Respiratory Pathogens in Monkeys

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Respiratory disease in a dynamic colony of nonhuman primates during a 4-year period was due primarily to infections caused by *Klebsiella pneumoniae*, *Diplococcus pneumoniae*, *Bordetella bronchiseptica*, *Pasteurella multocida*, and *Haemophilus influenzae*. The principal secondary invaders were *Escherichia coli*, *Staphylococcus aureus*, and streptococci. A high fatality rate was associated with infections caused by each of the primary pathogens, and females appeared to be more susceptible than males. Incidence of respiratory disease was greatest in the fall and early winter; however, at all times newly colonized monkeys had a higher infection rate than conditioned monkeys. Infections were occasionally confined only to the lungs and were sometimes present without grossly observable lung lesions. The information given on susceptibility of 10 species of nonhuman primates to respiratory infections provides a basis for developing disease models.

Historically, bacterial infections have been the primary cause of death in monkeys maintained in laboratory colonies (22, 23). As shown in recent reports (7, 13), bacterial infections of the gastrointestinal tract are still a major problem in newly imported and laboratory maintained primates. Although specific outbreaks of respiratory infections in monkeys have been described (6, 8, 9, 11, 17, 19), a systematic examination of the etiologic agents of respiratory disease in a large group of nonhuman primates has not been done. Therefore, it is the purpose of this report to summarize the findings from 8,781 monkeys, representing 10 major primate species, maintained at the National Center for Primate Biology.

Clinical signs of respiratory disease varied from crusting of the nares to marked dyspnea, prostration, and often death. At autopsy, involvement of the lungs was found to vary from slight congestion to red or gray hepatization of single lobes or entire lungs. In many cases, the respiratory pathogens did not cause detectable macroscopic changes in the respiratory tract but produced bacteremia, meningitis, or generalized hemorrhages. These infections, although not respiratory, are included in this report since the primary invasion route was considered to be via the respiratory tract.

MATERIALS AND METHODS

Identification and conditioning of primate species. The population studied consisted of 8,781 monkeys brought to the National Center for Primate Biology

colony between January 1964 and December 1967. The species examined were: *Aotus trivirgatus* (South America); *Cercocebus atys* and *Cercopithecus aethiops* (Africa); *Macaca fascicularis*, *M. mulatta*, *M. nemistrina*, *M. radiata*, *M. speciosa*, *Presbytis cristatus*, and *P. entellus* (Southeast Asia).

Upon arrival, each animal was weighed, tattooed, tuberculin-tested, and the majority examined for enteric pathogens. After evaluation of the physical condition of the shipment, mass treatment with antimicrobial agents was instituted if considered necessary. The prophylactic treatment for 3- to 4-kg animals usually consisted of 400,000 to 1,000,000 units of penicillin, often accompanied with 200 mg of streptomycin, administered intramuscularly (im) for 7 consecutive days. Appropriate alterations were made for smaller animals. If respiratory infections were suspected, sufficient tetracycline was added to the drinking water so that each animal received approximately 30 mg per day. Supportive treatment to improve hydration and health consisted of giving balanced salt solutions daily in the drinking water and administering im a vitamin preparation bi-weekly. After being fed cubed monkey chow (Purina) for 2 weeks, all animals were placed on the laboratory's standard monkey ration which contained isoniazid in an amount that provided approximately 20 mg per kg per day for each animal.

During the early part of the study, monkeys were gang caged in groups of 20 to 25 individuals. Later, newly imported animals were caged in groups of 10. As facilities became available, newly imported animals were caged in groups of two to three during the conditioning period and then recaged in groups of 10 upon entry into the stable colony.

Specimen collections. Calcium alginate swabs (Colab Laboratories, Inc., Chicago Heights, Ill.) were used to obtain specimens from the nares, nasopharynx, and exudates in the thoracic and abdominal

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cavities. Swabs were placed in 3.0 ml of Trypticase soy broth for immediate transport to the laboratory where they were inoculated directly onto eosin methylene blue (EMB) agar, blood agar, and phenyl ethyl alcohol agar prepared with rabbit or sheep blood. After incubation of the inoculated plates at 37 C. for 18 to 24 hr, representative colonies were picked for identification. Stained preparations were made of the incubated transport broth prior to subculture on appropriate media. Blood, spinal fluid, pericardial fluid, and tissues were inoculated directly into beef infusion broth (24) and subcultured onto selective and differential media after growth was detected. Primary cultures in broth were discarded as negative only if no evidence of growth appeared during 10 days of incubation.

Identification of species. Cultures of *Klebsiella pneumoniae* were identified presumptively on EMB agar. Nonmotile, gram-negative rods which gave typical reactions on triple sugar iron (TSI) agar hydrolyzed urea, and grew on Simmons citrate agar were inoculated into Worfel-Ferguson broth and subsequently examined with polyvalent and specific *Klebsiella* antisera (types 1 to 6). Further biochemical tests, when necessary, were based on those of Edwards and Ewing (4).

Diplococcus pneumoniae appeared with typical morphology in stains of the primary culture in broth or as characteristic colonies on blood agar plates. Suspect organisms, even in mixed culture, were examined for capsular type with specific antisera [Seruminstitute, Copenhagen (16); Difco Laboratories, Inc., Detroit, Mich.]. The omnisserum developed by Lund and Rasmussen (18) simplified identification of *D. pneumoniae* cultures. All *D. pneumoniae* isolates were susceptible to optochin.

Pasteurella multocida was seen in stained preparations as gram-negative, bipolar, ellipsoidal rods. Colonies on blood agar were small, translucent, and nonhemolytic. *P. multocida* was separated from other species of the genus since it produced indole and hydrogen sulfide (lead acetate paper). *P. multocida* was nonmotile at 18 to 22 C and did not grow on MacConkey agar, ferment maltose, or hydrolyze urea (2, 10).

Bordetella bronchiseptica was presumptively identified by the presence of gram-negative rods which produced small colonies on blood agar plates in 24 hr and small, colorless, opalescent colonies on EMB agar after 24 to 48 hr of incubation at 37 C. Neither acid nor hydrogen sulfide was produced in TSI agar. Identification was based on the rapid hydrolysis of urea, nitrate reduction, growth on Simmons citrate agar, motility, and the failure to ferment glucose and lactose (27).

Haemophilus influenzae was identified by characteristic colonial morphology on chocolate agar (2, 10) and further identified by Quellung reaction as type A or B with specific antisera (Difco).

Streptococcus and *Staphylococcus* species were isolated by using standard procedures (2, 10). Coagulase tests were performed routinely on *S. aureus* cultures.

Antibiotic susceptibility tests. The susceptibility of

isolates to antimicrobial agents was determined on Trypticase (BBL) soy agar or blood agar by using the disc technique. Only sensitivity discs (BBL) with high antibiotic concentrations were used to determine susceptibility, i.e., chloramphenicol, 30 µg; cephalothin, 30 µg; dihydrostreptomycin, 10 µg; furazolidone, 100 µg; erythromycin, 15 µg; kanamycin, 30 µg; neomycin, 30 µg; novobiocin, 30 µg; penicillin, 10 units; polymyxin B, 300 units; and tetracycline, 30 µg.

Culture for *Mycobacterium tuberculosis*. All animals showing positive tuberculin tests were sacrificed and necropsied using aseptic procedures. Representative lesions from the thoracic or abdominal cavities or both were homogenized in 3.0 ml of 0.2 % Fraction V bovine albumin; then 1.0 ml of the homogenate was suspended in a solution containing a final concentration of 500 units of penicillin per ml for 20 min at 37 C, was sedimented by centrifugation, and the pellet was resuspended to original volume in 0.2 % bovine albumin. One-tenth milliliter of the treated homogenate was used to inoculate both ATS slants and Dubos liquid medium; 0.02 ml was used to inoculate each quadrant of a Felsen plate containing 7H9 agar with 0, 0.1, 1, and 10 µg isoniazid per ml. In addition, 1.0 ml of the untreated homogenate was inoculated subcutaneously into the right inguinal region of a Hartley strain guinea pig. These animals were followed closely, noting changes in the inoculation site and body weight; they were tuberculin-tested at monthly intervals for a total observation period of 3 months. Representative lesions from guinea pigs were cultured in the same manner described above.

RESULTS

During the 4-year period from January 1964 through December 1967, 14,455 specimens from an available population of 8,781 monkeys were examined by using the procedures described. The major bacterial pathogens isolated were *K. pneumoniae*, *D. pneumoniae*, *P. multocida*, *B. bronchiseptica* and *H. influenzae* type B. The data in Table 1 show an overall infection rate of 7% in the 10 primate species examined. *K. pneumoniae* and *D. pneumoniae* were the principle etiologic agents responsible for disease in the total population; however, *P. multocida* was found as the principle respiratory pathogen in the South American owl monkey, *A. trivirgatus*. Members of *M. speciosa* were found to be relatively free of infection with all of these respiratory pathogens.

The high mortality associated with each of the infections is shown in Table 2. The overall mortality rate was 83% but ranged from a high of 88% for *K. pneumoniae* infections down to 71% for *B. bronchiseptica* infections.

The ratio of males to females in the total population was 1:1.13 (Table 3). However, the male to female ratio in animals infected with *K.*

TABLE 1. *Respiratory pathogens isolated from monkeys during a four-year period*

Monkey species	No. of monkeys in study	No. of monkeys infected with				
		<i>Klebsiella pneumoniae</i>	<i>Diplococcus pneumoniae</i>	<i>Pasteurella multocida</i>	<i>Bordetella bronchiseptica</i>	<i>Haemophilus influenzae</i>
<i>Aotus trivirgatus</i>	504	2	1	10	1	0
<i>Cerocebus atys</i>	203	8	11	8	2	0
<i>Cercopithecus aethiops</i> ..	197	1	9	5	9	0
<i>Macaca fascicularis</i>	767	38	18	16	5	0
<i>M. mulatta</i>	5,674	149	131	28	38	11
<i>M. nemistrina</i>	477	38	10	8	15	0
<i>M. radiata</i>	319	0	18	0	0	1
<i>M. speciosa</i>	187	1	0	0	1	0
<i>Presbytis cristatus</i>	105	11	1	0	7	0
<i>P. entellus</i>	348	14	26	0	2	0
All species.....	8,781	262	225	75	80	12

TABLE 2. *Fatal infections due to respiratory pathogens*

Bacterial pathogen	No. of monkeys		Per cent fatal infection
	Infected	Died	
<i>Klebsiella pneumoniae</i>	262	231	88
<i>Diplococcus pneumoniae</i> ...	225	185	82
<i>Bordetella bronchiseptica</i> ...	80	57	71
<i>Pasteurella multocida</i>	75	64	85
<i>Haemophilus influenzae</i>	12	9	75
Total infections.....	654	546	83

pneumoniae was 1:1.79, a statistically significant variation (Chi Square test) from the expected distribution ($P < 0.001$). The attack rates with *B. bronchiseptica*, *P. multocida*, and *H. influenzae* (type B) also suggest that females are more susceptible to infection than males. *D. pneumoniae* occurred in both sexes with the expected frequency. Nevertheless, the overall ratio of males to females infected with the five bacterial species was 1:1.44 ($P < 0.005$). A survey of conditions surrounding the infections has failed to show any circumstances which would influence the attack rate on a particular sex. Further, the infections with diplococci show the expected attack rate and serve to emphasize the greater susceptibility of females to the other respiratory pathogens, particularly *K. pneumoniae*.

Infections were detected more frequently in newly imported monkeys than in conditioned monkeys. The data in Table 4 have been arranged to illustrate differences in the infection rate in the initial 90-day conditioning period and in conditioned animals. These data show that in-

fections occurred approximately four times as often during the conditioning period as in fully conditioned animals.

Infections appeared in every month of the year, but the data in Table 5 show a greater incidence in the months of October through December. Respiratory infections in personnel could be expected to influence the onset and spread of these infections, but pharyngeal swabs from those in contact with the animals yielded cultures negative for the five primary pathogens.

The infection rate, which was 5% during the first year of study, increased to 12% in the second study year and was 10% in the third and fourth years (Table 6). As shown earlier, *K. pneumoniae* and *D. pneumoniae* ranked 1 and 2, respectively, in overall incidence, but the data in Table 6 show that on a year-to-year basis the rankings of these two major disease agents fluctuated.

The data in Table 7 are presented to show the source of many of the isolates. Bacterial pathogens were isolated from the blood in 60% of the infections. In only 23% of the cases was the infection confined to the lungs alone. Isolates from the spinal fluid alone were rather rare since the pathogens could often be found in other tissues. *B. bronchiseptica* produced infections which were confined to the lung in many cases, whereas *P. multocida* produced generalized infections which were usually characterized by bacteremia.

Dual infections with the primary respiratory pathogens were rarely found during the period of study. *D. pneumoniae* infections were complicated by concurrent infection with *K. pneumoniae* in seven cases, *P. multocida* in three cases, *B. bronchiseptica* in two cases, and *H. influenzae* in one case. However, mixed infections with other

TABLE 3. *Comparative susceptibility of males and females to infection with respiratory pathogens^a*

Bacterial pathogen	No. of monkeys				Ratio M:F
	Total infected	Males infected	Females infected	Sex not determined	
<i>Klebsiella pneumoniae</i>	262	93	166	3	1:1.79
<i>Diplococcus pneumoniae</i>	225	102	111	12	1:1.09
<i>Bordetella bronchiseptica</i>	80	31	46	3	1:1.48
<i>Pasteurella multocida</i>	75	29	44	2	1:1.52
<i>Haemophilus influenzae</i>	12	4	7	1	1:1.75
Total infections.....	654	259	374	21	1:1.44

^a Total colony population consisted of 3,941 males and 4,452 females (sex was not recorded for 388 animals) for M:F ratio of 1:1.13.

TABLE 4. *Relationship of time in quarters to infection with respiratory pathogens*

Bacterial pathogen	No. of monkeys infected	
	Less than 90 days ^a	More than 90 days ^a
<i>Klebsiella pneumoniae</i>	153	109
<i>Diplococcus pneumoniae</i>	137	88
<i>Bordetella bronchiseptica</i>	59	21
<i>Pasteurella multocida</i>	29	46
<i>Haemophilus influenzae</i>	3	9
Total infections ^b	381	273

^a Length of time in quarters.

^b Animals in quarters less than 90 days had an average monthly population of 385 and an infection rate of 7.9 per month giving an infection ratio of 1:49. Animals in quarters more than 90 days had an average monthly population of 1,197 and an infection rate of 5.7 per month, giving an infection ratio of 1:210.

organisms such as *Escherichia coli*, *Proteus* species, alpha- and beta-streptococci, or staphylococci were often observed. Concomitant enteric infections were also regularly found; *Shigella* species were isolated from 68 monkeys and *Salmonella* species from 36 monkeys infected with the five respiratory pathogens. It is questionable, then, which was the primary infection and which was the secondary invader in a weakened and more susceptible host.

Beta-streptococci were found to cause either generalized or respiratory infections in 147 animals, whereas staphylococci were similarly associated with 336 infections. In many cases these organisms were found only in the upper respiratory tract and represented a subclinical infection. Beta-streptococci were often group A (bacitracin discs), and the majority of the

staphylococci were coagulase-positive *S. aureus*. However, these infections were usually not severe unless found in conjunction with one of the major respiratory pathogens.

E. coli was the most common organism found in dual infections. Further, this organism was isolated from a total of 696 pneumonic or generalized infections. The general importance of this gram-negative bacillus in disease of the nonhuman primate is questionable; however, the infection may represent secondary invasion after a primary viral or mycoplasmal disease. For example, spinal fluids from 69 animals contained *E. coli* (53 in pure culture); but 56 of these animals showed indication of a viral infection [hemorrhagic disease similar to that described by Palmer et al. (20)]. Very few of the *E. coli* isolates could be typed with specific antisera (Difco) for the infant diarrheal types.

K. pneumoniae isolates were typed with specific antisera (Difco) to determine the association of particular strains with epidemics or clinical signs of disease. The data in Table 8 show that types 1 and 2 were found in 95% of the cases and that type 2 occurred with the greatest frequency; however, severity of disease caused by these two types could not be differentiated.

The ratio of infection to mortality with the various *D. pneumoniae* types is shown in Table 9. A total of 17 serologically differentiated strains were isolated with types 33, 9, 19, and 1, being found most frequently in that order. A high fatality rate was associated with each of the strains and attests to the seriousness of diplococcal pneumonias in monkey populations.

During the course of the study, *M. tuberculosis* was isolated from 24 monkeys which were positive tuberculin reactors when tested on arrival or during the conditioning period. One *M. fascicularis*, one *M. radiata*, and 22 *M. mulatta* gave positive tuberculin tests and were culturally

TABLE 5. Monthly incidence of respiratory pathogens during four-year period

Month	Avg population	No. of monkeys infected						Percentage
		<i>Klebsiella pneumoniae</i>	<i>Diplococcus pneumoniae</i>	<i>Pasteurella multocida</i>	<i>Bordetella bronchiseptica</i>	<i>Haemophilus influenzae</i>	Total	
January.....	1,428	28	13	6	0	1	48	3.4
February.....	1,484	24	12	3	4	1	44	3.0
March.....	1,487	18	10	3	11	0	42	2.8
April.....	1,536	18	13	9	6	2	48	3.1
May.....	1,540	18	28	5	3	6	60	3.9
June.....	1,568	18	19	4	7	0	48	3.1
July.....	1,621	10	5	1	9	0	25	1.5
August.....	1,595	14	14	8	10	0	46	2.9
September.....	1,575	11	23	6	5	0	45	2.9
October.....	1,564	21	33	11	14	0	79	5.1
November.....	1,696	35	27	16	8	1	87	5.1
December.....	1,901	46	28	3	3	1	81	4.3

TABLE 6. Yearly incidence of respiratory pathogens

Bacterial pathogen	No. of cases ^a			
	1964	1965	1966	1967
<i>Klebsiella pneumoniae</i>	4	63	123	72
<i>Diplococcus pneumoniae</i> ...	20	23	59	123
<i>Pasteurella multocida</i>	4	14	19	38
<i>Bordetella bronchiseptica</i> ..	6	11	38	25
<i>Haemophilus influenzae</i> ...	0	2	9	1
Total infections.....	34	113	248	259

^a The average monkey population was 632 in 1964, 908 in 1965, 2,294 in 1966, and 2,498 in 1967.

TABLE 7. Source of specimens yielding respiratory pathogens on culture

Bacterial pathogen	Number of cases			
	Blood	Lung only	Spinal fluid only	Nasopharyngeal swabs
<i>Klebsiella pneumoniae</i>	154	61	1	27
<i>Diplococcus pneumoniae</i> ...	149	39	6	26
<i>Pasteurella multocida</i>	59	8	1	4
<i>Bordetella bronchiseptica</i> ..	20	38	0	21
<i>Haemophilus influenzae</i> ...	9	2	0	0

positive. One infection in an *M. mulatta* was due to a strain fully resistant to 10 µg of isoniazid per ml of culture medium, and five other animals were infected with tubercle bacilli resistant to 0.1 µg of the drug.

Although encountered rarely, other respiratory pathogens were isolated. *Pasteurella hemolytica*

TABLE 8. *Klebsiella pneumoniae* types isolated from 262 monkeys

<i>Klebsiella pneumoniae</i>	No. of cases
Type 1.....	83
Type 2.....	166
Type 3.....	4
Type 4.....	0
Type 5.....	1
Type 6.....	1
Not typable.....	4
Not typed.....	3

was isolated from specimens taken at autopsy from two *M. mulatta* and one *P. cristatus*. *P. pseudotuberculosis* was isolated from fatal infections in two *A. trivirgatus* and one *P. entellus*. Fungal infections were found even more rarely, but two pulmonary infections with *Nocardia asteroides* and one generalized infection with *Coccidioides immitis* were observed. Each was proven by isolation and characterization of the organism (5, 10).

Antibiotic susceptibilities of the major respiratory pathogens did not change during the course of the study. Most of the *K. pneumoniae* isolates were resistant to chloramphenicol, dihydrostreptomycin, and tetracycline. However, 167 of 192 isolates tested were sensitive to cephalothin, a drug which also gave the best therapeutic results. *D. pneumoniae* isolates were all sensitive to penicillin. *P. multocida* strains were generally susceptible to chloramphenicol, dihydrostreptomycin, penicillin, and tetracycline. *B. bronchiseptica* isolates, in contrast to other gram-negative isolates, were almost uniformly resistant to furazolidone and streptomycin. However, only one strain was found resistant to tetracycline.

TABLE 9. *Diplococcus pneumoniae* types isolated from 225 monkeys and the fatality rate associated with each type

<i>Diplococcus pneumoniae</i>	No. of fatalities/No. of cases
Type 1.....	13/15
Type 2.....	1/1
Type 3.....	5/5
Type 4.....	8/10 ^a
Type 6.....	4/10
Type 8.....	1/1
Type 9.....	36/50
Type 15.....	6/6
Type 18.....	5/6
Type 19.....	22/26
Type 21.....	1/1
Type 22.....	0/1 ^a
Type 23.....	0/2
Type 27.....	4/5
Type 28.....	1/1
Type 29.....	0/1
Type 33.....	63/67
Not typable.....	18/18

^a Mixed types in single infection.

Except in a few instances all strains were also susceptible to chloramphenicol and, to a lesser extent, cephalothin. *H. influenzae* isolates were susceptible to chloramphenicol, dihydrostreptomycin, tetracycline, and cephalothin.

DISCUSSION

A systematic study of acute bacterial respiratory disease in nonhuman primate species was carried out to establish background information which could be used to improve the health status of colonized animals and to provide disease models for study. Acute respiratory disease in newly imported animals often results from a lowered resistance to infection caused by the inherent stresses imposed by capture and shipment. However, disease in conditioned animals arises from persistence of pathogens in the host, cross-infection from newly imported animals, or possible cross-infection from personnel. Prophylactic administration of antibiotics to control enteric infections in newly imported animals may increase the probability of recolonization with gram-negatives as shown by the results of Tillotson and Findland (25). However, Johanson et al. (12) could not correlate the prevalence of gram-negatives in oropharyngeal flora to a factor other than severity of disease. Tillotson and Lerner (26) reported pneumonia due to *E. coli* in humans could be related to lesions in the kidney and gastrointestinal tract. In the present studies, the access of gram-negative bacteria could have been provided by lesions

in the gastrointestinal tract after infection with *Shigella* species; cocci could have gained entry to the lower respiratory tract by aspiration. The conditions, then, that would favor respiratory infections by *E. coli*, *S. aureus*, and alpha- and beta-streptococci are stress, antibiotic therapy, or primary infections of viral, mycoplasmal or bacterial etiology (14, 15, 21).

Attack rates based on bacteriologically confirmed disease may be somewhat misleading in that not all ill animals were cultured due to the immediate need to preserve groups of animals. From clinical signs, preliminary identification of the etiologic agent, and experience with antibiotic susceptibilities of the isolates, specific therapy was instituted immediately to save ill animals and prevent spread of disease. For example, colonization of *P. entellus* was difficult due to explicit nutritional requirements (3) plus susceptibility to diplococcal and klebsiella infections. The rather chronic klebsiella infection, when detected, was immediately treated with cephalothin. Diplococcal infections, on the other hand, were often acute in all species with death occurring before clinical signs could be observed. However, when pathogens were isolated, cage-mates were treated prophylactically, and in some instances an entire room of 180 animals was placed on the prophylactic regimen. The infection rate, then, would be higher than that shown by the report of bacteriologically confirmed cases. This "weighing" of results may be responsible for the significantly higher infection rate in females, but the data on *D. pneumoniae* infections would tend to refute such a conclusion.

Due to the susceptibility of nonhuman primates to bacterial infections of the gastrointestinal and respiratory tracts, basic management of colonies must include control of population density, introduction of new animals, and movement of animals between groups. Semi-isolation of a socially oriented, free-ranging primate in a comparatively confining cage will not necessarily provide the optimal conditions for study of infectious diseases; more realistic data may be obtained in group cages which provide more space and conditions for social interaction.

Of the species of primates susceptible to natural infections with respiratory pathogens, several could be chosen to define a disease model for further study. Austrian (1) has suggested that the development of such models is necessary to the study of pathogenic mechanisms of bacteria in the respiratory tract. The data in this paper provide the overall background of species susceptibility that should be useful in establishing models for studying specific bacterial infections of the respiratory tract.

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