Gerodontology, Volume 1, Number 2, 1982

Age-Associated Lesions in Barrier-Reared Male Sprague-Dawley Rats: A Comparison Between Hap: (SD) and Crl:COBS[R]CD[R](SD) Stocks[1,6]

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Age-associated lesions were characterized in two outbred stocks of barrier-reared male Sprague-Dawley rats. Seventy-two virgin Hap:(SD) between 6-29 months of age and 113 retired breeder Crl:COBS[R]CD[R](SD) between 12-38 months of age were evaluated for the presence of lesions in all major organ systems. Rats of both stocks developed a spectrum of neoplastic, inflammatory and degenerative diseases with highest prevalence in the oldest age groups. In general, the shorter-lived Hap:(SD) rats had greater incidences and severity of lesions when compared to Crl:COBS[R]CD[R]SD of similar ages. Many of these differences were not apparent when the two stocks were compared over their respective life spans. The study provides baseline pathology data relevant to the use of these rats in gerontologic research.

The so-called "Sprague Dawley rat" has been used in scientific research for more than 50 years. (The copyright to the name "Sprague Dawley" is owned by Harlan Industries, Indianapolis, Indiana.) This outbred stock was developed by R.W. Dawley, and, for many years, was produced commercially by Sprague-Dawley, Inc., Madison, Wisconsin [25; 44]. Today, rats of Sprague Dawley (SD) origin are produced by many commercial breeders and are among the most widely used laboratory rats.

SD rats from different sources may have little in common except a similar stock designation because they are outbred and hence have heterogeneous genetic backgrounds. Furthermore, their life histories may differ markedly with respect to husbandry, nutrition, intercurrent infectious diseases, and breeding status. Failure to define or control environmental variables such as these can complicate or invalidate experimental results, particularly where long-term studies are in progress [4; 16].

The selection of a stock or strain of rats for research on aging, and the interpretation of experimental results, requires knowledge of the spontaneous lesions which can develop [20; 23; 35; 43]. Studies focussing on the gerontologic pathology of the Fischer 344 (F344) [19] and BN/BI, WAG/Rij and F1 hybrid (WAG/Rij x BN/BI) [12] are in the current literature. Additionally, there have been reports of neoplastic and non-neoplastic lesions in F344 [31] and the Osborne-Mendel strains [32]. These latter studies were done on control animals from a variety of toxicology studies, and rats were not kept beyond 24 months of age, thus eliminating the population of senescent animals of particular interest to experimental gerontologists.

This is a report of age-associated lesions in Hap:(SD) and Crl:COBS[R]CD[R](SD) rats, two widely used commercially produced stocks of SD origin. The report extends existing information about the gerontologic pathology of SD rats [7; 18; 49; 58].

Methods

Animals

Hap:(SD) (Hap). The breeding nucleus of Hap:(SD) rats for aging research was derived by hysterectomy from NIH colony stock in 1975. The rats were foster-nursed on germfree NIH Sprague Dawley rats and reared axenically in isolators. At 3-4 weeks of age, rats were inoculated orally with a bacterial "cocktail" consisting of 2 strains of streptococci, 2 strains of lactobacilli, one strain of nonpathogenic *Klebsiella pneumoniae* (formerly *Aerobacter aerogenes*), *Escherichia coli* and *Fusobacterium*. These rats were reared to adulthood within isolators at Harlan Industries, Indianapolis, Indiana.

From this breeding colony, cohorts of 50-150 male rats were weaned at 4 weeks of age, removed from the isolators and entered into a barrier aging colony. Litter sizes were not controlled.

Rat cohorts were housed 2-3 animals per cage in polypropylene or polycarbonate cages (19 in. x 10.5 in. x 18 in.) with autoclaved hardwood chip bedding. Bedding was changed 1-2 times per week. Animal rooms had an ambient temperature of 23°C, relative humidity of 40-60%, a 12/12 hr. light/dark cycle and 12-15 air changes per hour. Rats were fed non-certified autoclavable rodent laboratory chow (Purina 5010: protein minimum-23%, fat minimum-4.5%, fiber maximum-6.0%) *ad libitum*. Water was supplied in bottles

[1]Supported in part by National Institutes of Health grants RR 00200 and AG-00368, and by contract NO-1-AG 6-2136. The authors gratefully acknowledge the technical assistance of Gail Renard, Lois Craig, and Jane Haack; and the advice of Dr. D.H. Ringler, Dr. G.D. Abrams, and Dr. R.C. Adelman.

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and acidified with HCL to pH 2.5-3.0. Insecticides were not used in the animal rooms. Cages were recombined when rats died or were removed for testing. Shipping crates had agar *feed-soft diet* and hardwood bedding chips.

Crl:COBS[R]CD[R](SD) (CD). CD rats have been produced continuously at the Charles River Breeding Laboratories (CRBL), Wilmington, Massachusetts since 1955. Conventional production started in 1950 with a small breeding nucleus that was obtained from Sprague Dawley, Inc. The CRBL conventional colony was rederived in 1955 and was colonized in gnotobiotic isolators with the following rodent flora supplied by Dr. Russell W. Schaedler: *Lactobacillus acidophilus, Lactobacillus salivarius, Streptococcus fecalis,* a Group N anaerobic streptococcus, *Escherichia coli* variety *mutobilis, Bacteroides distasonis,* a *Ciostridium* species and an obligately anaerobic fusiform-shaped bacterium.

Groups of 50 or 100 12-month-old male retired breeders were set up monthly, housed 10 per cage, and held at CRBL until 24-26 months of age for subsequent use in research. The cages were stainless steel and were supplied with heat-sterilized hardwood bedding. Soiled bedding was vacuumed from the cages weekly and fresh bedding was added. The rats were fed Charles River Rat and Mouse Diet 4RF (Agway: protein minimum-22%, fat minimum-5%, fiber maximum-4%) *ad libitum.* Drinking water, acidified to pH 2.5-3.0 with HCL was supplied by an automatic system. Room temperature and other aspects of environment were comparable to those provided to Hap rats.

Pathology

Hap. Seventy-two rats were selected at random for necropsy from cohorts of the following ages (in months): 6-11 (14 rats), 12-17 (13 rats), 18-23 (11 rats) and 24-29 (34 rats). Animals were placed in filter-covered containers behind the barrier and shipped in a temperature-controlled van to the University of Michigan. Time between shipment and necropsy examination was 24 hours or less, and rats remained in their filter crates until they were removed for euthanasia. Necropsy examinations were done between 9:00 am and 3:00 pm.

Following clinical examination after removal from the crate, each rat was anesthetized with methoxyflurane, weighed, and the abdomen opened; the animals were killed by exsanguination through the abdominal aorta.

CD. One hundred and thirteen rats were necropsied at the following ages (in months): 12-17 (18 rats), 18-23 (16 rats), 24-29 (34 rats) and 30-39 (45 rats). Fifty-six of the rats, younger than 26 months, were selected randomly from among the cohort groups at CRL, and were shipped to us by air freight in filter covered cardboard transport crates. They were necropsied immediately on arrival. Fifty-seven of the rats were sent in a single shipment when they were 26 months old. They were held in an isolated conventional animal room, housed in groups of 3 or 4 in filter covered polycarbonate shoebox cages, and fed a rodent diet (Teklad[R], 1148 Mouse/Rat Diet) virtually identical in composition to that fed at CRBL. The rats were killed and necropsied as significant lesions became evident clinically, or, in a few instances, as they became moribund or died spontaneously.

Hap & CD. Some or all of the following organs were collected for microscopic examination: turbinates, trachea, lung, tongue, salivary gland, esophagus, stomach (squamous and glandular), duodenum, jejunum, ileum, cecum, terminal colon, liver, pancreas, heart, thoracic and abdominal aorta, spleen, mesenteric lymph node, thymus, adrenal, thyroid, pituitary, testis, prostate, seminal vesicle, preputial gland, kidney, urinary bladder, eye, harderian gland, skin, brain, vertebral column, semimembranosus muscle, tympanic bullae and any organ with a gross lesion. Organs were fixed in 10% buffered neutral formalin and eyes in Zenker's fixative; lungs were inflated with formalin. Tissues were embedded in paraffin, sectioned at 6 nm and stained with hematoxylin and eosin. The following special stains also were done on selected cases: Congo red, Masson's trichrome, von Kossa, Giemsa and Gomori's methenamine silver.

Parasitology

Hap. An anal tape impression was examined microscopically for pinworm ova. Fecal pellets were suspended in a saturated sodium nitrate solution and a coverslip flotation preparation examined for endoparasite ova and cysts. A 4 cm. piece of dorsal skin was removed at necropsy, placed in a petri dish and examined under a dissecting microscope for ectoparasites.

CD. Endoparasite examination was done only as follows: 18-23 months, 4 rats; 24-29 months, 3 rats; 30-39 months, 4 rats. Ectoparasite examination of skin was not performed.

Microbiology

Hap. A retrograde nasal aspirate (using trypticase soy broth) and the right cranial lobe of lung (removed aspectically) were cultured for *Mycoplasma pulmonis.* Lung, nasal aspirate, a calcium alginate swab of pharynx and terminal colon contents were cultured using standard bacteriologic techniques.

CD. The lung was cultured as above.

Serology

Hap. Serum samples were heated for 30 minutes at 56°C, diluted 1:5, and shipped to a commercial laboratory (Microbiological Associates, Bethesda, Maryland) for detection of antibodies to the following rodent viruses: hemagglutination inhibition (HAI) antibodies to pneumonia virus of mice (PVM), reovirus-3, GDVII (mouse poliovirus), Kilham rat virus (KRV) and Toolan's H-1; complement fixation (CF) antibodies to Sendai virus, mouse adenovirus, lymphocytic choriomeningitis virus (LCM) and rat coronavirus (RCV).

CD. Serology was not performed on the rats characterized in this paper. During the period of study, in-house serologic testing was done by CRBL on animals within their aging colony. Sera were tested for antibodies to the following rodent viruses: HAI antibodies to KRV, Toolan's H-1, Sendai, reovirus-3, PVM; CF antibodies to sialodacryoadenitis (SDA) virus. Indirect immunofluorescent antibody test and CF for LCM were performed by Dr. Pravin Bhatt, Yale University, School of Medicine, New Haven, Connecticut.

Statistical analysis of data

Statistical analyses were performed only on the lesion data from 12-17, 18-23, and 24-29 month old animals since these were the three age groups in which both CD and Hap rats were examined. Six to 11 month old CD rats were not included in the study, and, in the 30-38 month old group, there were no Hap survivors.

The probability values are reported (Tables 1-3) as Fisher exact probabilities for a 2 x 2 table. This statistic reflects the probability of observing a result as extreme or more extreme under the null hypothesis of no difference.

Results

Life expectancy

The 50% survival age for Hap rats in the cohorts studied was 24 months and maximum survival was 29 months [15]. The 50% survival age for CD rats in the cohorts studied was not determined. However, at 24 months of age, there was less than 10% mortality [17]. Maximum survival age was 38 months.

Pathology

Statistical comparison of the incidence of age-associated lesions was made only between comparable age groups (12-29 months). In general, Hap rats had significantly higher incidences of a number of neoplasms, degenerative and inflammatory lesions (Tables 1-3). However, as CD rats became senescent between 30-38 months, many of the age-associated lesions seen in the shorter-lived Haps became prevalent in CDs.

Neoplasms (Table 1)

Neoplasms were uncommon in both stocks before 18 months of age. Only three tumors were present in rats in the younger age groups: embryonal nephroma (Hap, 6-11 months), cutaneous pilomatricoma (Hap, 12-17 months) and islet cell tumor of pancreas (CD, 12-17 months). After 18 months, there was a rapid increase in the incidence of neoplasms, especially those involving the endocrine system. At the end of their respective life spans, rats from both stocks had similar high incidence of pituitary and adrenal gland tumors while only CDs developed neoplasia of the pancreatic islets.

Adenomas of the anterior pituitary were classified as chromophobe, acidophil or basophil, recognizing that such classification did not reflect cell of origin or hormonal activity [1]. The only overt indicator of hormone production by the neoplastic cells was secretory gynecomastia (5.6% incidence in Hap, 8.0% in CD) suggestive of prolactin production. If all anterior pituitary adenomas were combined, the incidence of 25.1% in Hap and 18.3% in CDs is comparable to that of many inbred strains [1] but lower than the 48% reported for CD males [51]. In the comparable age groups, Haps had a significantly greater incidence of chromophobe adenomas.

Adrenal cortical adenoma was found in roughly 20% incidence in both stocks with no difference between the comparable age groups. The neoplasm was classified according to the criteria of Hollander and Snell [36]. Foci of altered cells in the cortex which did not compress adjacent normal cells were classified as hyperplasia and therefore nonneoplastic with the knowledge that in the future they may be discovered to be analogous to the "neoplastic nodule" of rat liver [37; 57].

Pheochromocytoma, a tumor of the adrenal medulla, was a common neoplasm in both stocks with a higher incidence in 12-29 month old Haps. Although the division between neoplasia and medullary hyperplasia was not always clear-cut, medullary chromaffin cellular alterations were considered to be neoplastic if there were atypia, loss of normal architecture or compression of adjacent normal medullary cells or the zona reticularis. The difficulty of differentiating neoplastic and hyperplastic adrenal medulla has been addressed in rats [12; 36] and in man [56]. In our study, one pheochromocytoma in Hap rats metastasized to the mesenteric lymph nodes. Ganglioneuromas, as reported in F344 rats [52], were not seen.

Pancreatic islet cell tumors, some producing clinical signs and laboratory findings suggestive of insulin secretion (hypoglycemic shock), were common in CD rats (17.6%) and absent in Hap animals. Conversely, Hap animals had a significantly higher incidence of conglomerate islets, and islet hyperplasia was present in 33.8% of Haps as compared to 13.0% of CDs over their respective life spans. Islet hyperplasia and conglomerate islets have been associated with abnormal glucose tolerance tests in virgin SD rats [34].

Adenoma of the kidney was more frequent in Haps than CDs, both in comparable age groups and over the life span. The incidence of this tumor in Haps is considerably higher than reported in the literature for most inbred strains [1]. A smaller number of rats of both stocks had renal carcinomas; two of the oldest CDs had sarcomas. Lipomatous tumors as described in Osborne-Mendel rats [32] were not seen.

Benign mammary tumors are common in females of many rat stocks and strains, but males, including CD males, are usually affected only at a 1-2% incidence [1; 51; 55]. Throughout their life span, the CD rats (retired breeder) of this study continued to follow this typical pattern whereas the Hap rats (virgins) had an 11.1% incidence. In this study, both the classic fibroadenoma and well circumscribed tumors composed solely of whorls and bundles of dense collagen and arising in the ventral subcutaneum were seen. These were considered to be of mammary origin.

In the F344 rat, interstitial cell tumors of testis [19; 31] and monocytic leukemia [19; 31; 48; 54] are age-associated neoplasms occurring at a high incidence. Hap rats did not develop these neoplasms; CD rats had interstitial cell testicular tumors at 8.3% incidence and leukemias at 8.7% incidence. These neoplasms were prevalent primarily in 30-38 month old CDs.

Nonneoplastic lesions

The results of this study are in agreement with Berg's [7] finding that the major nonneoplastic lesions of aging SD rats are chronic glomerulonephropathy polyarteritis nodosa, chronic myocarditis, radiculoneuropathy, and skeletal muscle degeneration.

Major lesions (Table 2). CHRONIC GLOMERULONEPHROPATHY. Chronic glomerulonephropathy of the type identical to that reviewed by Gray [33] was widespread both in CD and Hap rats. The incidence was 91.2% and 88.9% respectively. Comparing the 12-29 month old rats, Haps had significantly more severe renal disease while CD rats had a greater proportion of minimally affected kidneys. This difference disappeared when the 30-38 month old CDs were included.

POLYARTERITIS NODOSA (PAN). The onset of this condition was age related since it did not occur before 18 months in Hap rats and 24 months in CD rats. For comparable age groups, Haps had a significantly higher incidence of PAN. However, the prevalence was close to 50% (20 to 45) in 30-38 month old CD rats, more than twice that in 24-29 month old CDs. For both stocks the most commonly affected organs were testis, spleen, mesentery, pancreas, and tongue, but vessels in many other organs also were involved. Lesions ranged from acute to chronic and were typical of PAN [4]. The incidence of PAN (23.9% and 23.6% respectively of all the CD and Hap rats examined) was lower than that reported by Berg [7] for SD rats up to 30 months old (60%) and was comparable to that of other SD rats [68] and of several inbred strains [12]. Arterial lesions of identical histological appearance but not acknowledged as PAN were described in 33-34 month old conventional SD virgin males [65]. An early onset of PAN in breeder CD rats analogous to that reported [64] in Sch:Sprague-Dawley$^{(R)}$ (SD) did not occur. Indeed, the onset was later than in the virgin Haps.

Table 1

Neoplasms in HAP and CD Rats

Type of Neoplasm	Age (Months) 6-11 HAP	12-17 CD	12-17 HAP	18-23 CD	18-23 HAP	24-29 CD	24-29 HAP	Sig.[3]	30-38 CD	Incidence[7] CD	Incidence[7] HAP
ENDOCRINE SYSTEM											
Adrenal:											
Cortical adenoma	0/14[1] (0)[2]	0/15 (0)	2/11 (18.2)	1/12 (8.3)	3/11 (27.3)	5/24 (20.8)	10/34 (29.4)	–[6]	12/37 (32.4)	18/88 (20.5)	15/70 (21.4)
Cortical adenocarcinoma	0/14 (0)	0/15 (0)	0/11 (0)	0/12 (0)	1/11 (9.1)	0/24 (0)	2/34 (5.9)	–	0/37 (0)	0/88 (0)	3/70 (4.3)
Pheochromocytoma	0/14 (0)	0/15 (0)	0/11 (0)	0/12 (0)	2/11 (18.2)	3/24 (12.5)	14/34 (41.2)	**[5]	10/37 (27.0)	13/88 (14.8)	16/70 (22.9)
Pituitary:											
Chromophobe adenoma	0/13 (0)	0/19 (0)	0/8 (0)	1/11 (9.1)	2/6 (33.3)	3/27 (11.1)	8/29 (27.6)	*[4]	12/36 (33.3)	16/93 (17.2)	10/56 (17.9)
Acidophil adenoma	0/13 (0)	0/19 (0)	0/8 (0)	0/11 (0)	0/6 (0)	1/27 (3.7)	3/29 (10.3)	–	0/36 (0)	1/93 (1.1)	3/56 (5.4)
Basophil adenoma	0/13 (0)	0/19 (0)	0/8 (0)	0/11 (0)	0/6 (0)	0/27 (0)	1/29 (3.4)	–	0/36 (0)	0/93 (0)	1/56 (1.8)
Adenocarcinoma	0/13 (0)	0/19 (0)	0/8 (0)	0/11 (0)	0/6 (0)	1/27 (3.7)	0/29 (0)	–	1/36 (2.8)	2/93 (2.2)	0/56 (0)
Adenoma - pars intermedia	0/13 (0)	0/19 (0)	0/8 (0)	0/11 (0)	0/6 (0)	0/27 (0)	1/29 (3.4)	–	0/36 (0)	0/93 (0)	1/56 (1.8)
Thyroid:											
Medullary thyroid tumor	0/14 (0)	0/16 (0)	0/13 (0)	0/12 (0)	1/10 (10.0)	1/25 (4.0)	5/34 (14.7)	–	4/45 (8.9)	5/98 (5.1)	6/71 (8.5)
Follicular adenoma	0/14 (0)	0/16 (0)	0/13 (0)	0/12 (0)	0/10 (0)	1/25 (4.0)	0/34 (0)	–	0/45 (0)	1/98 (1.0)	0/71 (0)
Parathyroid:											
Adenoma	0/9 (0)	0/7 (0)	0/9 (0)	0/6 (0)	0/11 (0)	0/11 (0)	1/26 (3.8)	–	0/28 (0)	0/52 (0)	1/55 (1.8)
URINARY SYSTEM											
Kidney:											
Adenoma	0/14 (0)	0/17 (0)	0/13 (0)	0/12 (0)	2/11 (18.2)	0/29 (0)	13/34 (38.2)	**	3/44 (6.8)	3/102 (2.9)	15/72 (20.8)
Carcinoma	0/14 (0)	0/17 (0)	0/13 (0)	0/12 (0)	0/11 (0)	0/29 (0)	4/34 (11.8)	–	2/44 (4.5)	2/102 (2.0)	4/72 (5.6)
Embryonal nephroma	1/14 (7.1)	0/17 (0)	0/13 (0)	0/12 (0)	0/11 (0)	0/29 (0)	0/34 (0)	–	0/44 (0)	0/102 (0)	1/72 (1.4)
Transitional cell papilloma	0/14 (0)	0/17 (0)	0/13 (0)	0/12 (0)	0/11 (0)	0/29 (0)	1/34 (2.9)	–	0/44 (0)	0/102 (0)	1/72 (1.4)
Fibrosarcoma	0/14 (0)	0/17 (0)	0/13 (0)	0/12 (0)	0/11 (0)	0/29 (0)	0/34 (0)	–	1/44 (2.3)	1/102 (1.0)	0/72 (0)
Undifferentiated sarcoma	0/14 (0)	0/17 (0)	0/13 (0)	0/12 (0)	0/11 (0)	0/29 (0)	0/34 (0)	–	1/44 (2.3)	1/102 (1.0)	0/72 (0)
Urinary Bladder:											
Metastatic renal carcinoma	0/11 (0)	0/15 (0)	0/11 (0)	0/12 (0)	0/9 (0)	1/21 (4.8)	0/31 (0)	–	0/33 (0)	1/81 (1.2)	0/62 (0)
GENITAL SYSTEM											
Testis:											
Interstitial cell tumor	0/13 (0)	0/16 (0)	0/12 (0)	0/12 (0)	0/11 (0)	2/27 (7.4)	0/34 (0)	–	6/41 (14.6)	8/96 (8.3)	0/70 (0)
Preputial Gland:											
Squamous cell carcinoma	0/14 (0)	0/12 (0)	0/12 (0)	0/11 (0)	0/11 (0)	0/15 (0)	0/28 (0)	–	1/13 (7.7)	1/51 (2.0)	0/65 (0)
Vas Deferens:											
Mesothelioma	0/13 (0)	0/16 (0)	0/12 (0)	0/12 (0)	0/11 (0)	0/27 (0)	1/34 (2.9)	–	0/41 (0)	0/96 (0)	1/70 (1.4)
Mammary Gland:											
Fibroadenoma/ fibroma	0/14 (0)	0/22 (0)	0/13 (0)	1/12 (8.3)	2/11 (18.2)	0/34 (0)	6/34 (17.6)	*	0/45 (0)	1/113 (0.9)	8/72 (11.1)

Table 1 Continued

Type of Neoplasm	Age (Months) 6-11 HAP	12-17 CD	12-17 HAP	18-23 CD	18-23 HAP	24-29 CD	24-29 HAP	Sig.	30-38 CD	Incidence CD	Incidence HAP
ALIMENTARY SYSTEM											
Liver:											
Neoplastic nodule	0/13 (0)	0/20 (0)	0/13 (0)	0/12 (0)	0/10 (0)	2/27 (7.4)	0/34 (0)	–	2/45 (4.4)	4/104 (3.8)	0/70 (0)
Hepatocellular carcinoma	0/13 (0)	0/20 (0)	0/13 (0)	0/12 (0)	0/10 (0)	2/27 (7.4)	1/34 (2.9)	–	1/45 (2.2)	3/104 (2.9)	1/70 (1.4)
Hemangioma	0/13 (0)	0/20 (0)	0/13 (0)	0/12 (0)	0/10 (0)	0/27 (0)	1/34 (2.9)	–	1/45 (2.2)	1/104 (1.0)	1/70 (1.4)
Capillary hemangiosarcoma	0/13 (0)	0/20 (0)	0/13 (0)	0/12 (0)	0/10 (0)	0/27 (0)	1/34 (2.9)	–	0/45 (0)	0/104 (0)	1/70 (1.4)
Pancreas:											
Islet cell tumor	0/13 (0)	1/21 (4.8)	0/13 (0)	0/12 (0)	0/11 (0)	9/32 (28.1)	0/34 (0)	**	9/43 (20.9)	19/108 (17.6)	0/71 (0)
Mouth:											
Squamous cell carcinoma	0/14 (0)	0/22 (0)	0/13 (0)	0/12 (0)	0/11 (0)	0/34 (0)	1/34 (2.9)	–	0/45 (0)	0/113 (0)	1/72 (1.4)
Palate-squamous papilloma	0/14 (0)	0/22 (0)	0/13 (0)	0/12 (0)	0/11 (0)	1/34 (2.9)	0/34 (0)	–	0/45 (0)	1/113 (0.9)	0/72 (0)
Esophagus:											
Infiltration of parotid neurofibrosarcoma	0/12 (0)	0/15 (0)	0/13 (0)	0/12 (0)	0/9 (0)	0/20 (0)	0/27 (0)	–	1/45 (2.2)	1/92 (1.1)	0/61 (0)
Stomach:											
Squamous cell carcinoma	0/14 (0)	0/16 (0)	0/13 (0)	0/12 (0)	0/10 (0)	0/28 (0)	1/33 (3.0)	–	0/44 (0)	0/100 (0)	1/70 (1.4)
Squamous papilloma	0/14 (0)	0/16 (0)	0/13 (0)	0/12 (0)	0/10 (0)	0/28 (0)	1/33 (3.0)	–	0/44 (0)	0/100 (0)	1/70 (1.4)
Salivary Glands:											
Benign mixed tumor	0/13 (0)	0/18 (0)	0/12 (0)	0/12 (0)	0/11 (0)	0/24 (0)	0/32 (0)	–	1/42 (2.4)	1/96 (1.0)	0/68 (0)
Parotid Neurofibrosarcoma	0/13 (0)	0/18 (0)	0/12 (0)	0/12 (0)	0/11 (0)	0/24 (0)	0/32 (0)	–	1/42 (2.4)	1/96 (1.0)	0/68 (0)
HEMIC AND LYMPHATIC SYSTEM											
Spleen:											
Leukemia, myelomonocytic	0/14 (0)	0/12 (0)	0/13 (0)	0/12 (0)	0/11 (0)	0/26 (0)	0/33 (0)	–	7/42 (16.7)	7/92 (7.6)	0/71 (0)
Leukemia, lymphocytic	0/14 (0)	0/12 (0)	0/13 (0)	0/12 (0)	0/11 (0)	0/26 (0)	0/33 (0)	–	1/42 (2.4)	1/92 (1.1)	0/71 (0)
Hemangioma	0/14 (0)	0/12 (0)	0/13 (0)	0/12 (0)	0/11 (0)	0/26 (0)	2/33 (6.1)	–	0/42 (0)	0/92 (0)	2/71 (2.8)
Capillary hemangiosarcoma	0/14 (0)	0/12 (0)	0/13 (0)	0/12 (0)	0/11 (0)	0/26 (0)	1/33 (3.0)	–	0/42 (0)	0/92 (0	1/71 (1.4)
Mesenteric Lymph Node:											
Pheochromocytoma (metastatic)	0/12 (0)	0/11 (0)	0/8 (0)	0/6 (0)	1/9 (11.1)	0/4 (0)	0/26 (0)	–	0/4 (0)	0/25 (0)	1/55 (1.8)
INTEGUMENTARY SYSTEM											
Skin:											
Basal cell tumor	0/13 (0)	0/22 (0)	0/11 (0)	0/12 (0)	0/9 (0)	0/34 (0)	1/29 (3.4)	–	0/45 (0)	0/113 (0)	1/62 (1.6)
Pilomatricoma	0/13 (0)	0/22 (0)	1/11 (9.1)	0/12 (0)	0/9 (0)	0/34 (0)	0/29 (0)	–	0/45 (0)	0/113 (0)	1/62 (1.6)
Trichoepithelioma	0/13 (0)	0/22 (0)	0/11 (0)	0/12 (0)	0/9 (0)	0/34 (0)	1/29 (3.4)	–	1/45 (2.2)	1/113 (0.9)	1/62 (1.6)
Sebaceous gland adenoma	0/13 (0)	0/22 (0)	0/11 (0)	0/12 (0)	0/9 (0)	1/34 (2.9)	0/29 (0)	–	1/45 (2.2)	2/113 (1.8)	0/62 (0)
Squamous papilloma	0/13 (0)	0/22 (0)	0/11 (0)	0/12 (0)	0/9 (0)	1/34 (2.9)	1/29 (3.4)		3/45 (6.7)	4/113 (3.5)	1/62 (1.6)
Dermal fibroma	0/13 (0)	0/22 (0)	0/11 (0)	0/12 (0)	0/9 (0)	4/34 (11.8)	1/29 (3.4)	–	5/45 (11.1)	9/113 (8.0)	1/62 (1.6)
Lipoma	0/13 (0	0/22 (0)	0/11 (0)	0/12 (0)	0/9 (0)	0/34 (0)	0/29 (0)	–	1/45 (2.2)	1/113 (0.9)	0/62 (0)
Hemangiosarcoma	0/13 (0)	0/22 (0)	0/11 (0)	0/12 (0)	0/9 (0)	1/34 (2.9)	0/29 (0)	–	0/45 (0)	1/113 (0.9)	0/62 (0)

Table 1 Continued

Type of Neoplasm	Age (Months) 6-11 HAP	12-17 CD	12-17 HAP	18-23 CD	18-23 HAP	24-29 CD	24-29 HAP	Sig.	30-38 CD	Incidence CD	Incidence HAP
RESPIRATORY SYSTEM											
Lung:											
Pulmonary adenoma	0/14 (0)	0/17 (0)	0/13 (0)	0/12 (0)	0/11 (0)	0/28 (0)	1/34 (2.9)	–	0/44 (0)	0/101 (0)	1/72 (1.4)
Papillary Adenocarcinoma	0/14 (0)	0/17 (0)	0/13 (0)	0/12 (0)	0/11 (0)	0/28 (0)	1/34 (2.9)	–	0/44 (0)	0/101 (0)	1/72 (1.4)
Leukemia cells in alveolar capillaries	0/14 (0)	0/17 (0)	0/13 (0)	0/12 (0)	0/11 (0)	0/28 (0)	0/34 (0)	–	1/44 (2.3)	1/101 (1.0)	0/72 (0)
CENTRAL NERVOUS SYSTEM											
Brain-Cerebellum:											
Reticulum cell sarcoma	0/14 (0)	0/16 (0)	0/12 (0)	0/12 (0)	0/11 (0)	0/27 (0)	0/33 (0)	–	1/43 (2.3)	1/98 (1.0)	0/72 (0)
MUSCULOSKELETAL SYSTEM											
Perivertebral tumor hemangiosarcoma	0/14 (0)	0/22 (0)	0/13 (0)	0/12 (0)	0/11 (0)	0/34 (0)	1/34 (2.9)	–	0/38 (0)	0/106 (0)	0/72 (1.4)
MISCELLANEOUS											
Neurogenous sarcoma	0/14 (0)	0/22 (0)	0/13 (0)	0/12 (0)	0/11 (0)	1/34 (2.9)	0/34 (0)	–	0/38 (0)	1/106 (0.9)	0/72 (0)

[1]Number with lesion/number examined; [2]( ) = percent with lesion; [3]Sig. = statistical significance (12-29 month old HAP and CD); [4]*$p<0.05$; [5]**$p<0.01$; [6]– = not statistically significant; [7]all age groups.

CHRONIC MYOCARDITIS. Chronic myocarditis occurred in 85.9% of CD rats and in 73.2% of Hap rats and was more prevalent with increasing age. The myocardial changes were identical to those reported by Fairweather [22] and included some or all of the following: myofiber degeneration, atrophy, fibrosis, and mononuclear infiltrates. In 6-11 month old Hap rats, the prevalence was 30.8%, similar to that of F344 rats [19]. Most published reports indicate that the age of onset of chronic myocarditis in rats is 13 months and older [22]. Clinical signs or lesions related to cardiac insufficiency were not present in either SD stock.

RADICULONEUROPATHY. In agreement with Burek [12], early and advanced lesions were found most consistently in the nerve roots comprising the cauda equina, especially in the lumbar vertebrae. In all affected rats, histologic lesions were identical to those described by other investigators [7; 8; 30]. Compared with younger Hap age groups, the prevalence of radiculoneuropathy was elevated markedly in rats older than 17 months. Nine of 11 Hap rats of the 18-23 month old group had histologic evidence of radiculoneuropathy, and all 34 of the 24-29 month old animals were affected. In the CDs, the only animals examined for radiculoneuropathy were those 30-38 months old, and 90.9% were affected. In both stocks, clinical signs of posterior paresis or paralysis were considered to be related to the degenerative CNS lesions. Bilateral hind limb paresis or paralysis was present in all of the 30-38 month old CD rats and in 50% of the 24-29 month old Haps but not in the younger Hap age groups. Rats with paralysis often exhibited urinary incontinence and constipation. Affected animals in the younger age groups had the histologic changes without clinical signs.

SKELETAL MUSCLE DEGENERATION AND ATROPHY. Gross and histologic evidence of skeletal muscle damage in the hind limbs most often follows the onset of radiculoneuropathy and is generally considered to be of neurogenic origin [14; 60]. Skeletal muscle degeneration and atrophy were not seen in 6-23 month old Hap or 12-23 month old CD rats. In Hap animals, sarcolemmal proliferation occurred independently of myofiber degeneration in 9.1% and 30% respectively of the rats in the 12-17 and 18-23 month old groups. The significantly lower incidence of skeletal muscle degeneration in 12-29 month old CD rats suggests that radiculoneuropathy was not as extensive in this stock until the rats reached senescence.

Other nonneoplastic lesions (Table 3). URINARY SYSTEM. Other than glomerulonephropathy, Hap rats had the following renal lesions at greater than 10% incidence: calculi (calcium-magnesium-ammonium phosphate) in the pelvic ureter, epithelial hyperplasia of the pelvic ureter, pyelonephritis and hydronephrosis. These lesions occurred most frequently in the 24-29 month old Haps. Calculi and ureteral epithelial changes did not occur in any CDs, and the incidences of pyelonephritis and hydronephrosis in CDs were 2.0% and 3.9% respectively.

Urolithiasis is associated in many species with ascending urinary infections and hydronephrosis. Additionally, urolithiasis and uroepithelial tumors of the ureter and urinary bladder have been closely correlated in BN/BIRij rats [11]. In this strain, males had high incidences of urinary bladder tumors and calculi while females had high incidences of ureteral tumors and calculi.

HEMIC AND LYMPHATIC SYSTEM. The mesenteric lymph node was selected as a representative of the lymphatic system in Hap rats. Changes occurring with age were by and large similar to those catalogued in Wistar rats [3; 62]. In the thymus of Hap rats, atrophy was present in approximately 50% of the rats in the 12-17 month old group and over 80% in animals older than 18 months. Fatty infiltration also became more common after this age. Both these findings are similar to those of Wagner [62]; however, the cystic changes she reported in older Wistars were uncommon in the Haps. Node and thymus were examined only in a small proportion of the CDs. Functional studies in conventional Zml:ZM(SD) rats (50% survival rate of 14 months and maximal life span of 23 months) indicated that immunocompetence in males as measured by colloidal carbon clearance and xenograft skin grafts declined but macrophage

migration inhibition was unaffected by age [9].

In the spleen, extramedullary hematopoiesis was a common finding in all age groups, being over 50% even in rats (Haps) less than 12 months old. Myelopoiesis, erythropoiesis and megakaryocyte production were present in varying proportions. Pigment of the type characterized by Ward and Reznik-Schuller [63] was present in the majority of both stocks.

CENTRAL NERVOUS SYSTEM. Vacuolation of the neuropil of the type described in rats, mice and hamsters [46] was present in the brain and spinal cord in all age groups of both stocks, increasing with age. Vacuolar change was significantly higher in 12-29 month old Haps in the cerebellum but not in the cerebrum. Cellular reaction was minimal to absent in the brain. In the cervical and thoracic spinal cords of Hap, but not CD, rats, gitter cell reaction was associated with the vacuoles in animals older than 18 months. Degenerative myelopathy of the type described by Burek, et al. [14] occurred in over 50% of the 24-29 month old Haps.

Neuron loss, alterations of glial cells and a number of other age-associated changes have been reported in the rat brain [20; 26; 50]. However, many of these abnormalities are not readily apparent on light microscopic examination of H & E sections.

CARDIOVASCULAR SYSTEM. (Heart). Myocardial degeneration, atrophy and fibrosis (chronic myocarditis) were the principal lesions. All others were present at a low incidence. Valvular endocardiosis, seen in older rats of both stocks, affected primarily the atrioventricular valves and histologically resembled the lesion in aging dogs [40]. Subendocardial mesenchymal cell proliferation—seen in one 12-17 month old Hap rat—corresponded to "endocardial disease" reported by Boorman, et al. [10].

(Arteries). Arteriosclerosis consisting of subintimal and medial calcification occurred in the intrapulmonary branches of the pulmonary artery and the thoracic aorta of both stocks but only in one old animal of each stock in the coronary arteries. CD retired breeders had a 13.9% incidence of medial sclerosis of pulmonary arteries as compared to 5.6% of the virgin Haps, but this calcific lesion was not comparable to the "premature arteriosclerosis" reported in repeatedly bred Sch:Sprague-Dawley[R] (SD) rats [64].

Thickening of the aortic intima of aged rats by subendothelial accumulation of amorphous, granular or fibrillar material and cellular debris has been reported. This lesion is most obvious by ultrastructural examination of the aorta and by the use of special stains with light microscopy [28; 42]. We did not examine our rat aortas for this specific change.

RESPIRATORY SYSTEM. (Lung). In Hap rats, inflammatory lesions of chronic lymphocytic bronchitis and interstitial pneumonia occurred more frequently in older animals and could be associated epizootiologically with significant titers to a series of murine viruses, principally Sendai and rat coronavirus (see serology results). The presence of these agents signifies increasing "permeability" of the barrier housing system, a common problem in such housing systems [5] and a severe one in aging rat colonies which cannot be renewed periodically.

Mycoplasma pulmonis, which has been associated with a spectrum of upper and lower respiratory tract lesions, was not isolated from the lung or nasopharyngeal area of any Hap rat in this study. A proportion of CD rats over 26 months of age, as mentioned in Methods, was removed from the barrier housing system and housed conventionally until euthanasia. This change in husbandry and subsequent contamination of the animals with murine viruses and bacteria was responsible for the rapid increase after 24 months of age in pulmonary inflammatory lesions including purulent bronchopneumonia. Smaller, inactive-looking peribronchial and perivascular lymphocytic aggregates unassociated with the pulmonary lesions occurred in all ages of rats. Such bronchial-associated lymphoid tissue (BALT) is a normal finding in rat lungs [29; 59].

Alveolar histiocytosis had a higher incidence in 12-29 month old Haps but was present in all age groups. This lesion consisted of collections of foamy macrophages within subpleural alveoli. Occasionally the macrophages were multinucleated; in some alveoli, the macrophages and multinucleated giant cells surrounded cholesterol clefts, presumably from degenerated histiocytes. Large collections of histiocytes were recognizable grossly as subpleural white plaques. An age-related incidence was not as clear in either of our stocks as it was in SD rats of Flodh, et al. [24] which had more severe lesions and higher prevalence in 22 month than in 6 or 9 month old animals.

(Upper respiratory tract). Inflammatory lesions in the trachea and turbinates paralleled those in the lungs.

ENDOCRINE SYSTEM. (Adrenal). Foci of cellular alteration in all zones of the cortex were common in both stocks though beginning in Haps at a younger age and present in a significantly higher incidence in 12-29 month old rats. Sinusoidal dilatation in the adrenal cortex and medulla occurred in rats older than 24 months and was especially prevalent in 30-38 month old CDs (32.4%). Bland sinusoidal thrombi were often associated with sinusoidal dilatation and occasionally with pheochromocytoma.

(Thyroid). Hyperplasia of parafollicular ("C") cells was present in older rats of both SD stocks with the characteristic difference between Haps and CDs. The progession of C cell lesions from hyperplasia to neoplasia has been well illustrated [21] and seemed identical in our rats although the tumor incidence was less than 10% and there was no difference between 12-29 month old Haps and CDs. The ability of medullary thyroid carcinoma from WAG/Rij rats to secrete calcitonin, even after transplantation, has been documented [47].

(Parathyroid). Over 50% of both stocks developed hyperplasia toward the end of their life spans. This lesion is regarded as secondary renal hyperparathyroidism by a number of investigators [7; 38; 53] and correlated well with the time course of glomerulonephropathy in this study. Hyperplasia is uncommon in rats with minimal chronic renal disease such as WAG/Rij [12]; it is also uncommon in male F344 rats (1.4%-Coleman, et al. [19]; 8%-Goodman, et al. [31]).

GENITAL SYSTEM. (Testis). The most common testicular lesion in the older age groups was patchy degeneration of the seminiferous tubules, often accompanied by dystrophic calcification. Interstitial edema was a common microscopic finding in Haps. An extreme form of testicular edema was hydrocoele, presenting grossly as an accumulation of clear, amber-colored fluid beneath the tunica albuginea. Hydrocoele has been documented previously only in 24-26 month old FW49 Bierach albino rats [45]. It was not described in 3-26 month old CD rats [39].

(Prostate). The most frequent finding in all age groups was concretions in the acinar lumens. Inflammatory lesions increased with age and were accompanied by epithelial hyperplasia. Dysplasia was minimal and neoplasms did not occur in any age group of either stock.

(Preputial gland). Inflammatory lesions ranging from focal mononuclear infiltrates to chronic abscesses, squamous metaplasia, duct dilation and patchy atrophy, were more frequent in older rats but did occur in all age groups. One or both glands were affected. Differences in preputial gland lesions between retired breeder CDs and virgin Haps were not striking.

DIGESTIVE SYSTEM. (Liver). Bile duct hyperplasia and fibrosis variably accompanied by mononuclear infiltrates [37] increased with age in both stocks. This pattern was similar to that of F344 rats [19]. Areas of hepatocellular altera-

Table 2

Major Nonneoplastic Lesions in HAP and CD Rats

	Age (Months)										
	6-11	12-17		18-23		24-29			30-38	Incidence[8]	
Lesion	HAP	CD	HAP	CD	HAP	CD	HAP	Sig.[3]	CD	CD	HAP
CHRONIC GLOMERULO-NEPHROPATHY											
Minimal	6/14[1] (42.9)[2]	13/17 (76.5)	6/13 (46.2)	7/12 (58.3)	3/11 (27.3)	8/29 (27.6)	2/34 (5.9)	**[4]	10/44 (22.7)	38/102 (37.3)	17/72 (23.6)
Moderate	2/14 (14.3)	0/17 (0)	3/13 (23.1)	2/12 (16.7)	4/11 (36.4)	13/29 (44.8)	14/34 (41.2)	—[6]	14/44 (31.8)	29/102 (28.4)	23/72 (31.9)
Severe	1/14 (7.1)	0/17 (0)	2/13 (15.4)	1/12 (0)	3/11 (27.3)	7/29 (24.1)	18/34 (52.9)	**[5]	19/44 (43.2)	26/102 (25.5)	24/72 (33.3)
TOTAL	9/14 (64.3)	13/17 (76.5)	11/13 (84.6)	9/12 (75.0)	10/11 (90.9)	28/29 (96.6)	34/34 (100.0)	—	43/44 (97.7)	92/102 (91.2)	64/72 (88.9)
POLYARTERITIS NODOSA											
Totals for Age Group	0/14 (0)	0/22 (0)	0/13 (0)	0/12 (0)	3/11 (27.2)	7/34 (20.6)	14/34 (41.2)	*	20/45 (44.4)	27/113 (23.9)	17/72 (23.6)
CHRONIC MYOCARDITIS	4/13 (30.8)	9/16 (56.3)	8/13 (61.5)	8/12 (66.7)	8/11 (72.7)	25/27 (92.6)	32/34 (94.1)	—	43/44 (97.7)	85/99 (85.9)	52/71 (73.2)
RADICULONEUROPATHY											
Cervical Spinal Cord	0/13 (0)	NE[7]	0/12 (0)	NE	0/11 (0)	NE	11/33 (33.3)	—	NE	NE	11/69 (15.9)
Thoracic Spinal Cord	0/14 (0)	0/8 (0)	0/12 (0)	0/12 (0)	0/11 (0)	0/13 (0)	0/30 (0)	—	8/27 (29.6)	8/60 (13.3)	0/67 (0)
Cauda Equina (Lumbar)	1/11 (9.1)	NE	2/12 (16.7)	NE	9/11 (81.8)	NE	34/34 (100.0)	—	20/22 (90.9)	20/22 (90.9)	46/68 (67.6)
SKELETAL MUSCLE DEGENERATION											
Sarcolemmal Proliferation	0/14 (0)	0/14 (0)	1/11 (9.1)	0/12 (0)	3/10 (30.0)	4/23 (17.4)	29/34 (85.3)	**	16/36 (44.4)	20/85 (23.5)	33/69 (47.8)
Myofiber Degeneration and Atrophy	0/14 (0)	0/14 (0)	0/11 (0)	0/12 (0)	0/10 (0)	3/23 (13.0)	26/34 (76.5)	**	20/36 (55.6)	23/85 (27.1)	26/69 (37.7)

[1]Number with lesion/number examined; [2]( ) = percent with lesion; [3]Sig. = statistical significance (12-29 month old HAP and CD); [4]**$p<0.05$; [5]**$p<0.01$; [6]— = not statistically significant; [7]NE = not examined; [8]all age groups.

tion—eosinophilic, basophilic, and clear cell foci—and neoplastic nodules are considered preneoplastic stages in hepatic carcinogenesis [6; 37; 66; 67]. Liver cell foci were present in older rats of both stocks at incidences ranging roughly from 4-21% (Table 3). Livers of individual animals often contained more than one type of focus. Neoplastic nodules (listed under neoplasia) were rare in CDs (3.8% incidence) and absent in Haps. Likewise, hepatocellular carcinomas were rare in both stocks (Table 1).

The stocks differed markedly from each other in the incidence of telangiectasis, with the lesion common in 24 month and older CD rats and rare even in the oldest Haps.

(Gastrointestinal tract). The GI tract essentially had no significant changes except for the stomach. Gastric lesions were present in the majority of rats of both stocks. Typical stomach lesions were in the fundus and consisted of deep mucosal fibrosis with gland dilation and atrophy, variably accompanied by mast cells and eosinophils in the muscularis mucosae and submucosa. Burek [12] briefly mentions that these lesions were "not common" in the rats in his study. In our experience, this finding increased dramatically with age (93.9% of the oldest Haps, 88.6% of the oldest CDs).

The squamous portion of the stomach was free of ulcers throughout the rats' life span.

(Pancreas). Changes in the exocrine pancreas were identical to those reviewed in the literature [2; 4]. These lesions had no apparent effect on the clinical health of the animals, e.g. steatorrhea or other signs of pancreatic insufficiency were not evident.

Islet lesions have been discussed under neoplasia.

(Salivary glands). Although not tabulated, glands were examined in a number of rats from both stocks. Most rats had no lesions. In the older animals, there were occasional areas of acinar vacuolation and focal interstitial collections of mononuclear cells.

SPECIAL SENSES. (Eye). Retinal degeneration had a higher incidence in 12-29 month old Haps than CDs, with 72.7% of the oldest Haps so affected. This lesion, which occurs in other stocks and strains, is considered by some to be light-induced although rats may have a degree of genetic susceptibility [61]. In aging F344 rats, peripheral retinal degeneration occurs even at low light levels, but exposure to moderate light (32 foot candles) exacerbates the lesion [41]. Photoreceptor degeneration of known heritability occurs early in life (60 days) in strains such as the RCS [27].

PIGMENT. Golden brown granular to amorphous pigment having the staining characteristics of lipofuscin and/or hemosiderin pigment [63] was present in a variety of organs and tissues (Table 3) of both stocks.

Parasitology

Hap. All rats were consistently negative for endo- and ectoparasites.

Table 3

Other Nonneoplastic Lesions in HAP and CD Rats

Lesion	Age (Months) 6-11 HAP	12-17 CD	12-17 HAP	18-23 CD	18-23 HAP	24-29 CD	24-29 HAP	Sig.[3]	30-38 CD	Incidence[9] CD	Incidence[9] HAP
URINARY SYSTEM											
Kidney:											
Pyelonephritis	0/14[1] (0)[2]	0/17 (0)	0/13 (0)	0/12 (0)	0/11 (0)	1/29 (3.4)	11/34 (32.4)	**[5]	1/44 (2.3)	2/102 (2.0)	11/72 (15.3)
Hydronephrosis	0/14 (0)	1/17 *(5.9)	0/13 (0)	0/12 (0)	0/11 (0)	2/29 (6.9)	10/34 (29.4)	–[6]	1/44 (2.3)	4/102 (3.9)	10/72 (13.9)
Cortical tubular vacuolization	0/14 (0)	0/17 (0)	1/13 (7.7)	0/12 (0)	0/11 (0)	3/29 (10.3)	0/34 (0)	–	1/44 (2.3)	4/102 (3.9)	1/72 (1.4)
Microabscess	0/14 (0)	0/17 (0)	0/13 (0)	0/12 (0)	1/11 (9.1)	0/29 (0)	0/34 (0)	–	0/44 (0)	0/102 (0)	1/72 (1.4)
Calcific concretions -cortex and medulla	1/14 (7.1)	1/17 (5.9)	3/13 (23.1)	0/12 (0)	0/11 (0)	2/29 (6.9)	1/34 (2.9)	–	4/44 (9.1)	7/102 (6.9)	5/72 (6.9)
Hematoma	0/14 (0)	0/17 (0)	0/13 (0)	0/12 (0)	0/11 (0)	0/29 (0)	0/34 (0)	–	2/44 (4.5)	2/102 (2.0)	0/72 (0)
Lipochrome/lipofuscin pigment-cortical tubules	12/14 (85.7)	16/17 (94.1)	13/13 (100.0)	8/12 (66.7)	11/11 (100.0)	25/29 (86.2)	34/34 (100.0)	–	43/44 (97.7)	92/102 (90.2)	70/72 (97.2)
Kidney-Pelvis:											
Calculus	0/14 (0)	0/17 (0)	0/13 (0)	0/12 (0)	1/11 (9.1)	0/29 (0)	12/34 (35.3)	**	0/44 (0)	0/102 (0)	13/72 (18.1)
Epithelial hyperplasia -pelvic ureter	0/14 (0)	0/17 (0)	0/13 (0)	0/12 (0)	0/11 (0)	0/29 (0)	8/34 (23.5)	**	0/44 (0)	0/102 (0)	8/72 (11.1)
Epithelial dysplasia -pelvic ureter	0/14 (0)	0/17 (0)	0/13 (0)	0/12 (0)	0/11 (0)	0/29 (0)	2/34 (5.9)	–	0/44 (0)	0/102 (0)	2/72 (2.8)
Chronic nonsuppurative pyelitis	0/14 (0)	0/17 (0)	0/13 (0)	0/12 (0)	0/11 (0)	0/29 (0)	3/34 (8.8)	–	0/44 (0)	0/102 (0)	3/72 (4.2)
No significant changes	2/14 (14.3)	1/17 (5.9)	0/13 (0)	4/12 (33.3)	0/11 (0)	0/29 (0)	0/34 (0)	–	0/44 (0)	5/102 (4.9)	2/72 (2.8)
Urinary Bladder:											
Chronic cystitis	0/11 (0)	0/15 (0)	0/11 (0)	1/12 (8.3)	0/9 (0)	0/21 (0)	1/31 (3.2)	–	4/33 (12.1)	5/81 (6.2)	1/62 (1.6)
Epithelial hyperplasia	0/11 (0)	0/15 (0)	0/11 (0)	0/12 (0)	0/9 (0)	0/21 (0)	1/31 (3.2)	–	0/33 (0)	0/81 (0)	1/62 (1.6)
Squamous metaplasia	0/11 (0)	0/15 (0)	0/11 (0)	0/12 (0)	0/9 (0)	0/21 (0)	1/31 (3.2)	–	0/33 (0)	0/81 (0)	1/62 (1.6)
No significant changes	11/11 (100.0)	15/15 (100.0)	11/11 (100.0)	11/12 (91.7)	9/9 (100.0)	20/21 (95.2)	30/31 (96.8)	–	29/33 (87.9)	75/81 (92.6)	61/62 (98.4)
HEMIC AND LYMPHATIC SYSTEM											
Spleen:											
Extramedullary hematopoiesis	8/14 (57.1)	11/12 (91.7)	9/13 (69.2)	10/12 (83.3)	8/11 (72.7)	16/26 (61.5)	32/33 (97.0)	–	34/42 (81.0)	71/92 (77.2)	57/71 (80.3)
Lymphoid hyperplasia	0/14 (0)	0/12 (0)	0/13 (0)	1/12 (8.3)	0/11 (0)	3/26 (11.5)	1/33 (3.0)	–	0/42 (0)	4/92 (4.3)	1/71 (1.4)
Lymphoid depletion	0/14 (0)	0/12 (0)	0/13 (0)	0/12 (0)	1/11 (9.1)	1/26 (3.8)	0/33 (0)	–	3/42 (7.1)	4/92 (4.3)	1/71 (1.4)
Neutrophils-sinusoids	0/14 (0)	0/12 (0)	1/13 (7.7)	0/12 (0)	1/11 (9.1)	1/26 (3.8)	0/33 (0)	–	3/42 (7.1)	4/92 (4.3)	2/71 (2.8)
Plasma cells-sinusoids	0/14 (0)	0/12 (0)	0/13 (0)	0/12 (0)	0/11 (0)	0/26 (0)	1/33 (3.0)	–	0/42 (0)	0/92 (0)	1/71 (1.4)
Fibrosis-sinusoids	0/14 (0)	0/12 (0)	0/13 (0)	0/12 (0)	2/11 (18.2)	0/26 (0)	0/33 (0)	–	0/42 (0)	0/92 (0)	2/71 (2.8)
Thrombosis-sinusoids	0/14 (0)	0/12 (0)	0/13 (0)	0/12 (0)	0/11 (0)	0/26 (0)	1/33 (3.0)	–	1/42 (2.4)	1/92 (1.1)	1/71 (1.4)
Necrosis	0/14 (0)	0/12 (0)	0/13 (0)	0/12 (0)	0/11 (0)	0/26 (0)	0/33 (0)	–	1/42 (2.4)	1/92 (1.1)	0/71 (0)
Nodular hyperplasia	1/14 (7.1)	0/12 (0)	0/13 (0)	0/12 (0)	0/11 (0)	0/26 (0)	0/33 (0)	–	0/42 (0)	0/92 (0)	1/71 (1.4)
Fibrosis-capsule	0/14 (0)	0/12 (0)	0/13 (0)	0/12 (0)	1/11 (9.1)	0/26 (0)	1/33 (3.0)	–	0/42 (0)	0/92 (0)	2/71 (2.8)

Table 3 Continued

	Age (Months)										
	6-11	12-17		18-23		24-29			30-38	Incidence	
Lesion	HAP	CD	HAP	CD	HAP	CD	HAP	Sig.	CD	CD	HAP
Spleen (cont.):											
Hemosiderin, lipochrome/ lipofuscin pigment	11/14 (78.6)	10/12 (83.3)	12/13 (92.3)	9/12 (75.0)	10/11 (90.9)	19/26 (73.1)	33/33 (100.0)	–	30/42 (71.4)	68/92 (73.9)	66/71 (93.0)
No significant changes	2/14 (14.3)	1/12 (8.3)	0/13 (0)	2/12 (16.7)	0/11 (0)	2/26 (7.7)	0/33 (0)	**	7/42 (16.7)	12/92 (13.2)	2/71 (2.8)
Mesenteric Lymph Node:											
Lymphoid depletion	0/12 (0)	0/11 (0)	0/8 (0)	2/6 (33.3)	0/9 (0)	0/4 (0)	4/26 (15.4)	–	1/4 (25.0)	3/25 (12.0)	4/55 (7.3)
RE hyperplasia	0/12 (0)	1/11 (9.1)	1/8 (12.5)	0/6 (0)	1/9 (11.1)	1/4 (25.0)	5/26 (19.2)	–	0/4 (0)	2/25 (8.0)	7/55 (12.7)
Medullary hemorrhage	0/12 (0)	0/11 (0)	1/8 (12.5)	1/6 (16.7)	3/9 (33.3)	1/4 (25.0)	7/26 (26.9)	–	0/4 (0)	2/25 (8.0)	11/55 (20.0)
Erythrophagocytosis	0/12 (0)	0/11 (0)	1/8 (12.5)	0/6 (0)	3/9 (33.3)	0/4 (0)	10/26 (38.5)	**	0/4 (0)	0/25 (0)	14/55 (25.5)
Mast cells-cortex and medulla	1/12 (8.3)	1/11 (9.1)	0/8 (0)	1/6 (16.7)	4/9 (44.4)	1/4 (25.0)	8/26 (30.8)	–	0/4 (0)	3/25 (12.0)	13/55 (23.6)
Cystic change-medulla	0/12 (0)	0/11 (0)	0/8 (0)	0/6 (0)	0/9 (0)	0/4 (0)	11/26 (42.3)	*	0/4 (0)	0/25 (0)	11/55 (20.0)
Lipochrome/lipofuscin pigment	2/12 (16.7)	0/11 (0)	5/8 (62.5)	2/6 (33.3)	7/9 (77.8)	0/4 (0)	18/26 (69.2)	**	0/4 (0)	2/25 (8.0)	32/55 (58.2)
No significant changes	10/12 (83.3)	9/11 (81.8)	2/8 (25.0)	1/6 (16.7)	0/9 (0)	3/4 (75.0)	2/26 (7.7)	**	3/4 (75.0)	16/25 (64.0)	14/55 (25.5)
Thymus:											
Atrophy	2/11 (18.2)	2/12 (16.7)	4/9 (44.4)	0/6 (0)	4/5 (80.0)	2/7 (28.6)	19/22 (86.4)	**	10/11 (90.9)	14/36 (38.9)	29/47 (61.7)
Fatty infiltration	1/11 (9.1)	0/12 (0)	0/9 (0)	0/6 (0)	4/5 (80.0)	2/7 (28.6)	13/22 (59.1)	*	9/11 (81.1)	11/36 (30.6)	18/47 (38.3)
Mast cells	0/11 (0)	0/12 (0)	2/9 (22.2)	0/6 (0)	0/5 (0)	0/7 (0)	5/22 (22.7)	*	1/11 (9.1)	1/36 (2.8)	7/47 (14.9)
Plasma cells	0/11 (0)	0/12 (0)	0/9 (0)	0/6 (0)	0/5 (0)	0/7 (0)	1/22 (4.5)	–	0/11 (0)	0/36 (0)	1/47 (2.1)
Cyst	0/11 (0)	0/12 (0)	0/9 (0)	0/6 (0)	0/5 (0)	0/7 (0)	1/22 (4.5)	–	0/11 (0)	0/36 (0)	1/47 (2.1)
Lipochrome/lipofuscin pigment	0/11 (0)	0/12 (0)	1/9 (11.1)	0/6 (0)	0/5 (0)	0/7 (0)	2/22 (9.1)	–	0/11 (0)	0/36 (0)	3/47 (6.4)
No significant changes	9/11 (81.8)	10/12 (83.3)	4/9 (44.4)	6/6 (100.0)	1/5 (20.0)	4/7 (57.1)	1/22 (4.5)	**	1/11 (9.1)	21/36 (58.3)	19/47 (31.9)
Bone Marrow (Vertebral):											
Hypoplastic	0/14 (0)	0/8 (0)	0/12 (0)	0/12 (0)	0/10 (0)	0/13 (0)	1/34 (2.9)	–	2/27 (7.4)	2/60 (3.3)	1/70 (1.4)
Active	14/14 (100.0)	8/8 (100.0)	12/12 (100.0)	12/12 (100.0)	10/10 (100.0)	13/13 (100.0)	33/34 (97.1)	–	25/27 (92.6)	58/60 (96.7)	69/70 (98.6)
CENTRAL NERVOUS SYSTEM											
Brain-Cerebrum:											
Vacuolization-gray/white matter, minimal or no reaction	2/14 (14.3)	1/16 (6.3)	1/12 (8.3)	5/11 (45.5)	2/11 (18.2)	12/26 (46.2)	17/34 (50.0)	–	31/43 (72.1)	49/69 (51.0)	22/71 (31.0)
Internal hydrocephalus	0/14 (0)	0/16 (0)	1/12 (8.3)	0/11 (0)	0/11 (0)	1/26 (3.8)	0/34 (0)	–	0/43 (0)	1/96 (1.0)	1/71 (1.4)
Arteriosclerosis	0/14 (0)	0/16 (0)	0/12 (0)	0/11 (0)	0/11 (0)	0/26 (0)	0/34 (0)	–	1/43 (2.3)	1/96 (1.0)	0/71 (0)
Satellitosis	0/14 (0)	0/16 (0)	0/12 (0)	0/11 (0)	0/11 (0)	1/26 (3.8)	0/34 (0)	–	0/43 (0)	1/96 (1.0)	0/71 (0)
Abscess	0/14 (0)	0/16 (0)	0/12 (0)	0/11 (0)	0/11 (0)	1/26 (3.8)	0/34 (0)	–	0/43 (0)	1/96 (1.0)	0/71 (0)
Gliosis	0/14 (0)	0/16 (0)	0/12 (0)	0/11 (0)	0/11 (0)	0/26 (0)	0/34 (0)	–	3/43 (7.0)	3/96 (3.1)	0/71 (0)
Focal poliomalacia	0/14 (0)	0/16 (0)	0/12 (0)	0/11 (0)	0/11 (0)	0/26 (0)	0/34 (0)	–	1/43 (2.3)	1/96 (1.0)	0/71 (0)
Calcification	0/14 (0)	0/16 (0)	0/12 (0)	0/11 (0)	0/11 (0)	0/26 (0)	0/34 (0)	–	1/43 (2.3)	1/96 (1.0)	0/71 (0)
No significant changes	12/14 (84.7)	15/16 (93.8)	10/12 (83.3)	6/11 (54.5)	9/11 (81.8)	13/26 (50.0)	17/34 (50.0)	–	7/43 (16.3)	41/96 (42.7)	48/71 (67.6)

Table 3 Continued

Lesion	Age (Months) 6-11 HAP	12-17 CD	12-17 HAP	18-23 CD	18-23 HAP	24-29 CD	24-29 HAP	Sig.	30-38 CD	Incidence CD	Incidence HAP
Brain-Cerebellum:											
Vacuolization-all layers, minimal or no reaction	1/14 (7.1)	0/16 (0)	2/12 (16.7)	1/12 (8.3)	10/11 (90.9)	10/27 (37.0)	28/33 (84.8)	**	33/43 (76.7)	44/98 (44.9)	41/70 (58.6)
Anomaly, granular layer	0/14 (0)	0/16 (0)	0/12 (0)	0/12 (0)	0/11 (0)	0/27 (0)	0/33 (0)	–	1/43 (2.3)	1/98 (1.0)	0/70 (0)
Purkinje cell degeneration	0/14 (0)	0/16 (0)	0/12 (0)	0/12 (0)	0/11 (0)	0/27 (0)	0/33 (0)	–	1/43 (2.3)	1/98 (1.0)	0/70 (0)
No significant changes	13/14 (92.9)	16/16 (100.0)	10/12 (83.3)	11/12 (91.7)	1/11 (9.1)	17/27 (63.0)	5/33 (15.2)	**	9/43 (20.9)	53/98 (54.1)	29/70 (41.4)
Brain-Medulla:											
Vacuolization	3/14 (21.4)	NE[7]	7/12 (58.3)	NE	8/11 (72.7)	NE	30/34 (88.2)	–	NE	NE	48/71 (67.6)
Gliosis	0/14 (0)	NE	0/12 (0)	NE	1/11 (9.1)	NE	1/34 (2.9)	–	NE	NE	2/71 (2.8)
Senile plaques	0/14 (0)	NE	1/12 (8.3)	NE	0/11 (0)	NE	0/34 (0)	–	NE	NE	1/71 (1.4)
No significant changes	11/14 (78.6)	NE	5/12 (41.7)	NE	2/11 (18.2)	NE	4/34 (11.8)	–	NE	NE	22/71 (31.0)
Cervical Spinal Cord:											
Vacuolization-no cellular reaction	7/13 (53.8)	NE	12/12 (100.0)	NE	7/11 (63.6)	NE	3/33 (9.1)	–	NE	NE	29/69 (42.0)
Vacuolization-gitter cell reaction	0/13 (0)	NE	1/12 (8.3)	NE	4/11 (36.4)	NE	13/33 (39.4)	–	NE	NE	18/69 (26.1)
Degenerative myelopathy	0/13 (0)	NE	0/12 (0)	NE	0/11 (0)	NE	17/33 (51.5)	–	NE	NE	17/69 (26.4)
No significant changes	6/13 (46.2)	NE	0/12 (0)	NE	0/11 (0)	NE	1/33 (3.0)	–	NE	NE	7/69 (10.1)
Thoracic Spinal Cord:											
Vacuolization-no cellular reaction	7/14 (50.0)	0/8 (0)	10/12 (83.3)	3/12 (25.0)	8/11 (72.7)	6/13 (46.2)	2/30 (6.7)	–	19/27 (70.4)	28/60 (46.7)	27/67 (40.3)
Vacuolization-gitter cell reaction	1/14 (7.1)	0/8 (0)	0/12 (0)	0/12 (0)	3/11 (27.3)	0/13 (0)	8/30 (26.7)	**	0/27 (0)	0/60 (0)	12/67 (17.9)
Degenerative myelopathy	0/14 (0)	0/8 (0)	0/12 (0)	0/12 (0)	0/11 (0)	0/13 (0)	20/30 (66.7)	**	1/27 (3.7)	1/60 (1.7)	20/67 (29.9)
No significant changes	6/14 (42.9)	8/8 (100.0)	2/12 (16.7)	9/12 (75.0)	0/11 (0)	7/13 (53.8)	0/30 (0)	**	5/27 (18.5)	29/60 (48.3)	8/67 (11.9)
Cauda Equina (Lumbar):											
Vacuolization-no cellular reaction	0/11 (0)	NE	2/12 (16.7)	NE	0/11 (0)	NE	0/34 (0)	–	6/22 (27.3)	6/22 (27.3)	2/68 (2.9)
Vacuolization-gitter cell reaction	0/11 (0)	NE	1/12 (8.3)	NE	1/11 (9.1)	NE	0/34 (0)	–	0/22 (0)	0/22 (0)	2/68 (2.9)
No significant changes	10/11 (90.9)	NE	7/12 (58.3)	NE	2/11 (18.2)	NE	0/34 (0)	–	2/22 (9.1)	2/22 (9.1)	19/68 (27.9)
CARDIOVASCULAR SYSTEM											
Heart:											
Valvular endocardiosis	0/13 (0)	1/16 (6.3)	0/13 (0)	2/12 (16.7)	1/11 (9.1)	1/27 (3.7)	6/34 (17.6)	–	3/44 (6.8)	7/99 (7.1)	7/71 (9.9)
Chronic vegetative endocarditis	0/13 (0)	0/16 (0)	0/13 (0)	0/12 (0)	0/11 (0)	0/27 (0)	1/34 (2.9)	–	0/44 (0)	0/99 (0)	1/71 (1.4)
Endocardial (mural) thrombosis	0/13 (0)	0/16 (0)	0/13 (0)	0/12 (0)	0/11 (0)	0/27 (0)	0/34 (0)	–	1/44 (2.3)	1/99 (1.0)	0/71 (0)
Subendocardial mesenchymal cell proliferation	0/13 (0)	0/16 (0)	1/13 (7.7)	0/12 (0)	0/11 (0)	0/27 (0)	0/34 (0)	–	0/44 (0)	0/99 (0)	1/71 (1.4)
Myxoid material-subendocardial	0/13 (0)	1/16 (6.3)	0/13 (0)	2/12 (16.7)	0/11 (0)	1/27 (3.7)	0/34 (0)	–	3/44 (6.8)	7/99 (7.1)	0/71 (0)
Fibrosis-subepi-and subendocardial	0/13 (0)	0/16 (0)	0/13 (0)	0/12 (0)	0/11 (0)	0/27 (0)	2/34 (5.9)	–	1/44 (2.3)	1/99 (1.0)	2/71 (2.8)
Vacuolization-myocardium	0/13 (0)	0/16 (0)	1/13 (7.7)	0/12 (0)	1/11 (9.1)	0/27 (0)	0/34 (0)	–	1/44 (2.3)	1/99 (1.0)	2/71 (2.8)
Dystrophic calcification	0/13 (0)	0/16 (0)	0/13 (0)	0/12 (0)	0/11 (0)	0/27 (0)	0/34 (0)	–	2/44 (4.5)	2/99 (2.0)	0/71 (0)
No significant changes	9/13 (69.2)	6/16 (37.5)	4/13 (30.8)	4/12 (33.3)	3/11 (27.3)	2/27 (7.4)	2/34 (5.9)	–	1/44 (2.3)	13/99 (13.1)	18/71 (25.4)

Table 3 Continued

Lesion	Age (Months) 6-11 HAP	12-17 CD	12-17 HAP	18-23 CD	18-23 HAP	24-29 CD	24-29 HAP	Sig.	30-38 CD	Incidence CD	Incidence HAP
Aorta (Thoracic):											
Basophilic degeneration-tunica media	0/11 (0)	0/8 (0)	0/10 (0)	0/12 (0)	0/8 (0)	0/14 (0)	3/30 (10.0)	–	2/27 (7.4)	2/61 (3.3)	3/59 (5.1)
Cartilagenous metaplasia-tunica media	0/11 (0)	0/8 (0)	2/10 (20.0)	0/12 (0)	0/8 (0)	0/14 (0)	1/30 (3.3)	–	2/27 (7.4)	2/61 (3.3)	3/59 (5.1)
Calcification-tunica media	0/11 (0)	0/8 (0)	1/10 (10.0)	0/12 (0)	0/8 (0)	1/14 (7.1)	1/30 (3.3)	–	1/27 (3.7)	2/61 (3.3)	2/59 (3.4)
Vacuolization-tunica media	0/11 (0)	0/8 (0)	0/10 (0)	1/12 (8.3)	0/8 (0)	0/14 (0)	1/30 (3.3)	–	0/27 (0)	1/61 (1.6)	1/59 (1.7)
Subintimal fibrous plaques	0/11 (0)	0/8 (0)	0/10 (0)	0/12 (0)	0/8 (0)	1/14 (0)	0/30 (0)	–	1/27 (3.7)	2/61 (3.3)	0/59 (0)
No significant changes	11/11 (100.0)	8/8 (100.0)	7/10 (70.0)	11/12 (91.7)	8/8 (100.0)	12/14 (85.7)	25/30 (83.3)	–	22/27 (81.5)	53/61 (86.9)	51/59 (86.4)
Pulmonary Arteries:											
Calcification-tunica media	0/14 (0)	0/17 (0)	0/13 (0)	0/12 (0)	2/11 (18.2)	7/28 (25.0)	2/34 (5.9)	–	7/44 (15.9)	14/101 (13.9)	4/72 (5.6)
Medial hypertrophy	0/14 (0)	0/17 (0)	0/13 (0)	0/12 (0)	2/11 (18.2)	3/28 (10.7)	2/34 (5.9)	–	2/44 (4.5)	5/101 (5.0)	4/72 (5.6)
Osseous metaplasia-media and intima	0/14 (0)	0/17 (0)	0/13 (0)	0/12 (0)	1/11 (9.1)	0/28 (0)	0/34 (0)	–	0/44 (0)	0/101 (0)	1/72 (1.4)
Cartilagenous metaplasia -tunica media	0/14 (0)	0/17 (0)	0/13 (0)	0/12 (0)	0/11 (0)	0/28 (0)	0/34 (0)	–	1/44 (2.3)	1/101 (1.0)	0/72 (0)
No significant changes	14/14 (100.0)	17/17 (100.0)	13/13 (100.0)	12/12 (100.0)	8/11 (72.7)	21/28 (75.0)	32/34 (94.1)	–	37/44 (84.1)	87/101 (86.1)	67/72 (93.1)
Coronary Arteries:											
Arteriosclerosis	0/13 (0)	0/16 (0)	0/13 (0)	0/12 (0)	0/11 (0)	0/27 (0)	1/34 (2.9)	–	1/44 (2.3)	1/99 (1.0)	1/71 (1.4)
Vacuolization-tunica media	0/13 (0)	0/16 (0)	0/13 (0)	0/12 (0)	1/11 (9.1)	0/27 (0)	0/34 (0)	–	0/44 (0)	0/99 (0)	1/71 (1.4)
No significant changes	13/13 (100.0)	16/16 (100.0)	13/13 (100.0)	12/12 (100.0)	10/11 (90.9)	27/27 (100.0)	33/34 (97.1)	–	43/44 (97.7)	98/99 (99.0)	69/71 (97.2)
Other Arteries:											
Medial calcification-testicular	0/13 (0)	0/16 (0)	0/12 (0)	0/12 (0)	0/11 (0)	2/27 (7.4)	0/34 (0)	–	0/41 (0)	2/96 (2.1)	0/70 (0)
Medial calcification-splenic	0/14 (0)	0/12 (0)	0/13 (0)	0/12 (0)	0/11 (0)	0/26 (0)	0/33 (0)	–	1/41 (2.4)	1/91 (1.1)	0/71 (0)
Arteriosclerosis-renal	0/14 (0)	0/17 (0)	0/13 (0)	0/12 (0)	0/11 (0)	0/29 (0)	0/34 (0)	–	4/44 (9.1)	4/102 (3.9)	0/72 (0)
Organs with Polyarteritis Nodosa:											
Testis	0/13 (0)	0/16 (0)	0/12 (0)	0/12 (0)	1/11 (9.1)	7/27 (25.9)	12/34 (35.3)	–	20/41 (48.8)	27/96 (28.1)	13/70 (18.6)
Spleen	0/14 (0)	0/12 (0)	0/13 (0)	0/12 (0)	1/11 (9.1)	4/26 (15.4)	5/33 (15.2)	–	12/42 (28.6)	16/92 (17.4)	6/71 (8.5)
Mesentery	0/14 (0)	0/22 (0)	0/13 (0)	0/12 (0)	2/11 (18.2)	6/34 (17.6)	5/34 (14.7)	–	10/45 (22.2)	16/113 (14.2)	7/72 (9.7)
Pancreas	0/13 (0)	0/21 (0)	0/13 (0)	0/12 (0)	2/11 (18.2)	3/32 (9.4)	1/34 (2.9)	–	7/43 (16.3)	10/108 (9.3)	3/71 (4.2)
Tongue	0/13 (0)	0/5 (0)	0/11 (0)	0/2 (0)	0/10 (0)	4/16 (25.0)	3/32 (9.4)	–	1/43 (2.3)	5/66 (7.6)	3/66 (4.5)
Urinary bladder	0/11 (0)	0/15 (0)	0/11 (0)	0/12 (0)	0/9 (0)	2/21 (9.5)	0/31 (0)	–	1/33 (3.0)	3/81 (3.7)	0/62 (0)
Brain	0/14 (0)	0/16 (0)	0/12 (0)	0/11 (0)	0/11 (0)	1/26 (3.8)	0/34 (0)	–	1/43 (2.3)	2/96 (2.1)	0/71 (0)
Salivary glands	0/13 (0)	0/18 (0)	0/12 (0)	0/12 (0)	0/11 (0)	0/24 (0)	0/32 (0)	–	2/42 (4.8)	2/96 (2.1)	0/68 (0)
Kidney	0/14 (0)	0/17 (0)	0/13 (0)	0/12 (0)	0/11 (0)	0/29 (0)	0/34 (0)	–	2/44 (4.5)	2/102 (2.0)	0/72 (0)
Liver	0/13 (0)	0/20 (0)	0/13 (0)	0/12 (0)	0/10 (0)	0/27 (0)	0/34 (0)	–	2/45 (4.4)	2/104 (1.9)	0/70 (0)
Thymus	0/11 (0)	0/12 (0)	0/9 (0)	0/6 (0)	0/5 (0)	0/7 (0)	1/22 (4.5)	–	2/11 (18.2)	2/36 (5.6)	1/47 (2.1)
Seminal vesicle	0/14 (0)	0/17 (0)	0/12 (0)	0/12 (0)	0/9 (0)	0/23 (0)	0/31 (0)	–	1/37 (2.7)	1/89 (1.1)	0/66 (0)
Lymph node	0/12 (0)	0/11 (0)	0/8 (0)	0/6 (0)	0/9 (0)	0/4 (0)	0/26 (0)	–	1/4 (25.0)	1/25 (4.0)	0/55 (0)

Table 3 Continued

Lesion	Age (Months) 6-11 HAP	12-17 CD	12-17 HAP	18-23 CD	18-23 HAP	24-29 CD	24-29 HAP	Sig.	30-38 CD	Incidence CD	Incidence HAP
Organs with Polyarteritis Nodosa (cont.):											
Cecum	0/14 (0)	0/3 (0)	0/10 (0)	NE	1/11 (9.1)	0/14 (0)	1/33 (3.0)	–	0/21 (0)	0/38 (0)	2/68 (2.9)
Extra-hepatic artery	0/13 (0)	0/20 (0)	0/13 (0)	0/12 (0)	1/10 (10.0)	0/27 (0)	1/34 (2.9)	–	0/45 (0)	0/104 (0)	2/70 (2.9)
Skeletal muscle	0/14 (0)	0/14 (0)	0/11 (0)	0/12 (0)	0/10 (0)	0/23 (0)	1/34 (2.9)	–	0/36 (0)	0/85 (0)	1/69 (1.4)
Adrenal	0/14 (0)	0/15 (0)	0/11 (0)	0/12 (0)	1/11 (9.1)	0/24 (0)	0/34 (0)	–	0/37 (0)	0/88 (0)	1/70 (1.4)
Stomach	0/14 (0)	0/16 (0)	0/13 (0)	0/12 (0)	0/10 (0)	0/28 (0)	1/33 (3.0)	–	0/44 (0)	0/100 (0)	1/70 (1.4)
RESPIRATORY SYSTEM											
Lung:											
Peribronchial lymphocytic aggregates	7/14 (50.0)	10/17 (58.8)	9/13 (69.2)	6/12 (50.0)	9/11 (81.8)	15/28 (53.6)	19/34 (55.9)	–	19/44 (43.2)	50/101 (49.5)	44/72 (61.1)
Peribronchial lymphocytic aggregates with germinal centers	0/14 (0)	0/17 (0)	0/13 (0)	0/12 (0)	1/11 (9.1)	3/28 (10.7)	10/34 (29.4)	*	3/44 (6.8)	6/101 (5.9)	11/72 (15.3)
Perivascular lymphocytic aggregates	3/14 (21.4)	4/17 (23.5)	3/13 (23.1)	3/12 (25.0)	2/11 (18.2)	14/28 (50.0)	19/34 (55.9)	–	8/44 (18.2)	29/101 (28.7)	27/72 (37.5)
Alveolar histiocytosis	6/14 (42.9)	5/17 (29.4)	6/13 (46.2)	0/12 (0)	4/11 (36.4)	3/28 (10.7)	9/34 (26.5)	*	14/44 (31.8)	22/101 (21.8)	25/72 (34.7)
Alveolar histiocytosis with cholesterol granuloma	0/14 (0)	0/17 (0)	1/13 (7.7)	0/12 (0)	0/11 (0)	0/28 (0)	4/34 (11.8)	*	0/44 (0)	0/101 (0)	5/72 (6.9)
Septal calcification	0/14 (0)	0/17 (0)	1/13 (7.7)	0/12 (0)	0/11 (0)	3/28 (10.7)	0/34 (0)	–	0/44 (0)	3/101 (3.0)	1/72 (1.4)
Mesothelial hypertrophy	1/14 (7.1)	0/17 (0)	0/13 (0)	0/12 (0)	0/11 (0)	1/28 (3.6)	0/34 (0)	–	0/44 (0)	1/101 (1.0)	1/72 (1.4)
Adenomatosis	0/14 (0)	0/17 (0)	0/13 (0)	0/12 (0)	0/11 (0)	1/28 (3.6)	0/34 (0)	–	1/44 (2.3)	2/101 (2.0)	0/72 (0)
Hydrothorax	0/14 (0)	1/17 (5.9)	0/13 (0)	0/12 (0)	0/11 (0)	1/28 (3.6)	0/34 (0)	–	3/44 (6.8)	5/101 (5.0)	0/72 (0)
Pleural fibrosis	0/14 (0)	0/17 (0)	0/13 (0)	0/12 (0)	0/11 (0)	1/28 (3.6)	0/34 (0)	–	0/44 (0)	1/101 (1.0)	0/72 (0)
Foreign body giant cell	0/14 (0)	0/17 (0)	0/13 (0)	0/12 (0)	0/11 (0)	1/28 (3.6)	0/34 (0)	–	0/44 (0)	1/101 (1.0)	0/72 (0)
Lipochrome/lipofuscin pigment-peribronchial and perivascular	0/14 (0)	0/17 (0)	0/13 (0)	0/12 (0)	0/11 (0)	0/28 (0)	9/34 (26.5)	**	0/44 (0)	0/101 (0)	9/72 (12.5)
Bronchopneumonia	0/14 (0)	0/17 (0)	0/13 (0)	0/12 (0)	0/11 (0)	9/28 (32.1)	1/34 (2.9)	*	17/44 (38.6)	26/101 (25.7)	1/72 (1.4)
Interstitial pneumonia	0/14 (0)	0/17 (0)	2/13 (15.4)	0/12 (0)	2/11 (18.2)	9/28 (32.1)	7/34 (20.6)	–	17/44 (38.6)	26/101 (25.7)	11/72 (15.3)
Chronic bronchitis	0/14 (0)	0/17 (0)	0/13 (0)	0/12 (0)	0/11 (0)	0/28 (0)	2/34 (5.9)	–	0/44 (0)	0/101 (0)	2/72 (2.8)
No significant changes	2/14 (14.3)	3/17 (17.6)	1/13 (7.7)	4/12 (33.3)	1/11 (9.1)	4/28 (14.3)	3/34 (8.8)	–	8/44 (18.2)	19/101 (18.8)	7/72 (9.7)
Turbinates:											
Subepithelial lymphoid nodules	1/13 (7.7)	NE	3/12 (25.0)	NE	0/11 (0)	NE	1/34 (2.9)	–	NE	NE	5/70 (7.1)
Coagulative necrosis-epithelium	0/13 (0)	NE	2/12 (16.7)	NE	2/11 (18.2)	NE	1/34 (2.9)	–	NE	NE	5/70 (7.1)
Cholesteatoma	1/13 (7.7)	NE	0/12 (0)	NE	0/11 (0)	NE	0/34 (0)	–	NE	NE	1/70 (1.4)
Rhinitis	2/13 (15.4)	NE	6/12 (50.0)	NE	5/11 (45.5)	NE	14/34 (41.2)	–	NE	NE	27/70 (38.6)
No significant changes	9/13 (69.2)	NE	4/12 (33.3)	NE	6/11 (54.5)	NE	18/34 (52.9)	–	NE	NE	37/70 (52.9)

Table 3 Continued

Lesion	Age (Months) 6-11 HAP	12-17 CD	12-17 HAP	18-23 CD	18-23 HAP	24-29 CD	24-29 HAP	Sig.	30-38 CD	Incidence CD	Incidence HAP
Trachea:											
Dilated submucosal glands	1/13 (7.7)	2/16 (12.5)	3/13 (23.1)	0/11 (0)	5/11 (45.5)	4/24 (16.7)	12/32 (37.5)	*	4/43 (9.3)	10/94 (10.6)	21/69 (30.4)
Calcification-cartilage	6/13 (46.2)	13/16 (81.3)	8/13 (61.5)	10/11 (90.9)	7/11 (63.6)	20/24 (83.3)	28/32 (87.5)	–	42/43 (97.7)	85/94 (90.4)	49/69 (71.0)
Calcification-mucosa	0/13 (0)	0/16 (0)	1/13 (7.7)	0/11 (0)	0/11 (0)	0/24 (0)	0/32 (0)	–	0/43 (0)	0/94 (0)	1/69 (1.4)
Hyaline droplets-epithelium	0/13 (0)	0/16 (0)	0/13 (0)	0/11 (0)	0/11 (0)	0/24 (0)	1/32 (3.1)	–	0/43 (0)	0/94 (0)	1/69 (1.4)
Lipochrome/lipofuscin pigment	0/13 (0)	0/16 (0)	0/13 (0)	0/11 (0)	1/11 (9.1)	1/24 (4.2)	0/32 (0)	–	4/43 (9.3)	5/94 (5.3)	1/69 (1.4)
Tracheitis, lymphocytic	0/13 (0)	0/16 (0)	0/13 (0)	0/11 (0)	2/11 (18.2)	1/24 (4.2)	8/32 (25.0)	*	9/43 (20.9)	10/94 (10.6)	10/69 (14.5)
No significant changes	7/13 (53.8)	3/16 (18.8)	4/13 (30.8)	1/11 (9.1)	3/11 (27.3)	4/24 (16.7)	4/32 (12.5)	–	1/43 (2.3)	9/94 (9.6)	18/69 (26.1)
ENDOCRINE SYSTEM											
Adrenal Cortex:											
Foci of cellular alteration	3/14 (21.4)	0/15 (0)	3/11 (27.3)	2/12 (16.7)	5/11 (45.5)	4/24 (16.7)	20/34 (58.8)	**	15/37 (40.5)	21/88 (23.9)	31/70 (44.3)
Sinusoidal dilatation	1/14 (7.1)	0/15 (0)	0/11 (0)	0/12 (0)	1/11 (9.1)	1/24 (4.2)	3/34 (8.8)	–	12/37 (32.4)	13/88 (14.8)	5/70 (7.1)
Thrombosis	0/14 (0)	0/15 (0)	0/11 (0)	0/12 (0)	0/11 (0)	0/24 (0)	4/34 (11.8)	–	12/37 (32.4)	12/88 (13.6)	4/70 (5.7)
Spindle cell proliferation	0/14 (0)	0/15 (0)	0/11 (0)	0/12 (0)	1/11 (9.1)	0/24 (0)	1/34 (2.9)	–	1/37 (2.7)	1/88 (1.1)	2/70 (2.9)
Capsular fibrosis	0/14 (0)	0/15 (0)	0/11 (0)	0/12 (0)	0/11 (0)	1/24 (4.2)	1/34 (2.9)	–	2/37 (5.4)	3/88 (3.4)	1/70 (1.4)
Necrosis	0/14 (0)	0/15 (0)	0/11 (0)	0/12 (0)	0/11 (0)	1/24 (4.2)	0/34 (0)	–	2/37 (5.4)	3/88 (3.4)	0/70 (0)
Hyaline droplets	0/14 (0)	0/15 (0)	0/11 (0)	0/12 (0)	0/11 (0)	0/24 (0)	1/34 (2.9)	–	0/37 (0)	0/88 (0)	1/70 (1.4)
Extra-cortical nodule	0/14 (0)	0/15 (0)	0/11 (0)	0/12 (0)	0/11 (0)	0/24 (0)	0/34 (0)	–	1/37 (2.7)	1/88 (1.1)	0/70 (0)
Lipochrome/lipofuscin pigment	4/14 (28.6)	3/15 (20.0)	4/11 (36.4)	5/12 (41.7)	9/11 (81.8)	11/24 (45.8)	31/34 (91.2)	*	22/37 (59.9)	41/88 (46.6)	48/70 (68.6)
Adrenal Medulla:											
Hyperplasia	0/14 (0)	0/15 (0)	1/11 (9.1)	0/12 (0)	1/11 (9.1)	1/24 (4.2)	3/34 (8.8)	–	0/37 (0)	1/88 (1.1)	5/70 (7.1)
Thrombosis	0/14 (0)	0/15 (0)	0/11 (0)	0/12 (0)	1/11 (9.1)	1/24 (4.2)	0/34 (0)	–	5/37 (13.5)	6/88 (6.8)	1/70 (1.4)
Extramedullary hematopoiesis	0/14 (0)	0/15 (0)	0/11 (0)	0/12 (0)	0/11 (0)	0/24 (0)	0/34 (0)	–	1/37 (2.7)	1/88 (1.1)	0/70 (0)
Purulent inflammation	0/14 (0)	0/15 (0)	0/11 (0)	0/12 (0)	0/11 (0)	1/24 (4.2)	0/34 (0)	–	0/37 (0)	1/88 (1.1)	0/70 (0)
No significant changes (cortex and medulla)	10/14 (71.4)	12/15 (80.0)	5/11 (45.5)	6/12 (50.0)	1/11 (9.1)	3/24 (12.5)	0/34 (0)	**	2/37 (5.4)	23/88 (26.1)	16/70 (22.9)
Pituitary:											
Colloid cyst	4/13 (30.8)	2/19 (10.5)	0/8 (0)	1/11 (9.1)	0/6 (0)	6/27 (22.2)	3/29 (10.3)	–	13/36 (36.1)	22/93 (23.7)	7/56 (12.5)
Colloid calcification	0/13 (0)	0/19 (0)	0/8 (0)	0/11 (0)	0/6 (0)	0/27 (0)	0/29 (0)	–	1/36 (2.8)	1/93 (1.1)	0/56 (0)
Hemosiderin	0/13 (0)	0/19 (0)	0/8 (0)	0/11 (0)	0/6 (0)	0/27 (0)	3/29 (10.3)	–	0/36 (0)	0/93 (0)	3/56 (5.4)
Thrombosis	0/13 (0)	0/19 (0)	0/8 (0)	0/11 (0)	0/6 (0)	0/27 (0)	1/29 (3.4)	–	0/36 (0)	0/93 (0)	1/56 (1.8)
Coagulative necrosis	0/13 (0)	0/19 (0)	0/8 (0)	0/11 (0)	0/6 (0)	0/27 (0)	1/29 (3.4)	–	0/36 (0)	0/93 (0)	1/56 (1.8)
Fibrinoid necrosis	0/13 (0)	0/19 (0)	0/8 (0)	0/11 (0)	0/6 (0)	0/27 (0)	0/29 (0)	–	1/36 (2.8)	1/93 (1.1)	0/56 (0)
Vacuolization-pars nervosa	0/13 (0)	0/19 (0)	0/8 (0)	0/11 (0)	1/6 (16.7)	1/27 (3.7)	3/29 (10.3)	–	1/36 (2.8)	2/93 (2.2)	4/56 (7.1)
No significant changes	9/13 (69.2)	17/19 (89.5)	8/8 (100.0)	10/11 (90.9)	3/6 (50.0)	18/27 (66.7)	12/29 (41.4)	–	13/36 (36.1)	58/93 (62.4)	32/56 (57.1)

Table 3 Continued

Lesion	Age (Months) 6-11 HAP	12-17 CD	12-17 HAP	18-23 CD	18-23 HAP	24-29 CD	24-29 HAP	Sig.	30-38 CD	Incidence CD	Incidence HAP
Thyroid:											
C-cell hyperplasia	0/14 (0)	0/16 (0)	5/13 (38.5)	0/12 (0)	8/10 (80.0)	5/25 (20.0)	15/34 (44.1)	**	15/45 (33.3)	20/98 (20.4)	28/71 (39.4)
Disparity in follicle size and colloid content	14/14 (100.0)	2/16 (12.5)	13/13 (100.0)	7/12 (58.3)	10/10 (100.0)	5/25 (20.0)	34/34 (100.0)	**	12/45 (53.3)	38/98 (38.8)	71/71 (100.0)
Concretions in follicle lumens	12/14 (85.7)	2/16 (12.5)	13/13 (100.0)	2/12 (16.7)	9/10 (90.0)	8/25 (32.0)	33/34 (97.1)	**	24/45 (53.3)	36/98 (36.7)	67/71 (94.4)
Keratin cyst	0/14 (0)	0/16 (0)	0/13 (0)	1/12 (8.3)	0/10 (0)	1/25 (4.0)	1/34 (2.9)	–	1/45 (2.2)	3/98 (3.1)	1/71 (1.4)
Lipochrome/lipofuscin pigment	1/14 (7.1)	0/16 (0)	3/13 (23.1)	0/12 (0)	7/10 (70.0)	4/25 (16.0)	31/34 (91.2)	**	12/45 (26.7)	16/98 (16.3)	42/71 (59.2)
No significant changes	0/14 (0)	14/16 (87.5)	0/13 (0)	1/12 (8.3)	0/10 (0)	2/25 (8.0)	0/34 (0)	**	8/45 (17.8)	25/98 (25.5)	0/71 (0)
Parathyroid:											
Hyperplasia	0/9 (0)	0/7 (0)	2/9 (22.2)	0/6 (0)	7/11 (63.6)	4/11 (36.4)	19/26 (73.1)	*	27/28 (96.4)	31/52 (59.6)	28/55 (50.9)
Calcification	0/9 (0)	0/7 (0)	0/9 (0)	0/6 (0)	0/11 (0)	0/11 (0)	0/26 (0)	–	1/28 (3.6)	1/52 (1.9)	0/55 (0)
No significant changes	9/9 (100.0)	7/7 (100.0)	7/9 (77.8)	6/6 (100.0)	4/11 (36.4)	7/11 (63.6)	6/26 (23.1)	*	1/28 (3.6)	21/52 (40.4)	26/55 (47.3)
GENITAL SYSTEM											
Testis:											
Seminiferous tubular degeneration with calcification	0/13 (0)	0/16 (0)	1/12 (8.3)	1/12 (8.3)	1/11 (9.1)	5/27 (18.5)	10/34 (29.4)	–	14/41 (34.1)	20/96 (20.8)	12/70 (17.1)
Hydrocoele	0/13 (0)	0/16 (0)	0/12 (0)	1/12 (8.3)	0/11 (0)	7/27 (25.9)	7/34 (20.6)	–	11/41 (26.8)	19/96 (19.8)	7/70 (10.0)
Interstitial edema (micro)	3/13 (23.1)	0/16 (0)	4/12 (33.3)	0/12 (0)	3/11 (27.3)	0/27 (0)	16/34 (47.1)	**	3/41 (7.3)	3/96 (3.1)	26/70 (37.1)
Necrosis	0/13 (0)	0/16 (0)	0/12 (0)	0/12 (0)	0/11 (0)	0/27 (0)	0/34 (0)	–	1/41 (2.4)	1/96 (1.0)	0/70 (0)
Thrombosis-interstitium	0/13 (0)	0/16 (0)	0/12 (0)	0/12 (0)	0/11 (0)	0/27 (0)	1/34 (2.9)	–	0/41 (0)	0/96 (0)	1/70 (1.4)
Fibrosis-capsule	0/13 (0)	0/16 (0)	0/12 (0)	0/12 (0)	0/11 (0)	0/27 (0)	2/34 (5.9)	–	0/41 (0)	0/96 (0)	2/70 (2.9)
Cryptorchidism	0/13 (0)	0/16 (0)	0/12 (0)	0/12 (0)	0/11 (0)	1/27 (3.7)	0/34 (0)	–	0/41 (0)	1/96 (1.0)	0/70 (0)
Lipochrome/lipofuscin pigment	0/13 (0)	0/16 (0)	1/12 (8.3)	0/12 (0)	0/11 (0)	0/27 (0)	4/34 (11.8)	**	0/41 (0)	0/96 (0)	5/70 (7.1)
No significant changes	10/13 (76.9)	16/16 (100.0)	8/12 (66.7)	11/12 (91.7)	7/11 (63.6)	18/27 (66.7)	8/34 (23.5)	**	19/41 (46.3)	64/96 (66.7)	33/70 (47.1)
Prostate:											
Concretions-lumens	6/13 (46.2)	10/17 (58.8)	6/9 (66.7)	3/11 (27.3)	7/9 (77.8)	5/25 (20.0)	25/32 (78.1)	**	16/43 (37.2)	34/96 (35.4)	44/63 (69.8)
Chronic prostatitis	3/13 (23.1)	3/17 (17.6)	1/9 (11.1)	0/11 (0)	1/9 (11.1)	10/25 (40.0)	14/32 (43.8)	–	9/43 (20.9)	22/96 (22.9)	19/63 (30.2)
Epithelial hyperplasia	1/13 (7.7)	0/17 (0)	0/9 (0)	0/11 (0)	2/9 (22.2)	3/25 (12.0)	11/32 (34.4)	*	7/43 (16.3)	10/96 (10.4)	14/63 (22.2)
Squamous metaplasia	0/13 (0)	1/17 (5.9)	0/9 (0)	0/11 (0)	0/9 (0)	0/25 (0)	2/32 (6.3)	–	5/43 (11.6)	6/96 (6.3)	2/63 (3.2)
Epithelial dysplasia	0/13 (0)	0/17 (0)	0/9 (0)	0/11 (0)	0/9 (0)	0/25 (0)	1/32 (3.1)	–	0/43 (0)	0/96 (0)	1/63 (1.6)
Atrophy	0/13 (0)	0/17 (0)	0/9 (0)	0/11 (0)	0/9 (0)	0/25 (0)	0/32 (0)	–	3/43 (7.0)	3/96 (3.1)	0/63 (0)
Pigmented macrophages	0/13 0)	0/17 (0)	0/9 (0)	0/11 (0)	0/9 (0)	0/25 (0)	1/32 (3.1)	–	0/43 (0)	0/96 (0)	1/63 (1.6)
No significant changes	6/13 (46.2)	6/17 (35.3)	2/9 (22.2)	8/11 (72.7)	1/9 (11.1)	12/25 (48.0)	3/32 (9.4)	**	10/43 (23.3)	36/96 (37.5)	12/63 (19.0)

Table 3 Continued

Lesion	Age (Months) 6-11 HAP	12-17 CD	12-17 HAP	18-23 CD	18-23 HAP	24-29 CD	24-29 HAP	Sig.	30-38 CD	Incidence CD	Incidence HAP
Preputial Gland:											
Chronic adenitis	2/14 (14.3)	8/12 (66.7)	2/12 (16.7)	7/11 (63.6)	4/11 (36.4)	7/15 (46.7)	23/28 (82.1)	–	13/13 (100.0)	35/51 (68.6)	31/65 (47.7)
Duct dilatation	3/14 (21.4)	6/12 (50.0)	1/12 (8.3)	5/11 (45.5)	3/11 (27.3)	9/15 (60.0)	7/28 (25.0)	*	11/13 (84.6)	31/51 (60.8)	14/65 (21.5)
Squamous metaplasia	0/14 (0)	1/12 (8.3)	0/12 (0)	0/11 (0)	0/11 (0)	1/15 (6.7)	0/28 (0)	–	3/13 (23.1)	5/51 (9.8)	0/63 (0)
No significant changes	11/14 (78.6)	3/12 (25.0)	10/12 (83.3)	2/11 (18.2)	5/11 (45.5)	3/15 (20.0)	5/28 (17.9)	–	0/13 (0)	8/51 (15.7)	31/65 (47.7)
Seminal Vesicle:											
Atrophy	0/14 (0)	0/17 (0)	0/12 (0)	0/12 (0)	0/9 (0)	1/23 (4.3)	9/31 (29.0)	*	5/37 (13.5)	6/89 (6.7)	9/66 (13.6)
Chronic inflammation	1/14 (7.1)	0/17 (0)	0/12 (0)	0/12 (0)	0/9 (0)	2/23 (8.7)	3/31 (9.7)	–	5/37 (13.5)	7/89 (7.9)	4/66 (6.1)
Concretions-lumens	0/14 (0)	0/17 (0)	0/12 (0)	0/12 (0)	0/9 (0)	1/23 (4.3)	0/31 (0)	–	1/37 (2.7)	2/89 (2.2)	0/66 (0)
Smooth muscle hypertrophy	0/14 (0)	0/17 (0)	0/12 (0)	0/12 (0)	0/9 (0)	1/23 (4.3)	0/31 (0)	–	0/37 (0)	1/89 (1.1)	0/66 (0)
Epithelial sloughing	0/14 (0)	0/17 (0)	0/12 (0)	0/12 (0)	0/9 (0)	0/23 (0)	0/31 (0)	–	1/37 (2.7)	1/89 (1.1)	0/66 (0)
Squamous metaplasia	0/14 (0)	0/17 (0)	0/12 (0)	0/12 (0)	0/9 (0)	0/23 (0)	0/31 (0)	–	1/37 (2.7)	1/89 (1.1)	0/66 (0)
No significant changes	13/14 (92.9)	17/17 (100.0)	12/12 (100.0)	12/12 (100.0)	9/9 (100.0)	19/23 (82.6)	20/31 (64.5)	–	26/37 (70.3)	74/89 (83.1)	54/66 (81.8)
Vas Deferens:											
Fat necrosis	0/13 (0)	3/16 (18.8)	0/12 (0)	0/12 (0)	0/11 (0)	1/27 (3.7)	4/34 (11.8)	–	1/47 (2.4)	5/96 (5.2)	4/72 (5.6)
Cyst	0/13 (0)	0/16 (0)	0/12 (0)	0/12 (0)	0/11 (0)	0/27 (0)	1/34 (2.9)	–	0/41 (0)	0/96 (0)	1/72 (1.4)
No significant changes	13/13 (100.0)	13/16 (81.2)	12/12 (100.0)	12/12 (100.0)	11/11 (100.0)	26/27 (96.3)	29/34 (85.3)	–	40/41 (97.6)	91/96 (94.8)	67/72 (93.1)
Mammary Gland:											
Gynecomastia	0/14 (0)	0/22 (0)	0/13 (0)	0/12 (0)	1/11 (9.1)	3/34 (8.8)	3/34 (8.8)	–	6/45 (13.3)	9/113 (8.0)	4/72 (5.6)
No significant changes	14/14 (100.0)	22/22 (100.0)	13/13 (100.0)	11/12 (91.7)	8/11 (72.7)	31/34 (91.2)	25/34 (73.5)	–	39/45 (86.7)	103/113 (91.2)	60/72 (83.3)
ALIMENTARY SYSTEM											
Liver:											
Eosinophilic foci	0/13 (0)	3/20 (15.0)	0/13 (0)	4/12 (33.3)	0/10 (0)	4/27 (14.8)	8/34 (23.5)	–	11/45 (24.4)	22/104 (21.2)	8/70 (11.4)
Clear cell foci	0/13 (0)	4/20 (20.0)	0/13 (0)	3/12 (25.0)	0/10 (0)	2/27 (7.4)	8/34 (23.5)	–	4/45 (8.9)	13/104 (12.5)	8/70 (11.4)
Basophilic foci	0/13 (0)	0/20 (0)	0/13 (0)	0/12 (0)	0/10 (0)	0/27 (0)	0/34 (0)	–	5/45 (11.1)	5/104 (4.8)	0/70 (0)
Bile ductule hyperplasia and fibrosis	2/13 (15.4)	12/20 (60.0)	11/13 (84.5)	9/12 (75.0)	10/10 (100.0)	15/27 (55.6)	27/34 (79.4)	–	34/45 (77.8)	71/104 (68.3)	50/70 (71.4)
Fatty change	0/13 (0)	4/20 (20.0)	2/13 (15.4)	1/12 (8.3)	4/10 (40.0)	10/27 (37.0)	12/34 (35.3)	–	12/45 (26.7)	27/104 (26.0)	18/70 (25.7)
Telangiectasis	0/13 (0)	1/20 (5.0)	0/13 (0)	1/12 (8.3)	0/10 (0)	6/27 (22.2)	1/34 (2.9)	*	18/45 (40.0)	26/104 (25.0)	1/70 (1.4)
Focal chronic hepatitis	1/13 (7.7)	1/20 (5.0)	0/13 (0)	0/12 (0)	1/10 (10.0)	2/27 (7.4)	0/34 (0)	–	1/45 (2.2)	4/104 (3.8)	2/70 (2.9)
Focal purulent hepatitis	0/13 (0)	0/20 (0)	1/13 (7.7)	0/12 (0)	2/10 (20.0)	0/27 (0)	1/34 (2.9)	–	0/45 (0)	0/104 (0)	4/70 (5.7)
Extramedullary hematopoiesis	1/13 (7.7)	0/20 (0)	0/13 (0)	0/12 (0)	2/10 (20.0)	2/27 (7.4)	1/34 (2.9)	–	8/45 (17.8)	10/104 (9.6)	4/70 (5.7)
Thrombosis	0/13 (0)	0/20 (0)	0/13 (0)	0/12 (0)	0/10 (0)	0/27 (0)	2/34 (5.9)	–	0/45 (0)	0/104 (0)	2/70 (2.9)

Table 3 Continued

Lesion	Age (Months) 6-11 HAP	12-17 CD	12-17 HAP	18-23 CD	18-23 HAP	24-29 CD	24-29 HAP	Sig.	30-38 CD	Incidence CD	Incidence HAP
Liver (cont):											
Chronic passive congestion	0/13 (0)	0/20 (0)	0/13 (0)	0/12 (0)	1/10 (10.0)	0/27 (0)	0/34 (0)	–	0/45 (0)	0/104 (0)	1/70 (1.4)
Hepatocyte atrophy	0/13 (0)	0/20 (0)	0/13 (0)	0/12 (0)	0/10 (0)	1/27 (3.7)	0/34 (0)	–	2/45 (4.4)	3/104 (2.9)	0/70 (0)
Coagulative necrosis	0/13 (0)	1/20 (5.0)	0/13 (0)	0/12 (0)	0/10 (0)	0/27 (0)	0/34 (0)	–	1/45 (2.2)	2/104 (1.9)	0/70 (0)
Cyst(s)	0/13 (0)	0/20 (0)	0/13 (0)	0/12 (0)	0/10 (0)	0/27 (0)	0/34 (0)	–	1/45 (2.2)	1/104 (1.0)	0/70 (0)
Capsular fibrosis	0/13 (0)	0/20 (0)	0/13 (0)	0/12 (0)	1/10 (10.0)	1/27 (3.7)	0/34 (0)	–	0/45 (0)	1/104 (1.0)	1/70 (1.4)
Syncytial giant cells-sinusoids	0/13 (0)	0/20 (0)	0/13 (0)	0/12 (0)	0/10 (0)	0/27 (0)	1/34 (2.9)	–	0/45 (0)	0/104 (0)	1/70 (1.4)
Lipochrome/lipofuscin pigment-Kupffer cells	0/13 (0)	0/20 (0)	0/13 (0)	0/12 (0)	0/10 (0)	0/27 (0)	1/34 (2.9)	–	0/45 (0)	0/104 (0)	1/70 (1.4)
No significant changes	10/13 (76.9)	3/20 (15.0)	2/13 (15.4)	0/12 (0)	0/10 (0)	1/27 (3.7)	3/34 (8.8)	–	0/45 (0)	4/104 (3.8)	15/70 (21.4)
Tongue:											
No significant changes	13/13 (100.0)	5/5 (100.0)	11/11 (100.0)	2/2 (100.0)	9/10 (90.0)	16/16 (100.0)	29/32 (90.6)	–	43/43 (100.0)	66/66 (100.0)	62/66 (93.3)
Teeth:											
Malocclusion	0/14 (0)	0/22 (0)	0/13 (0)	0/12 (0)	0/11 (0)	2/34 (5.9)	0/34 (0)	–	4/45 (8.9)	6/113 (5.3)	0/72 (0)
Peritoneal Cavity:											
Hemoperitoneum	0/14 (0)	0/22 (0)	0/13 (0)	0/12 (0)	0/11 (0)	2/34 (5.9)	0/34 (0)	–	0/45 (0)	2/113 (1.8)	0/72 (0)
Esophagus:											
No significant changes	12/12 (100.0)	15/15 (100.0)	13/13 (100.0)	12/12 (100.0)	9/9 (100.0)	20/20 (100.0)	27/27 (100.0)	–	44/45 (97.8)	91/92 (98.9)	61/61 (100.0)
Stomach:											
Fundic mucosal gland dilatation, atrophy and fibrosis	2/14 (14.3)	1/16 (6.3)	7/13 (53.8)	3/12 (25.0)	9/10 (90.0)	17/28 (60.7)	31/33 (93.9)	**	39/44 (88.6)	60/100 (60.0)	49/70 (70.0)
Calcification-muscularis propria and mucosa	0/14 (0)	1/16 (6.3)	1/13 (7.7)	0/12 (0)	0/10 (0)	0/28 (0)	0/33 (0)	–	1/44 (2.3)	2/100 (2.0)	1/70 (1.4)
Focal chronic gastritis	0/14 (0)	0/16 (0)	0/13 (0)	0/12 (0)	0/10 (0)	0/28 (0)	1/33 (3.0)	–	0/44 (0)	0/100 (0)	1/70 (1.4)
Focal chronic peritonitis	0/14 (0)	0/16 (0)	0/13 (0)	0/12 (0)	0/10 (0)	0/28 (0)	1/33 (3.0)	–	0/44 (0)	0/100 (0)	1/70 (1.4)
Trichobezoar	0/14 (0)	0/16 (0)	2/13 (15.4)	0/12 (0)	0/10 (0)	0/28 (0)	0/33 (0)	–	0/44 (0)	0/100 (0)	2/70 (2.9)
Paneth-like cells	0/14 (0)	0/16 (0)	0/13 (0)	0/12 (0)	0/10 (10.0)	0/28 (0)	0/33 (0)	–	0/44 (0)	0/100 (0)	1/70 (1.4)
Mucosal polyp	0/14 (0)	0/16 (0)	0/13 (0)	0/12 (0)	0/10 (0)	0/28 (0)	0/33 (0)	–	1/44 (2.3)	1/100 (1.0)	0/70 (0)
Inclusion bodies-glandular epithelium	0/14 (0)	0/16 (0)	0/13 (0)	0/12 (0)	1/10 (10.0)	0/28 (0)	0/33 (0)	–	0/44 (0)	0/100 (0)	1/70 (1.4)
Cardiac epithelium-erosion inflammation, cytoplasmic inclusion bodies	0/14 (0)	0/16 (0)	0/13 (0)	0/12 (0)	0/10 (0)	0/28 (0)	0/33 (0)	–	1/44 (2.3)	1/100 (1.0)	0/70 (0)
Cyst-cardiac epithelium	0/14 (0)	0/16 (0)	0/13 (0)	0/12 (0)	0/10 (0)	1/28 (3.6)	0/33 (0)	–	0/44 (0)	1/100 (1.0)	0/70 (0)
No significant changes	12/14 (85.7)	14/16 (87.5)	6/13 (46.2)	9/12 (75.0)	1/10 (10.0)	11/28 (39.3)	2/33 (6.1)	**	3/44 (6.8)	37/100 (37.0)	21/70 (30.0)
Duodenum:											
Deep mucosal fibrosis	0/13 (0)	0/14 (0)	0/13 (0)	0/11 (0)	0/10 (0)	0/25 (0)	1/33 (3.0)	–	0/31 (0)	0/81 (0)	1/69 (1.4)
No significant changes	13/13 (100.0)	14/14 (100.0)	13/13 (100.0)	11/11 (100.0)	10/10 (100.0)	25/25 (100.0)	32/33 (97.0)	–	31/31 (100.0)	81/81 (100.0)	68/69 (98.6)
Jejunum:											
Microherniation-crypts	0/14 (0)	NE	0/10 (0)	NE	0/11 (0)	0/9 (0)	1/31 (3.2)	–	0/5 (0)	0/14 (0)	1/66 (1.5)

Table 3 Continued

Lesion	Age (Months) 6-11 HAP	12-17 CD	12-17 HAP	18-23 CD	18-23 HAP	24-29 CD	24-29 HAP	Sig.	30-38 CD	Incidence CD	Incidence HAP
Jejunum (cont):											
No significant changes	14/14 (100.0)	NE	10/10 (100.0)	NE	11/11 (100.0)	9/9 (100.0)	30/31 (96.8)	–	5/5 (100.0)	14/14 (100.0)	65/66 (98.5)
Ileum:											
Focal chronic peritonitis	0/12 (0)	0/14 (0)	0/8 (0)	0/12 (0)	1/10 (10.0)	0/23 (0)	0/32 (0)	–	0/18 (0)	0/67 (0)	1/62 (1.6)
Atrophy-villi	0/12 (0)	0/14 (0)	0/8 (0)	0/12 (0)	0/10 (0)	0/23 (0)	1/32 (3.1)	–	0/18 (0)	0/67 (0)	1/62 (1.6)
Calcification-villi	0/12 (0)	0/14 (0)	0/8 (0)	0/12 (0)	1/10 (10.0)	0/23 (0)	0/32 (0)	–	0/18 (0)	0/67 (0)	1/62 (1.6)
Subacute ileitis	0/12 (0)	0/14 (0)	1/8 (12.5)	0/12 (0)	0/10 (0)	0/23 (0)	0/32 (0)	–	0/18 (0)	0/67 (0)	1/62 (1.6)
No significant changes	12/12 (100.0)	14/14 (100.0)	7/8 (87.5)	12/12 (100.0)	9/10 (90.0)	23/23 (100.0)	31/32 (96.9)	–	18/18 (100.0)	67/67 (100.0)	59/62 (95.2)
Cecum:											
Deep mucosal fibrosis	0/14 (0)	0/3 (0)	1/10 (10.0)	NE	1/11 (9.1)	0/14 (0)	4/33 (12.0)	–	3/21 (14.3)	3/38 (7.9)	6/68 (8.8)
No significant changes	14/14 (100.0)	3/3 (100.0)	9/10 (90.0)	NE	10/11 (90.9)	14/14 (100.0)	29/33 (87.9)	–	18/21 (87.5)	35/38 (92.1)	62/68 (91.2)
Colon:											
Deep mucosal fibrosis	0/14 (0)	0/13 (0)	1/12 (8.3)	0/9 (0)	2/9 (22.2)	0/18 (0)	1/30 (3.3)	–	0/20 (0)	0/60 (0)	4/65 (6.2)
Calcification-surface epithelium	0/14 (0)	0/13 (0)	0/12 (0)	0/9 (0)	1/9 (11.1)	0/18 (0)	1/30 (3.3)	–	1/20 (5.0)	1/60 (1.7)	2/65 (3.1)
No significant changes	14/14 (100.0)	13/13 (100.0)	11/12 (91.7)	9/9 (100.0)	6/9 (66.7)	18/18 (100.0)	28/30 (93.3)	–	19/20 (95.0)	59/60 (98.3)	59/65 (90.8)
Pancreas - Acini:											
Atrophy and/or fibrosis and duct dilatation	1/3 (2.7)	7/21 (33.3)	2/13 (15.4)	2/12 (16.7)	3/11 (27.3)	10/32 (31.3)	6/34 (17.6)	–	24/43 (55.8)	43/108 (39.8)	12/71 (16.9)
Hemosiderin-interstitial	5/13 (38.5)	7/21 (33.3)	2/13 (15.4)	6/12 (50.0)	3/11 (27.3)	14/32 (43.8)	16/34 (47.1)	–	32/43 (74.4)	59/108 (54.6)	26/71 (36.6)
Fatty infiltration	0/13 (0)	0/21 (0)	0/13 (0)	0/12 (0)	1/11 (9.1)	4/32 (12.5)	1/34 (2.9)	–	1/43 (2.3)	5/108 (4.6)	2/71 (2.8)
Periductal eosinophils and fibrosis	0/13 (0)	0/21 (0)	0/13 (0)	0/12 (0)	2/11 (18.2)	0/32 (0)	1/34 (2.9)	–	0/43 (0)	0/108 (0)	3/71 (4.2)
Inspissated debris-ducts	0/13 (0)	0/21 (0)	0/13 (0)	0/12 (0)	2/11 (18.2)	0/32 (0)	1/34 (2.9)	–	0/43 (0)	0/108 (0)	3/71 (4.2)
Nodular hyperplasia	0/13 (0)	0/21 (0)	0/13 (0)	0/12 (0)	1/11 (9.1)	0/32 (0)	1/34 (2.9)	–	0/43 (0)	0/108 (0)	2/71 (2.8)
Hyperplasia-ductules	0/13 (0)	0/21 (0)	0/13 (0)	0/12 (0)	1/11 (9.1)	0/32 (0)	0/34 (0)	–	0/43 (0)	0/108 (0)	1/71 (1.4)
Vacuolization	0/13 (0)	0/21 (0)	0/13 (0)	0/12 (0)	0/11 (0)	0/32 (0)	1/34 (2.9)	–	0/43 (0)	0/108 (0)	1/71 (1.4)
Pancreas - Islets:											
Hyperplasia	7/13 (53.8)	4/21 (19.0)	5/13 (38.5)	2/12 (16.7)	2/11 (18.2)	3/32 (9.4)	10/34 (29.4)	–	5/43 (11.6)	14/108 (13.0)	24/71 (33.8)
Conglomerate islets	1/13 (7.7)	0/21 (0)	1/13 (7.7)	0/12 (0)	2/11 (18.2)	0/32 (0)	8/34 (23.5)	**	0/43 (0)	0/108 (0)	2/71 (16.9)
Atrophy	0/13 (0)	0/21 (0)	0/13 (0)	0/12 (0)	0/11 (0)	0/32 (0)	1/34 (2.9)	–	0/43 (0)	0/108 (0)	1/71 (1.4)
Hyalinization	0/13 (0)	0/21 (0)	0/13 (0)	0/12 (0)	0/11 (0)	0/32 (0)	0/34 (0)	–	1/43 (2.3)	1/108 (0.9)	0/71 (0)
No significant changes (acini and islets)	6/13 (46.2)	14/21 (66.7)	6/13 (46.2)	6/12 (50.0)	4/11 (36.4)	15/32 (46.9)	11/34 (32.4)	–	10/43 (23.3)	45/108 (41.7)	27/71 (38.0)

Table 3 Continued

Lesion	Age (Months) 6-11 HAP	12-17 CD	12-17 HAP	18-23 CD	18-23 HAP	24-29 CD	24-29 HAP	Sig.	30-38 CD	Incidence CD	Incidence HAP
SPECIAL SENSES											
Eye-Cornea:											
Chronic purulent keratitis	0/6 (0)	0/13 (0)	0/6 (0)	0/11 (0)	0/5 (0)	0/9 (0)	2/11 (18.2)	–	NE	0/33 (0)	2/28 (7.1)
Ulcer	0/6 (0)	0/13 (0)	0/6 (0)	0/11 (0)	0/5 (0)	0/9 (0)	1/11 (9.1)	–	NE	0/33 (0)	1/28 (3.6)
Acanthosis	0/6 (0)	0/13 (0)	0/6 (0)	0/11 (0)	0/5 (0)	0/9 (0)	1/11 (9.1)	–	NE	0/33 (0)	1/28 (3.6)
No significant changes	6/6 (100.0)	13/13 (100.0)	6/6 (100.0)	11/11 (100.0)	5/5 (100.0)	9/9 (100.0)	8/11 (72.7)	–	NE	33/33 (100.0)[a]	25/28 (89.3)
Eye-Retina:											
Degeneration	0/6 (0)	0/13 (0)	0/6 (0)	0/11 (0)	1/5 (20.0)	0/9 (0)	8/11 (72.7)	**	NE	0/33 (0)	9/28 (32.1)
No significant changes	6/6 (100.0)	13/13 (100.0)	6/6 (100.0)	11/11 (100.0)	4/5 (80.0)	9/9 (100.0)	3/11 (27.3)	–	NE	33/33 (100.0)[a]	19/28 (67.9)
Harderian Gland:											
Chronic interstitial adenitis	1/8 (12.5)	0/14 (0)	0/7 (0)	0/11 (0)	3/10 (30.0)	0/15 (0)	11/31 (35.5)	**	1/4 (25.0)	1/44 (2.3)	15/56 (26.8)
Squamous metaplasia	0/8 (0)	0/14 (0)	0/7 (0)	0/11 (0)	0/10 (0)	0/15 (0)	1/31 (3.2)	–	0/4 (0)	0/44 (0)	1/56 (1.8)
Epithelial hyperplasia	0/8 (0)	0/14 (0)	0/7 (0)	0/11 (0)	0/10 (0)	0/15 (0)	1/31 (3.2)	–	0/4 (0)	0/44 (0)	1/56 (1.8)
No significant changes	7/8 (87.5)	14/14 (100.0)	7/7 (100.0)	11/11 (100.0)	7/10 (70.0)	15/15 (100.0)	20/31 (64.5)	–	3/4 (75.0)	43/44 (97.7)	41/56 (73.2)
Ear-External Ear:											
Hyperkeratosis	0/7 (0)	NE	0/7 (0)	NE	0/10 (0)	NE	6/32 (18.8)	–	NE	NE	6/56 (10.7)
No significant changes	7/7 (100.0)	NE	7/7 (100.0)	NE	10/10 (100.0)	NE	26/32 (81.2)	–	NE	NE	50/56 (89.3)
Ear-Typmanic Bullae:											
Otitis media	0/12 (0)	0/12 (0)	0/11 (0)	0/10 (0)	0/11 (0)	1/9 (11.1)	2/34 (5.9)	–	1/12 (8.3)	2/43 (4.7)	2/68 (2.9)
Eosinophilic debris	0/12 (0)	0/12 (0)	4/11 (36.4)	0/10 (0)	2/11 (18.2)	0/9 (0)	7/34 (20.6)	**	0/12 (0)	0/43 (0)	13/68 (19.1)
Pigmented macrophages	0/12 (0)	0/12 (0)	0/11 (0)	0/10 (0)	1/11 (9.1)	0/9 (0)	0/34 (0)	–	0/12 (0)	0/43 (0)	1/68 (1.47)
No significant changes	12/12 (100.0)	12/12 (100.0)	7/11 (63.6)	10/10 (100.0)	9/11 (81.8)	8/9 (88.9)	26/34 (76.5)	–	11/12 (91.7)	41/43 (95.3)	54/68 (79.4)
INTEGUMENTARY SYSTEM											
Skin:											
Hyperkeratosis	3/13 (23.1)	0/22 (0)	1/11 (9.1)	0/12 (0)	2/9 (22.2)	0/34 (0)	5/29 (17.2)	**	0/45 (0)	0/113 (0)	11/62 (17.7)
Acanthosis	0/13 (0)	0/22 (0)	1/11 (9.1)	0/12 (0)	0/9 (0)	0/34 (0)	3/29 (10.3)	*	0/45 (0)	0/113 (0)	4/62 (6.5)
Ulceration	0/13 (0)	0/22 (0)	0/11 (0)	0/12 (0)	0/9 (0)	0/34 (0)	2/29 (6.9)	–	0/45 (0)	0/113 (0)	2/62 (3.2)
Pododermatitis	0/13 (0)	0/22 (0)	0/11 (0)	0/12 (0)	0/9 (0)	2/34 (5.9)	0/29 (0)	–	7/45 (15.6)	9/113 (8.0)	0/62 (0)
Epidermal cyst	0/13 (0)	0/22 (0)	0/11 (0)	0/12 (0)	0/9 (0)	0/34 (0)	5/29 (17.2)	*	0/45 (0)	0/113 (0)	5/62 (8.1)
Granulomatous folliculitis	0/13 (0)	0/22 (0)	0/11 (0)	0/12 (0)	0/9 (0)	0/34 (0)	1/29 (3.4)	–	0/45 (0)	0/113 (0)	1/62 (1.6)
No significant changes	10/13 (76.9)	22/22 (100.0)	10/11 (90.9)	12/12 (100.0)	7/9 (77.8)	26/34 (76.5)	18/29 (62.1)	–	29/45 (64.4)	89/113 (78.8)	45/62 (72.6)

Table 3 Continued

Lesion	Age (Months) 6-11 HAP	12-17 CD	12-17 HAP	18-23 CD	18-23 HAP	24-29 CD	24-29 HAP	Sig.	30-38 CD	Incidence CD	Incidence HAP
MUSCULOSKELETAL SYSTEM											
Vertebral Bone:											
Prolapse of intervertebral disc	0/14 (0)	0/8 (0)	1/11 (9.1)	0/12 (0)	0/10 (0)	0/13 (0)	0/34 (0)	–	0/27 (0)	0/60 (0)	1/69 (1.4)
Hemorrhage in leptomeninges	0/14 (0)	0/8 (0)	1/11 (9.1)	0/12 (0)	0/10 (0)	0/13 (0)	0/34 (0)	–	0/27 (0)	0/60 (0)	1/69 (1.4)
No significant changes	14/14 (100.0)	8/8 (100.0)	10/11 (90.9)	12/12 (100.0)	10/10 (100.0)	13/13 (100.0)	34/34 (100.0)	–	27/27 (100.0)	60/60 (100.0)	68/69 (98.6)
Skeletal Muscle:											
Fatty infiltration	0/14 (0)	1/14 (7.1)	0/11 (0)	1/12 (8.3)	0/10 (0)	1/23 (4.3)	1/34 (2.9)	–	1/36 (2.8)	4/85 (4.7)	1/69 (1.4)
Interstitial myositis	0/14 (0)	0/14 (0)	0/11 (0)	1/12 (8.3)	0/10 (0)	0/23 (0)	0/34 (0)	–	0/36 (0)	1/85 (1.2)	0/69 (0)
Necrosis	0/14 (0)	0/14 (0)	0/11 (0)	0/12 (0)	0/10 (0)	0/23 (0)	0/34 (0)	–	1/36 (2.8)	1/85 (1.2)	0/69 (0)
No significant changes	14/14 (100.0)	13/14 (92.9)	10/11 (90.9)	10/12 (83.3)	7/10 (70.0)	16/23 (69.6)	5/34 (14.7)	*	15/36 (41.7)	54/85 (63.5)	36/69 (52.2)

[1]Number with lesion/number examined; [2]( ) = percent with lesion; [3]Sig. = statistical significance (12-29 month old HAP and CD); [4]*$p<0.05$; [5]**$p<0.01$; [6]– = not statistically significant; [7]NE = not examined; [8]Excludes 30-38 month old CD; [9]all age groups.

CD. Of a small number of animals examined for endoparasites, the following results were obtained: 18-23 months, 0/4; 24-29 months, 1 *Syphacia muris*/3; 30-39 months, 1 *Syphacia muris*/4. The pinworm infestation occurred after rats were removed from the barrier to conventional housing.

Bacteriology

Hap. The pathogen most consistently isolated was *Pseudomonas sp. (aeruginosia, fluorescens, cepacia and putida).* When a rat was a carrier, the organism was usually found in both the nasopharynx and colon. Carrier frequency was as follows: 6-11 months, 42.8%; 12-17 months, 58.3%; 18-23 months, 36.4%; 24-29 months, 47.1%. Other pathogens isolated less frequently were *Staphylococcus aureus* and *Corynebacterium sp.*

Mycoplasma was not isolated from any animal during the study duration.

CD. Mycoplasma was not isolated from any lung specimen although a number of rats in the older age groups which were housed outside of the barrier had typical lesions of murine respiratory mycoplasmosis. Tracheal and nasal washings, which are better specimens for *Mycoplasma* isolation than tissue, were not collected in the CDs. Bacterial pathogens isolated from the lung with low frequency (1-2 rats in the older, conventionalized age groups) were *Streptobacillus moniliformis, Pseudomonas aeruginosa* and *Staphylococcus aureus.*

Serology

Hap. Significant antibody titer to murine viruses were present in all age groups. Animals usually had antibodies to more than one agent. Incidences of virus titers were: PVM - 72.9%, Sendai -56.1%, RCV - 42.4%, Toolan's H-1 -5.7%, reo 3 -1.4%, KRV -1.4%.

CD. During the period of study, aging colony animals within the barrier at CRL had antibodies to SDA, Toolan's H-1, Sendai and PVM.

Discussion

The two SD stocks in this study exhibited the entire spectrum of murine age-associated lesions [4; 7]. Some of the lesions were incidental with no effect on the animals' general health while others contributed significantly to morbidity and mortality. Additionally, many lesions were found in combination in older rats.

The two stocks, in a number of instances, differed markedly in their expression of lesions with increasing age. Part of the difference may relate to the variation in longevity of Hap and CD rats. A number of neoplasms and nonneoplastic lesions developed at an earlier age in Haps, indicating that senescence occurred more rapidly in this stock than in the longer-lived CDs. However, longevity cannot be the sole explanation for the occurrence of lesions unique to one stock and their rarity or absence in the other stock, e.g. islet cell tumors in CDs, kidney adenomas in Haps, ureteral calculi in Haps, and hepatic telangiectasis in CDs.

Although we have identified statistically significant differences in incidences of neoplastic and nonneoplastic lesions, we emphasize the need to interpret these results cautiously. As Burek and Hollander [13] have pointed out, substantial variability in age-associated lesions can occur even within highly inbred strains which have been reared under identical conditions in a single institution. The SD rats we have reported on here were outbred. They consisted of retired breeder and virgin groups. Other variables were the location of the colonies, cage size, group size, diet, handling, husbandry, lighting and air changes. Thus, it would seem prudent to recognize that multiple factors could have contributed to the differences in lesions between the two stocks.

Many of these variables are, at present, unavoidable. The

SD populations described in this paper accurately represent the outbred rats currently available from commercial breeders in the United States to investigators in experimental gerontology. Baseline pathology and longevity data on commercially available stocks are essential for investigators who are using or wish to select these rats for gerontologic research projects but do not have the resources to establish their own baseline data. Use of well defined, high quality aged SD rats can minimize many of the deficiencies found in earlier gerontologic research [20] employing the rat as a model for aging studies.

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