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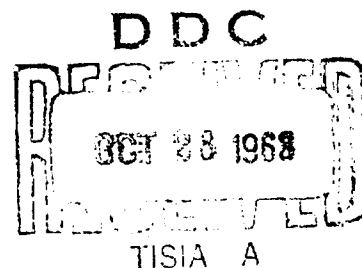
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TECHNICAL MANUSCRIPT 83

SPONTANEOUS SIMIAN GIANT-CELL PNEUMONIA WITH COEXISTENT B-VIRUS INFECTION

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BIOLOGICAL LABORATORIES
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SPONTANEOUS SIMIAN GIANT-CELL PNEUMONIA
WITH COEXISTENT B-VIRUS INFECTION

Peter J. Soto, Jr.

George A. Deauville

Pathology Division
DIRECTOR OF MEDICAL RESEARCH

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ABSTRACT

A morphologic study of three cases of giant-cell pneumonia is presented. These are most interesting in that a coexistent B-virus infection was present in two. A pure case of B-virus infection is included for comparison.

The pathogenesis of giant-cell pneumonia is discussed, with emphasis on the lack of clinical evidence of measles. The pathogenesis and pathology of B-virus is also discussed.

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I. INTRODUCTION

Giant-cell pneumonia (G.C.P.) as an abnormal response to an infection with the measles virus is now a well-documented entity in man, usually limited to children,¹⁻⁷ but recently described in an adult.⁸ It is an interstitial pneumonia characterized by the presence of specific syncytial-type epithelial giant cells containing nuclear and cytoplasmic inclusions. Similar giant cells may be seen in virtually all other nonlymphoid tissues. A second type of giant cell, the Alagna or Warthin-Finkeldey cell, usually unaccompanied by inclusions, may be seen in the lymphoid tissues including the lymph nodes, spleen, thymus, and lymphoid collections in the intestinal tract.

Spontaneous G.C.P. has been briefly described in two cynomolgus (Macaca philippinensis) monkeys⁹ and its reported incidence in the rhesus (Macaca mulatta) and green (Cercopithecus aethiops sabaeus) monkey is equally rare,^{10,11} although the studies of Peebles, et al.,¹² and more recently those of Meyer,¹³ have conclusively shown that antibodies to the measles virus were present in virtually all of their cynomolgus and rhesus monkeys within a relatively short period of time after capture.

It is the purpose of this manuscript to describe in detail three more cases of G.C.P. in rhesus monkeys, two of which are most interesting in that an infection with B-virus was also present. To our knowledge, this is the first reported instance in which these two viruses were present in the same host with concurrent pathological manifestations. A case representing pure B-virus infection is included for comparison.

II. MATERIAL AND METHODS

All monkeys referred to in this communication were obtained from India and brought to the United States by airplane and eventually to the animal farm at Fort Detrick, Maryland. During the period of flight and transport to Fort Detrick, the monkeys were housed ten per crate. The time interval from capture to arrival at Fort Detrick could not be determined, since no record was kept as to when a monkey was caught and how long it was held in India before being shipped to the United States.

Upon arrival at the animal farm, each monkey is routinely given 300,000 units of bicillin intramuscularly and 0.2 cubic centimeter of 1:10 dilution of old tuberculin intrapalpebrally.

During the reception period, the animals are tattooed for identification, examined externally for lesions, and only random monkeys are examined for the presence of the characteristic oral ulcer of B-virus infection. The tuberculin reactors are euthanized with pentobarbital sodium as soon as the test is read.* However, nonreactor monkeys with mouth lesions of B-virus are quarantined until the ulcers heal and then issued for experimental use.

The monkeys are housed two per cage. These cages are so constructed that feeding and cleaning offer no problem and ample room is provided. Excellent visibility is afforded for observing the condition of the monkeys.

The four monkeys reported here were approximately three years old and their weights varied from 2.5 to 3.0 kilograms. They were all considered to be clinically well and none had a rash during the short period in which they were observed. This period usually encompassed several days. Because these four animals were tuberculin reactors, they were euthanized and the tissues obtained at autopsy were fixed in buffered formalin and stained with hematoxylin and eosin.

III. PATHOLOGICAL OBSERVATIONS

A. CASE 1 (MONKEY X-27)

1. Gross Pathology

The left eyelids were covered by a yellow exudate and the upper lid (site of tuberculin test) was hyperemic.

The lungs were unremarkable except for marked focal areas of atelectasis and congestion. The lymph nodes in the hilar areas of the lungs as well as those in the abdomen were enlarged. The remaining viscera were not remarkable. No gross evidence of tuberculosis was found.

2. Microscopic Changes

Multiple sections of the lungs confirmed the gross impression of atelectasis and congestion. The adjacent aerated areas revealed septal thickening and a mononuclear cell infiltrate. The most distinctive feature observed was the proliferation of large numbers of the characteristic

* In conducting the research reported herein, the investigators adhered to "Principles of Laboratory Animal Care" as established by the National Society for Medical Research.

syncytial epithelial giant cell containing acidophilic nuclear and cytoplasmic inclusions identical to those seen in measles. The giant cells contained as many as 15 nuclei, and generally the inclusions did not completely fill the nuclei. The cytoplasmic inclusions varied considerably in size, with the largest about seven microns in diameter (Figure 1). Occasionally, mononuclear cells contained nuclear inclusions. Many of the giant cells were lying free in the air sac lumina and a few could be seen still attached to the alveolar wall. Intermingled with these giant cells were neutrophils and lymphocytes.

The majority of the bronchioles and larger bronchi also shared in this giant-cell reaction. Many giant cells with inclusions were still attached to the mucosa, while others were free in the lumen. There was little associated inflammatory reaction in the bronchi. However, many of the bronchioles exhibited necrosis of the epithelium with smudged giant cells.

A cross section of the lung mite (Pneumonyssus spp.) was observed in a dilated bronchus and here the usual attendant infiltration of eosinophils and lymphocytes was present. Giant cells containing nuclear and cytoplasmic inclusions were also present among these inflammatory cells.

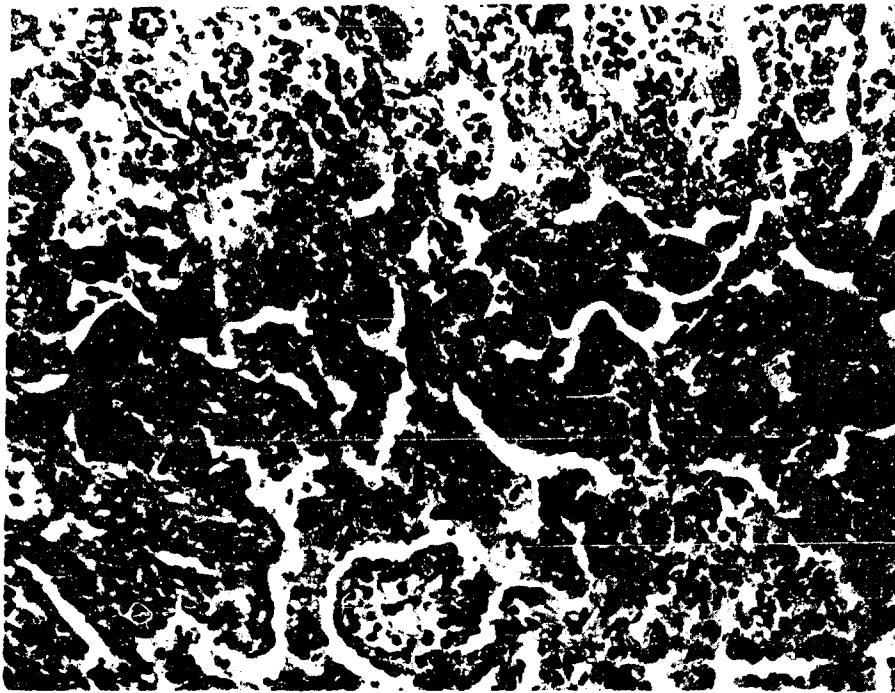
Characteristic Warthin-Finkeldey giant cells containing as many as 25 nuclei were present in several tracheobronchial and abdominal lymph nodes. All nodes showed reactive hyperplasia and several of the tracheobronchial group contained carbon and brown mite pigment. No inclusions were seen.

The kidney was most interesting in that two giant cells without definite inclusions were seen in the pelvic epithelium (Figure 2).

The hepatic parenchymal cells exhibited minimal cloudy swelling, and several bile ducts contained purplish cytoplasmic bodies in the lining cells, some of which measured up to six microns (Figure 3). These bodies did not resemble the inclusions observed in the lungs.

The pancreas disclosed several abortive giant cells that appeared to be arising from the acinar cells and contained as many as eight nuclei free of inclusions. The ducts were unremarkable. The spleen and esophagus were unremarkable. Sections of the eyelid showed chronic inflammation. No evidence of tuberculosis was found in any organ examined.

A



B

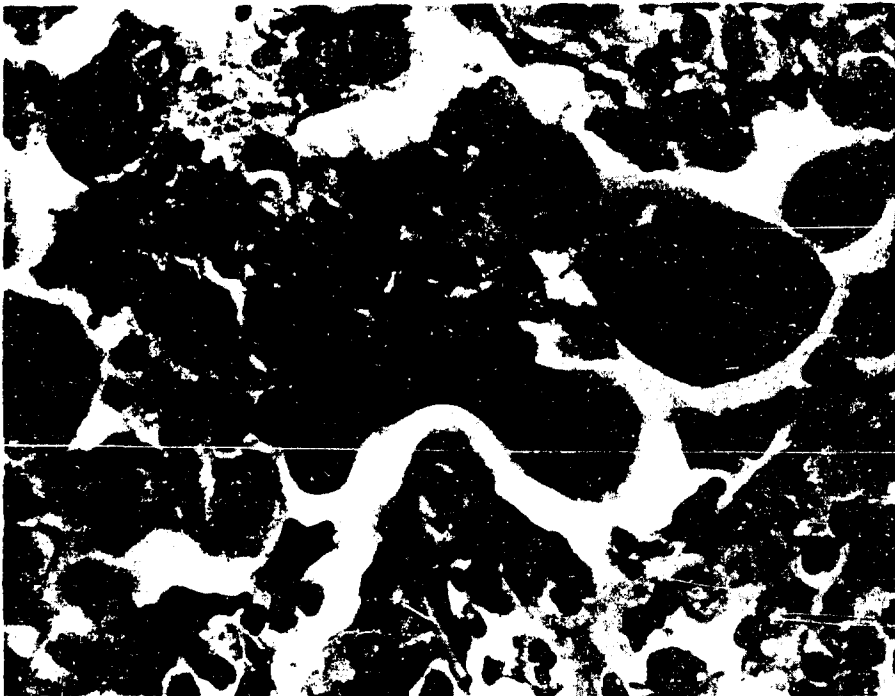


Figure 1. Lung, Case 1. A. Marked interstitial inflammation and thickening of alveolar septa. Numerous multinucleated syncytial giant cells arising from the alveolar septa. Nuclear inclusions are readily seen at this power. 220X. B. Higher magnification of A. Large giant cells with very prominent nuclear and cytoplasmic inclusions. 710X.

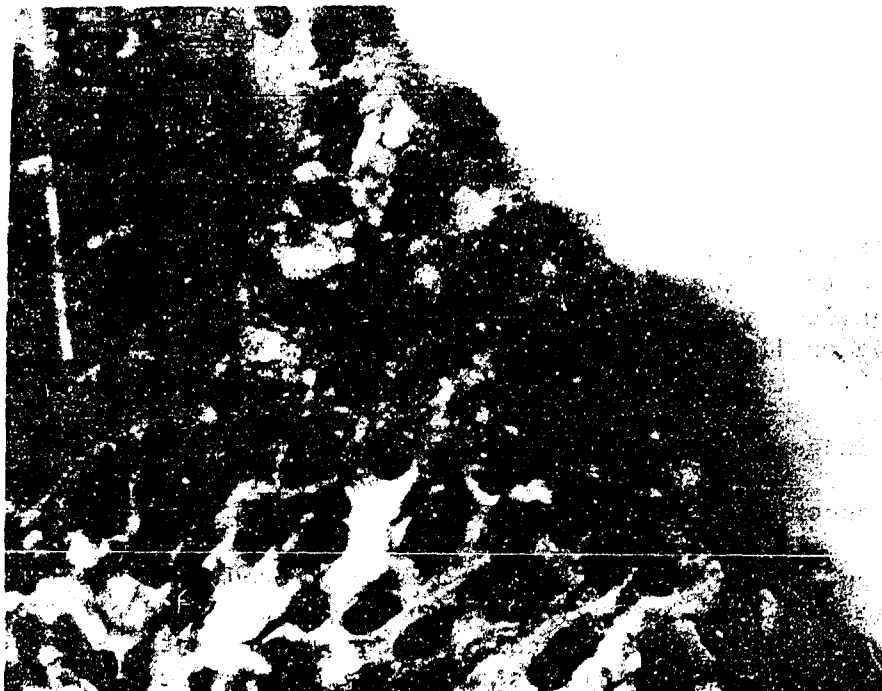


Figure 2. Kidney, Case 1. Two large multinucleated giant cells arising at the free edge of the epithelial lining of the renal pelvis. No inclusions were observed in these giant cells. 840X.

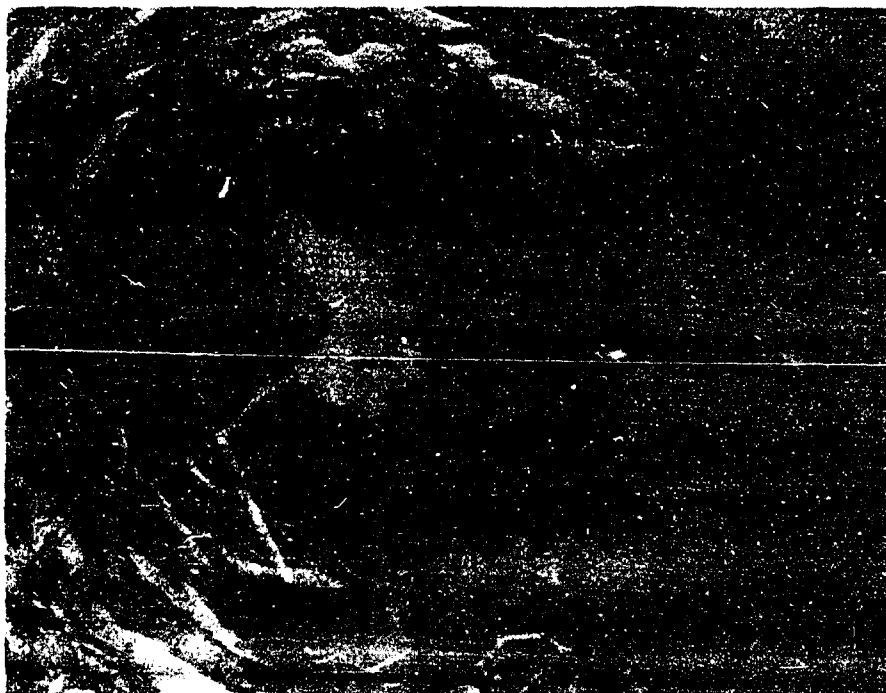


Figure 3. Liver, Case 1. Two bile ducts of intermediate size containing enigmatic cytoplasmic bodies. 710X.

B. CASE 2 (MONKEY W-40)

1. Gross Pathology

The site of tuberculin test in the right upper eyelid was mildly inflamed. Present near the apex of the tongue was a lesion indicative of B-virus infection. The ulcer measured about one centimeter in diameter and had a shallow, yellow, necrotic base. No lesions were noted on the buccal mucosa or lips. The axillary lymph nodes were slightly enlarged and congested.

The lungs and other viscera were not remarkable.

2. Microscopic Changes

The pulmonary changes in this case differed from those of the previous case in that here the inflammatory reaction and giant cell formation were confined to the bronchi, bronchioles, and the immediate peribronchial tissue. The giant cells contained both nuclear and cytoplasmic inclusions. However, a few contained only cytoplasmic inclusions. Many giant cells were seen in the stage of budding off into the lumen. Mite pigment was seen in juxtaposition to most of the bronchioles, as were small lymphoid collections.

The lymph nodes were hyperplastic and several contained Warthin-Finkeldey giant cells (Figure 4).

The tongue lesion consisted of a necrotic, amorphous, pale plaque in which ghosts of squamous cells were evident. An infiltrate of neutrophils, lymphocytes, and large macrophages accompanied this change. At the edges of the plaque, numerous squamous cells contained acidophilic nuclear inclusions typical of B-virus.^{14,15} These inclusions filled the nuclei and were surrounded by a thin rim of marginated chromatin. In the more necrotic area, the inclusions took on a smudged, amphophilic appearance. In several instances, the nuclei aggregated to form giant cells. The inflammatory reaction extended into the musculature of the tongue, but did not involve the sublingual glands.

The liver did not show any evidence of B-virus infection, but did contain cytoplasmic bodies in the bile duct epithelial cells similar to those described in the preceding case.

The spleen, heart, colon, and kidney, including the pelvic epithelium, were not remarkable. However, the pancreas revealed a similar pattern of pseudogiant cell formation as described in the above case.

Sections of the eyelid showed early granulation tissue infiltrated with chronic inflammatory cells.

No evidence of tuberculosis was found in any organ examined.

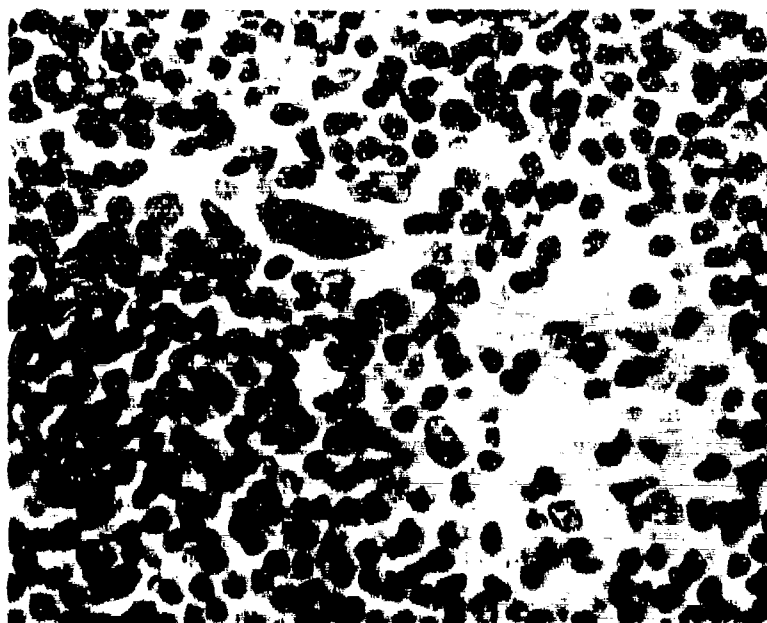


Figure 4. Lymph Node, Case 2. A typical Warthin-Finkeldy giant cell. 710X.

C. CASE 3 (MONKEY 104M)

1. Gross Pathology

In Case 3 the chief features were confined to the lungs and mouth. The lungs contained areas of pneumonic consolidation involving large areas of virtually all lobes. The picture was that of a bacterial pneumonia.

The tongue contained several large plaques typical of B-virus. Geographically, these lesions were quite extensive and encompassed most of the lingual surface and extended posteriorly to involve the epiglottis. Laterally, the buccal mucosa was also involved, with multifocal small and large areas of superficial ulceration. These changes were also seen on the lips.

2. Microscopic Changes

Multiple sections of the lungs revealed a picture of extensive bronchopneumonia. The less involved alveoli were filled with edema fluid rich in fibrin. However, hyaline membranes typically seen in viral pneumonias were not present. Scattered throughout all areas of the lungs were large syncytial giant cells containing inclusions of measles. An occasional single cell contained inclusions as well. The luminal of several large bronchi contain necrotic debris, acute inflammatory cells, and smudged giant cells. The intact epithelial cells of the bronchi showed early giant-cell formation with nuclear and cytoplasmic inclusions. Mite pigment was present.

Multiple sections of the tongue, epiglottis, and buccal mucosa revealed extensive necrosis involving the entire thickness of the mucous membrane (Figure 5). An infiltrate consisting of neutrophils and lymphocytes was also evident. Acidophilic nuclear inclusions with margination of the chromatin were seen in single cells as well as in individual cells in collections of two to eight cells (Figure 6). The quality of the inclusions was best appreciated at the junction of the necrotic and relatively intact epithelium. Encysted sarcosporidia were also observed in the musculature of the tongue. The lips showed essentially the same changes. Moreover, the inflammatory reaction extended to the hair shafts of the adjacent skin and nuclear inclusions were seen in the epithelial lining cells.

In several areas, the inflammatory process spread to involve the sublingual glands. Here the acinar lining cells had apparently undergone a change that resulted in a multinucleated, abortive, giant cell obliterating the lumen in most instances and containing definite nuclear inclusions of the type that were interpreted as being due to measles. This impression is further supported by the fact that occasionally one of these transformed glands contained small pink cytoplasmic inclusions measuring two to six microns (Figure 7). Most probably this change in the sublingual glands represents a dual infection, with B-virus causing the initial injury and the measles virus invading the glands later. We saw no evidence of cytoplasmic inclusions in any of the cells containing the typical herpes nuclear inclusions.

A survey of the central nervous system revealed one collection of astrocytes and round cells in the pons at the level of the mid-portion of the fourth ventricle. Various levels of the cord were unremarkable except for two focal collections of oligodendroglial cells in the grey matter in juxtaposition to a vessel at the cervical level. No inclusions were seen.

The renal pelvis did not exhibit giant-cell formation as in Case 1, but many of the epithelial cells contained eosinophilic cytoplasmic bodies of varying sizes and shapes (Figure 8). No nuclear inclusions were seen in these cells.



Figure 5. Tongue, Case 3. The edge of a typical plaque of B-virus infection with relatively intact epithelium to the left. The dark areas in the necrotic zone represent inclusion-bearing cells. 71X.

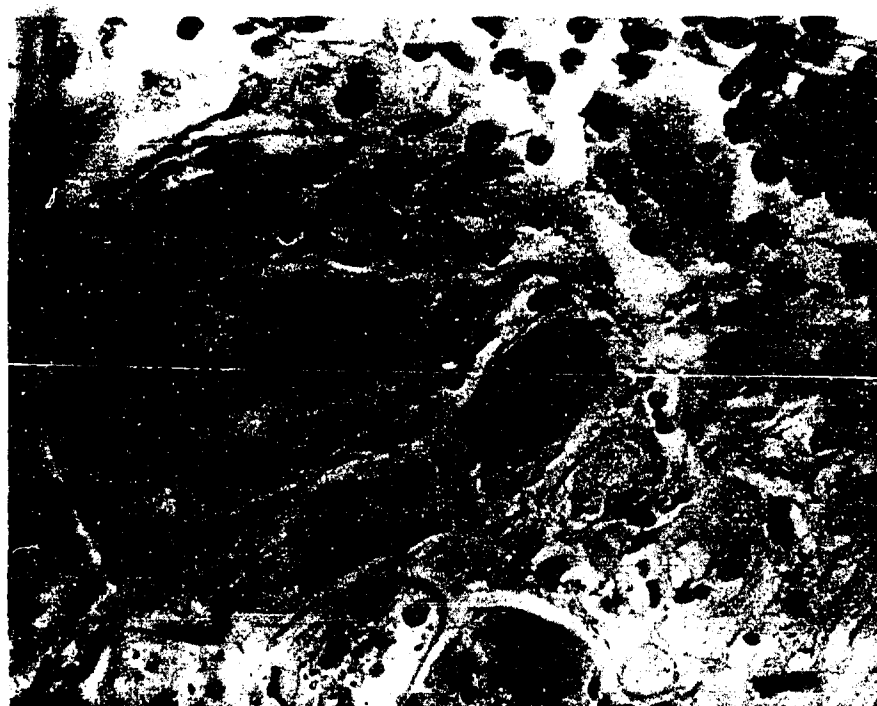


Figure 6. Tongue, Case 3; Typical B-Virus Giant Cell on the Right. The nuclei contain acidiophilic inclusions with associated margination of the chromatin. The nuclei of single cells also contain characteristic type-A inclusions. 710X.

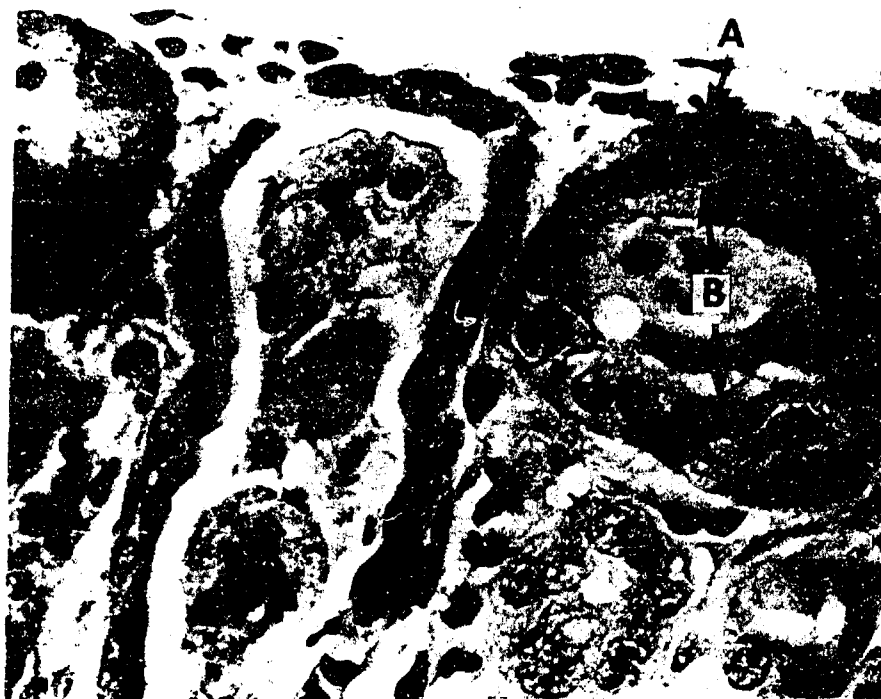


Figure 7. Tongue, Case 3; Sublingual Glands Showing Giant Cell Transformation. Arrow A indicates nuclear inclusion and arrow B cytoplasmic inclusions. 710X.

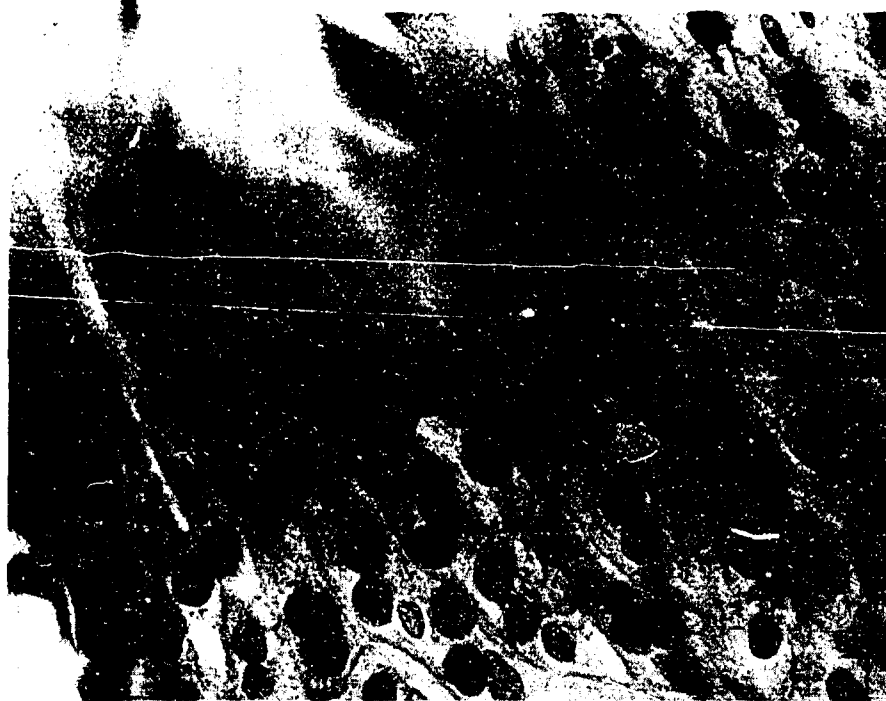


Figure 8. Kidney, Case 3. Many of the transitional epithelial cells of the renal pelvis contain eosinophilic cytoplasmic bodies of varying sizes and shapes resembling those described by Bolande. 710X.

Sections of the colon, liver, major salivary glands, heart and spleen revealed no changes of B-virus or measles. No evidence of tuberculosis was observed.

D. CASE 4 (MONKEY 48M)

1. Gross Pathology

As in the preceding case, the changes in Case 4 were confined to the lungs and mouth and were essentially the same in degree and extent, except that the herpetic lesions were present on the hard palate and alveolar ridge.

2. Microscopic Changes

The pulmonary changes were those of a necrotizing bronchopneumonia. No giant cells were observed, but many macrophages were seen in the air sacs.

The histological features of the tongue, mucous membranes, and lips and nose were similar to those in the preceding case. However, here the inflammatory response was not as brisk. Inflammatory cells did extend into the sublingual glands, but no inclusions or transformed acini complexes were seen.

The other significant changes were confined to the central nervous system. Specifically, in the pons several foci of perivascular cuffing, glial cell proliferation, chiefly astrocytic, accompanied by minimal, focal demyelination, were observed (Figures 9, 10). However, no inclusions were seen. Other areas revealed collections of round cells encroaching on a neurone, but no true neuronophagia was seen. The medulla also showed one vessel with minimal cuffing. The cervical cord was not remarkable. No evidence of tuberculosis was found.



Figure 9. Pons, Case 4; A Large Vessel with Prominent Perivascular Cuffing. 220X.

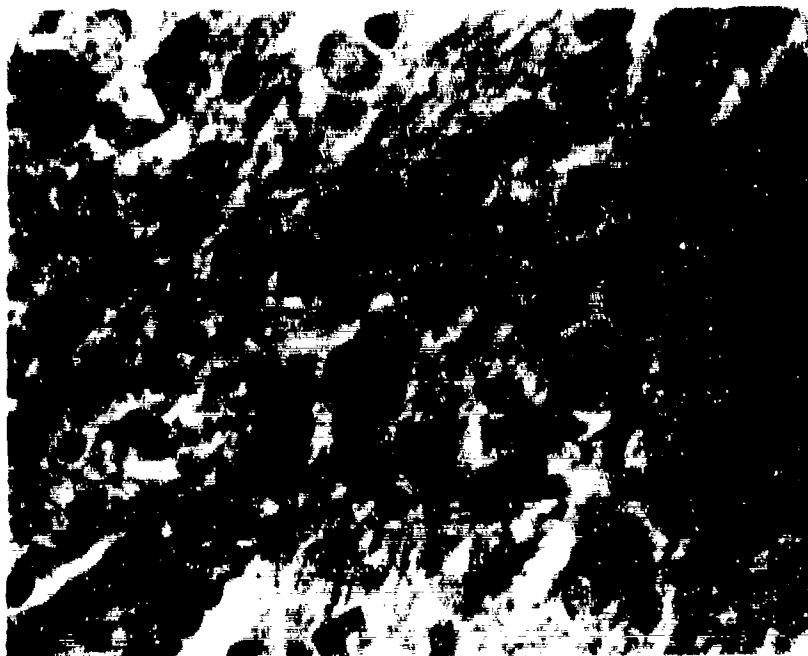


Figure 10. Pons, Case 4; A Circumscribed Collection of Mononuclear Cells and Astrocytes. No inclusions were seen. 710X.

IV. DISCUSSION

Although both the rhesus and cynomolgus monkeys are excellent hosts for the experimental production of measles,^{12,16} its occurrence as a spontaneous clinical or pathological entity is apparently rare, as judged by the paucity of reports. However, there is now abundant and irrefutable evidence that these two monkeys as well as other simian species do, in fact, become infected without showing apparent evidence of clinical disease as we know it in man. This conclusion is based on the serological observations of Peebles,¹² and more recently those of Meyer.¹³ Both of these studies clearly showed that monkeys tested immediately after capture in their native habitat did not have antibodies to the measles virus. However, after the animals had been held in captivity for various periods of time, the majority developed antibodies. Meyer¹³ found that all of the rhesus monkeys developed antibodies within eight weeks after capture. Both investigations strongly indicate that the monkeys became infected through association with humans and not as a result of "jungle" measles as has been suggested.¹⁷ Moreover, these studies readily explain the erratic and inconsistent results described in the literature when blood or throat washings from measles patients were introduced into these animals in an attempt to produce the disease experimentally.

Other evidence that monkeys latently harbor an agent indistinguishable from the measles virus is offered by Ruckle¹⁸ and Frankel,¹⁹ who recovered this virus from uninoculated tissue culture derived from the kidneys of healthy animals. This agent, initially called MINIA (monkey intranuclear inclusion agent), has now been shown to be identical to the measles virus.¹¹ The fact that one of our monkeys (Case 1) contained two giant cells within the pelvic epithelium, although without demonstrable inclusions, suggests the site in which this virus latently resides in the kidney. It may also explain the isolation of the measles virus from urine.²⁰

The cytoplasmic eosinophilic bodies seen in the renal pelvic epithelium of Case 3 closely resemble those described by Bolande²¹ and others²² in exfoliated cells in urinary sediment. Their identity is still a subject of much work. However, it has been shown that they are not measles inclusion bodies,²³ but most probably represent a degenerative change, as they can be seen in numerous unrelated conditions, including neoplastic and inflammatory.²²

In 1945, Pinkerton¹ suggested that giant-cell pneumonia was an atypical expression of infection with the measles virus in an individual who, for immunological or other reasons, did not develop the typical rash and related clinical features. It was not until 1959 that this hypothesis was proved correct when Enders⁵ isolated the measles virus from three cases of G.C.P. in whom the typical rash did not appear, but the pathological changes were indistinguishable from those cases showing the typical rash. It seems logical to assume that G.C.P. also occurs in the benign form of measles but not to the extent seen in debilitated individuals.

The giant-cell response in the lungs of our cases is morphologically identical to that seen in humans dying of the disease. The presence of the typical Warthin-Finkeldey giant cell in the lymph nodes also supports the diagnosis of measles. The lack of clinical evidence of the disease in our cases, especially the rash, is most interesting. One can only speculate regarding this fact, and the possibilities appear to fall into three categories:

(a) By analogy, the monkeys reported here could have been in the prodromal stage of measles and consequently would not show the rash.

(b) Monkeys do not develop the full clinical picture when the disease is spontaneous compared with the essentially complete clinical disease acquired experimentally. By analogy, this would place the monkey in the same category as those debilitated humans dying of measles-G.C.P. without a rash.

(c) Monkeys do develop the typical signs and symptoms but they go unrecognized. This is quite possible, especially when such large numbers of animals are at hand that individual observation is impractical if not impossible.

Moreover, if we assume that a rash develops in spontaneous measles as it does in the experimental disease, then the difficulty in recognizing the rash is compounded by the fact that the exanthema occurs mainly on the trunk and extremities and only scantily or not at all on the face. Furthermore, abundance of hair on the face makes recognition more difficult.

This question of inapparent disease could be resolved by deliberately exposing antibody-free monkeys to humans with measles in the very early stage of the rash or to debilitated individuals with measles. The exposed animals could then be monitored very closely both clinically and serologically.

In a preliminary attempt to resolve the question of inapparent disease by observing the cage mates of Cases 1 and 2, the cage mate of Case 1 (measles alone) remained in good health for approximately two months and was then issued for experimental use. During this period, random checks were made and no rash or other symptoms were observed.

The cage mate of Case 2 (measles and B-virus) was observed for approximately three months and during this period did not develop a rash or a lesion typical of B-virus.

Similar follow-ups were not possible for Cases 3 and 4 because they occurred approximately two years earlier and the fate of their cage mates is not recorded.

Although naturally occurring cases of B-virus infection have been described only in rhesus monkeys,^{14,15} there is abundant serologic evidence that apparently healthy cynomolgus monkeys also became infected and that the disease is more widespread in both species than previously realized.²⁴⁻²⁷ Moreover, isolation of this virus from tissue culture derived from normal monkey kidney cells²⁷ indicates the significance of this agent from an interpretive viewpoint. Thus it seems that the virus can remain latent in the tissue of normal monkeys for long periods of time.

In most cases, specific eosinophilic nuclear inclusions are readily seen in the tongue and associated structures, as they were in three of our cases. On the other hand, inclusions are uncommon in the liver and central nervous system, but gliosis and perivascular cuffing are common in the latter. None of our cases had hepatic changes. However, one did show changes in the pons and medulla compatible with B-virus infection.

It is interesting to note that no inclusions or specific changes were seen in the kidneys in Keeble's^{14,15} or our cases although, as mentioned earlier, the virus has been recovered from uninoculated renal tissue cultures.

We feel that Case 3 deserves special comment because of the presence of cytoplasmic and nuclear inclusions in the acini of the sublingual glands. As suggested, this may well represent a dual infection with B-virus and measles. Giant cells with inclusions have been described in the tongue in a case of fatal measles in man.⁵

The amphophilic bodies seen in the cytoplasm of the bile duct epithelial cells in two of our cases also remain a subject of speculation, as we have seen them in a small number of rhesus monkeys that showed no evidence of B-virus or measles. These cytoplasmic bodies may well represent degenerating nuclei rather than a specific entity.

Since the rhesus monkey is commonly used in experimental work, and the true incidence of G.C.P. is not known, one can only theorize as to the effect the latter would have on an experimental model, especially one in which the properties of aerosols and aerosol-induced infections are studied. It may well be that G.C.P. is much more common than we suspect; this may be due in part to the obliteration of the morphologic hallmarks of the disease by bacterial superinfection seen so commonly in fatal viral pneumonias.²⁸

In studies of B-virus, it should be emphasized that monkeys, or tissues derived therefrom, should be handled with extreme care because of the real danger of acquiring this infection. As is well known, the disease is almost uniformly fatal in man and deaths have resulted from monkey bites as well as from the handling of tissue culture of monkey kidney cells.

No discussion of G.C.P.-measles complex would be complete without a comment on its relationship to distemper. Several experimental and serological investigations have yielded conflicting information regarding the morphologic and antigenic similarities of these two viruses. The available evidence indicates that they are closely allied; however, the extent of antigenic overlap has not been determined.

It is well known that distemper produces a morphologic pattern in animals of the families Canidae and Mustelidae not unlike that seen in measles.²⁹ To our knowledge, distemper has not been seen naturally or produced experimentally in monkeys, although Dalldorf unsuccessfully attempted to produce it in the rhesus.³⁰ However, it should be noted that antibodies to distemper have been found in monkeys in relatively low titers.¹¹

A possible explanation for the lack of tuberculosis in any of the animals is the fact that the intrapalpebral tuberculin test is not uncommonly accompanied by false positives and false negatives.

V. SUMMARY

Three cases of spontaneous G.C.P. in the rhesus monkey, two with associated B-virus infection, are described. To our knowledge, this is the first instance in which these two viruses have been described in the same host.

We feel our cases have all the morphologic hallmarks of measles and the relationship to distemper is briefly mentioned.

Several possible theories are offered to explain the lack of clinical evidence of measles in our cases as well as in those seen by others.

The possible detrimental role that monkey measles may play in experiments in which the lung is the target organ is discussed.

The extreme hazard in working with monkeys because of overt or latent B-virus infection is mentioned.

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