts.

In molluscum contagiosum the pathological changes in the epidermal cells are evidenced by hypertrophy and hyperplasia (Macallum) which are followed by degenerative activities (Plate 24, Fig. 5). Somewhat the same course of events is observed in warts and condyloma acuminatum. Contagious epithelioma of fowls, or fowlpox, is a disease with two names, each of which suggests a pathological process different from that indicated by the other. At one time this morbid condition was believed to be neoplastic in nature, but at present the tendency is to consider it closely allied to other pock diseases. In spite of the presence of warty growths that characterize the disease, one should remember that a destruction of tissue with vesicle formation also occurs (Plate 26, Fig. 8).

In lesions of infectious myxomatosis of rabbits first described by Sanarelli, the subepidermal tumor-like masses have attracted most attention. Interesting changes, however, have been observed also in the epidermis where a marked swelling and then a complete dissolution of the cells take place. In this disease it appears that proliferative phenomena predominate in the corium and subcutaneous tissues to such an extent that tumor-like masses are formed, while in the epidermis retrograde changes with vesicle formation prevail (Plate 26, Figs. 1–3).

The virus of vesicular stomatitis injected in the pads of guinea pigs causes rapid destruction of epithelial cells, and within 18 to 24 hours after inoculation, vesicles are already well developed. While at this time many swollen cells are still present in the lesions, mitotic figures, amitotic giant cells, and other evidences of proliferation are either absent or present in small numbers (Plate 26, Fig. 7). I have not had the opportunity of examining lesions earlier than 18 hours after inoculation, consequently I do not know whether an appreciable amount of proliferation precedes so rapid a destruction of cells as that observed in this disease. In the light of what is now known con-

cerning the bacteriophage, it is conceivable, however, that such a proliferation may occur.

The lysis* of bacteria by bacteriophage, as the name applied to the phenomenon suggests, has been considered the most important feature of the action of this agent on microörganisms. D'Herelle, Hadley, and others, however, have spoken of an initial stimulation of bacteria as evidenced by an increase in rate of their multiplication. It has also been observed repeatedly that the size of individual cells increases considerably under the influence of phage. The constancy or the importance of this swelling as a factor in the disappearance of bacteria has not been generally accepted. Moreover, it has been suggested that swollen bacteria are very resistant to dissolution and disappear, if at all, very slowly.

The extent of swelling of individual bacteria, the relative proportion of swollen cells, as well as the actual relation between the swelling and the lysis, are difficult to establish by the usual methods of observation. Consequently, Dr. Bronfenbrenner, with the assistance of Mr. Rosenberger, investigated the matter cinematographically. The following is a brief description of their findings: After a short period of lag, bacilli under the influence of phage began to multiply at a rate noticeably exceeding that of normal organisms photographed under similar conditions. Many cells failed to complete their division and filaments having a length of from 10 to 20 times that of normal bacteria were frequently observed. By the end of the first hour of growth, occasional cells had already begun to swell, and by the end of the third hour the majority of bacteria in the field appeared more or less swollen. The swelling continued slowly until about the fifth hour, when, one by one, the bacteria suddenly and quickly disappeared, leaving little, if any, evidence of their former existence (Plate 28, Figs. 1–3).

Bronfenbrenner has also shown that in stained preparations the cytoplasm of swollen bacteria takes the dye less intensely and less evenly than does the cytoplasm of normal cells, in consequence of which it frequently appears segmented or beaded (Plate 28, Fig. 2). These observations were substantiated by photographs of unstained bacteria made by means of ultra-violet light. The rapid melting

* The description of the pathological picture observed in bacteria undergoing lysis is taken from Bronfenbrenner, Muckenfuss, and Hetler's paper, "The study of intimate mechanism of the lysis of bacteria by bacteriophage," *Am. J. Path.*, 1927, iii, 562.

away of the bacteria recorded cinematographically together with observations on the appearance of swollen bacteria in stained and unstained preparations probably indicates that the cytoplasm of bacteria under the influence of phage is liquefied within the cells prior to the disappearance of their membranes.

From the observations recorded it seems that in lesions produced by the majority of viruses, phenomena related to stimulation, proliferation, and degeneration of cells, as well as those connected with inflammation, occur. In some cases, all of the phenomena do not appear, because under the existing conditions it is impossible for certain of them to take place. For instance, in diseases that attack nerve cells, as in rabies, no proliferation of the involved cells has been described. In such diseases the first response of the affected cells is probably an alteration in their metabolism or a necrobiosis. Nor does inflammation in the form of cellular exudate always occur, either because certain tissues are involved, *e. g.*, the epidermis in molluscum contagiosum, or because certain hosts, *e. g.*, plants and bacteria, cannot respond to injury in this manner. Finally, in diseases in which all the phenomena occur, one frequently experiences difficulty in determining the order of their occurrence. In some diseases, however, and under certain conditions in others, the pathological changes apparently take place in the following order: (1) hypertrophy and hyperplasia,* (2) degeneration or necrobiosis, and (3) inflammation in the form of cellular or other exudation.

## Relation of Proliferation, Degeneration, and Inflammation to the Formation of Inclusion Bodies

Inasmuch as typical inclusion bodies are frequently observed in cells before any evidences of inflammation in the immediate neighborhood are discernible, it appears that these structures are not directly related to the products of inflammation, *e. g.*, engulfed leucocytes.

Although the question is still open as to whether the incitants of many virus diseases are structurally related to their significant inclusions (enveloped by them), and in spite of the contention of certain workers that inclusions represent parasites, it seems most likely

* Some workers may contend that these changes are the first responses to many kinds of injury and constitute evidences of degeneration. Be that as it may, in any event they are evidences of stimulation and proliferation.

that at least the major portion of the constituents of these peculiar bodies are in some manner related to the phenomena of proliferation and degeneration of host cells. Furthermore, in the majority of instances they appear to be more closely connected with hypertrophy and hyperplasia of cells than with retrograde changes. In rabies, a disease in which little or no proliferation of affected cells occurs, degenerative processes or altered cell metabolism may be responsible for the formation of inclusions. In morbid conditions, however, where proliferation precedes, or at least goes hand in hand with degeneration, and where inclusions are found in actively growing and dividing cells (Plate 22, Figs. 1 and 3; Plate 23, Figs. 1 and 8; Plate 24, Fig. 7) it seems not unlikely that the cellular activity induced by the viruses may lead to the formation of the inclusions either through the overproduction or the modification of some substance or substances normally present in cells, or in consequence of the retention of material ordinarily excreted. These views receive further support from observations concerning the size of cells affected by viruses. In certain instances their diameter increases from 7 to 400 microns (Plate 24, Figs. 1–4). Such an enhancement of size forces one to admit that the changes giving rise to it cannot result from degeneration alone and can take place only in living cells with a fairly active metabolism.

According to these views, inclusion bodies constitute the visible manifestations of a series of activities taking place in living and frequently in growing cells under the stimulating and degrading influences of certain viruses. In most instances the structural relation of the incitants to their specific inclusions is an open question. The distinctive differences observed in inclusions may be dependent upon the species of host, the type of cell and its portion affected, and the nature of the stimulus in the form of virus or its activity. It is true that proliferation and degeneration of cells are observed in some virus diseases and also in diseases other than those caused by viruses without the occurrence of typical inclusions in affected cells. The nature of the stimulus which determines the type and extent of changes taking place in these diseases probably accounts for the absence of inclusions under these conditions.

## Summary

There are diseases caused by certain peculiar incitants, viruses, that produce in their hosts pathological changes not entirely unlike those found in other diseases, yet sufficiently different from them in regard to phenomena related to proliferation and degeneration to warrant placing such agents in a group by themselves. If proliferative phenomena predominate, pathological conditions such as warts, molluscum contagiosum, and tumors result. If destructive or retrograde changes prevail, diseases such as varicella, vesicular stomatitis, and lysis of bacteria are the consequence.

Cells affected by many of the diseases in the group exhibit intracellular changes sufficiently characteristic to be spoken of as inclusion bodies. These structures are probably closely related to the proliferative and degenerative phenomena induced in cells by the action of viruses.

The views expressed in the present paper concerning the pathological conditions observed in virus disease are consistent with living or with lifeless incitants multiplying either intra- or extracellularly. The pathological changes, however, as well as other phenomena, emphasize the fact that in virus diseases an intimate type of parasitism exists.


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## DESCRIPTION OF PLATES

### PLATE 22

FIGS. 1 and 2. Epithelial cells affected by the virus of contagious epithelioma; the pink-staining masses in the cytoplasm represent Bollinger bodies. Fig. 1 also shows the result of amitotic division of the nucleus. Zenker's fixative; eosin and methylene blue stain. × 1700.

FIGS. 3 and 4. Cells, probably endothelial leucocytes, in the interstitial tissue of a rabbit's testicle affected by Virus III. The inclusions are represented by the pink intranuclear masses. Fig. 3 represents an amitotic giant cell. Zenker's fixative; eosin and methylene blue stain. × 1700.

FIGS. 5–7. Human epithelial cells injured by the virus of varicella. The pink masses in the nuclei are the characteristic inclusions. Fig. 7 represents an amitotic giant cell. Zenker's fixative; eosin and methylene blue stain. × 1700.

FIGS. 8–11. These figures represent a, b, e, and g respectively of Abb. 8 in Lauda and Luger's article on herpes simplex, *Ergbn. inn. Med. u. Kinderheilk.*, 1926, xxx, 377, and show the initial stages of oxychromatic nuclear degeneration.

FIGS. 12 and 13. These figures represent a and b respectively of Abb. 9 in Lauda and Luger's article on herpes simplex (see above), and show oxychromatic nuclear degeneration fully developed.

FIGS. 14 and 15. These figures represent 2 cells of Abb. 10 in Lauda and Luger's article on herpes simplex (see above), and show the end stages of oxychromatic nuclear degeneration.

FIGS. 16 and 17. Vaccine bodies — Guarnieri bodies — in the cytoplasm of corneal epithelial cells of a rabbit, 48 hours post inoculation. Zenker's fixative; eosin and methylene blue stain. × 1700.

FIG. 18. Represents one cell from Abb. 18 of Lipschütz's article on the herpes group of diseases, *Arch. Dermatol. u. Syph., Orig.*, 1921, cxxxvi, 428. The cell, corneal epithelial cell of a rabbit inoculated with herpes simplex virus, shows an acidophilic nuclear inclusion. Sublimate alcohol fixation; hämalaun eosin stain; Zeiss 1/12 im. and oc. 4.

FIG. 19. Represents an amitotic giant cell in human genital herpes. From Abb. 10 in Lipschütz's article (see above). Sublimate alcohol fixation; Giemsa's stain; Zeiss 1/12 im. and oc. 4.

FIG. 20. Represents a human epithelial cell affected by the virus of herpes zoster. From Abb. 1 in Lipschütz's article (see above). The characteristic change is the acidophilic mass in the nucleus. Sublimate alcohol fixation; Giemsa's stain; Zeiss im. and oc. 4.

FIG. 21. Reproduction of a cell from Fig. 5, Plate V, of Negri's article on rabies, *Z. Hyg., u. Infectionskrankh.*, 1903, xliii, 507, and shows a cell from Ammon's horn of a dog that died of rabies 15 days post infection. In the cytoplasm is a typical Negri body. Zenker's fixative; Mann's stain; Zeiss 2 mm. and oc. 6.

FIG. 22. Reproduction of a cell from Fig. 15, Plate II, of Bosc's article on sheep-pox, *Centr. Bakt., 1. Abt., Orig.*, 1903, xxxiv, 413, 517, 666. It is an epithelial cell with a cytoplasmic inclusion and vacuolated nucleus. Flemming's fixative; magenta phenol picro-indigo-carmine stain; Zeiss 1/12 im.

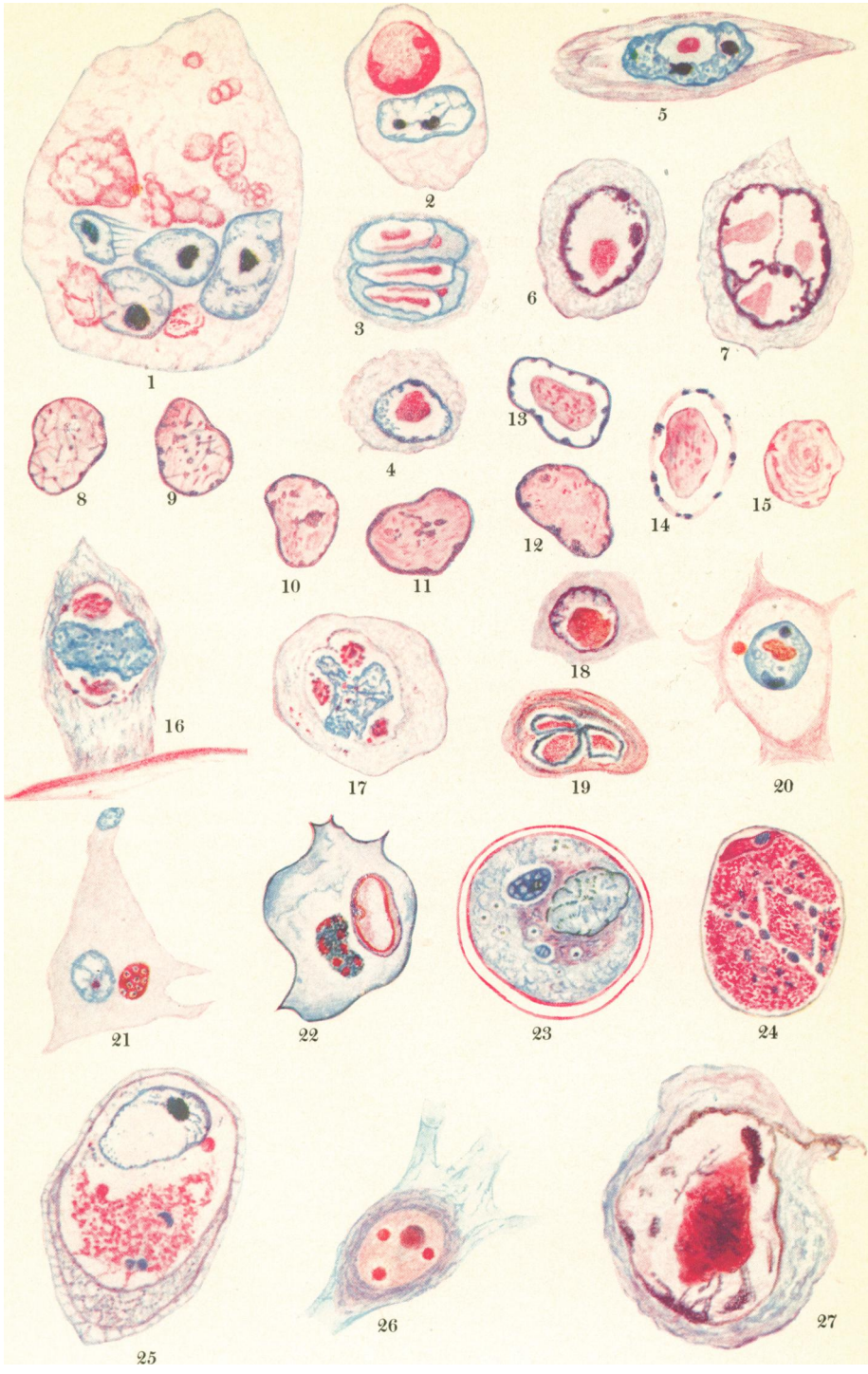
FIG. 23. Represents Fig. 5 (slightly modified) of Plate XXVIII illustrating Weissenberg's article on lymphocystic disease of fish, von Prowazek's Handbuch der pathogenen Protozoen, 1921, Leif. 9, 1344. The cell, 27 microns in diameter, shows several cytoplasmic inclusions. Acetic alcohol fixation; hematoxylin and Biondi stain. × 1025.

FIG. 24. Reproduction from Plate XVI illustrating Lipschütz's article on molluscum contagiosum, *Arch. Dermatol. u. Syph.*, 1911, cvii, 387, represents an epithelial cell with its nucleus compressed and pushed to the periphery and with its cytoplasm practically replaced by a so-called molluscum body. Sublimate alcohol fixation; Giemsa's stain; Leitz im. 1/12 and oc. 8.

FIG. 25. Epithelial cell of rabbit affected by the virus of infectious myxomatosis. The cell is swollen, the nucleus is vacuolated, and the cytoplasm contains a large granular pink-staining mass in the midst of which are several blue coccoid bodies. Zenker's fixative; eosin and methylene blue stain. × 1700.

FIG. 26. Reproduction of Fig. 5, Plate II, illustrating Joest's chapter on Borna disease in Kolle and von Wassermann's Handbuch der pathogenen Mikroorganismen, Jena, Fischer, 2nd ed., 1913, vi, 251. Ganglion cell from Ammon's horn showing pink nuclear inclusions. Lentz's stain; Zeiss im. 1/12 and oc. 3.

FIG. 27. Reproduction of one cell from Fig. 1, Plate 33, illustrating Cole and Kuttner's article on salivary gland virus of guinea pigs in *J. Exp. Med.*, 1926, xliv, 855. It is a swollen duct cell with eosin-staining nuclear inclusion from a submaxillary gland of a full grown pig. Zenker's fixative; eosin and methylene blue stain. × 1700.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## PLATE 23

FIG. 1. Tobacco mosaic. "Young palisade cell containing striate material radiating from the nucleus and a crescent-shaped body (A) adjacent to nucleus." (After Rawlins and Johnson, *Am. J. Bot.*, 1925, xii, 19.)

FIG. 2. "Leaf cell containing mitotic figure, crescent-shaped body (A), and striate material." (After Rawlins and Johnson.)

FIG. 3. "Cell of a short glandular trichome containing a body (A) of the same type shown in Fig. 4." (After Rawlins and Johnson.)

FIG. 4. "Cell of a short glandular trichome showing striate material and vacuolate body (A) containing a dark-staining granule." (After Rawlins and Johnson.)

FIG. 5. Intracellular body (marked X) in rosette-diseased wheat. (After McKinney, Eckerson, and Webb, *J. Agric. Res.*, 1923, xxvi, 605.)

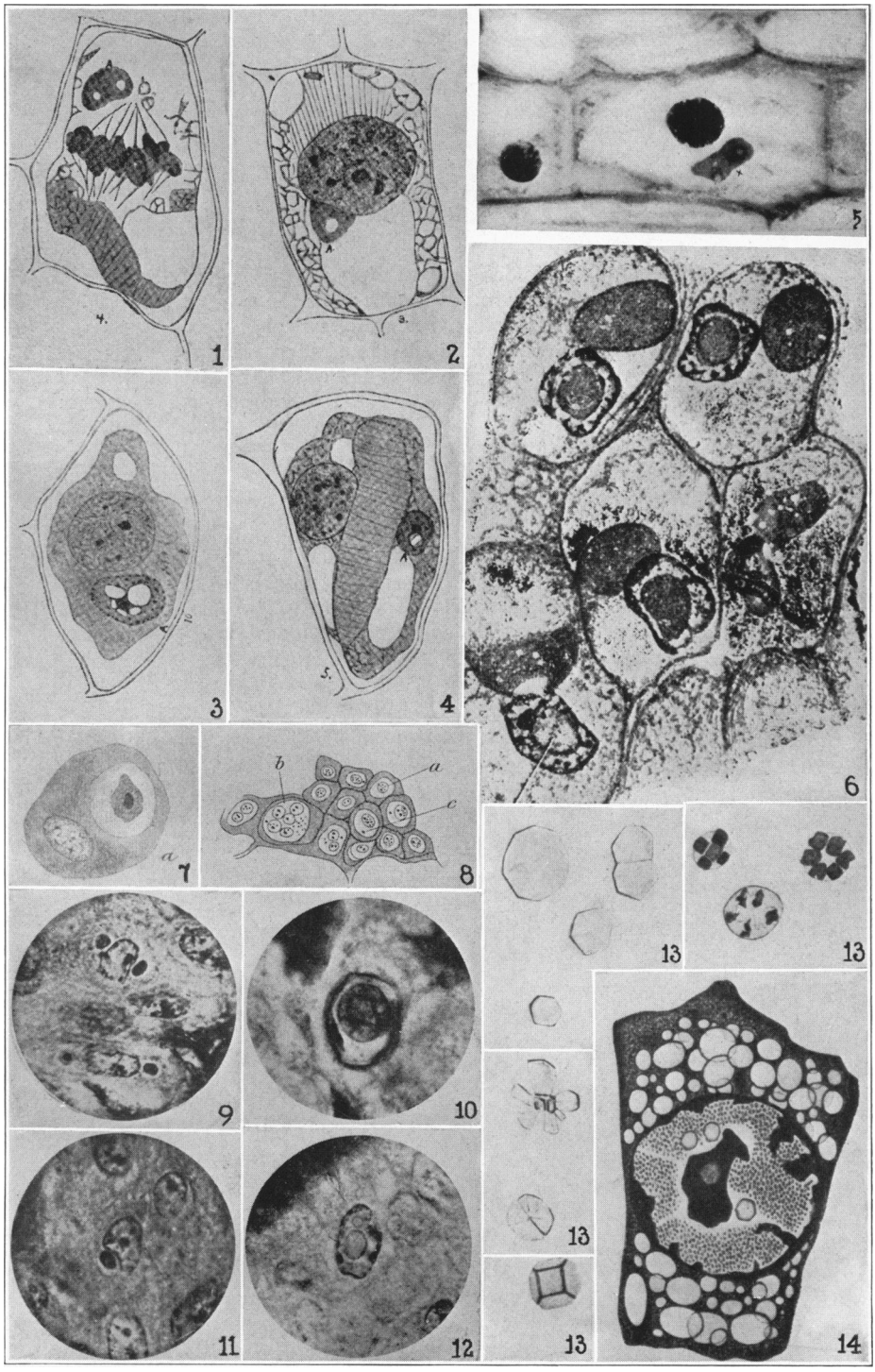
FIG. 6. Shows nuclear and cytoplasmic inclusions in paravaccinia. Reproduction of Fig. 12, Plate III, in Lipschütz's article on paravaccinia, *Arch. Dermatol. u. Syph., Orig.*, 1919–20, cxxvii, 193.

FIG. 7. Reproduction from Guarnieri's article on vaccinia in 1892 showing a vaccine body in the cytoplasm.

FIG. 8. Reproduction from Weigert's article on smallpox in 1874 showing amitotic giant cells and bodies in cytoplasm of affected cells similar to the ones later described by Guarnieri.

FIGS. 9–12. Cells showing nuclear and cytoplasmic inclusions in smallpox. (After Councilman, Magrath, and Brinckerhoff, *J. Med. Res.*, 1904, xi, 12.)

FIGS. 13 and 14. Polyhedral bodies in jaundice of silkworms. (After von Prowazek, *Centr. Bakt., 1. Abt., Orig.*, 1912–13, lxvii, 268.)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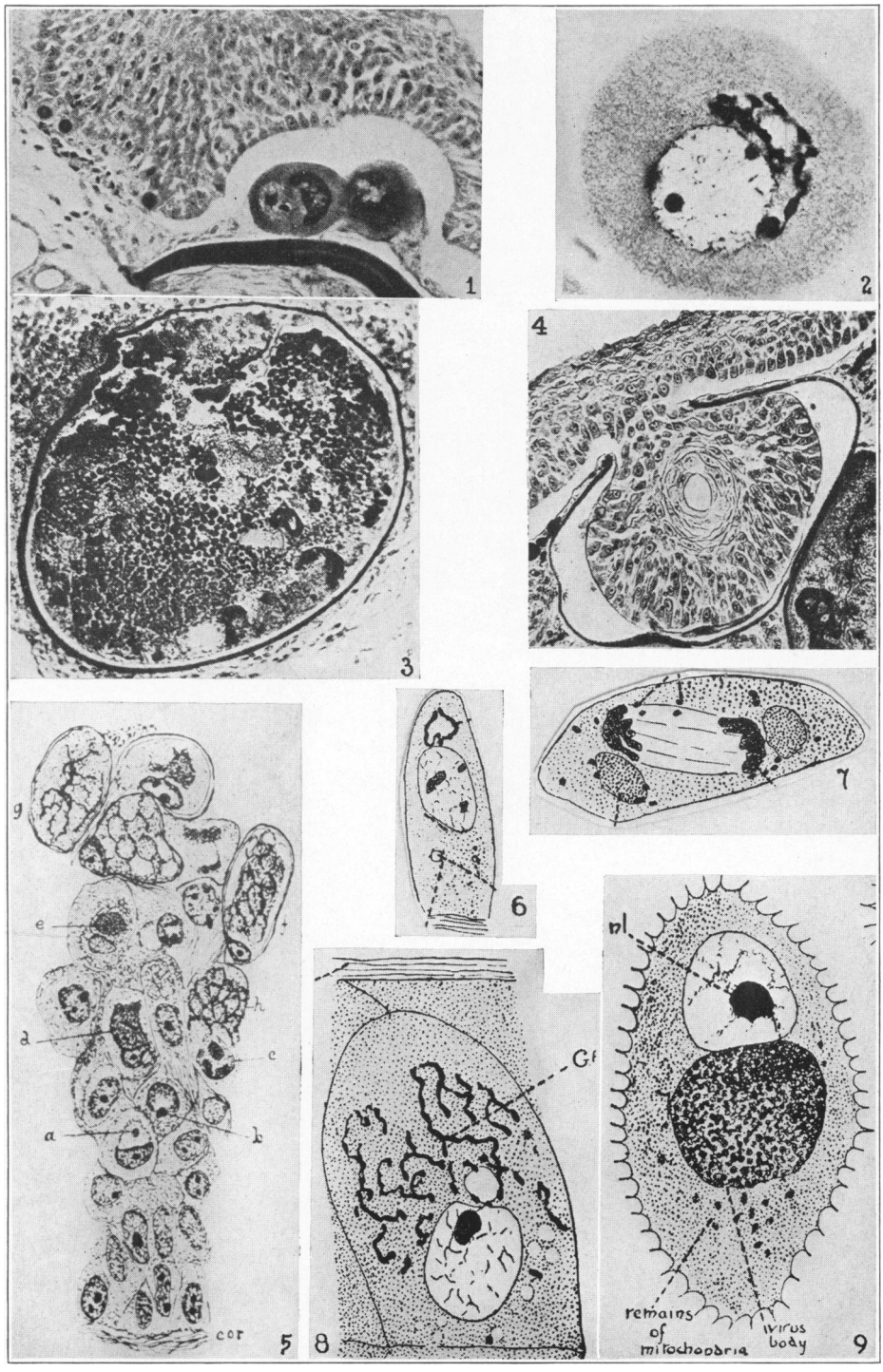
## PLATE 24

FIGS. 1–4. Illustrations by Joseph (1918) showing the remarkable increase in size of cells affected by the virus of lymphocystic disease of fish. In Fig. 1, there are three small dark cells showing the early effect of the virus, and two large ones exhibiting the picture presented at a later stage. Fig. 3 presents a cell going to pieces. Fig. 4 shows new cells filling the space left by one degenerated cell. Fig. 1 = × 250; Fig. 2 = × 650; Fig. 3 = × 200; Fig. 4 = × 200.

FIG. 5. Reproduction from Macallum's (1892) article showing the changes that take place in epidermal cells under the influence of molluscum contagiosum virus.

FIGS. 6–9. Reproductions from Ludford and Findlay's article (1926) on fowlpox. Fig. 6 shows small vacuole with minute adherent granules. Fig. 7 represents a cell with a mitotic figure and two virus bodies. Fig. 8 shows reversal of Golgi apparatus. Fig. 9 presents a well developed virus body in a greatly swollen cell.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pl
remains of mitochondria
virus body

## PLATE 25

FIG. 1. Reproduction of illustration by Guarnieri (1892) showing hyperplasia and hypertrophy of corneal cells with vaccine bodies caused by the action of vaccine virus.

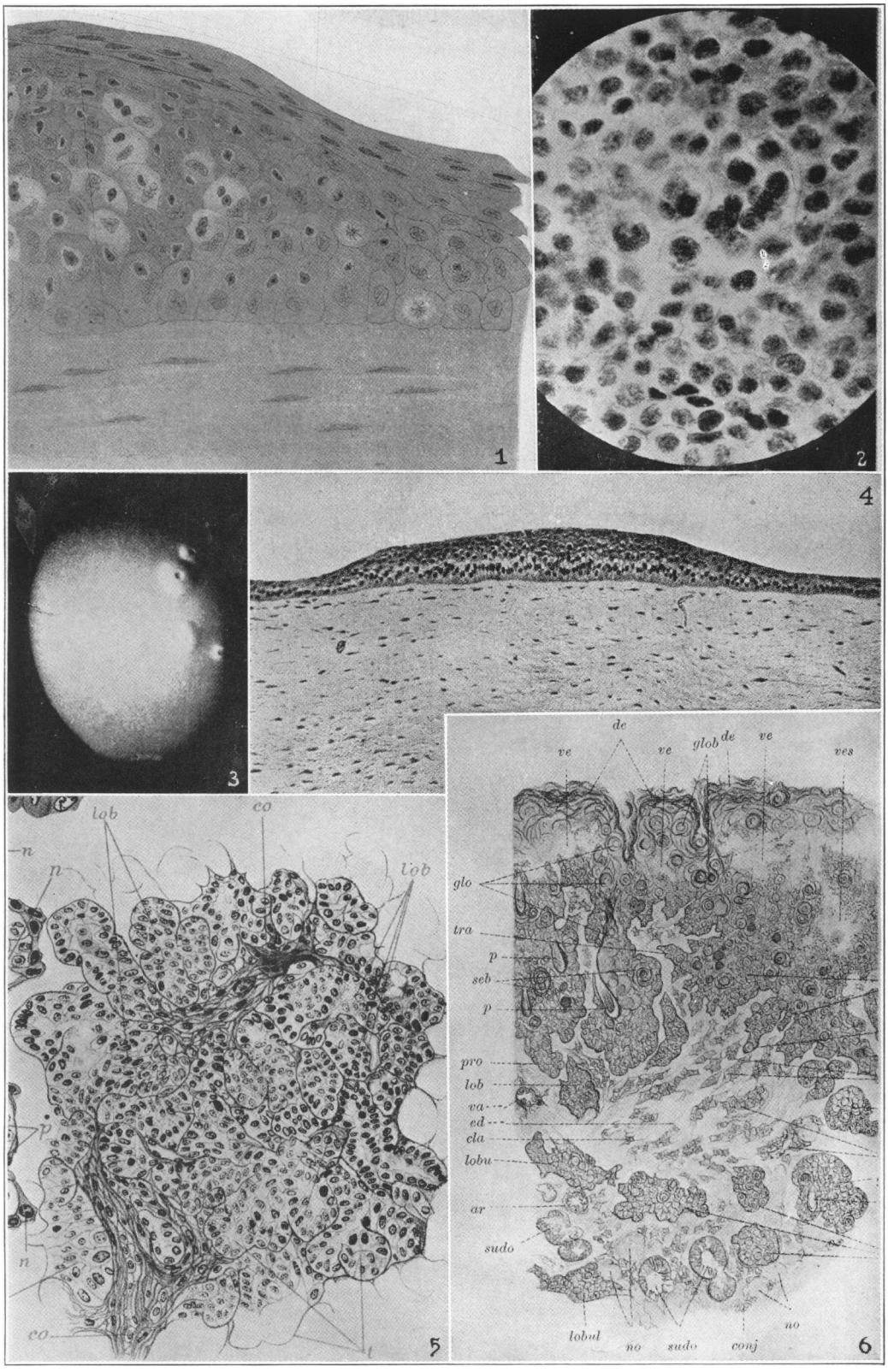
FIG. 2. Reproduction of illustration by von Wasielewski (1901) showing hyperplasia and hypertrophy of corneal cells with amitotic giant-cell formation caused by the action of vaccine virus.

FIG. 3. Illustration by Paul (1916) showing the effect of smallpox virus on the corneal cells of a rabbit 86 hours after inoculation.

FIG. 4. Illustration by Paul (1916) showing hyperplasia and hypertrophy of corneal cells caused by smallpox virus 48 hours after inoculation. No evidence of inflammation at this time.

FIG. 5. "Sheep-pox adenoma" of lungs. (After Bosc, 1903.)

FIG. 6. Hyperplasia and hypertrophy of cells in the skin caused by the virus of sheep-pox. (After Bosc, 1903.)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## PLATE 26

FIG. 1. Epidermal cells covering a myxomatous mass in the corium (virus myxomatosum, Sanarelli). Some of the epithelial cells are swollen and contain cytoplasmic inclusions. × 375.

FIG. 2. Epidermal cells undergoing dissolution. Compare with Fig. 1. × 125.

FIG. 3. Complete dissolution of epidermal cells. Compare with Figs. 1 and 2. × 125.

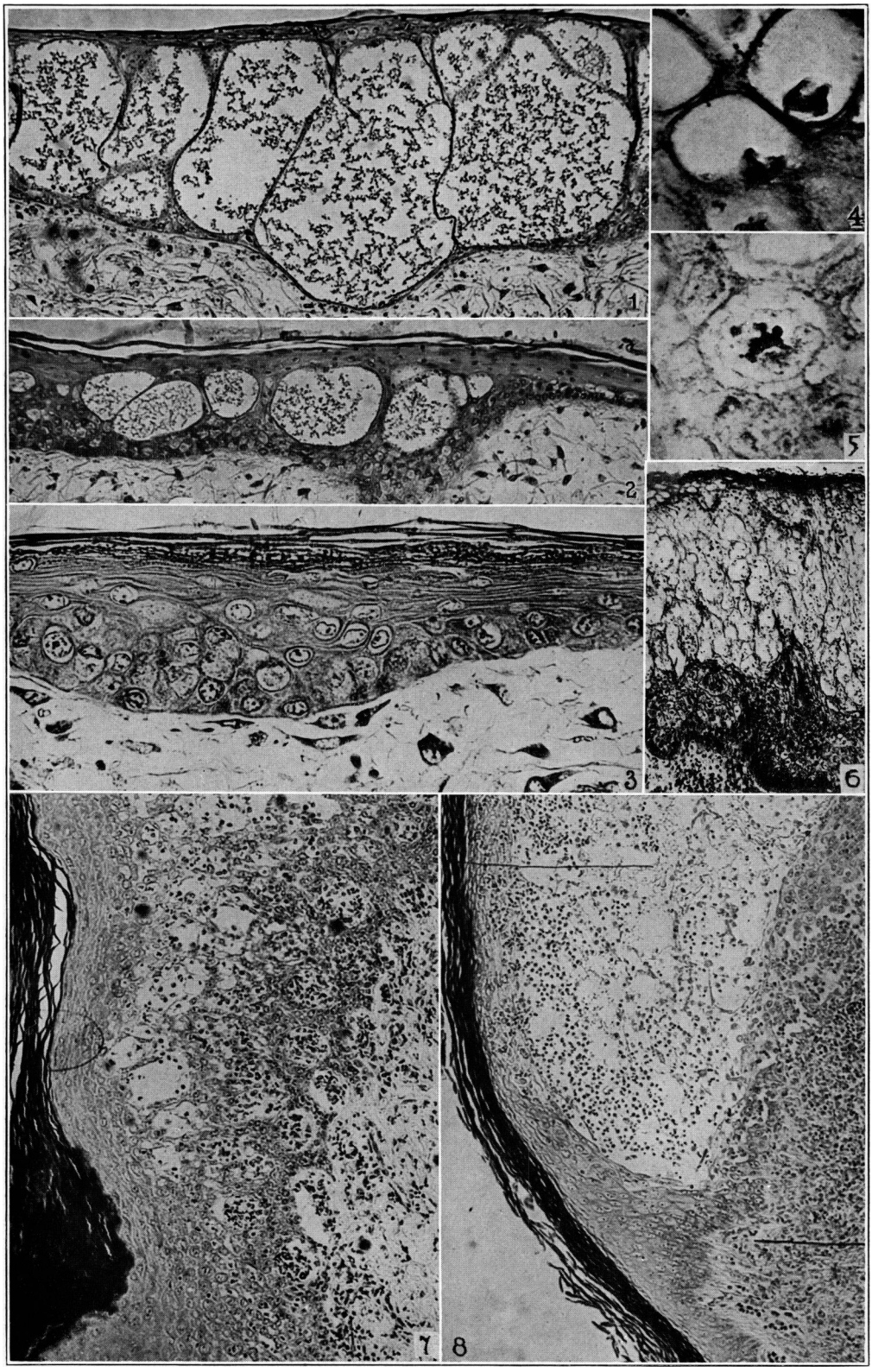
FIG. 4. "Degenerated cells showing vacuolation of protoplasm and shrivelling of nuclei." (After Councilman, Magrath, and Brinckerhoff, 1904.)

FIG. 5. "Reticular degeneration of epithelial cell." (After Councilman, Magrath, and Brinckerhoff.)

FIG. 6. "Early vesicle showing formation of epithelial reticulum." (After Councilman, Magrath, and Brinckerhoff.)

FIG. 7. Vesicle in pad of guinea pig 18 hours after inoculation with virus of vesicular stomatitis. Reticulum formed by degenerated cells. × 125.

FIG. 8. Vesicle formation that frequently occurs in contagious epithelioma or fowl-pox. × 125.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## PLATE 27

FIG. 1. "Crown tissue from rosette-diseased plant" (wheat). "Note the cells containing intracellular bodies in addition to the nuclei and also the granular nature of the cells which have become necrotic." (After McKinney, Eckerson, and Webb, *J. Agric. Res.*, 1923, xxvi, 605.)

FIG. 2. "Crown tissue from healthy plant." Compare with Fig. 1. (After McKinney, Eckerson, and Webb.)

FIG. 3. "Section of an early stage of a fruit blister showing the brown necrosis of the epidermal cells and the hyperplasia of the subepidermal cells." (After Gardner, *J. Agric. Res.*, 1925, xxx, 871.)

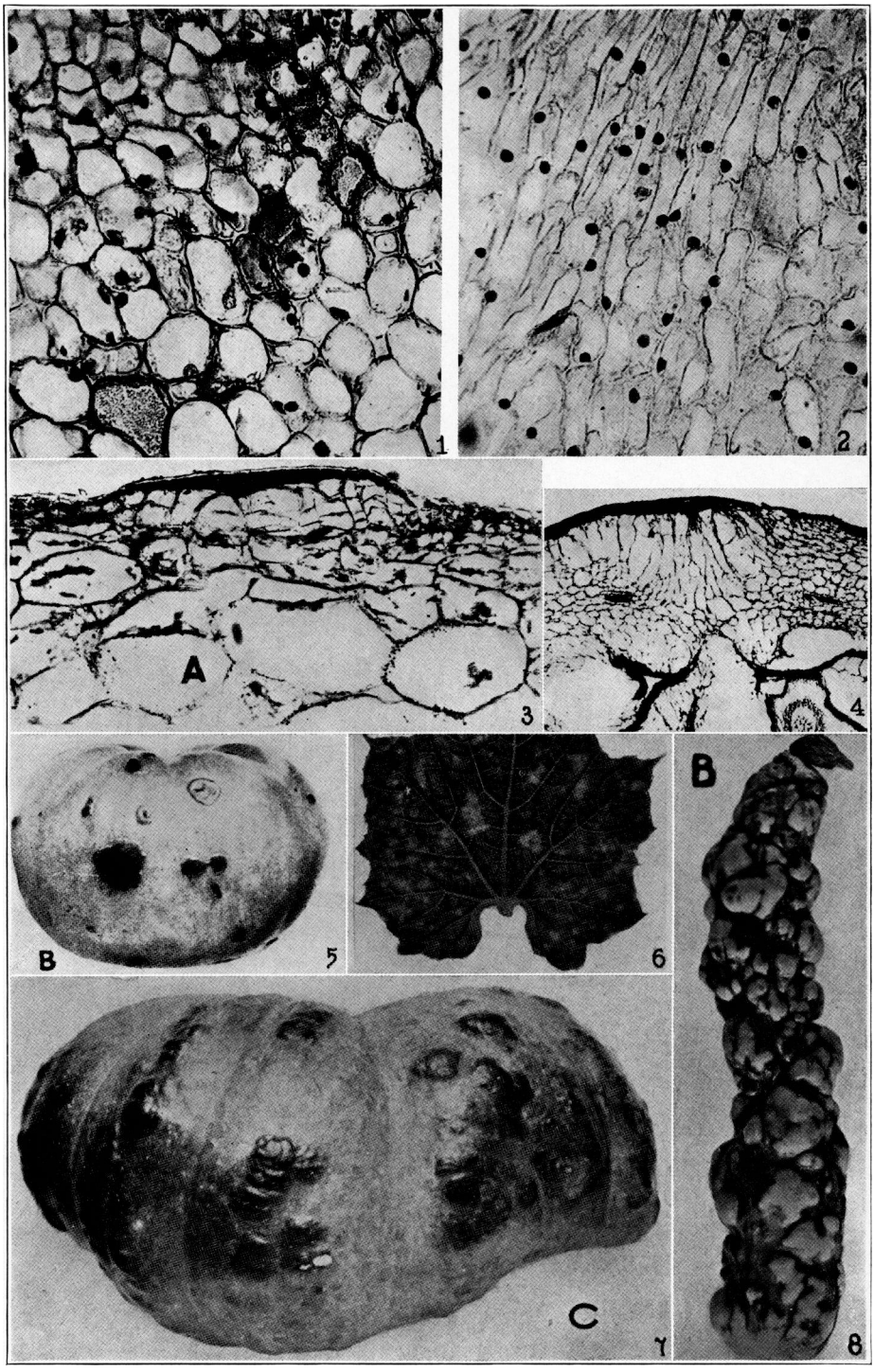
FIG. 4. "Section of a pericarp lesion resulting from necrosis and collapse of an area of subepidermal cells and hypertrophy of the cells immediately beneath the necrotic area." (After Gardner.)

FIG. 5. "Surface blisters on a mosaic tomato." (After Gardner.)

FIG. 6. Mosaic leaf of a gourd. (After Doolittle, *U. S. Dept. Agric. Bull., No. 879*, 1920.)

FIG. 7. "Mosaic fruit of pumpkin, showing large dark-green swellings on a yellow background." (After Doolittle.)

FIG. 8. Mosaic disease of Summer Crookneck squash. (After Doolittle.)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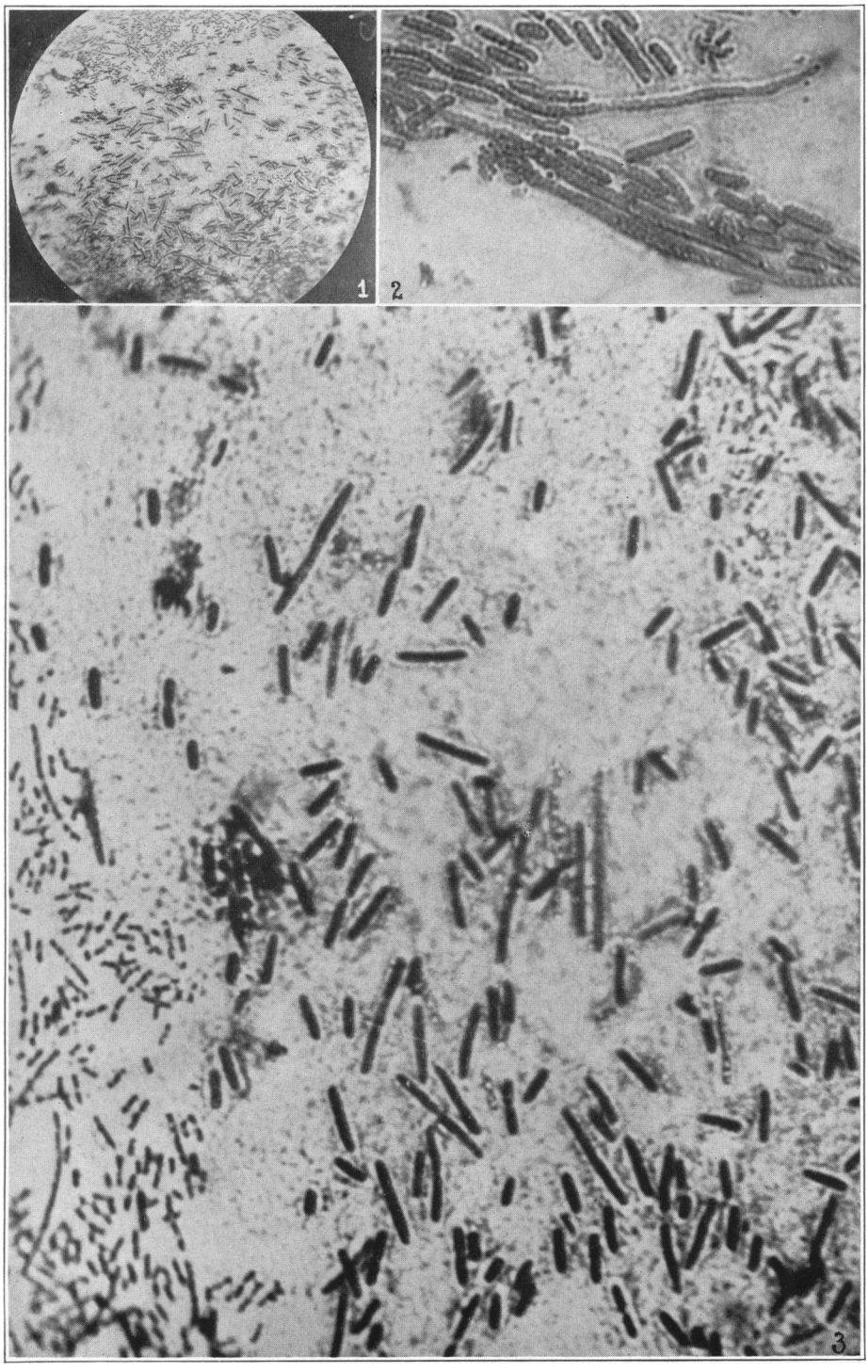
## PLATE 28

FIGS. 1 and 3. Fig. 3 is an enlargement of Fig. 1. At the left side of Fig. 3 are normal bacteria. The large organisms in the center of the picture show the swelling induced by the action of bacteriophage. Pictures supplied by J. J. Bronfenbrenner.

FIG. 2. Stained preparation of bacteria undergoing lysis. The protoplasm is beaded and segmented. Picture supplied by J. J. Bronfenbrenner.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