

The Natural Incidence of Renal Diseases in Various Species of Nonhuman Primates

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Introduction

In an attempt to clearly delineate renal disease patterns among various species of nonhuman primates, all renal materials available from routine necropsies at Delta Regional Primate Research Center were reviewed from 1975 to 1979. Pathological entities discovered are described.

Materials and Methods

Kidney tissues from 504 animals representing 8 nonhuman primate species were reviewed. Monkeys and apes not involved in studies of the kidney or urinary tract, coming to autopsy because of dying of natural causes, were examined. In most cases, gross appearance of kidney and other associated organs were noted but in many other cases, no careful attention has been paid but tissues were invariably examined histologically. The exact age of these animals is not known because most of the animals are caught in the wild and then brought to the primate center or transferred from other centers under the same circumstances. Tissue was fixed in 10% formalin, embedded in paraffin and 10 μ m sections stained with hematoxylin and eosin. Histologic examination of kidney sections include evaluation of the thickness of cortex and medulla in the specimen. Alterations of vessels are especially at the corticomedullary junction and in the afferent arterioles as far as glomeruli,

the cellularity, the condition of the basement membrane, capsular lining epithelium, focal or diffuse necrosis of glomerulus were examined. Tubular lumen size, size of cells, cytoplasmic deposits and particular segment affected were also included. Fibrous interstitium in both cortex and medulla were included for microscopic examination for comparative study.

Results

Kidney tissues from 504 animals representing eight nonhuman primate species were reviewed (Table 1). The kidney tissues were examined mostly derived from animals spontaneously dying at the center, majority of animals came with various pathologic conditions, i.e., gastrointestinal disturbances due to bacterial and parasitic diseases, respiratory diseases, septicemia, and trauma.

Since the purpose of the study was to determine the incidence of renal diseases in various species of nonhuman primates, histopathologic diagnosis of renal pathology seen in monkeys based on species and total number of animals examined were relevant and the data obtained are summarized (Table 2).

Two species of nonhuman primate, namely *macaque* and *Sanguinus mystax* were the major animals represented at Delta Regional Primate Center followed by *Saimiri sciurens*, *Papio* sp., *Erythrocebus patas*, *Macaca fascicularis*, *Cercopithecus aethiops*

and *Pan* spp. Although variable numbers of kidney tissues were examined, incidence of renal diseases seen in various species of nonhuman primates observed can be generalized.

Macaca Species : Among 200 *macaques* necropsied at Delta Primate Center, approximately 40% of the animals showed varying degrees of renal pathology. All group of ages ranging from juvenile to adults were encountered. More than 60% of *macaques* necropsied were females. Purulent nephritis was most common condition encountered comprising more than 50 cases. The capsule of the effected kidneys was edematous and had a slightly yellowish blue. The kidneys were hyperemic in medullary portions. The cortex but not the medulla was beset with many small greyish yellow foci which contain a droplet of pus microscopically, in the early stages, bacteria were obvious in the glomeruli and intertubular capillaries, and later they can be found in many abscesses in the collecting parts of the involved nephrons. Embolic suppurative nephritis due to septicemia was also seen; isolated large abscesses in the monkey kidney may result from confluence of small ones, but such abscess was more likely a development for a septic embolus, the initial ischemic infarct being destroyed by suppuration which may or may not be sequestered. If healing of embolic suppurative nephritis occurs, the varying degree of scarring were resulted. The central portions of the scars were of dense fibrous tissue containing a few lymphocytes. Near the margins, some atrophic tubules persist; some of these were indilated and contain hyaline casts. Six cases of chronic pyelonephritis were diagnosed based on previous report^{5,6}. The inflammatory infiltrate was mainly lymphocytic with mononuclear cells. It was irregular and consisted of wedge-shaped areas with the apex toward the papilla (Fig. 1). Fibrosis with tubular loss and localization of the inflammation were common. Although most frequently associated etiologic agent was the *E. coli* followed by *Proteus mirabilis*, gram negative bacillus, a member of family vibriaceae *Aeromonas hydrophilia* has

been isolated consistently among rhesus monkeys dying at the Center during 1978 and 1979. Most positive isolates occurred in animals housed in free ranging outdoor corrals.⁴ The bacterial organisms were readily demonstrable in renal tubules by both light and electron microscopy (Fig. 2). The pleomorphic bacilli measures approximately 0.2 μm in diameter and found in cytoplasm among the degranulated endoplasmic reticulum. Although slight degree of mitochondrial degeneration such as loss of cristae and swollen capsule were seen, endoplasmic reticulum networks were mostly damaged and free ribosomes were found through the perinuclear space (Fig. 2).

Other common renal lesion seen in association with purulent nephritis was embolic type nephritis characterized by multifocal abscessation of renal parenchyma. The lesion was most often associated with *E. coli* colonies involving glomeruli (Fig. 3). Subacute to chronic interstitial nephritis was often characterized by interstitial inflammation, and fibrosis with tubular loss and dilation. This was apparently results as a sequela of purulent nephritis.

The toxic nephrosis (25 cases) was most common condition found apparently due to toxic plant ingestion. It can be focal or diffuse affecting nuclei of collecting tubules. Necropsy often revealed large amounts of grass in the stomach. This was often seen in adult pregnant females and may be attributable to toxic metabolites although no toxicologic analyses of these plants have been made.

No neoplastic or parasitic renal diseases were found in rhesus monkeys necropsied in this series.

Sanguinus mystax: Among 167 *Sanguinus mystax* necropsied, 60 of various age groups of animals showed renal diseases. The types of renal diseases seen are summarized (Table 3). Most common type of renal disease seen was the focal suppurative nephritis. *E. coli* and *Aeromonas hydrophilia* were most commonly cultured. In the interstitium surrounding the glomeruli and tubules were areas of lymphocyte and plasma cell infiltration Extensive fibrosis with tubular atrophy was common.

The second most common type of renal lesion

seen in six cases was exudative type of glomerulonephritis followed by embolic type of glomerulonephritis possibly due to generalized septicemia. Proliferative focal glomerulonephritis was the predominant lesion in two cases. Hypercellularity of the glomerular tuft, with an increased mesangial and endothelial cells, was often seen (Fig. 4). Capillary lumina were narrowed, with various degrees of wall thickening. Occasionally, there were microfilaria within the glomerular tufts (Fig. 5). There were various degree of adhesion between parietal and visceral layer of Bowman's capsule. Some discrete sclerosis of the tuft was seen in all cases. Only three cases of pyelonephritis were seen. Extensive interstitial exudate consisted of neutrophils although some areas contained lymphocytes and plasma cells. The renal pelvis had purulent exudate.

One renal hypoplasia case was observed among 187 *S. mystax* necropsied. Several cases of nephrogenic immaturity were observed among neonatal mortality experienced at the Center. One case was characterized by renal tubular hyalinization and amyloidosis (Fig. 7).

***Saimiri sciureus*:** The most frequent seen lesion among squirrel monkeys dying at the Primate Center was the acute purulent nephritis. Three other monkeys had pyelonephritis. Glomerulonephritis was seen in most of squirrel monkeys of both sexes and ages. Based on light microscopy three had membranoproliferative glomerulonephritis and other two had exudative glomerulonephritis. While chronic inflammatory cells were often associated with diseased glomeruli, fusion of epithelial foot processes associated with proteinuria was seen in some forms of glomerulonephritis. Several cases of tubular nephrosis associated with septicemia and toxemia and hemorrhagic nephritis were also observed. Tubular dilatation with proliferation glomerulonephritis was also observed. All of these animals came from a long term irradiation project but the lesions seen were not attributable to irradiation nor other experimental procedure.

***Papio spp*:** Among 20 *Papio sp.* of various age and sexes autopsied, the most common renal lesions

seen were minor, circumscribed, cellular infiltrates affecting cortical interstitia, predominantly at the corticomedullary junction. No glomerular lesions were found in baboons autopsied at Delta Primate Center. One female adult baboon had purulent nephritis and pyelonephritis.

***Erythrocebus patas*:** More than 12 renal tissues were examined in connection with Delta virus research project. Only three cases had multifocal necrotic nephritis. Intranuclear inclusion bodies were found in the tubular epithelium suggesting viral etiology of this condition. Other patas renal tissues examined after biopsy showed only a minor lymphocytic cellular infiltrate on the corticomedullary junction; no significant renal diseases were found.

***Macaca fascicularis*:** Routine necropsies of 10 *Macaca fascicularis* showed only minor renal lesions such as circumscribed lymphocyte cell infiltrate and a minor pyelonephritis lesion. No significant renal lesions were found.

***Cercopithecus aethiops*:** Routine necropsies of 10 vervet monkeys showed minor renal lesions such as focal histiocyte cellular infiltrates and a minor suppurative nephritis. Two sections showed rather diffuse renal congestion and focal areas of hemorrhage. One other renal section revealed fatty droplets in the convoluted tubules. No other renal lesions were found.

***Pan spp*:** Only five chimpanzees were necropsied during 1977 to 1979. Although three other renal sections were examined, no significant renal lesions were found, other than focal areas of chronic interstitial nephritis, seen in one adult chimpanzee. Overall renal diseases incidence, though a limited animals were necropsied, was low.

Discussion

The deleterious effect of infectious agents on the structure and function of the kidney has long been recognized. The direct invasion of the renal parenchyma of these agents with resultant pyelonephritis and the direct involvement of the glomeruli subsequent to systemic infection with certain strains of nephrogenic *E. coli* and other organisms

Table 1. Renal Tissues Examined from Various Species of Nonhuman Primates

Species	No. of renal tissues examined
<i>Macaca mulatta</i>	200
<i>Saimiri sciureus</i>	80
<i>Erythrocebus patas</i>	12
<i>Cercopithecus aethiops</i>	10
<i>Pan spp.</i>	5
<i>Papio spp.</i>	20
<i>Macaca fascicularis</i>	10
<i>Sanguinus mystax</i>	167

Total no. of species : 8

Total no. of kidneys examined : 504

with resultant glomerulonephritis are the two well known classic renal disease mechanism caused by infectious agents.¹³ Although urinary tract infections have been documented in various species of nonhuman primates⁶⁾ very little information is available concerning comparative aspects of disease and species susceptibility. Recent symposium on

Table 2. Renal Disease Incidence Among Necropsies

Animal	Autopsies	Renal pathology
<i>Macaca mulatta</i>	200	80(40%)
<i>Sanguinus mystax</i>	167	60(35%)
<i>Saimiri sciureus</i>	80	35(43%)
<i>Papio spp.</i>	20	2(10%)
<i>Erythrocebus patas</i>	12	3(25%)
<i>Macaca fascicularis</i>	10	2(20%)
<i>Cercopithecus aethiops</i>	10	5(50%)
<i>Pan spp.</i>	5	2(40%)

renal pathology in nonhuman primates emphasizes this.²⁾

Although variable denominator of nonhuman primates have been necropsied, there were clear renal disease patterns possibly due to hereditary or species susceptibility among old and new world species of monkeys. Purulent nephritis occurred more often in rhesus monkeys whereas in *Sanguinus mystax* and *Saimiri sciureus* glomerulonephritis predominates. Among old world monkeys, baboons

Table 3. Classification of Nephritis Observed in the Nonhuman Primates

Type of nephritis	<i>Macaques</i>	<i>S. Mystax</i>	<i>Saimiri Sciureus</i>	<i>Papio sp.</i>	<i>Erythrocebus patas</i>	<i>M. Fascularis</i>	<i>Pan spp.</i>
Glomerulonephritis							
Exudative		6	2				
Embolic	6	3					
Proliferative	3	2	3				
Deposition		1					
Interstitial nephritis							
Purulent	50	28	20			3	
Lymphocytic	20	6	3	3	3		1
Granulomatous							
Toxic tubular nephrosis							
Pyelonephritis							
Purulent	6	3	3	1			
Others							
Renal immaturity		6					
Renal hypoplasia		1	1				

(*Papio sp.*) were free against the renal infectious diseases; virtually no renal diseases were seen among 200 necropsy.³⁾ This is not the case with *Macaques* although environmental and host factors have been altered considerably in rhesus monkeys housed at the Center.

Aeromonas hydrophilia is a gram negative bacillus, etiologic agent of red leg disease in frogs has been described in human infection. *Aeromonas hydrophilia* has been first time implicated as the cause of acute diarrhea and gastrointestinal disorders in nonhuman primates.⁴⁾ It's been isolated not only from rhesus monkeys but also from other species such as *Sanguinus mystax*, *Erythrocehus patab* and *Saimiri sciuresus*. It is considered to be an important nephrogenic agent especially among primates housed in the corral situation.

Parasitic infection must be considered as possible etiology cause in glomerulonephritis especially in wild caught *Sanguinus mystax*. High incidence of microfilarial parasites, *Dipetalonema gracile* in this species may account for direct and indirect (immunopathologic) role in predisposing glomerulonephritis. The microfilaria visualized within the glomeruli may sensitize the host and antibodies may

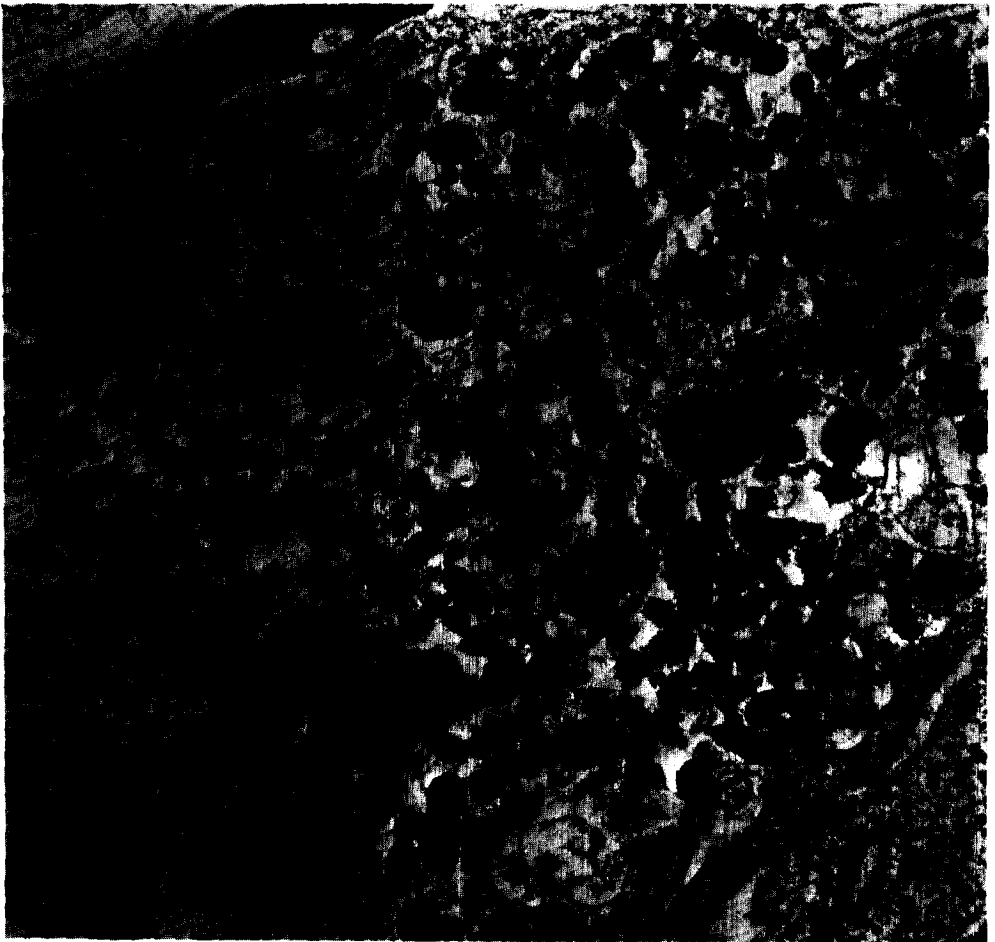
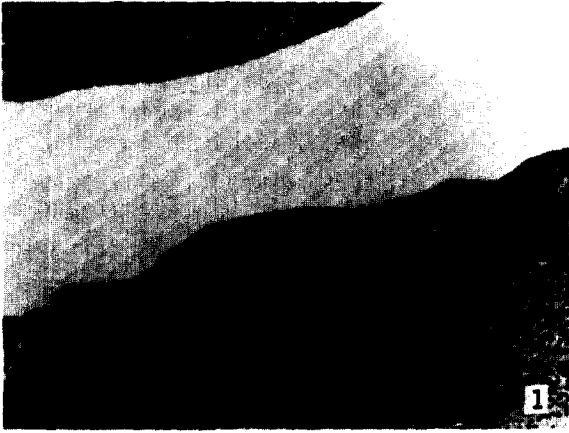
have deposited within basement membrane which may also attract neotrophics and other mononuclear cells.

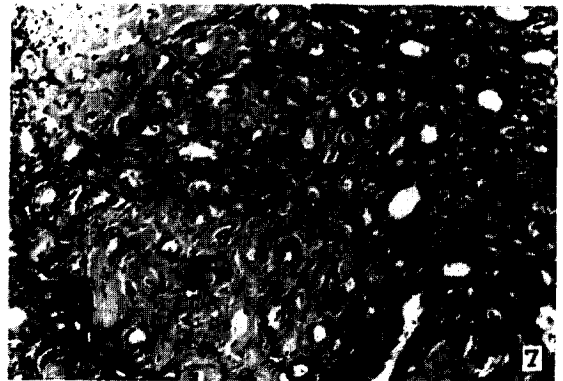
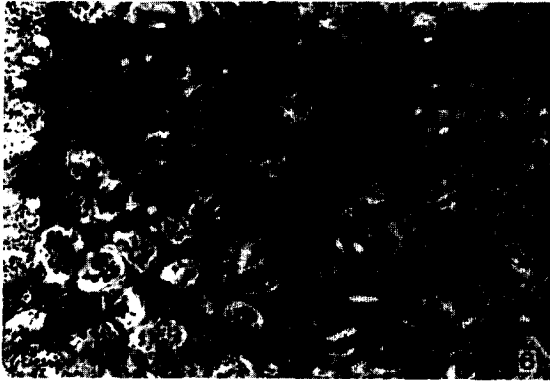
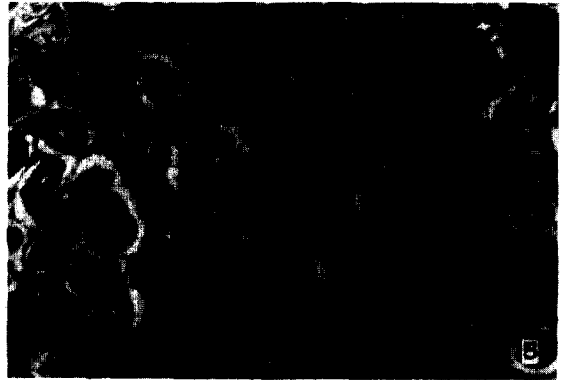
Conclusion

The renal pathology was investigated in 504 routine autopsies representing eight nonhuman primate species. *Macaque* species (200) and *Sanguinus mystax* (167) followed by *Saimiri sciereus* species (80) represent majority of animals represented. Most common renal diseases seen were purulent interstitial nephritis followed by toxic tubular nephrosis, glomerulonephritis and pyelonephritis. A characteristic disease pattern has been emerged among different species of nonhuman primates; more interstitial nephritis occur in *Macaques* versus New World monkeys whereas more glomerulonephritis occur in *Sanguinus mystax* and other New World monkeys versus baboons and other Old World monkey species although overall renal disease incidence remains relatively low. *Aeromonas hydrophilia* is first time recognized as an important etiological agent for renal disease among free ranging out door monkeys.

Legends for Figures

- Fig. 1.** Chronic pyelonephritis observed in an adult rhesus monkey. Note the numerous lymphocytes infiltrated throughout the submucosal layer of the papilla. H & E. $\times 100$.
- Fig. 2.** *Aeromonas hydrophilia* organisms visualized by electron microscopy. The bacterial cellular capsule, cell wall and plasma membrane is discernible. $\times 2000$.
- Fig. 3.** Embolic glomerulonephritis-note the bacterial colonies found within the necrotized glomerular mesangium. H & E. $\times 100$.
- Fig. 4.** Proliferative glomerulonephritis seen in one of the *Sanguinus mystax*. Note the hypercellularity of the glomerula tufts with increased mesangial and endothelial cells. H & E. $\times 150$.
- Fig. 5.** Note the microfilarial parasite, *Dipetalonema gracile*, found within the glomeruli. Also note the nephrosis associated with it. H & E. $\times 100$.
- Fig. 6.** Nephrogenic immaturity seen among neonatal birth accomanied by pulmonary immaturity in a mystax. H & E. $\times 60$.
- Fig. 7.** Note the hyalinization of renal tubules and chronic nephritis associated with it. Congo red stain was positive for amyloidosis. H & E. $\times 100$.





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각종 Nonhuman primate에 자연 발생한 신장질병에 대한 연구

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초 목

Nonhuman primate에 자연 발생하는 신장질병에 대한 병리학적 연구를 위해 *Macaque* (200), *Sanquinus mystax* (15), *Saimiri sciureus* (80) 등 8종에서 총 504두를 일반 병리부검에 의해 조사하였다.

가장 빈발하는 신장 질병은 화농성, 간질성, 신장염이며 다음은 독성 신세노판염, 신사구체신염 및 신우신염 등이었다.

도표 3에서 비교된 바와 같이 nonhuman primate의 각 종류에 따라서 특성적인 신장염 소견을 보여주었다. 야외 원숭이 사육장에서 기르는 원숭이 군에서는 *Aeromonas hydrophilia*가 처음으로 중요한 본 질병의 원인체로 발견되었다.