INFECTIOUS MYXOMATOSIS OF RABBITS

OBSERVATIONS ON THE PATHOLOGICAL CHANGES INDUCED BY VIRUS MYXOMATOSUM (SANARELLI)

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PLATES 34 TO 37

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In 1927, a preliminary report (1) was made concerning certain features of a disease designated by Sanarelli as infectious myxomatosis of rabbits. The purpose of the present communication is to amplify the previous report and to record some results of subsequent work.

Infectious myxomatosis is a malady indigenous to rabbits of South America and was first described by Sanarelli (2) in 1898. The disease, as he saw it, was characterized by the presence of nodules in the skin in the neighborhood of the eyes, nose, mouth, ears, and genitalia. A conjunctivitis, accompanied by a profuse purulent discharge, resulted from the involvement of the skin around the eyes. The disease ran a rapid course, death of the animals usually occurring within 1 or 2 weeks after infection. Upon palpation the tumors were firm and on section revealed a gelatinous consistency. Histologically they were found to be comprised of gelatinous material, large stellate cells, and blood vessels. The lymph nodes and spleen were enlarged, and, in histological preparations of the latter, nests of the large stellate cells were observed. The presence of the virus was demonstrated in the secretions from the eyes, in the tumors, in the various organs, and in the blood. Besides spreading spontaneously, the malady proved to be transmissible by experimental inoculation. Many kinds of animals, including man, were inoculated. The rabbit, however, was the only susceptible host found. Sanarelli was unable to cultivate the etiological agent on artificial media, nor was he able to see it by means of the microscope. In view of these facts, he concluded that *Virus myxomatosum* is similar in nature to rabic virus.

Since Sanarelli's original communication only 10 papers (see bibliography) dealing with the infectious myxoma of rabbits have appeared. A detailed review of these reports, with the exception of Findlay's (11),

was made by Hobbs (10) in 1928. Therefore, only the results of previous work that are particularly interesting or that have a bearing on the experiments to be presented at this time will be described.

Moses, Hobbs, and Findlay have shown that the myxoma virus is capable of passing through filters impervious to ordinary bacteria. No worker has been able to cultivate the etiological agent on artificial media in the absence of living host cells. The rabbit is the only known susceptible host. Even the wild hares (*Lepus braziliensis*) of Brazil are resistant to the virus (Moses, 1911).

Splendore, 1909, reported the presence of trachoma-like bodies in the tumor cells. In 1911, Moses stated that he was unable to confirm Splendore's observations concerning these bodies. Aragão, 1911, recorded his observations of certain bodies, *Chlamydozoa myxomae*, within the hypertrophic nuclei of the tumor cells. In 1927, this investigator repudiated his work concerning the nuclear inclusions and stated that the etiological agent is represented by small round granules, *Strongyloplasma myxomae*, situated within the cytoplasm of infected cells. Rivers, 1927, reported that he was able to find large granular acidophilic inclusion bodies in the cytoplasm of epithelial cells covering the myxomatous masses. Hobbs, 1928, confirmed Rivers' observations concerning the presence of these inclusions in the epithelial cells. Lipschütz, 1927, described within the cytoplasm of the swollen tumor cells, the presence of many small bodies which, inasmuch as they seemed to differ from chlamydozoa and strongyloplasms, he designated *Sanarellia cuniculi*. Findlay, 1929, failed to confirm Rivers' observations regarding the presence of cytoplasmic inclusions in epithelial cells. He was able, however, to find Lipschütz's *Sanarellia cuniculi* in the tumor cells.

Although Sanarelli in 1898 described the myxomatous masses in the skin as tumors and found that in infected animals the spleen and lymph nodes were enlarged and that at times an orchitis occurred, certain workers have been unable to confirm his observations. For instance, Aragão, 1927, stated that the myxomatous swellings are not true tumors but remarkable collections of oedema due to an infectious agent. Furthermore, he observed no involvement of the lymph nodes and spleen. Findlay, 1929, reported that "the nodular lesions are thus due, not to an active proliferation of the tissue elements, but simply to the myxomatous changes in the tissues." Moreover, he found "no enlargement of the lymph-glands or spleen." Also, according to him, "the testicles, apart from congestion, were normal even when the scrotum was affected."

From the above brief review of the reports dealing with infectious myxomatosis of rabbits, it is obvious that many conflicting statements and opinions exist. Nevertheless, the disease is so characteristic and so fatal that there is no doubt but that all of the investigators studied the same malady. In fact, many of them were dealing with the same

strain of virus, which originally came from the Oswaldo Cruz Institute in Brazil.

In a preliminary report, 1927, I described for the first time certain changes observed in epidermal cells covering myxomatous masses induced by *Virus myxomatosum*:

> Upon microscopic examination the first change noted in the epidermal cells is an increase in their size. Then, small pink, granular areas appear in the cytoplasm. These areas rapidly increase in size and frequently involve most of the cytoplasm. In the center of the acidophilic masses, blue, round or rod-shaped bodies are often seen. . . . The disease process in the epidermal cells progresses until there is complete dissolution of the cells. At this time distinct vesicles appear in the epidermis. . . .

Because of the involvement of the epidermis, a fact that had not been observed previously, I raised the question in my preliminary note as to whether I was dealing with more than one virus. Since that time work on the myxoma has been continued and now it seems advisable to record certain observations that may be of interest.

Methods and Materials

Virus.—The myxoma virus was obtained by Dr. C. E. Simon from Dr. A Moses of the Oswaldo Cruz Institute, Brazil. In May, 1926, Dr. Simon sent the virus to Dr. A. Carrel who gave it to me for study.

Methods of Inoculation.—Animals were inoculated epidermally, intradermally, subcutaneously, intravenously, and intranasally. A few animals were allowed to contract the disease through contact with infected rabbits. Except for the tumors that arose at the sites of inoculation, the disease picture was the same following all types of inoculation.

Cultures.—Infectious blood and bits of the tumors and different organs were tested for sterility by means of the usual aerobic and anaerobic cultures. No bacterium of etiological significance was encountered. In approximately 50 per cent of the rabbits that died of the myxoma, *P. lepiseptica* was obtained from some organ or tissue. Sufficient animals, however, with sterile tumor masses, blood, and organs were studied to convince one that the changes to be described in this paper were not induced by *P. lepiseptica*. In working with the myxoma, one should endeavor to use rabbits that are not carriers of *P. lepiseptica*.

Fixation and Staining.—Tissues used for histological studies were obtained from rabbits sacrificed by the intravenous injection of air. The tissues were fixed in Zenker's (5 per cent acetic acid) fluid and stained with eosin and methylene blue and according to Giemsa's method.

EXPERIMENTAL

The course of infectious myxomatosis and the histological findings are not materially influenced by the manner in which the disease is contracted. When the virus is rapidly passed in series from rabbit to rabbit, however, it kills the animals so promptly that sufficient time does not elapse for the formation of large and characteristic lesions. Therefore, if large tumors and metastases are desired for study, a virus that has been stored for a long time should be employed.

During a period of 4 years, approximately 100 rabbits have been used for various studies of the myxoma virus. Of these animals, 25 have been carefully autopsied and the tissues have been examined histologically. The results of each autopsy will not be given in detail. The findings in different tissues and organs will be described and the relative frequency of the involvement of these organs and tissues will be noted.

Skin

In every susceptible animal the epidermis, corium, and subcutaneous tissues were involved. The appearance of primary and secondary lesions in the skin is illustrated in Figs. 1–7. Such lesions are elevated, round or oval masses, the centers of which may take on a purplish color. Upon palpation the masses are firm and at times have the consistency of cartilage. The affected skin around the genitalia, however, frequently presents the appearance of oedematous tissue (Figs. 6, 7). If the lesions have progressed sufficiently, evidences of vesiculation can be found (Figs. 1, 5). In fact, fluid can be obtained from the vesicles by means of capillary pipettes. If the animals survive long enough, the vesicles are replaced by crusts which cap the tumor nodules (Fig. 5).

On sectioning the tumors one finds them firm, and hard to cut. The epidermis is thickened or shows evidences of vesiculation. The corium and subcutaneous tissues consist of a tough, pinkish, gelatinous material freely supplied with blood vessels. The tumors may be attached to the underlying muscles.

Histological examination reveals the following course of events in the epidermis. The cells increase in number and size (Fig. 9). Then small acidophilic granules appear in the cytoplasm. These rapidly increase in number and eventually replace the major portion of the normal cytoplasm. Among the acidophilic granules round or rod-shaped blue bodies may be seen (Figs. 21, 23). The nuclei become swollen or vacuolated (Fig. 23) and the chromatin is fragmented. Finally the cells undergo dissolution and vesicles appear in the epidermis (Figs. 10, 11).

In the involved corium and subcutaneous tissues an amorphous-looking material is seen in which large stellate or polygonal cells (Figs. 12, 24, 25), many polymor-

phonuclear leucocytes, and multinucleated cells (Figs. 12, 14) are found. The nuclei of the polygonal cells are swollen, and the chromatin is fragmented (Fig. 25). Dividing cells and mitotic figures are not numerous, but they do occur. Many of the so-called tumor cells are strikingly phagocytic. The cytoplasm of these cells contains a large number of granules. Whether some of the granules are similar to those described by Lipschütz and Findlay is not known. It seems, however, that the majority of the bodies represents not virus particles, but ingested material. The myxomatous masses are abundantly supplied with blood vessels, many of which are surrounded by the large polygonal cells (Fig. 12). At times the endothelial cells of the capillaries also seem to be involved (Figs. 12, 13) and are not unlike the large cells seen in other parts of the tumor.

TEXT-FIG. 1. Chain of axillary lymph nodes draining site of primary inoculation of the skin with myxoma virus. The glands were hypertrophic, hemorrhagic and firm. Histological examination of the 4 larger glands revealed the fact that the lymphocytes had been completely replaced by "myxoma" cells. Natural size.

In the epidermis and in the corium affected by the virus it appears that more than a myxomatous metaplasia of the cells already present occurs. Evidences of growth and destruction of cells are found.

Lymph Glands

Examination of the axillary and popliteal lymph glands was a routine procedure of each autopsy. If the animal is inoculated in the skin over the lateral surface of the thorax and upper part of the abdomen, it is usual to find the axillary glands on the same side involved. Glands in the other axilla and in the popliteal spaces, in a great many instances, also show evidences of involvement. A marked degree of hypertrophy is the first change noted; at times the increase in size is tenfold. Then discrete red areas appear on the surface of the glands. Finally the nodes become very firm and hemorrhagic throughout (Text-fig. 1).

Histological examination reveals that the early changes in the lymph glands are characterized by an increase in the lymphatic tissue, *i.e.*, lymphocytes. Then in the lymph sinuses around the periphery of the glands phagocytic cells make their appearance (Fig. 18), many of which are multinucleated. Soon the lymphocytes begin to disappear, and, if sufficient time elapses, the glands become devoid of such cells. At this stage of the disease, the large lymph nodes consist of cells resembling those found in the subcutaneous myxomatous nodules (Fig. 19). These cells are not normal; they have hypertrophic nuclei with fragmented chromatin, and in their cytoplasm different kinds of granules are present, many of which seem to have been ingested. On studying the sections one obtains the impression that these cells arise from the reticulum of the glands. Mitotic figures are not numerous. Nevertheless, they do occur. If the cells that comprise these "metastases" or altered lymph glands arise from the reticulum, their number can be accounted for only upon the assumption that a multiplication of the cells of the reticulum takes place under the stimulus of the virus. In addition to the type of cells just described, many polymorphonuclear leucocytes are seen.

Spleen

The spleen may be enlarged or it may be of normal size. On histological examination nests of large stellate cells are not infrequently observed. In two rabbits, many of the blood vessels in the spleen were surrounded by myxomatous tissue (Figs. 17, 20) composed of cells similar to those described in the "metastases" in the lymph glands. Around each myxomatous nodule was a compact ring of cells, many of which seemed to be spleen cells crowded together by the growth of the myxoma. Other cells in this dense mass doubtless represented the results of host reaction to the infection.

Lungs

As a rule, lesions characteristic of the myxoma were not observed in the lungs. Occasionally a pneumonic process caused by *P. lepiseptica* was encountered. In sections of the lungs from one rabbit, however, numerous myxomatous nodules (Fig. 15) were seen in the vicinity of blood vessels and bronchi. The myxomatous tissue was similar in nature to that observed elsewere in the body. Moreover, the epithelial cells of the bronchi in close proximity to the myxomas showed evidences of hyperplasia, and, in the cytoplasma of these abnormal cells, changes similar to those seen in epidermal cells were noted.

Inasmuch as the myxoma virus is regularly found in the secretions from the eyes and nose and in the blood, it is difficult to state in what manner the virus that caused the lesions in the lungs obtained entrance.

Testicles

In the majority of the rabbits the scrotal skin is affected, but it is unusual for the testicle to be attacked by the virus. In 4 rabbits, however, myxomatous

changes in the interstitial tissue of the testicle accompanied by a necrosis of the tubules was encountered.

Epididymis

The epididymis (Fig. 8) is involved more frequently than is the testicle. Within the connective tissue, myxomatous masses similar to those in the subcutaneous tissue are found. In one rabbit the epithelial cells lining different parts of the epididymis showed intracellular changes similar to those described in the epidermal cells, *i.e.*, an increase in number and size, and the presence of acidophilic cytoplasmic inclusions (Figs. 16, 22).

Tunica Vaginalis

It is not unusual to find hemorrhagic myxomatous nodules in the tunica vaginalis (Fig. 8).

Ovary and Uterus

Autopsies were performed on 3 female rabbits inoculated with myxoma virus. No lesions were found in the ovaries and uterus. If a large number of infected female rabbits were examined, it is possible that lesions might be encountered in these organs.

Pancreas, Liver, Kidney, Adrenals

No myxomatous nodules were observed in the pancreas, kidney, liver and adrenals.

Concerning the Presence of More than One Virus

The peculiar changes in the epidermis that accompany the myxomatous masses in the underlying tissue induced me to raise the question in my preliminary note (1) whether the observed pathological picture resulted from the combined activity of two viruses. Findlay (11), failing to find the changes in the epidermis described by me, again raised the question as to whether I was dealing with two viruses, one of which is indigenous to American rabbits and is not found in British rabbits. Furthermore, he suggested that one of the agents may be so labile that it is unable to withstand shipment from America to England.

During the last 4 years, I have tried in many ways to demonstrate the presence of more than one virus in the myxoma material and have been unable to do so. Vaccine virus and Virus III have been elimi-

nated as possible contaminants by passage of the myxoma through rabbits immune to these agents. Fowl-pox also is not a contaminant, inasmuch as an emulsion of the myxomatous tissue will produce no disease in fowls. The myxomatous material is innocuous for mice, rats, guinea pigs, and monkeys. Therefore, if two viruses are present in the myxomas, both are specific for the rabbit.

In view of the fact that different viruses are not equally stable, an emulsion of myxomatous tissue in 50 per cent glycerol, and citrated infectious blood were stored on ice for 1 and 2 years respectively in the hope of eliminating in this manner one of the viruses in case two were present. Lesions resulting from inoculations with these materials showed the phenomena in the epidermis that gave rise to the question regarding the presence of two viruses. Therefore, if there are two viruses in the material with which I have been working, then both are extremely resistant to aging and storage or a large number of the rabbits that I have inoculated during the past 4 years have been carriers of the second or contaminating virus. The facts that I have adduced do not conclusively exclude the possibility of the presence of two viruses. Nevertheless, in view of them, such a possibility seems unlikely.

DISCUSSION

The fact that maladies induced by viruses are characterized by hyperplasia and necrosis was discussed in a previous paper (12). In the majority of the virus diseases both of these phenomena are observed. In some, however, hyperplasia may play the important rôle, while in others necrosis dominates the picture. Such a lack of balance between the growth and destruction of tissue accounts for the fact that the activity of some viruses gives rise to certain kinds of tumors, *e.g.*, Rous' sarcoma, while the operation of others lead to vesicular lesions, *e.g.*, variola and foot-and-mouth disease.

Many of the viruses are highly species specific. Virus III attacks only rabbits; the salivary-gland virus is active only in the guinea pig; hog cholera is infectious only for swine; each polyhedral disease has its specific caterpillar host; the tumor-forming activity of the Rous sarcoma seems to be limited to chickens; certain mosaic viruses produce pathological changes in one kind of plant. This marked degree

of specificity, however, is not exhibited by all viruses. For instance, vaccinia and rabies may be induced in many kinds of animals.

A close relation exists between the viruses and host cells. This fact is emphasized by the lack of evidence to demonstrate that these active agents are capable of multiplication in the absence of living susceptible host cells, and by the presence in many instances of specific inclusion bodies in the affected cells. The relation between the viruses and cells may be not only close but specific in that certain types of cells alone are directly injured by the disease-inciting agent. For example, in rabies and poliomyelitis, it appears that nerve cells are the susceptible elements. Such cell specificity however, is not observed in vaccinia and herpes febrilis, diseases in which cells of ectodermal and mesodermal origin are involved.

The ease with which virus diseases spread from one host to another varies. Some are contagious, *e.g.*, variola and foot-and-mouth disease; others are only inoculable, *e.g.*, rabies and Rous' sarcoma; while yet others are capable of being transferred only by means of grafts, as is the case with certain infectious chloroses of plants.

The infectious myxoma of rabbits described in the present paper is one of the first maladies placed in the virus group. Moreover, when the available facts are closely examined, it is found to be one of the most interesting and characteristic of the lot. It is highly species specific, contagious, attacks cells of ectodermal and mesodermal origin, and causes hyperplasia and necrosis—the predominance of necrosis in the epidermis leads to vesicles, while the preponderance of hyperplasia in the subcutaneous and other tissues results in tumor-like masses. Moreover, inclusion bodies are found in epithelial cells involved. Finally, the causal agent is filterable, has not been cultivated in the absence of living host cells, and is very resistant to the action of certain chemicals and to long periods of storage.

Infectious myxomatosis, acquired spontaneously or induced experimentally, regularly exhibits foci of metastatic activity of the causal agent. These are always seen in the skin, particularly around the eyes, mouth, nose, and genitalia. The lymph glands draining the site of inoculation are usually involved. Other lymph nodes also may be affected. The epididymis and testicle with its tunic are not infrequently attacked. In an occasional animal, many metastases occur

around the blood vessels of the spleen and rarely multiple metastases are found in the lungs. Inasmuch as the virus is always found in the blood, the word metastases, when used in connection with this disease, does not necessarily mean that multiple lesions arise through the transportation of affected cells from one part of the body to another. The metastases described above probably represent the results of the activity of the virus operating in different parts of the animal.

There is no adequate explanation of the fact that Hobbs and I found changes in the epidermal cells associated with cytoplasmic inclusions, while Findlay in England observed none. Nor is it easy to understand why only a few workers have noted involvement of the lymph glands. In any event, the results of the work reported at the present time indicate that the rabbits in New York over a period of 4 years when infected with *Virus myxomatosum* as a rule exhibited involvement of the lymph glands.

The exact nature of the stellate, polygonal, or myxomatous cells is not known. Lipschütz, (9) speaks of them as histiocytes, while Findlay (11) describes them as "hypertrophied connective-tissue cells." Furthermore, the nature of the inclusions in the epithelial (1) and connective tissue cells (9, 11) is still an open question, as is the case with many of the inclusion bodies in the virus diseases.

I can not agree with the statement of Findlay (11) and Aragão (8) that no active proliferation of tissue elements results from infection with the myxoma virus. The evidence obtained from my work is convincing that both growth and destruction of tissues occur in this disease. Of course the cells evidencing multiplication may be those already present in the tissues. Moreover, a myxomatous change may take place in these cells as a result of the virus activity, but such an occurrence does not alter the fact that an increase in the number of cells also results from the operation of the virus and that this increase plays a part in the formation of the nodules or tumor-like masses. These facts, however, are not proof that the myxomatous masses are true neoplasms similar to cancer in man. In fact, some investigators are not convinced that the exact relation of Rous' sarcoma to true neoplasms has been determined.

In certain respects the myxoma of rabbits resembles the Rous sarcoma of chickens. In others, however, it is quite different. If, as

some believe, the Rous sarcoma appears to be more closely related to true neoplasms than to diseases induced by highly contagious agents, then the myxoma, upon further study, may serve to bridge the gap between the Rous tumor and other virus maladies, and to indicate that, after all, no great difference exists between tumor-forming viruses and those causing vesicular or destructive lesions.

SUMMARY

The virus of infectious myxomatosis of rabbits (Sanarelli) induces multiple lesions in the skin, lymph glands, tunica vaginalis, epididymis, testicle, spleen, and lungs.

Growth and destruction of cells in the epidermis overlying the myxomatous masses leads to the formation of vesicles. Cytoplasmic inclusions are found in affected epidermal cells. Occasionally, similar inclusions are seen in other involved epithelial cells. The nature of the inclusions is an open question.

In the myxomatous masses situated in the subcutaneous and other tissues, evidences of alteration and growth of certain cells are observed.

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EXPLANATION OF PLATES

PLATE 34

FIG. 1. Primary "tumor" surrounded by secondary nodules. Several vesicles cap the primary growth.

FIG. 2. Multiple primary tumors induced by rubbing the virus on the freshly shaved skin. The central portions of some of the nodules reveal a purplish tint.

FIG. 3. Involvement of the eyelids accompanied by a white, purulent discharge.

FIG. 4. Metastatic nodule in lip.

FIG. 5. Metastatic nodule in skin over shoulder. The growth is capped by a vesicle undergoing desiccation.

FIG. 6. Oedema around the vaginal orifice.

FIG. 7. Oedema of prepuce and scrotum.

FIG. 8. Four metastatic nodules, three in the tunic, one in the epididymis.

PLATE 35

FIGS. 9, 10, 11. Involvement of epidermis characterized by hyperplasia of the epithelial cells followed by necrosis resulting in vesicles. × 375, × 125, × 125 respectively.

FIG. 12. Section through a subcutaneous nodule comprised of gelatinous material, large polygonal cells, giant cells, blood vessels, and polymorphonuclear leucocytes. × 250.

FIG. 13. Enlargement of capillary, indicated by arrow in Fig. 12, showing involvement of endothelial cells. × 1000.

FIG. 14. Higher magnification of giant cell shown in Fig. 12. × 1000.

PLATE 36

FIG. 15. Metastasis in the lung. The epithelium of the bronchus near the myxomatous tissue is hyperplastic and contains cytoplasmic inclusions. × 150.

FIG. 16. Represents the involvement of epithelial cells in the epididymis which is characterized by hyperplasia and cytoplasmic inclusions. Compare with Fig. 22. × 300.

FIG. 17. Metastasis around blood vessel in spleen. × 125.

FIG. 18. Early lesion in lymph node. Note changes in cells lining the lymph sinus and the presence of large phagocytic cells within the sinus. × 250.

FIG. 19. Complete replacement of lymph node by myxomatous tissue. × 250.

PLATE 37

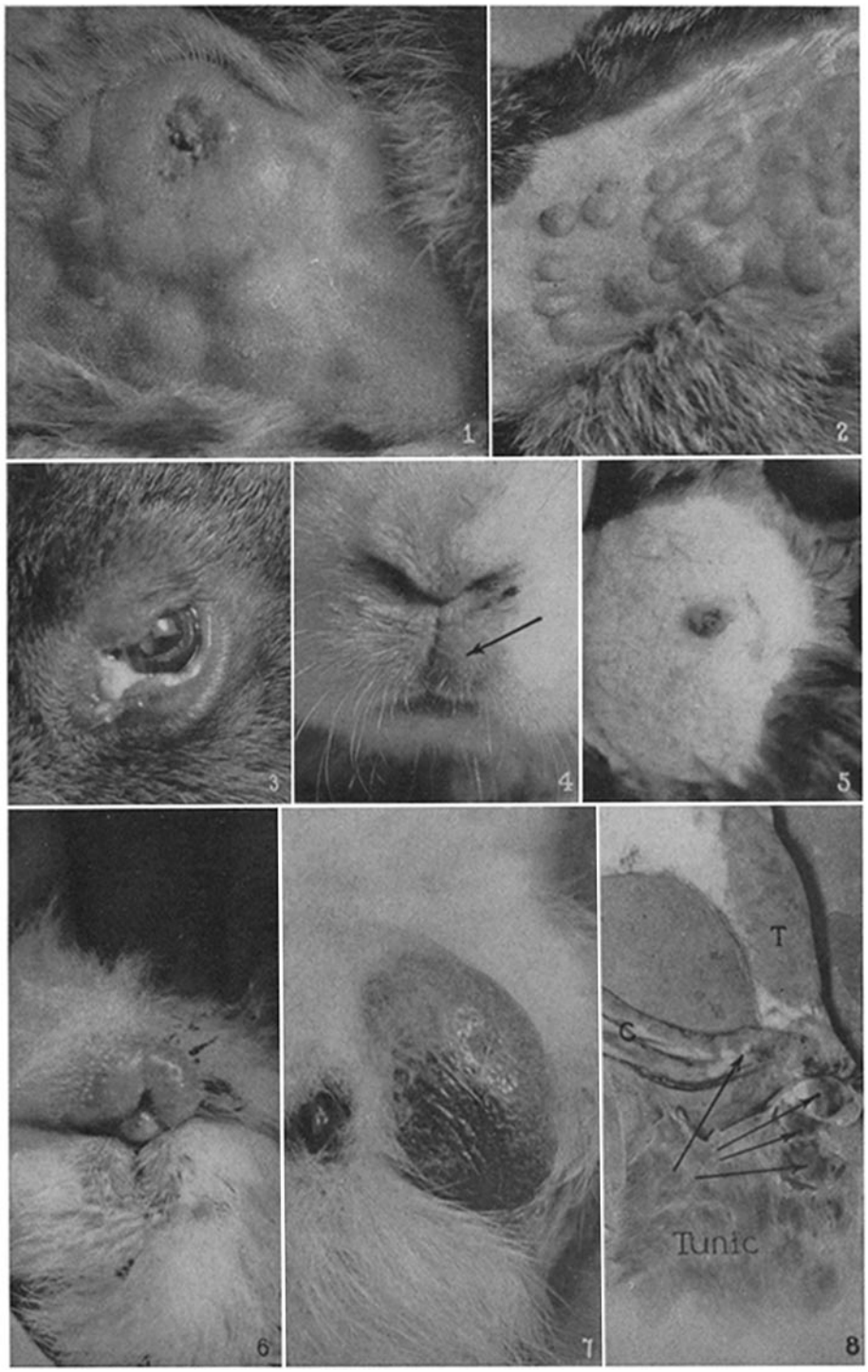
FIG. 20. Metastasis in spleen. Eosin and methylene blue. × 125.

FIG. 21. Acidophilic cytoplasmic inclusions in epidermal cells. Eosin and methylene blue. × 800.

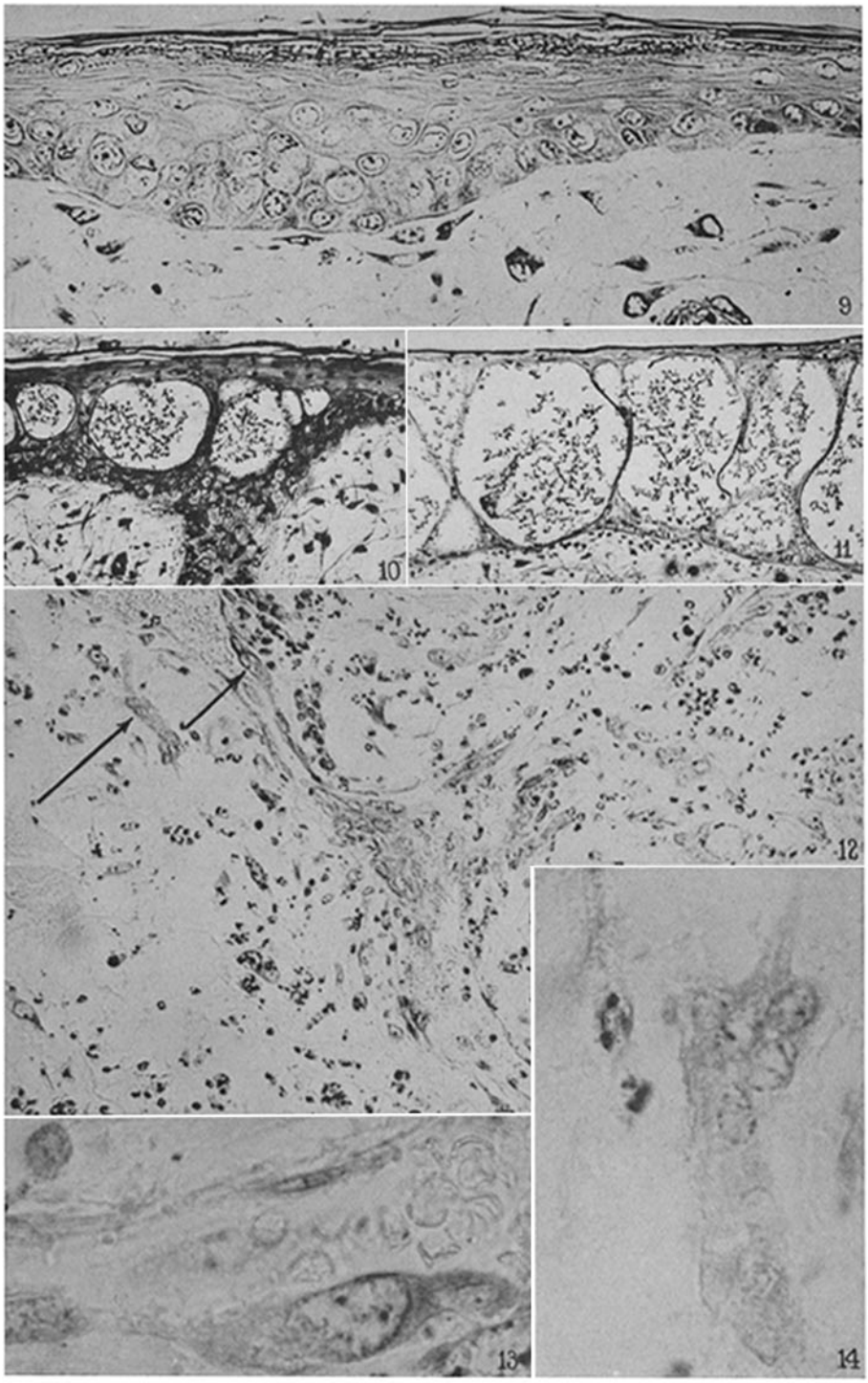
FIG. 22. Acidophilic cytoplasmic inclusions in epithelial cells of epididymis. Compare with Fig. 16. Eosin and methylene blue. × 1000.

FIG. 23. Epidermal cell with vacuolated nucleus and granular acidophilic cytoplasmic inclusion in which are situated three blue coccoid bodies. Giemsa. × 1500.

FIGS. 24, 25. Myxoma cells. Note fragmentation of chromatin. Giemsa, and eosin and methylene blue respectively. × 1500.



(Rivers: Infectious myxomatosis of rabbits)



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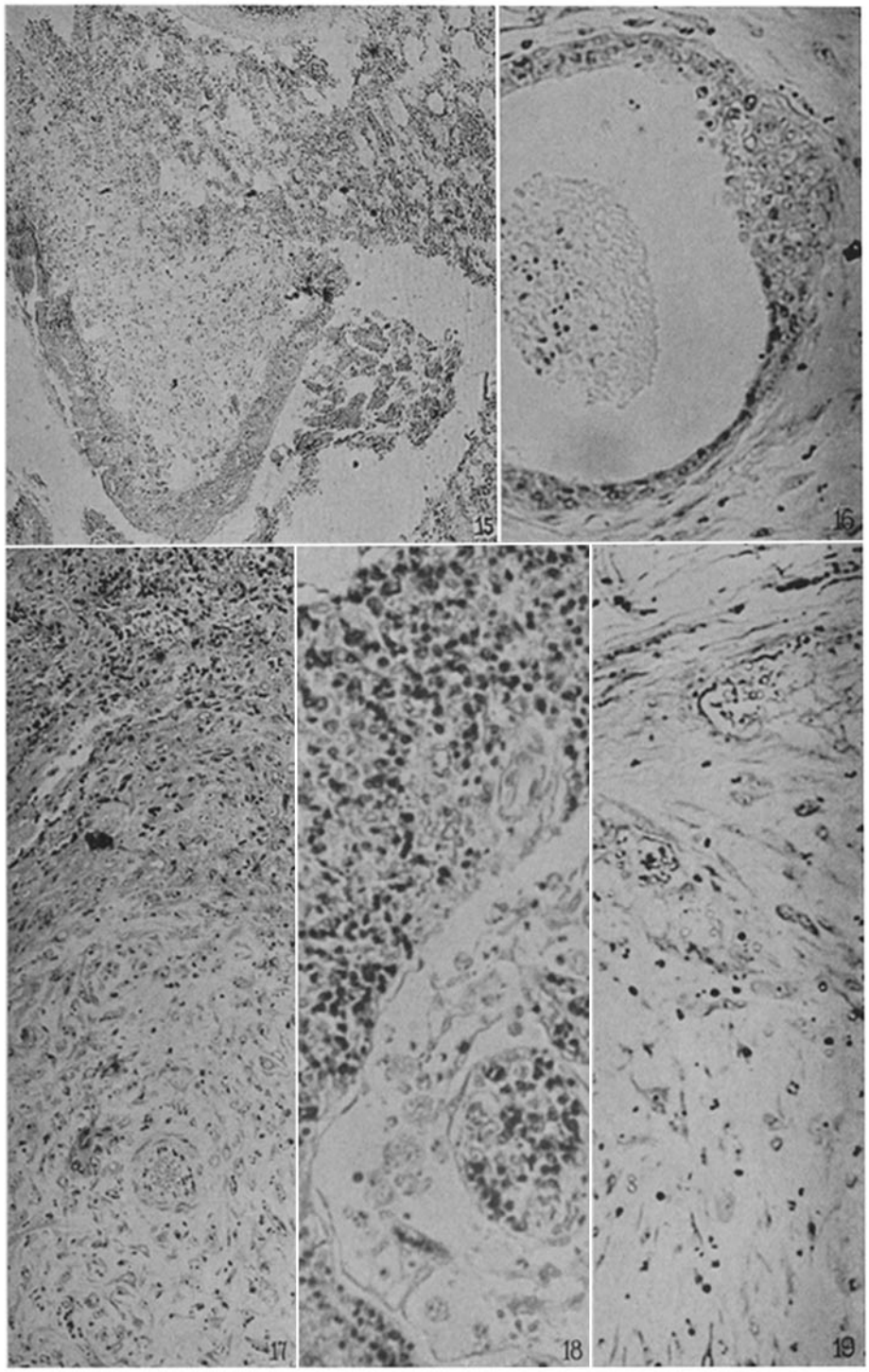

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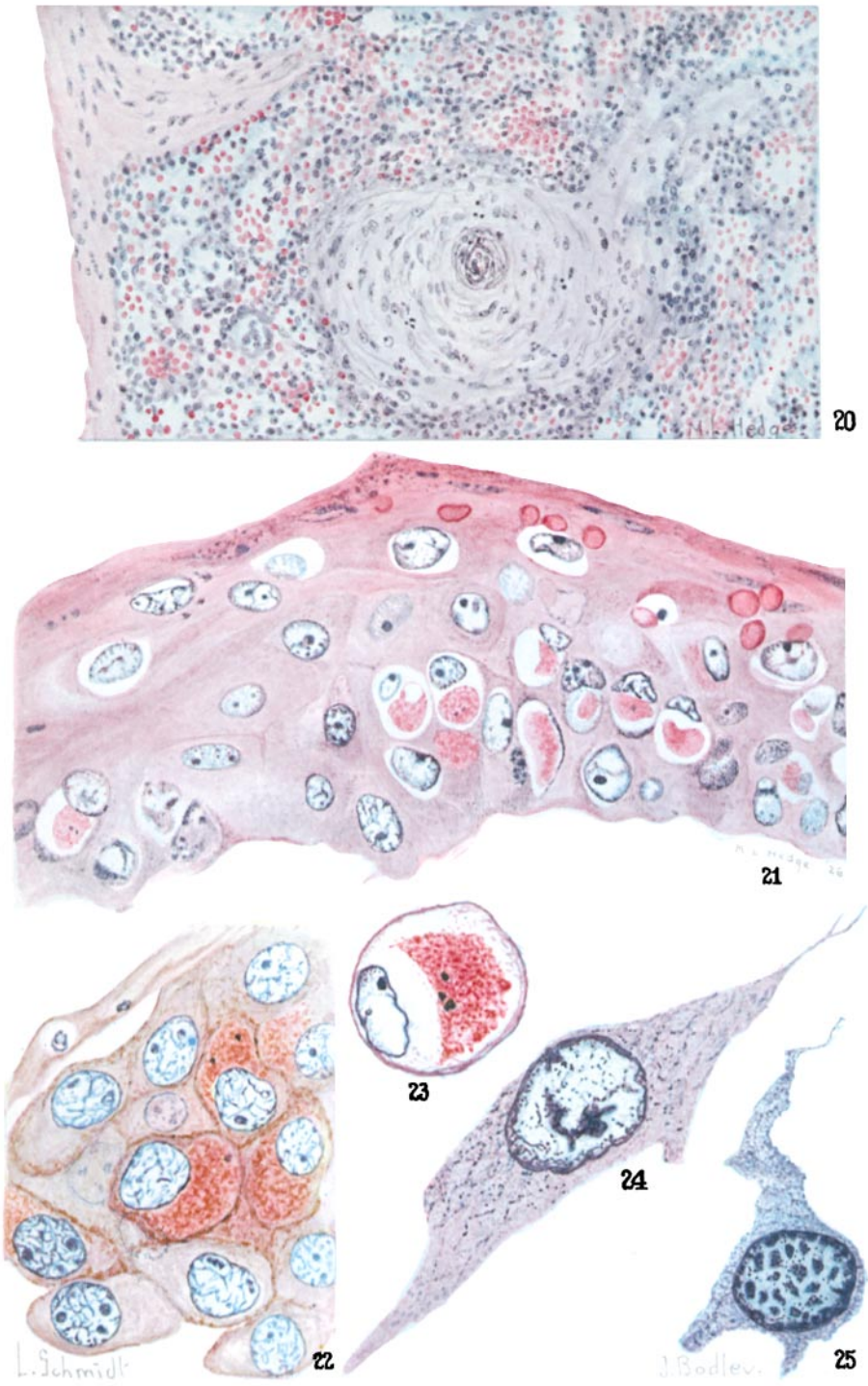

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