gest that fluctuations of the host's reactivity to a given infection might occur independent of immunological phenomena. The actual reactivity of the host to a given amount of toxic material and not the absolute potency of the material determines the degree of toxic manifestations during the infection. It can be assumed that such hyperreactivity phenomena need not necessarily be manifested by obvious toxic reactions but may result in subtle disturbances of various systems of the host. It is suggested that physiological and pharmacological studies on such models may be a fruitful approach towards an understanding of pathophysiologic processes in infection. As our experiments show, such studies may also provide information on the relationship between invasive and pathogenic mechanisms.

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Zusammenfassung

Es wird einleitend darauf hingewiesen, dass mehr und mehr die Bedeutung von unspezifischen Faktoren für die Resistenz gegen Infektionen erkannt wird. Solche Faktoren können wohl auch in der Pathogenese von Infektionskrankheiten eine Rolle spielen, so zum Beispiel eine erhöhte Sensibilität gegen Endotoxin, die während den verschiedensten experimentellen Infektionen in Tieren nachgewiesen werden kann. An Hand von Experimenten an Mäusen wird dargestellt, in welchem Ausmass eine vorausgehende Impfung mit BCG den Ablauf einer nachfolgenden Infektion mit *Salmonella typhimurium* in verschiedenster Weise beeinflussen kann. Dies hängt weitgehend davon ab, ob grosse oder kleine Dosen zur Infektion verwendet werden.

Some Remarks Concerning the Ecology of Bedsonia Infections

By K. F. MEYER*

In 1953 in a discussion of the nomenclature of the psittacosis group, sponsored by the New York Academy of Sciences, it was recommended that the system be changed so that the investigator who first elucidated the morphologic, physiologic, and immunologic properties of this group – Sir SAMUEL BEDSON – would be properly recognized (MEYER[1]). It was proposed that the group name *Miyagawanella*, adopted in Bergey's Manual of Determinative Bacteriology, composed by a committee of the American Society of Bacteriologists, be replaced by *Bedsonia*, since the virus of lymphogranuloma venereum can scarcely be regarded as the prototype of the group.

One cannot be satisfied easily in finding even some simple term for reference to members of this group; neither rickettsia nor virus is a perfect fit. In the following remarks they will be given the questionable term virus, since no common appropriate twilight term is at hand.

The recognition of new antigenic relatives of the psittacosis and lymphogranuloma venereum (LGV) viruses has catalyzed investigations on a much broadened front in laboratory and field studies. The relationships of the old and new members, the natural and experimental infections, the virus particles, and the antigenic and chemical structures have aroused a new wave of curiosity and study. The group has been well reviewed recently from several points of view (WEISS[2]; WENNER[3]; MEYER and EDDIE[4]; BEDSON[5]), and this seems the time to integrate the old and new information.

General Characteristics of the Group

During the past 20 years, elaborate and painstaking studies, first of the psittacosis virus, then lymphogranuloma venereum, and later other avian and mammalian viruses, have established the widespread existence of distinct biologic groups which share striking characteristics:

They are large intracellular parasites, responsible for diverse, spontaneous, generalized or local, clinical or latent infections in man, birds, and mammals. They are readily stained by basophilic dyes. They are antigenically related, as evidenced in the complement fixation, cross immunity, and toxin neutralization tests. They are, with one exception, capable of producing pneumonitis in the laboratory mouse when introduced by the intranasal route. They grow well in the yolk sac of the embryonated egg. They are susceptible to the action of certain drugs. The usual infections are probably latent; among susceptible species infection may be commonplace, initially taking place in the young. Mortality rates vary; epidemics sometimes occur. More often the tendency is recovery, with the development

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[1] K. F. MEYER, Ann. N. Y. Acad. Sci. *56*, 545 (1953).

[2] E. WEISS, Ann. Rev. Microbiol. *9*, 227 (1955).

[3] H. A. WENNER, Advanc. Virus Res. *5*, 39 (1958).

[4] K. F. MEYER and B. EDDIE, Chapter 6 in *Progress in Psittacosis Research and Control* (Ed. by F. R. BEAUDETTE, Rutgers University Press, New Brunswick, New Jersey, 1958), p. 52.

[5] S. P. BEDSON, J. R. Inst. Pub. Health Hyg. *22*, 67, 99, 131 (1959).

of some immunity after the benign illness or inapparent infection. Immunity is seldom absolute and fully virulent or weakly virulent Bedsonias survive in varying, usually small, numbers in tissues of the host. In the usual host species, after infection the virus persists in reticulo-endothelial cells, suggesting a parasitic partnership in existence for a long evolutionary period. It may remain confined to the internal organs until either some unusual stress on the host or vitality of the parasite, when it may find its way through excreta to a new host. Whenever the stability is disturbed, for whatever reason – starvation, crowding, breeding, illness – the virus may multiply and find release to the external environment. Large reservoirs can be assumed to exist in nature; the balanced partnership between the psittacosis-ornithosis viruses and their avian hosts suggests this. Either acutely ill, or more frequently inapparently infected, hosts potentially threaten the health and welfare of several known species of animals, including man, and possibly others yet undiscovered.

Ecology of Human Bedsonia Infection

The Bedsonias were first recognized over 50 years ago, when HALBERSTAEDTER and VON PROWAZEK made their classical observation on trachoma in Java. By direct transmission of conjunctival scrapings from man, they succeeded in infecting orang utans; in the scrapings from these animals and from patients they noted the epithelial cell inclusions with which their names are now associated. With great perspicacity these workers suggested that the inclusion bodies represent intracellular colonies of the causal agent. These early morphologic studies led to recognition of another form of inclusions, the initial bodies, which LINDNER regarded as an early stage in the development of the mature Halberstaedter-Prowazek-Körper. The significance of these early studies on trachoma became more clear when BEDSON, BLAND, and CANTI proved that the obligate intracellular parasites causing avian and human psittacosis develop through a complex series of morphologic changes. Observations with the light microscope suggested binary fission as the mode of reproduction. THYGESON, studying trachoma, made observations similar to those of HALBERSTAEDTER and VON PROWAZEK and of LINDNER and reemphasized the initial body that matures to a mass of elementary bodies. Quite recently LITWIN[6], in an excellent study on the morphology of the growth cycle of a mammalian member of the Bedsonia group, the feline pneumonitis virus, in the chorioallantoic ectoderm of chick embryos with respect to infectivity, elementary particle counts in light and electron microscopy, has furnished an explanation of the early studies with the trachoma inclusion bodies: Early and late phases of the obligate intracellular growth cycle are analogous to those of bacteria, and the trachoma psittacosis-lymphogranuloma viruses multiply by binary fission. The causative agents of trachoma and of inclusion conjunctivitis from infections in China, Gambia, Saudi Arabia, Egypt, and the U.S.A. have been propagated in the yolk sac of embryonated eggs 6- to 8-days old (COLLIER[7]). Further evidence has been furnished that the trachoma virus belongs to the Bedsonia group. BELL *et al.* have shown that the intravenous inoculation of concentrated viable elementary bodies of trachoma are toxic to mice. This observation recalls the historically interesting fact that the existence of thermolabile endotoxin in a member of this group was first recognized in lymphogranuloma venereum.

How did the LGV virus find its place in the Bedsonia group? Again, through morphologic studies. GAMMA recognized large cytoplasmic bodies in cells from infected lymph nodes, and a few years later GAY PRIETO described small corpuscles differing from the GAMMA-FAVRE bodies. By showing some of the cytoplasmic corpuscles to be Castaneda-positive, FINDLAY proved more conclusively than GAY PRIETO the relationship of these bodies to the infective agent in the pus of climatic buboes. A few years before, HELLERSTRÖM and WASSÉN had produced a bacteria-free meningitis in rhesus monkeys by injecting bubo pus. MIYAGAWA *et al.* demonstrated, in filtration experiments, that the presence of these bodies paralleled infectivity, a fact already by then established for the prototype of the Bedsonia group – the psittacosis virus. FINDLAY *et al.*, and later RAKE and JONES, suggested a possible cycle of development similar to that described for trachoma and the psittacosis viruses. This relationship was confirmed further when the LGV virus grew luxuriantly in the embryonated hen egg. Its host range in experimental infections was broader than that of trachoma, but narrower than that of the psittacosis virus. Few strains isolated from human material, with or without monkey passage, induce fatal meningitis in mice on intracerebral inoculation. Variations in virulence of Bedsonias was also first recognized for the LGV virus.

The third Bedsonia infection host specific to man, inclusion conjunctivitis, is transmitted through venereal contact. It is from the genital sources that the acute self-limiting infection of the conjunctiva arise.

Trachoma, lymphogranuloma venereum, and inclusion conjunctivitis all suggest that the parasitism that they represent is of long standing in the human host. The flare-ups do not have the violence of the usual reaction of a host encountering a new parasite.

It is not certain whether pneumonitis should be included as a fourth human-host-specific Bedsonia infection. Transmission from one human being to another

[6] J. LITWIN, J. infect. Dis. *105*, 129 (1959).
[7] L. H. COLLIER, Brit. med. Bull. *15*, 231 (1959).

has been considered supportive, but the outbreaks have been few, the mortality rates high, the origin focal, and the spread slow and not far.

In the spring of 1940 a man died in a hospital in San Francisco 17 days after onset of bronchopneumonia. Three nurses attending this patient became similarly ill 17 to 19 days later, bronchopneumonia intervened, and after a stormy course two of these nurses died. The remaining nurse recovered slowly. Two laboratory workers who tested tissues from these patients for virus contracted a similar disease and recovered. The isolated strain, known as the S. F. strain of human pneumonitis virus, exhibited one puzzling characteristic: it failed to infect mice when injected intravenously but had a highly active heatlabile endotoxin.

A severe outbreak of pneumonitis in the Louisiana bayous was transmitted from person to person, spreading among attendants in fatal cases and only to those in attendance within 48 h of death of the patients. A highly toxic virus pathogenic for several species of mammals, including guinea pigs, and birds was isolated from sputum and blood in two fatal cases. That these illnesses could have originated in some extrahuman source, possibly egrets, has recently been suggested by TREUTING, one of the investigators of the outbreaks.

The third episode of apparent person-to-person transmission was reported from Chicago in 1944. Two men, a physician and a dental student, contracted an illness similar to those in the Louisiana outbreak. The agent isolated from the lungs of the patients, to become known as the Illinois human pneumonitis virus, on the basis of toxin neutralization tests, resembles the Louisiana strain.

In recent years there have been no reports of pneumonitis outbreaks from Louisiana, despite some discovered reservoirs in nature and the unchanged life habits and customs of bayou residents. One may speculate that the infection does occur, but is unrecognized, since it is not distinguishable clinically from other virus pneumonias or minor respiratory ailments and could be expected to respond to antimicrobial therapy as they do. Or that the kaleidoscope turned and some peculiar host-parasite relationship fell into place, producing in three different localities of the United States fatal bronchopneumonia caused by Bedsonias of exalted virulence. That secondary cases arose through personal contact points up the communicability of these viruses by the respiratory route in the late stage. Such outbreaks have occurred elsewhere and at other times. In several the initial illness was conclusively proven to have originated from extrahuman (avian) sources. Despite extensive surveys in the period before antibiotic therapy came into use proof could not be secured to support the hypothesis that aside from trachoma, lymphogranuloma venereum, and inclusion conjunctivitis, a specific human pneumonitis virus exists and may be exchanged from person to person. The hypothesis overlooks that the strains passed only from fatally infected patients and then only late in the course. This suggests an avian strain of unusually high virulence meeting man for the first time. Effective treatment seems to prevent this type of spread. The reported transmissions from person to person from 1899 to 1945 were of viruses of psittacine origin, more recently of columban origin.

The discovery of complement fixation reactions with the common group antigen in the course of serum surveys, for example in those in Holland and Scandinavian countries where lymphogranuloma venereum is rare, can justifiably be used to support the idea that human pneumonitis Bedsonia viruses exist. But careful studies in rural and some urban areas indicate that many extrahuman sources could account for these subclinical infections. So far as is known now, one must still look for birds, including poultry, as the source of most human psittacosis.

Relation of Avian Bedsonias to Human Disease

In 1929–30, psittacosis was widespread in Europe and America due to the dissemination of a large collection of infected Amazon parrots, and the interest aroused by more than 700 cases of what had previously been regarded as an exceedingly rare disease led to careful investigations and to isolation of the virus which is the prototype of the Bedsonia group. Within the next few years investigations showed that most of the sporadic human cases and small outbreaks affected people in contact with the parakeet (*Melopsittacus undulatus*), a native of Australia, rather than with the South American parrot. Through the years the abundant growth of the trade in parakeets has increased the incidence of psittacosis. Wherever these cage birds are bred and raised—in the United States, Germany, Japan, the Netherlands, Switzerland, Great Britain—they are the principal sources of this infection. The epizootiology of psittacosis in aviary-bred parakeets, seagulls (petrels), and pigeons is fairly well understood: the continuity of the virus's survival is perpetuated in the nest. In observations in Australia there is good evidence of fatal and nonfatal epizootics in wild parrots. The highly virulent strain responsible for the 1938–39 fatal epidemics was transmitted from one species to another, but the 1957 nonfatal epizootic did not seem to affect other species. Of 98 species of birds belonging to 9 orders, 20 families, and 62 genera found to be naturally infected, only 57 were psittacine (MEYER[8]).

To protect man against psittacosis, quarantine has been adopted, but large and small psittacine and other

[8] K. F. MEYER, Chapter 22 in, *Diseases of Poultry* (Ed. by H. E. BIESTER and L. H. SCHWARTE, Iowa State College Press, Ames 1959), p. 504.

cage birds are being smuggled into the United States to meet the popular demand, especially for Panama and Amazon parrots and cockatoos. In extensive field trials with tetracycline compounds, multiplication of the virus in the tissues of the birds has been stopped, and most birds have rid themselves of any virus on hand. Thus it seems possible to hope to import or to raise Bedsonia-free cage birds.

Preoccupation with the psittacine aspect has recently been distracted by the infection in poultry. The participation of pigeons, chickens, ducks, geese, pheasants, and particularly turkeys in the maintenance of this virus and in causing human infections has been recognized.

Pneumonitis (487 cases, 11 deaths) has broken out in poultry plants in Texas, New Jersey, Oregon, Wisconsin, British Columbia, where adult turkeys were processed for market. These occupational infections concern several groups, both physically and financially, and ornithosis in turkeys has become a subject of some intensive studies. Where turkeys were observed to have gross anatomical lesions on the viscera (plastic exudate over the liver, air sacs, and heart, teeming with Bedsonia elementary bodies highly virulent for mice), mild to frank clinical attack rates among the exposed workers have ranged from 20 to 70%. The disease is not always benign, as the case fatality rate (2·6%) indicates. Delay in treatment, the use of ineffective antimicrobial drugs (penicillin is not effective) and complications such as hepatitis and myocarditis in older people were responsible for the deaths. The ornithosis virus is destroyed within $3^1/_2$–5 min at 56°C, so that after proper cooking the carcass of the poultry can be considered safe. If turkeys and chickens are incubator-hatched, the virus cannot be perpetuated in the nest as usual. Although on several breeding ranches the infection has reappeared annually as a latent infection in the young birds or poults, it has manifested itself as a frank destructive poultry disease during the breeding and egg laying period. How this happens has not been understood, but in recent studies at the Hooper Foundation, feather mites belonging to the Glyciphagidae, Analgesidae, and Cheyletidae collected from litter or bedding six months after contact with live turkeys or chickens were proven contaminated or infected with Bedsonia agents. Emulsified mites produced nonfatal infections in white mice on intraperitoneal inoculation in the first passage. On further intranasal mouse passage the focal pulmonary areas of consolidation contained typical elementary bodies, and fatal infections were produced on intracerebral or intraperitoneal injection. These have been pathogenic for parakeets and guinea pigs and are antigenically indistinguishable from typical avian Bedsonia. If virus-carrying arthropods survive in the nest, the seasonal recurrence of ornithosis in incubator-hatched poultry could be readily explained.

Ornithosis among pigeons is a common infection causing morbidity but little mortality. The prevalence of isolated infections among pigeon fanciers, owners of lofts or operators of squab farms is amply reflected in recently published records (MEYER[8]). Fatal infections in infants and occasionally in older people who had been spending considerable time in public parks frequented by pigeons and in people in contact with racing pigeons cast suspicion on the vast reservoir of free-flying pigeons as a public health hazard.

Finally, scattered reports from Czechoslovakia, Austria, Germany, Yugoslavia, and U.S.S.R. indicate that ducks and geese can convey psittacosis to man.

Relation of Mammalian Bedsonias to Human Disease

The discovery that viruses of this group can cause disease other than pneumonitis in mammals other than man has been increasingly evident in recent years. The number of species is increasing, and the clinical manifestations more and more various. The mammalian Bedsonias can destroy domesticated animals, and those constituting a distinct hazard in animal economy have been studied to some extent. Whether the so-called meningopneumonitis virus recovered from ferrets inoculated with throat washings obtained from cases of suspected influenza is actually a parasite of this animal must remain unascertained. Pathogenicity and toxin neutralization tests have shown this virus to be related to the pigeon viruses. The murine pneumonitis virus is indigenous to certain stocks of laboratory mice, feline pneumonitis is a highly infectious disease of cats, and the viruses isolated are apparently species specific. Viruses have been isolated from infected opossums (common opossum, *Didelphio paraguayensis;* wooly opossum, *Caluremys laniger;* brown masked opossum, *Metachisus medicaudatus*), but have not been studied extensively. Those isolated from cattle in the United States and Japan, causing diseases described as bovine enteritis, encephalomyelitis, pneumonia, and abortion, may be closely related to each other. The localization in the central nervous system and the pulmonary tissues has been an interesting complication of a more generalized and usually minor infection. Serologic surveys have indicated a fairly widespread infection affecting 8–100% of adult cattle. Enzootic abortion of ewes in Great Britain and the United States occurs during the last 2 or 3 weeks of gestation. The Bedsonia induce pathogenic lesions in the fetal membranes and the aborted fetus, where they are readily demonstrable in large numbers. The pathogenesis is incompletely defined. Whether the same virus causes ovine pneumonitis remains to be learned. Recently reports from Japan describe pneumonitis in goats caused by a Bedsonia. In the biology of this organism found in mammals two facts are outstanding: Most of them are

highly pathogenic to guinea pigs, but rarely for parakeets or ricebirds.

Human infections directly traceable to infected animals are either unrecognized or infrequent or account for some otherwise unexplained serologic reactions. One laboratory infection with the virus of enzootic abortion of ewes and one with that of bovine encephalomyelitis are on record. Feline pneumonitis has been considered a possible source of human pneumonitis. Further evidence that these viruses may cause unrecognized infection in man stem from the occurrence of complement-fixing antibodies among veterinary personnel in stockyards and packing plant employees.

This sketch of the Bedsonia group reveals that they can infect several members of the animal kingdom, including man. They vary in pathogenicity, virulence, and tissue tropism, causing either local or systemic infection. The ecologic relationships pose fascinating questions and offer a fresh challenge to the imagination of the biologist.

Zusammenfassung

Es wird vorgeschlagen, dass die Vertreter der Psittacosis-Lymphogranuloma-Trachoma-Gruppe der Mikrobakterien in Zukunft als *Bedsonia* bezeichnet werden. Die einzelnen Glieder dieser Gruppe erzeugen lokale und systemische Infektionen beim Menschen, Geflügel und einzelnen Säugetieren und nicht nur bei Papageien. Da die Pathogenität, die Virulenz und der Gewebetropismus grosse Unterschiede aufweisen, bietet das ecologische Studium der Infektionen viele anregende Probleme.

Zur Kenntnis des lamellaren Musters in ausgewachsenen und der Kristallgitterstruktur in jungen Chloroplasten

Von E. HEITZ*

I. Seit den ersten Arbeiten von MENKE[1] in denen er, ausgehend von polarisationsoptischen Untersuchungen im UV-Mikroskop[2] eine lamellare Struktur der Chloroplasten von *Anthoceros* nachweisen konnte, und auch für die Chloroplasten höherer Pflanzen (*Selaginella*, *Phaseolus*) dieselbe Grundstruktur angab, haben nach der Erfindung des Elektronenmikroskops eine ganze Reihe von Autoren diese Befunde an verschiedenen Pflanzen bestätigt und mit Hilfe des viel höheren Auflösungsvermögens dieses Mikroskops und vor allem bei Benutzung der neuen Einbettungs- und Scheidetechnik sehr genaue und in feinste Einzelheiten gehende Aufschlüsse geben können (COHEN und BOWLER[3], HODGE, MCLEAN und MERCER[4]; SAGER und PALADE[5]; LEYON[6], STEINMANN und SJÖSTRAND[7]; WOLKEN und PALADE[8] und andere).

Die von MENKE[1] gefundene Grundstruktur, wie sie bei den meisten Algen und dem genannten Lebermoose vorliegt, ist an Schnitten noch wenig, mindestens aber zu wenig genau im einzelnen untersucht worden (bzw. an nicht genügenden Präparaten oder Aufnahmen s. u.). Nur von WOHLFAHRT-BOTTERMAN[9] wird eine einwandfreie Aufnahme des Chloroplasten einer Dinoflagellate, *Amphidinium elegans*, gegeben (Abb. 1)[10]. Der Verfasser stellt fest, dass bei dieser Alge eine in bezug auf die Anordnung der Lamellen bisher nicht bekannte «Struktur der Chloroplasten» vorliegt. Der Chloroplast besteht hier «aus einer Vielzahl distinkter, parallel verlaufender Lamellenpakete, die sich gesetzmässig jeweils aus 4 Membranen zusammensetzen. Die beiden inneren dieser Membranen sind dicker und kontrastreicher als die beiden äusseren»[11]. Die von WOHLFAHRT-BOTTERMANN[9] gegebene Abbildung 6c, welche Schnitte durch fast einen ganzen und drei verschieden grosse Stücke von Chloroplasten zeigt, belegt die Gesetzmässigkeit eindeutig. (Lediglich im Chloroplastenstück am rechten Bildrand enden links 4 Lamellenpakete mit zwei äusseren dünnen und nur *einer* von ihnen eingeschlossenen dicken Lamelle; dasselbe erkennt man auf der hier wiedergegebenen Abbildung 1: Etwa 9 Lamellenpakete bestehen aus zwei äusseren dünnen und zwei inneren dicken; bei drei dagegen – mit Pfeilen bezeichnet – ist nur *eine* innere dicke vorhanden.) Hier sei eine Abbildung von LEYON und WETTSTEIN[12] erwähnt. Ich möchte die Äusserung meiner Ansicht nicht unterdrücken, dass die beiden Verfasser auf Grund von besseren Aufnahmen (bzw. Präparaten) zu der Überzeugung hätten kommen müssen, dass bei der untersuchten Braunalge deren Lamellenpakete (von ihnen als grobe Lamellen bezeichnet) nicht aus vier *gleich* dicken

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[1] W. MENKE, Kolloid-Z. *85*, 256 (1938).

[2] W. MENKE, Naturwissenschaften *28*, 158 (1940).

[3] M. COHEN und E. BOWLER, Protoplasma *42*, 414 (1953).

[4] J. HODGE, J. MCLEAN und F. MERCER, J. biophysic. biochem. Cytol. *1*, 605 (1955).

[5] R. SAGER und G. PALADE, J. biophysic. biochem. Cytol. *3*, 463 (1957).

[6] H. LEYON, Svensk kemisk Tidskr. *68*, 70 (1956).

[7] E. STEINMANN und F. SJÖSTRAND, Exp. Cell Res. *8*, 15 (1955).

[8] J. WOLKEN und G. PALADE, Ann. N. Y. Acad. Sci. *56*, 873 (1953).

[9] K. GRELL und K. WOHLFARTH-BOTTERMANN, Z. Zellforsch. *47*, 7 (1957).

[10] Vgl. Abb. 1; nach einer mir in verdankenswerter Weise von Herrn Dr. WOHLFAHRT-BOTTERMANN zur Verfügung gestellten nicht veröffentlichten Originalphotographie.

[11] Gesperrt von HEITZ

[12] H. LEYON und D. WETTSTEIN, Z. Naturforsch. *9b* 471 (1954).