

RABBIT POX

II. PATHOLOGY OF THE EPIDEMIC DISEASE

BY HARRY S. N. GREENE, M.D.

(From the Laboratories of The Rockefeller Institute for Medical Research)

PLATES 22 TO 24

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The clinical manifestations of epidemic rabbit pox have been described.¹ The purpose of this paper is to record the results of pathological examinations.

Material and Methods

The epidemic of rabbit pox was preceded by an increase in gastrointestinal and nutritive disorders and infections of the upper respiratory tract with a consequent increase in the number of deaths due to those causes. These conditions were prevalent during the epidemic so that animals coming to autopsy represented not only deaths due to rabbit pox, but also deaths due to other causes and to rabbit pox complicated by other conditions.

During the epidemic, postmortem examinations were made on over 900 rabbits. These included deaths from various causes and animals killed for the purpose of obtaining material representing all stages of the disease uncomplicated by other conditions. The methods employed in the collection of material were outlined in the previous paper. Tissues were fixed in 10 per cent formalin, Zenker's and Helly's fluids and sectioned in paraffin. Sections were stained with hematoxylin and eosin; Giemsa's stain was also used in examinations made for inclusion bodies.

Gross Postmortem Findings

The postmortem picture was not always characteristic and in some cases diagnosis was questionable, owing to the absence of distinctive macroscopic lesions or to the confusion created by other conditions prevalent at the time. As a rule, however, marked alteration in the gross appearance of tissues and organs and the occurrence of widespread focal lesions in the skin or elsewhere made identification of the disease possible.

¹ Greene, H. S. N., *J. Exp. Med.*, 1934, **60**, 427.

Areas of focal infiltration and necrosis were nearly always present and formed the most definite evidence of infection. Apart from the skin (Figs. 1, 2), mouth (Figs. 8, 9) and upper respiratory tract, they occurred with the greatest frequency in the liver, spleen and lungs, but were found in every organ of the body with the exception of the brain and kidneys.

The general appearance of animals dying from fulminating infections necessarily differed from that of animals in which the course of disease was more protracted. As a general rule, however, animals were well nourished with an abundance of fat in normal depots, and only in those cases associated with obstruction of the pharynx or with extensive ulceration of the tongue and mouth was extreme emaciation found.

Subcutaneous tissues were often markedly edematous and pea-sized nodules of necrosis were occasionally found in fat and connective tissue. Muscle and serous membranes rarely showed clearly defined focal lesions but small miliary hemorrhages were common (Fig. 3).

Lesions within the Abdominal Cavity

The peritoneal cavity usually contained an excess of free fluid which in rare cases was blood-stained. Small areas of fat necrosis were common in the omental, mesenteric and retroperitoneal fat, and occasionally characteristic pearly white nodules of pin-head size were scattered over the surface of the peritoneum.

Stomach and Intestine.—The stomach was usually filled with food, and in many cases, although autopsy quickly followed death, digestion and perforation of the walls had occurred. Small petechial hemorrhages were occasionally found on the surface of the cecum and small bowel, but otherwise focal lesions were extremely rare.

In some cases, the intestines were distended with fluid and gaseous material and the anal region stained with diarrheal discharges. In others the cecum and upper portion of the colon were filled with masses of fecal material which were hard and dry or of a stiff, putty-like consistency. These masses were of variable extent and usually they were separated by accumulations of a thick tenacious mucoid material. Occasionally, this condition was found in the lower portion of the small as well as in the large intestine. It was also present in animals dying of other causes before and during the epidemic so that it cannot be regarded as peculiar to rabbit pox. It is rather evidence of an abnormality connected with the epidemic and accentuated by pox infection.

Liver.—The liver was always involved and usually had a characteristic appearance. In typical cases it was moderately enlarged, firm in consistency and pale yellow or yellowish brown in color with a profusion of translucent pearly white or opaque grey nodules a millimeter or more in diameter scattered over its surface and distributed throughout the organ (Fig. 5); nodules were occasionally found in the wall of the gall bladder. In some instances, these small lesions were accompanied by larger irregular areas of necrosis measuring as much as 0.5 cm. in

diameter. In other cases the liver was markedly enlarged and showed an extreme degree of yellowish red mottling suggestive of passive congestion. In fulminating cases, characteristic nodules were usually absent.

Spleen.—The spleen was invariably affected, and as a rule was moderately enlarged, dark red in color, firm and showed a few small areas of necrosis comparable with those found in the liver (Fig. 6).² The greatest enlargement occurred in fulminating cases and in those associated with secondary infection. Under these conditions the spleen was soft and considerable blood and pulp could be scraped from its cut surface. Exceptionally, the organ was normal in size, a dirty greyish brown in color and showed numerous focal lesions.

Kidneys and Adrenals.—The kidneys were enlarged and pale but characteristic macroscopic lesions were never demonstrated. The adrenals were usually large and greyish yellow in color; they were soft and showed a loss of architectural definition suggestive of autolysis, but occasionally distinct areas of focal necrosis were found.

Genitalia.—In the female the ovaries and uterus were often riddled with focal lesions. Infection of the uterus was frequently accompanied by a purulent exudate and abscesses were sometimes found in the wall. This was particularly true of animals which had recently aborted or given birth to young. The testicles of the male were always enlarged, and in most instances contained numerous focal and diffuse areas of necrosis varying from minute nodules to lesions a centimeter or more in diameter. Edema and hemorrhage were present in some cases.

Lesions within the Thorax

The pleural and pericardial cavities usually contained an excess of clear fluid and occasionally were markedly distended. Purulent exudates were not seen. Focal lesions were common on pleural surfaces but rare on the pericardium.

Lungs.—The lungs showed a variety of conditions. Visible or palpable lesions were nearly always present but occasionally the lungs were normal in appearance. The most constant lesion was a small subpleural nodule, and in some instances these were peppered thickly over all surfaces (Fig. 4). In early and uncomplicated infections, these translucent or pearly white nodules were frequently the only lesions present. More advanced cases showed typically necrotic, miliary nodules and occasionally larger pea-sized areas of necrosis with irregular patches of consolidation (Fig. 7). These areas of consolidation frequently measured a centimeter or more in diameter on the pleural surface and extended into the underlying tissue of the lung as a conical or wedge-shaped mass. They were greyish yellow or a dirty greenish grey color and sometimes were surrounded by a narrow zone of

² The spleens shown in Figs. 5 and 6 are from Belgian hares. The enlargement is more marked than was generally observed at autopsy and is due in part to a coincident abnormality of the spleen found among animals of this breed in our colony.

hemorrhage or congestion as in the case of an infarct. Occasionally these were the only macroscopic lesions found. Diffuse consolidation of one or more lobes was seen in some animals but was less frequent than other lesions.

The trachea and bronchi appeared normal in early cases. In more advanced cases, they usually contained an abundance of white frothy material which rarely was blood-stained.

Heart.—The heart was usually pale in color, soft and relaxed. In other instances it was normal in appearance. In a few cases marked distension of all chambers with fluid blood was noted. Rarely focal lesions were found in the myocardium.

Thymus.—The thymus was generally enlarged and occasionally markedly edematous. Petechial hemorrhages were of almost constant occurrence and focal areas of necrosis were common.

Lesions of Miscellaneous Organs

Lymph Nodes.—Lymph nodes were not universally affected. The most pronounced abnormalities were found in the pharyngeal and deep cervical nodes and in the superficial nodes in general, especially the popliteals. As a rule, these nodes were swollen and edematous and frequently showed characteristic focal lesions; occasionally they were dark red in color or contained petechial hemorrhages. In contrast with this, characteristic changes were rarely seen in the thoracic and abdominal nodes. Occasionally they were slightly swollen and edematous but, as a rule, no gross alterations could be detected.

Bone Marrow and Periosteum.—The bone marrow was always abundant but showed many variations in color and consistency. Frequently it was reddish grey in color with small scattered hemorrhages and larger greyish areas of necrosis. Under such conditions it was generally of normal consistency. In many instances it was uniformly grey in color and cheese-like in consistency. Rarely it was dark red and fluid.

The periosteum often showed greyish red elevated thickenings interspersed with areas of hemorrhage. These lesions were most common in the periosteum of the flat bones of the skull.

Thyroid and Parathyroids.—The thyroid, as a rule, was small and pale and often showed focal lesions. Parathyroids were likewise generally small but focal lesions were much less common.

Brain and Spinal Cord.—The brain ordinarily showed no other abnormality than an engorgement of pial vessels. In a few cases there was a slight increase in the amount of cerebrospinal fluid, and in one animal the ependyma of the lateral ventricles was markedly granular.

The spinal cord was usually normal in appearance. In a few instances it was slightly swollen and edematous.

Submaxillary Gland.—The submaxillary gland was almost invariably enlarged and contained localized and diffused areas of necrosis.

Microscopic Findings

Both in the gross and microscopically, the most distinctive lesion in all organs and tissues was the sharply circumscribed nodule or papule. More diffuse lesions arising either from the coalescing of adjoining nodules or the simultaneous affection of large areas were also common. Microscopically, the composition of these lesions varied somewhat with their location and age but, in general, affected areas showed comparable histological changes.

The fully developed nodule or papule was found to be made up of a central area of necrosis in which cell outlines and cell types were completely lost, surrounded by a zone of mononuclear cell infiltration. This zone and the neighboring tissues were usually edematous and occasionally hemorrhagic. In the more diffuse lesions the focal character was entirely lost, large areas of tissue were infiltrated, necrosis was widespread and edema was marked. Both types were found together in fatal infections, but among animals killed in early stages of the disease there was a notable tendency for the lesions of a given animal to be limited to either the discrete or the diffuse form.

Skin and Mucous Membrane.—Characteristic lesions of the various types were found in the corium and subcutaneous tissues. The epithelial changes characteristic of small pox in man were not found. In early lesions the epidermis remained intact and unaltered. Pathological changes were demonstrable only in those cases associated with large necrotic areas in the corium. These consisted in atrophy and degeneration and suggested secondary nutritional or pressure disturbances rather than the localization of the specific cause of the disease in the epidermis itself.³

Similar lesions were found in the mucous membranes of the mouth and pharynx but in this situation focal lesions were generally larger and diffuse edematous infiltrations were of more frequent occurrence.

A large amount of material from fatal cases of infection and from animals killed at earlier stages of the disease was examined with a view to determining the pathogenesis of focal and diffuse lesions. It was found that in both cases the lesions began as a vascular or perivascular process affecting blood vessels and lymphatics, but the devel-

³ In a recent epidemic of a disease presenting identical clinical signs and symptoms, the lesions of the skin were not limited to the corium, but were also found in the epidermis where they consisted of focal epithelial degeneration, vacuolization and vesicle formation. This disease was less contagious and far less fatal than that described in this report.

opment of the lesion was most clearly defined in the case of the smaller blood vessels. In the earliest lesions the endothelium of affected vessels was swollen and granular and occasionally detached. There was no apparent alteration in the walls of the vessel, but the perivascular tissues were slightly distended with a serous exudate and contained a few cells grouped in loose collar formation about the affected vessels. The cells were chiefly large mononuclears with some lymphocytes and occasional polymorphonuclear and red blood cells. There was also an appreciable tendency to the accumulation of leucocytes in the lumen of the vessel, and occasionally cells were seen penetrating the vessel wall.

As the lesion progressed, the process assumed either a focal or diffuse form. In the case of focal lesions (Fig. 14), the accumulation of cells increased both inside and outside of the vessel. The walls of the vessel showed hyaline changes and eventually the outlines of the vessel were lost. The cells at the center of the nodule thus formed became necrotic and disintegrated so that cell outlines and cell types were no longer recognizable. At this stage, the lesion was composed of a central area of necrosis surrounded by a zone of mononuclear cells of variable extent. This zone and the adjacent tissues were edematous as a rule, and occasionally hemorrhagic.

Lesions of this type varied from extremely minute granules to masses a centimeter or more in diameter. They were widely scattered or in close proximity to one another but, as a rule, the intervening tissues were little if at all affected.

Diffuse lesions differed from the focal in that, from the beginning, there was a more widespread involvement of blood vessels and lymphatics with less tendency to the concentration of cellular elements about affected vessels. In typical cases, cells and fluid were spread diffusely through the tissues (Fig. 13); mononuclear cells still predominated but there was considerable increase in the relative number of polymorphonuclear and red blood cells. Widespread edema and extensive necrosis of tissues were characteristic features of these lesions and hemorrhage was a frequent occurrence.

There was no truly pustular stage in the development of either focal or diffuse lesions. With the extension of the necrosis in the deeper layers of the skin, the blood supply to adjacent tissues was cut off or

impaired, giving rise to an anemic necrosis which frequently extended well beyond the limits of the specific lesion. In this way many focal lesions extended to the surface with the formation of ulcers covered by crusts, while confluent and diffuse lesions gave rise to mass necrosis or gangrene followed by sloughing of larger masses of tissue.

There was no evidence that a pyogenic or other secondary infection played any part in the production of these lesions. Focal and diffuse reactions had a common mode of origin, but from the beginning they pursued a different course. Evidently the difference was mainly one of degree and was referable to the extent of the vascular injury on the one hand, and the ability of the animal to limit the action of the causative agent on the other. As a rule, given animals showed a tendency to one type of reaction or the other, but with the progress of the disease focal lesions frequently became confluent and occasionally gave way to an outspoken diffuse reaction.

Lungs.—The lungs showed focal and diffuse lesions comparable in all respects with those of the skin. Circumscribed areas of mononuclear infiltration were found in the vicinity of small blood vessels (Figs. 12, 15) and occurred with the greatest frequency near the pleural surface of the lung, but were also situated deep in its substance and occasionally were scattered profusely throughout a section. They were rarely as sharply circumscribed as those found in the skin, and frequently alveolar walls extending from such foci were infiltrated and swollen with exudate. Occasional sections showed thickening and infiltration of alveolar walls with no clearly defined focal lesions. This infiltration was sometimes widespread but more often occurred in scattered patches without relation to the bronchi. More diffuse lesions in which large areas were infiltrated with an exudate rich in mononuclear cells and fluid and containing many polymorphonuclears were common in more advanced cases of infection, but were also found in association with early focal infiltrations. Older lesions showed varying degrees of degeneration, and in fatal cases total necrosis of an entire lobe was not uncommon. Lesions of this kind were comparable with the areas of mass necrosis seen in the skin. In rare instances, there were also extensive areas of consolidation composed mainly of polymorphonuclear cells which appeared to be due to the action of some secondary invader.

In early cases of infection the peribronchial lymphatic tissue was generally hyperplastic, but the bronchi themselves showed no pathological alteration. In many fatal cases, however, their walls were infiltrated and necrotic and their lumina plugged with exudate and desquamated epithelial cells. The absence of primary bronchial changes and the great frequency of focal interstitial lesions would suggest that the infection spread through blood and lymphatic channels rather than through bronchial passages.

Liver.—The liver was occasionally engorged with blood but, as a rule, showed in addition to the focal and diffuse areas of infiltration and necrosis only an extreme degree of cloudy swelling. Early foci were closely associated with blood vessels in the portal spaces (Fig. 10) but older and more diffuse lesions extended into the liver parenchyma and resulted in extensive destruction of lobules. Fatty degeneration was marked in some cases but was also a common finding in animals which showed no evidence of pox infection. In fulminating infections, typical focal necroses were not found and the microscopic picture was that of an acute diffuse degeneration and necrosis involving the whole organ. Individual cells were swollen, granular and indistinct with pyknotic nuclei, and in scattered areas were definitely necrotic. Mononuclear infiltrations were absent.

Spleen, Lymph Nodes and Bone Marrow.—The spleen showed a varying degree of congestion, which in some cases was extreme. The sinuses were distended and contained an excessive number of mononuclear cells; polymorphonuclear leucocytes were rare. Immature leucocytes and nucleated red cells were common. Malpighian corpuscles were generally enlarged, edematous and contained cells larger and more granular than normal; rarely the corpuscles were reduced in size. Focal and diffuse areas of necrosis were found in many instances. Focal lesions were most frequent on the surface but were also found in Malpighian corpuscles. Occasionally necrosis was widespread throughout the organ, the pulp consisting of a homogeneous mass of degenerating cells and pigment, while the Malpighian corpuscles were represented by nests of nuclear detritus.

Superficial lymph nodes were generally hyperplastic with large active germinal centers. Their increased size, however, was in large part due to edema. Sinuses were distended with fluid and individual cells widely separated. The deep cervical nodes were most markedly affected and frequently showed cystic dilatation of their medullary sinuses. These changes were often accompanied by discrete and diffuse areas of necrosis and, in many instances, entire nodes were necrotic.

The bone marrow in many fatal cases was involved in so widespread a necrosis that many sections failed to show a single normal cell (Fig. 11). In other instances small focal necroses were scattered throughout and hemorrhages were common. In less affected areas vessels were engorged with blood, large and small mononuclear cells were abundant, while polymorphonuclear cells were rare.

Miscellaneous Organs.—Cloudy swelling in the kidneys was so marked that many tubules were completely occluded. Other tubular or glomerular changes did not occur and necrotic foci were never found.

The adrenals often showed focal areas of necrosis. Widespread degeneration and disintegration were common in fatal cases but may have been of postmortem origin. In animals killed and immediately autopsied, however, similar but less marked changes were found. Diffuse areas of necrosis were of rare occurrence.

Discrete and diffuse areas of necrosis were common in the testicle. In early lesions there were scattered patches of mononuclear cells in the interstitial tissue and around the tubules. These increased and eventually became necrotic. In

some instances, the necrosis was limited to small areas, while in others there was widespread necrosis of interstitial tissue and tubules.

The ovaries were usually hyperemic and frequently showed focal lesions. Simple cysts were also common. The walls of the uterus often contained multiple foci of necrosis and abscesses were occasionally found.

Necrotic foci, areas of hemorrhage and edema were frequent findings in the submaxillary gland, thyroid and thymus.

The walls of the gastrointestinal tract were generally hyperemic with small, scattered areas of hemorrhage and enlarged lymphoid follicles, but typical necrotic foci were not observed.

The heart showed no singular microscopic changes. Vacuoles were occasionally found in muscle fibers but cellular infiltrations or necrotic lesions were absent in the sections examined.

In other regions of the body muscle fibers were frequently separated by edema, and diffuse cellular infiltrations, hemorrhage and necrosis were common.

Many sections were taken from different parts of the brain, but aside from engorgement of vessels, no definite pathological changes were found.

Vascular Lesions.—Vascular damage was intimately associated with all lesions and formed the focus for the cellular infiltrations characteristic of the disease in all organs and tissues. Early changes consisting of swelling and desquamation of endothelial cells were found in small vessels and precapillaries in the vicinity of fresh infiltrations. In focal lesions the immediate surrounding tissues were infiltrated with mononuclear cells which, in some instances, could be observed migrating through the vessel wall. In diffuse lesions endothelial damage was more intense and more widespread. Later stages were characterized by hyaline degeneration and necrosis of the vessel wall. But in the larger vessels no distinctive lesion could be detected.

Inclusion Bodies.—A thorough search was made for inclusion bodies in specially cut and stained sections. Many tissues from animals in different stages of infection were examined, but in none were cytoplasmic or nuclear changes found which were sufficiently characteristic to be called inclusion bodies.

DISCUSSION

Epidemic rabbit pox is the most destructive contagious disease which we have encountered in the rabbit. Its extreme contagiousness and high mortality in certain classes of animals are comparable with the scourges of small pox in man and, in many other respects, the rabbit infection shows resemblances to this disease. In typical cases the characteristic features of small pox are duplicated and present the distinguishing signs of infection. The cutaneous eruption preceded by an erythematous rash and passing through the stages of papule, pustule and crust, the involvement of special organs, the complica-

tions and sequelae are similar in both diseases. The atypical forms of the two diseases also show similar modifications with lesions ranging from confluent eruptions to inconspicuous papules and systemic reactions varying from the complete absence of detectable symptoms to extreme prostration. The severity of the infection in pregnant and lactating females, the occurrence of abortions and the high mortality in young animals are especially significant.

Pathologically, the lesions in the skin of the rabbit were more deeply situated and resembled more closely those of the mucous membrane in man; they did not show the typical epithelial changes which have been described in the formation of vesicles and no typical inclusion bodies were found. In other respects the two diseases appear, both clinically and pathologically, to be essentially the same or identical. The absence of typical vesication and the failure to find inclusion bodies may be referable to the deep location and rapidly destructive nature of primary lesions. This assumption is borne out by subsequent experience with a less severe form of infection in which typical vesicles and inclusion bodies were present.

Characteristic lesions occurred with greatest frequency in the skin and mucous membranes of the mouth, nose and pharynx, in the lungs, liver, spleen, lymph nodes and bone marrow, and in the testicles and ovaries. In fatal cases of infection focal or diffuse lesions or both were nearly always present in these organs, but in some fulminating infections no lesions could be found in the skin.

Diffuse and focal lesions occurred together or as alternative processes, apparently depending upon the severity of the infection. In fulminating cases of disease, there was widespread degeneration and necrosis of cells comparable with those found in many infections and intoxications and in no way distinctive. The more common diffuse lesions, however, presented the characteristics of an acute inflammatory reaction in which extensive edema, a variable amount of hemorrhage, marked mononuclear but comparatively slight polymorphonuclear infiltration and widespread necrosis were distinctive features. Focal lesions consisted of clearly defined mononuclear infiltrations in which polymorphonuclear cells were almost entirely absent and edema and hemorrhage were less marked than in the diffuse form.

Focal lesions were intimately related to small blood vessels which usually showed varying degrees of endothelial damage. Diffuse lesions were also associated with vascular injury which, in cases not obscured by necrosis, was sometimes found widespread in small vessels and precapillaries. More frequently the damage was localized in single vessels, but was more intense than in focal lesions and accompanied by extensive edema and beginning necrosis in surrounding tissues, indicating that this type of diffuse lesion arose from extension of a focal process. In many fatal cases, however, necrosis was widespread and with loss of histological details, the original focal or diffuse nature of the lesion could not be determined. This was particularly true of pulmonary lesions which, in advanced cases, usually showed extensive consolidation with an exudate largely made up of mononuclear cells but also containing many polymorphonuclear cells and mass necrosis.

In view of the interest which has been manifested in the etiology of pneumonia in virus infections, it may be pointed out that lesions of this kind were not peculiar to the lungs. Similar processes were observed in the lesions of the skin which at times spread very rapidly with the development of a massive edema followed by necrosis and sloughing of the affected part. In these cases the exudate also contained a number of polymorphonuclear cells. Many of these animals survived, and it is worthy of note that the acute diffuse reaction was not followed by abscess formation as would be expected if the lesion were due to a secondary bacterial infection. Healing occurred as in the case of the typical focal lesion which supports the view that the diffuse reactions with edema, hemorrhage and infiltrations containing polymorphonuclear cells were produced by the action of the same agent which was concerned in the production of the focal lesions. From the information at hand, the action of a secondary invader cannot be excluded. At the same time, it must be remembered that the presence of a secondary invader does not prove that it played any essential part in the production of the lesion, and from the evidence available it appears that in this disease both the diffuse and the focal lesions were attributable to the same organism.

As a matter of fact, the diffuse reaction in the skin corresponds closely with the lesion usually obtained by a cutaneous or intracuta-

neous inoculation of vaccine virus, and any doubt concerning the etiology of pulmonary lesions is equally applicable to lesions of the skin, including those produced by inoculation with bacteria-free filtrates as well as the lesions seen in spontaneous infections.

Other lesions to which attention should be directed are those of the hematopoietic system, which in many fatal cases were so extensive that complete destruction of individual organs resulted. In such instances the spleen, bone marrow and many lymph nodes were so necrotic that microscopic identification depended rather on general outlines than on histological detail. The most constant finding, aside from the widespread necrosis in these organs, was the almost complete absence of polymorphonuclear cells. The sinuses of the spleen contained numerous mononuclear leucocytes but other forms were scanty, and in the bone marrow although their mononuclear antecedents were plentiful, polymorphonuclear cells themselves were extremely rare.

The remarkable healing of lesions of this disease in recovered animals is also worthy of mention. This was particularly noticeable in the organs of generation which, although most extensively affected, were repaired with restoration of spermatogenesis and ovulation. Cases were numerous in which clinical examination indicated universal and profound parenchymal damage. Yet such animals rapidly recovered normal functions and, in less than a month, were capable of active breeding service, and in general behavior could not be distinguished from normal animals.

Small pox was once regarded as among the most serious menaces to man, and in recognition of this fact protective measures were instituted which are unsurpassed by those employed against any other disease. Rabbit pox is clearly a serious menace to the rabbit and unless adequate precautions are taken, may seriously reduce the usefulness of the rabbit as an experimental animal. Typical cases of the disease are as easily detected as typical cases of small pox, but atypical and asymptomatic infections might escape detection or be mistaken for snuffles or for some innocuous disease. But because of their insidious and highly contagious nature they are a highly dangerous form of infection. Careful examination will, however, reveal sufficiently definite signs of infection in all forms of the disease to arouse suspicion or to make a positive diagnosis. From previous experience, it also

appears that if sporadic cases of infection are detected before the disease has become epidemic, the infection can be suppressed by the destruction or isolation of infected and exposed animals. Such measures are apparently of no avail during the height of an epidemic.

The probable origin of the epidemic will be discussed in a subsequent paper. It may be said, however, that available evidence indicates that the infection which was responsible for the present epidemic was not introduced from the outside but originated in the Institute and was either masked by some other disease or spread in atypical form and thus escaped attention until it reached the breeding colony as an outspoken epidemic disease.

Finally, clinical and pathological evidence lead to the conclusion that rabbit pox is comparable with small pox in man and that it is produced by an agent closely related to the virus of small pox.

SUMMARY AND CONCLUSIONS

The lesions found in animals with epidemic rabbit pox have been described in this paper. The most distinctive gross lesion in all organs and tissues was the small nodule or papule which was found to consist of mononuclear infiltration and necrosis. Diffuse lesions were also found in which the infiltration was widespread and accompanied by edema, hemorrhage and extensive necrosis of affected tissues and organs. The possibility of the diffuse lesions being due to the action of secondary invaders was considered, but available evidence indicated that the different types, including pneumonia, represented reactions to a single causative agent. Moreover, an intimate relationship was observed to exist between lesions and small blood vessels in which primary endothelial damage was usually apparent. The degree of vascular damage generally corresponded to the extent of the lesion and it is probable that this in turn corresponded to the dose of the causative agent.

The close analogy between the clinical manifestations and pathological processes of this disease in the rabbit and small pox in man led to the conclusion that the disease in the rabbit is essentially the same as small pox, and that it is probably produced by a virus closely related to the virus of small pox. Available evidence indicated that the infection originated in the Institute and that it spread in atypical form or

masked by some other disease until it reached the breeding colony as a clearly defined epidemic infection.

EXPLANATION OF PLATES

PLATE 22

FIG. 1. Undersurface of the skin from a fatal case of rabbit pox showing numerous papular lesions and a wide discolored zone of edematous infiltration. The variation in the size of individual lesions and the concentration of lesions in vascular areas as shown in this photograph were typical findings. Natural size.

FIG. 2. Undersurface of the skin from a fatal case of infection showing discrete lesions of the hemorrhagic type and their relationship to blood vessels. $\times 3/4$.

FIG. 3. Hind quarters of a young animal killed late in the course of disease. Areas of hemorrhage and mononuclear infiltration were widespread throughout the skeletal musculature. Natural size.

PLATE 23

FIG. 4. Lungs from a fatal case of infection in a young animal showing numerous subpleural miliary nodules. Similar lesions were found deep in the substance of the lung but pneumonic consolidation was absent. Natural size.

FIG. 5. Liver and spleen from a young animal. Small focal areas of necrosis are distributed profusely throughout the liver. The spleen is enlarged and shows a few scattered discrete lesions. Microscopically, the sinuses were distended with large degenerating mononuclear cells and Malpighian corpuscles were poorly defined and consisted of similar elements interspersed with nuclear detritus. Natural size.

FIG. 6. Spleen from an adult animal showing marked enlargement and large subcapsular foci of necrosis. Lesions of this kind were unusual. Natural size.

FIG. 7. Lungs from an adult animal showing diffuse consolidation and large subpleural nodules with umbilicated centers. Compare with Figs. 8 and 9. Natural size.

FIGS. 8 and 9. Tongue. Large umbilicated nodules were commonly found in this situation. Microscopically, they consisted of subepithelial mononuclear infiltration which extended deeply into the underlying muscle, but the epidermis itself showed no specific changes. Natural size.

PLATE 24

FIG. 10. Section of the liver from an animal killed during the course of the disease showing degeneration of parenchymatous cells and an early focus of mononuclear cell infiltration in the portal connective tissue. In other sections all stages in the further development of this lesion could be traced from a more pronounced infiltration involving neighboring lobules to final necrosis. $\times 275$.

FIG. 11. Section of bone marrow from a fatal case of infection in an adult

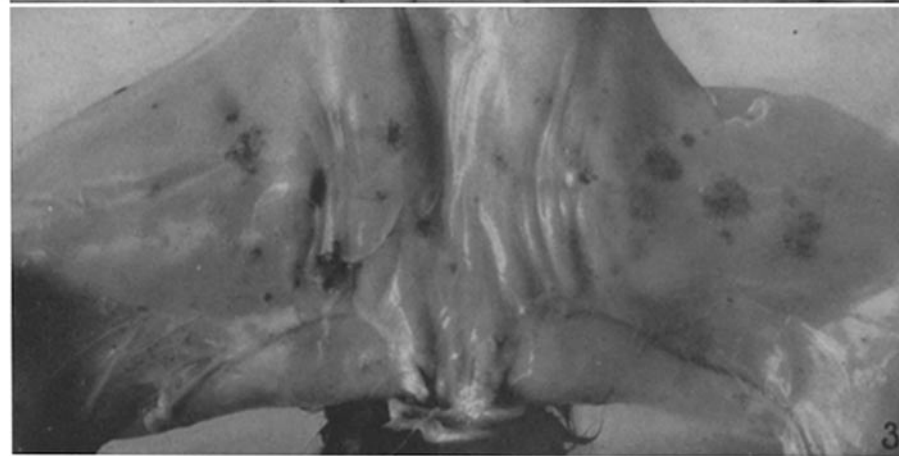
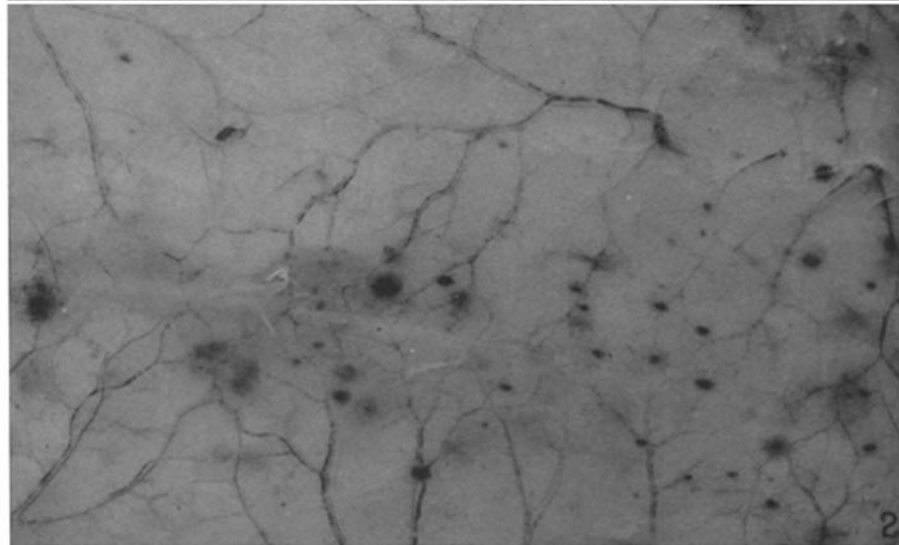
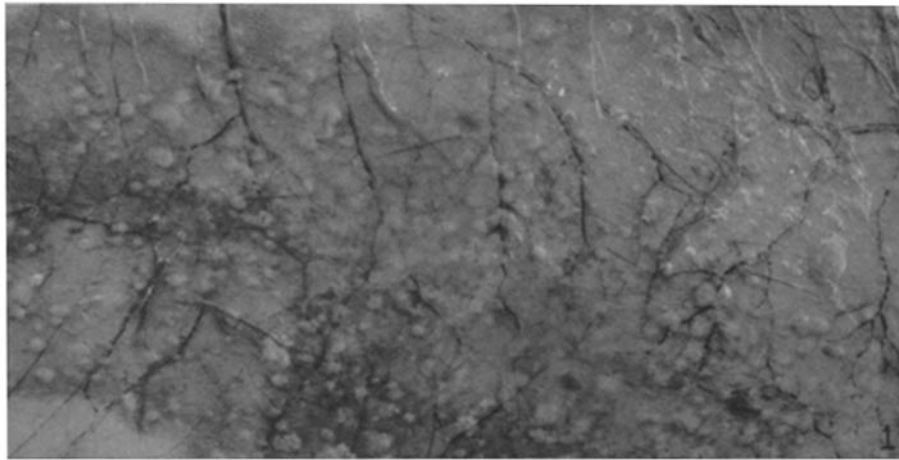
animal. There is widespread necrosis of hematopoietic tissue and no intact cells can be found. $\times 75$.

FIG. 12. Section of lung from an animal killed in an early stage of disease. The lesion is deep in the substance of the organ and consists of a focal mononuclear infiltration with exudation into the alveoli and extension of the infiltration in alveolar walls toward the pleural surface. A blood vessel near the pleural surface contains an excessive number of mononuclear cells. $\times 90$.

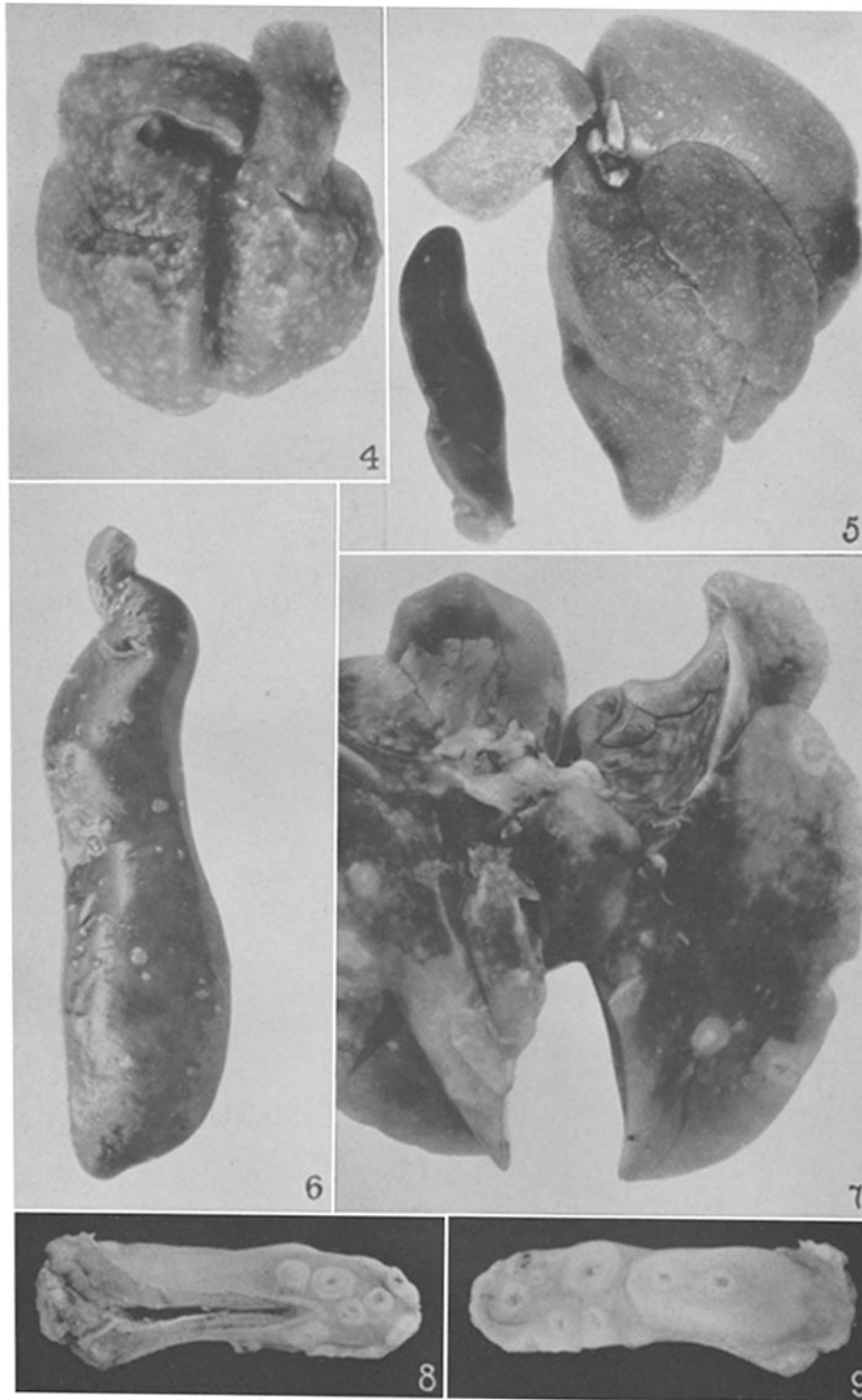
FIG. 13. Section of the lip showing a diffuse infiltration of deeper tissues including the muscle with mononuclear cells and fluid. $\times 130$.

FIG. 14. Section through an early lesion in the skin of the ear showing mononuclear infiltration about a small blood vessel in the corium, destruction of endothelial cells and hyaline changes in the vessel wall. There were no specific epithelial changes. $\times 130$.

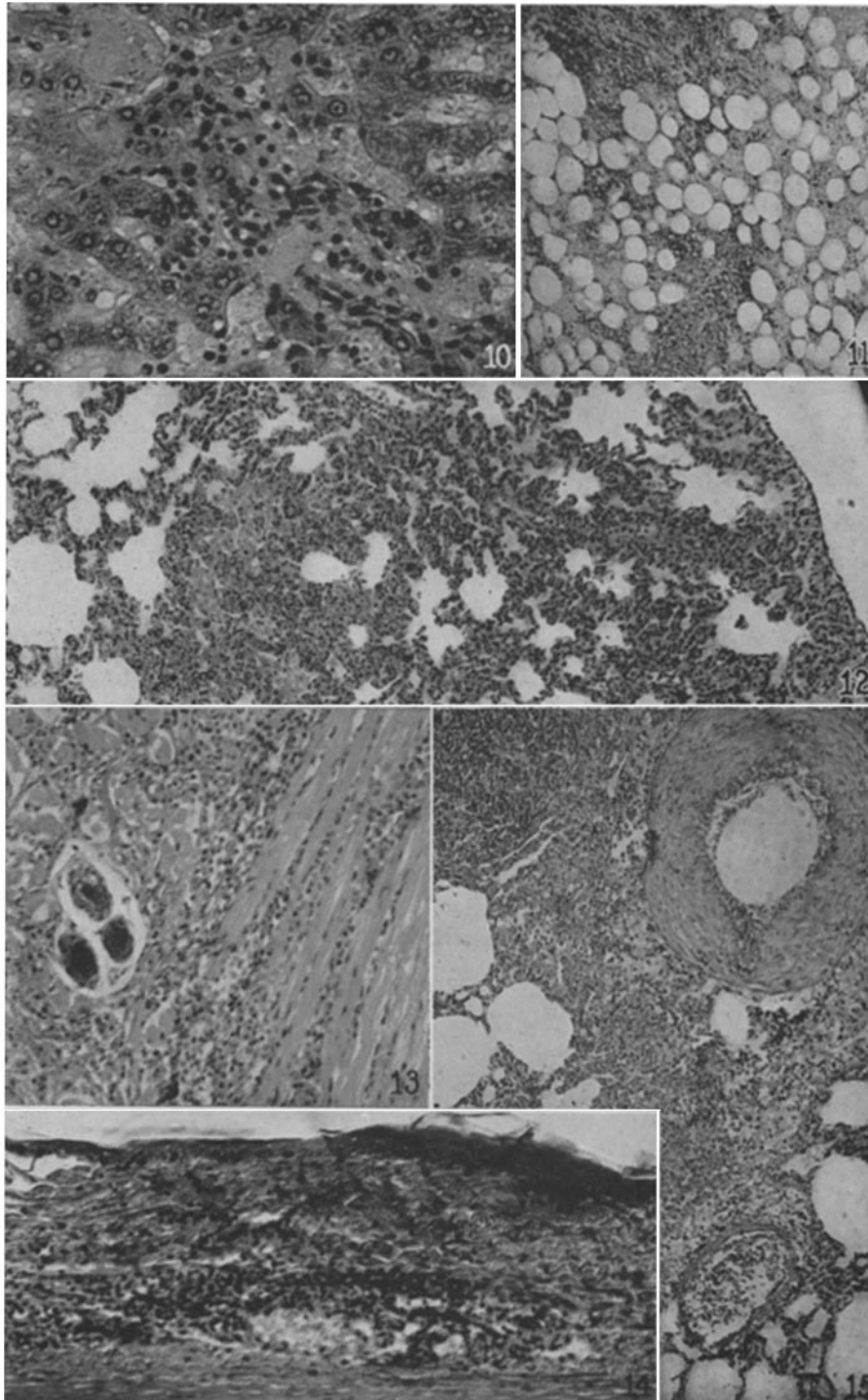
FIG. 15. Section through a lesion in the lung of an animal killed when the first external sign of infection was observed. The lesion has progressed to necrosis but has remained localized about two adjacent blood vessels which show advanced changes in the endothelial and muscular walls. $\times 75$.



(Greene: Rabbit pox. II)



(Greene: Rabbit pox. II)



Photographed by Louis Schmidt

(Greene: Rabbit pox. II)