TECHNICAL PROGRESS REPORT

COO/1487/7

The University of Chicago Contract No. AT(11-1) 1487

for the period June 14, 1971 to August 14, 1972

- (1) Histopathological changes in Laboratory Animals Exposed to Protracted Low-Level Total-Body Neutron and GammaRay Fluxes-a Continuing Study
- (2) The University of Chicago
Department of Pharmacology and Radiology
950 East 59th Street
Chicago, Illinois 60637
- (3) The program of research, completed and proposed, has been and will be in conjunction and collaboration with the Janus neutron study now being conducted by the Division of Biological and Medical Research, The Argonne National Laboratory, Argonne, Illinois. The program is identified there as the "Neutron and Gamma Ray Toxicity Studies." The portion of the study the proposer is concerned with is the evaluation of the gross and histopathological reasons for the morbidity and mortality of the exposed and control animals. Studies on the normal or stressed aging of mice and mastomys (*Paromys natalensis*) have been conducted and will continue. The purpose of these studies is to establish base lines for future evaluations of exposed animals.

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A major segment of the study, in part reported last year, (COO/1487/6) has been completed and is presented in appendix A of this report. It is entitled "Pathologic Observation of Aged Mastomys (*Praomys natalensis*) Variously Caged." The observations made a year ago have been considerably modified by the findings developed since that report was made. Over 3,000 tissues sections were examined and diagnosed in this study; about 1,000 the past year.

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A scoping study of aging BCF,(SPF) hybrid mice is underway. This study was initiated to establish a base line for the animals that are being exposed to the Janus neutron flux. At this time 206 have been studied histologically and a total of 380 have been autopsied. The 174 that have not yet been examined histologically will be completed as the sections are stained. About 7-10 tissues from each mouse were saved for examination. Over 1700 were studied and diagnosed during the past year. No report has yet been prepared but will be upon completion of the series.

About 50 mice, exposed to various patterns of neutron, have been examined histologically. There was about 500 tissue sections involved. A considerably larger number have been killed and await histological preparation. The proposer has participated in the autopsy sessions. The exposure to which these animals have been subjected is not known to the proposer. It is our practice to examine the animals "blind" so that there will be no unconscious bias. ✓

The proposer is presently receiving support from the National Institutes of Health on the following grant,

USPHS 5-PO6-FR-00409-04
and from this contract
AT (11-1) 1487

It is planned that this will be the final request for funds.

- (4) The scientific and professional activities and background of the proposer is given in the attached curriculum vitae and bibliography.

Appendix A

Pathologic Observations of Aged Mastomys

(Praomys natalensis) Variouslly Caged

John H. Rust,* R.J.M. Fry, Ward R. Richter*
and Everett Staffeldt

Introduction

A study of the possible pathologic effects of stressful caging conditions upon male and female mastomys (*Praomys natalensis*) was initiated in 1968 and now has been completed. This report is concerned with the gross and microscopic findings of those animals killed at 516-647 days, about 18 $2/3$ -21 $\frac{1}{2}$ months of age. Of the 333 animals started in this study, only 269 survived and have had a relatively complete histopathologic work-up. It was originally planned that 384 animals would be used. For various technical or other reasons, the remainder of the mastomys are not included. Most of these were discarded because of an inopportune death time and advanced autolysis of tissue, lost tissues and tissues destroyed in preparation. All histological work was done in the histology laboratory of the A. J. Carlson Animal Research Facility at the University of Chicago (supported by the USPHS 5-PO6-RR0409 (Research) grant). Material from younger animals, ie., approximately 4 and 9 months, has been saved and if possible, will be examined in their entirety at a later date.

The nominal design was given in detail in the grant request the period beginning June 15, 1971. It is essentially a 3 level block design, with 1 missing block, with three levels of caging area per animal, 4 cage-animal densities (both sexes alone or together in some case) and 3 sampling times (ages).

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The cages were modified, where necessary, to have equal areas.

The areas with the various cages were,

Gamma cage (round)	19.6 square inches
Breeder cage (B-20)	20.0 square inches
Breeder cage (B-35)	35.0 or 37.1 square inches
Breeder cage (B-60)	60.0 square inches
Mouse cage	35.0 square inches
Rat cage	63.0 square inches

(one mouse cage had 59.5 square inches and in the tabulations that follow later, it is listed as a B-60 cage in the case of 3 males only).

The initial cage density of animals and the various combination and the symbols used are,

Males

1 male ♂
2 males 2 ♂ ♂
3 males 3 ♂ ♂
6 males 6 ♂ ♂

Females

2 females 2 ♀ ♀
6 females 6 ♀ ♀

Mixed or paired

1 male and 1 female (♂♀) ♂ or ♀

The basic data derived are given in tables 1-9. It was also of interest to see how little the fate of the mastomys housed in groups depended upon their crowding or upon the number or sex of their cage mates.

The cage status of the mastomys reported on in this study, ie., numbers started and numbers surviving at the end of the study, and the range of their age at autopsy, in days, was:

(♂ ♀) (Mouse cage)	16 pairs started	age 561-645
	11 pairs at end	
	2 males at end	
	3 females at end	
2 ♀ ♀ (Mouse cage)	19 pairs started	age 561-647
	13 pairs at end	
	6 singles at end	
2 ♂ ♂ (Mouse cage)	17 pairs started	age 561-647
	11 pairs at end	
	6 singles at end	
3 ♂ ♂ (Mouse cage)	13 triplets started	age 561-639
	6 triplets at end	
	4 pairs at end	
	3 singles at end	
6 ♂ ♂ (Mouse cage)	6 sextuplets started	age 561-639
	4 quadruplets at end	
	2 triplets at end	
6 ♀ ♀ (Mouse cage)	4 sextuplets started	age 561
	1 quintuplet at end	
	1 quadruplet at end	
	1 triplet at end	
	1 pair at end	

2 ♂ ♂ (B-20 cage)	10 pairs started	609-631
	3 pairs at end	
	7 singles at end	
2 ♀ ♀ (B-20 cage)	11 pairs started	617-619
	5 pairs at end	
	6 singles at end	
♂ ♀ (B-20 cage)	18 pairs started	609-641
	8 pairs at end	
	6 males at end	
	4 females at end	
3 ♂ ♂ (B-20 cage)	7 triplets started	596-631
	1 triplet at end	
	4 pairs at end	
	2 singles at end	
3 ♂ ♂ (Rat cage)	12 triplets started	619-645
	4 triplets at end	
	6 pairs at end	
	2 singles at end	
6 ♂ ♂ (Rat cage)	5 sextuplets started	516-645
	1 quintuplet at end	
	1 quadruplet at end	
	1 triplet at end	
	1 pair at end	
	1 single at end	

Description of lesions observed

Disease entities, per se, were not usually encountered or identified. More often, it was a unique lesion which might or might not suggest an identifiable disease complex. The descriptions that follow will, therefore, be directed at lesions by organs rather than by disease complexes.

LUNGS - A rather frequent observation was a pneumonitis. Usually it was quite mild. The bronchial walls were mildly edematous with collections of lymphocytes, plasma cells and some macrophages. The infiltrate extended into the interlobular and alveolar septa. In the latter, a few neutrophils could be seen, but were not often the predominant cell type. No sex or treatment dependency was noted. One case of adenomatosis and several alveologenic adenomas were seen. The adenomas will be discussed under tumors.

No other changes were seen either at autopsy or microscopically.

HEART - Almost without exception there was a chronic valvulitis of varying degrees of severity in all valves available for inspection microscopically. The lesion was not sought for at autopsy, since the change was usually so slight that it is likely that the nodules could only be observed with some optical aid. The lesion could best be characterized as a nodular connective tissue proliferation with modest collagen formation. No sex or treatment difference was noted.

A common finding was a non-specific chronic interstitial myocarditis. It varied in severity from a few lymphocytes and monocytes in small clusters (by far the most common) to a severe diffuse infiltrate that involved all heart muscle. It was found in 24% of the females and in 15% of the males. There was no evidence that it was related to the stress of caging. (see Table 1 and 2).

LIVER - The livers were unusually free of lesions. No evidence of

hepatitis was seen either as an acute or a chronic manifestation. In spite of the heart lesions noted before, there was rarely any evidence of passive hyperemia or chronic congestion. No metastatic tumors were found. Hepatomas were seen in 15% of the females and 11% of the males (see table 7). No difference was noted relative to the caging. There were three hemangiomas, one case of telangectasis, and one case of cholangioma.

The hepatomas and lymphosarcomas involving the liver will be considered in the discussion of tumors. The mastomys have no gall bladder, so the absence of any mention is not an oversight.

KIDNEY - A very common lesion was a chronic interstitial nephritis. It was somewhat more common in the male, with 86% of the males animals with the lesion, and 63% in the females (see tables 3 and 4). Grossly the external surface of the kidney was often irregularly granular and pitted and were sometimes smaller in size (shriveled). Microscopically, the milder cases had focal collections, about vascular structures and interstitially, of lymphoid cells, monocytes and plasma cells. In the mild cases, the tubules were not noticeably altered. In the more severe cases a linear infiltrate extended from the capsule deep into the cortex with destruction or severe alteration of glomeruli and tubules. Many of the glomeruli were hyalinized and atrophic in the zone of the severe interstitial lesion and the tubules would often be replaced by proliferating interstitial connective tissue. Cysts were frequent in the severe cases and were filled with an eosinophilic protein material. Some tubules which escaped destruction were severely dilated or even cystic, and might contain some light granular pinkish material.

While the kidney lesions did range markedly in the degree of severity, on the average, it was only considered to be moderate. Kidneys were scored by degrees of severity, ie., mild-1, moderate-2, moderately severe-3, and severe-4, and it was determined that the description

of moderate was the most frequent used and averaging all of the values obtained supported this observation (see tables 3 and 4).

Another lesion which could possibly have been associated with the chronic interstitial nephritis was glomerulosclerosis. It is clear that they were not always associated, for only 77% of the males and 44% of the females had the lesion. This was less frequent than the interstitial disease.

Most of the glomeruli affected were of the membranous type with only a few being of the proliferative variety. Epithelial crescents were not seen though there was often a moderate degree of proliferation of Bowman's capsule and a few connective tissue strands attached to the glomerulus. Adhesions of the capsule to the tuft were localized and rarely extensive. The capillary tufts usually displayed "wireloops", were hyalinized and had a thickened basement membrane (mesangium). No amyloid disease was ever encountered. All in all, the lesions were of a moderate degree with surprisingly few that could be called moderately severe (see tables 3 and 4).

Vascular lesions were quite uncommon and when found, had minimal hyalinization of the intima and media of middle sized and small arteries. No necrotizing areas were observed. Intravascular thrombi were very uncommon. No amyloidosis was observed.

STOMACH - The most frequent observation was hyperkeratosis of the forestomach. The forestomach in this species is essentially a continuation of the oesophagus and is, therefore, lined with a stratified squamous epithelium. It is flattened and not folded like that of the rat. At least 95% of the animals displayed hyperkeratosis. It was so frequent that it is tempting to suggest that it is the normal situation. Even those animals that were not considered to have hyperkerotosis had one or two

layers of keratin overlaying the epithelium. Some animals, more notably the females, had very severe hyperkeratosis. The disorganization was such that on several occasions it was chosen to call the lesion a squamous cell adenoma (see table 9). It is recognized that they did not display all of the criteria needed for that classification, but were placed there somewhat in desperation. At autopsy, tightly massed hair balls were often found associated with or loosely attached to the excess keratin of the forestomach. On some occasions hair of the mastomys was found (microscopically) to be intertwined with the keratin.

On a few occasions, focal infiltrates of lymphocytes, monocytes and plasma cells were observed above the muscularis mucosae, most particularly at, or near the junction of the forestomach and the glandular stomach.

The glandular portions of the fundic stomach were relatively free of disease, the exception being a rare abscess, or a focal infiltrate, similar in nature to that in the forestomach, which lay above the muscularis mucosa and extended into the submucosa and the lamina propria between the gastric pits. Sections of the pyloric stomach (glandular) were rarely saved for examination.

Tumors were relatively common and will be discussed under that topic. The mastomys are a unique laboratory animals in that they have a large number of stomach tumors that develop with age.

THYROID - A most unusual and frequent finding was chronic thyroiditis. It was found most frequently in females, 91%. The males had the lesion only 77% of the time. The average degree of severity for females was moderately severe and in males only moderate. The system of scoring severity was one-fourth or less of the section of gland involved-1; one-fourth to one-half-2; one-half to three-fourths-3; and greater than three-fourths-4. The average for all females was 3.2 and for males 2.4. There seem to be no dependency upon caging (see table 5 and 6).

With one exception, the lesion was of the type called struma lymphomatosa, or Hashimoto's disease. The one exception was the granulomatous type. In the first type, the gland was grossly enlarged and microscopically the acini were, to varying degrees, replaced by lymphocytes. Sometimes they were in follicular collections, but commonly they were seen as sheets of cells overrunning the acini. The acinar epithelium was pale eosinophilic and usually moderately hyperplastic. On five occasions the hyperplasia was advanced enough to suggest papillary adenomas of the thyroid. The granulomatous type had giant cells among disrupted thyroid follicles forming granulomata. There was the suggestion of a foreign body reaction.

ADRENAL - The males and females had greatly differing lesions in the adrenal. The females had a degenerative lesion of the cortex which involved what might be termed the reticular zone. There is some question whether or not this analogy with higher mammals is valid. The degeneration was hydropic and often included "brown degeneration". The latter is thought to be like the ceroid deposition (ceroidogenesis) commonly seen in female mice of advanced age. The breadth of the lesion was extensive, and sometimes including what might be considered the fascicular zone in the most severely affected. In a substantial number of cases, there was a collar of cells at the base of the cortex often involving the medulla. The nuclei were pyknotic and the cytoplasm pale and vacuolated. These cells may well be associated with a zone analogous to the transitory cortex, or Howard-Miller's X-zone, of the young female mouse. This zone is replaced in the mature female mice by a juxtamedullary connective tissue band. It is possible that the cells observed were evidence of metaplasia or hyperplasia of such cells. The significance of their presence in the aging female mastomys is not known.

The zona glomerulosa, and commonly the zona fasciculata, was not changed so far as could be detected in the hematoxylin-eosin stained tissue. The medulla of the adrenal was not changed except for occasional hyper-volemia.

Tumors were seen rather frequently and will be discussed under that topic.

In the male mastomys, the degenerative lesion described above was quite infrequent. The collar of cells seen in the juxtamedullary zone was never seen in the male. Most frequently, there was a marked cortical hypertrophy. Over 90% of the males were affected. This probably is an underestimate since the diagnosis had to rest upon subjective observations. The cells appeared to be arising in the reticular zone, if that designation can be accepted. The zona glomerulosa did not seem to be involved (see tables 7 and 8).

PITUITARY - This endocrine gland was not uniquely changed except for a hyperplasia-adenoma lesion. It was quite difficult to decide which category should be selected. All hyperplastic pituitaries could be easily detected at autopsy. The pituitary would be so greatly enlarged as to break over or through the sella turcica. Whether or not the clinoid process was eroded as is observed in mice could not be determined. The frequency of the lesion 4.8% in males and 1.8% in females (see table 7). The hyperplastic lesion was observed in the zone analagous to the anterior lobe (pars distalis). An attempt is being made to identify the cell type but they appeared to have been the acidophile type. It seems quite possible that there may be both the alpha and epsilon cells present. Little is known about the pituitary gland cell distribution in this species.

OVARY - The ovary in the aging female mastomys is not greatly different from other rodents. Of the ovaries examined, 49% were atrophic and 10% were cystic. Tumors of the ovaries were not as

frequently seen in this study as in the aging female mouse.

MAMMARY GLAND - Only one mammary tumor was noted on the autopsy records. Unfortunately, the tissues from this case were lost in processing. From this one observation, however, it seems certain that neither mammary tumors or mastitis are common in the mastomys.

TUMORS - (see table 7)

THYMOMA - The thymoma is a relative common neoplasm in the mastomys. In the male 8.9%, and in the female 12%, of the animals in our series bore a thymoma which could easily be diagnosed either at autopsy or by microscope. In the mastomys, it has a characteristic appearance of the "starry-sky" lymphoma. In no other organ was such an arrangement found. It was thought, at first, that the punched out areas might be Hassal's corpuscles, but the evidence was not adequate to substantiate the notion. The thymomas were composed of relatively uniform, medium-sized cells with round to oval nuclei with a fine stippling, uniformly distributed chromatin. The nucleoli were small and inconspicuous. The cytoplasm was neutral (amphophilic) in color and slight in amount. The cell borders were indistinct and cohesive. The "starry-sky" areas were composed of histiocytes with abundant pale staining cytoplasm. Phagocytosis was not observed. The appearance of the thymoma was much like that of Burkitt's lymphoma or stem-cell lymphoma.

Rarely the lymphoma spread to distant organs such as the liver, kidney, or mesenteric lymph nodes. The "starry-sky" appearance was lost in such metastasis. The cell types maintained their identity with those in the thymus ranging from stem-cells (lymphoblasts) to mature lymphocytes. The histiocytic elements did not metastasize. Most commonly the cells were located as nodules about the portal triads or the central vein and were not commonly seen in the sinusoids except as very small clusters.

LYMPHOSARCOMAS - These tumors were found in both males and females, 3.8% and 3.7% respectively. They were too infrequent in occurrence to determine whether or not there was a treatment difference. The appearance of the spleen, in these cases, was unique among rodents. The white pulp (Malpighian corpuscle) was always quite distinctly free of the disease process, most characteristically a reactive type. The reactive corpuscle ie., a reticuloendothelial center about a sheathed artery with a distinct lymphoid collar, was almost always observed even in the absence of the disease. The lymphocytic hyperplasia of the lymphosarcomatous mastomys was confined to the cords of the red pulp. It was often difficult to determine from the spleen alone whether or not the disease was present. It may well be that some cases of lymphosarcoma were misdiagnosed if it is speculated that it was in an early stage of the disease development. In that situation, with no supporting observations in other tissues, the diagnosis of hematopoiesis was in truth lymphosarcoma. Those that were recorded as lymphosarcoma always had metastatic lesions in the liver, kidney, mesenteric nodes, mesenteric fat, adrenal and other organs.

The liver lesions were largely lymphoblastic or lymphocytic (more mature) and centered about vascular structures as collars or nodules. The sinusoids were relatively free of any cells except for some small collections and they were not associated with Kupfer cells. The kidney lesions were perivascular or periglomerular and rarely interstitial. The perirenal lymph nodes and fat were frequently involved. Adrenals on some occasions had foci between the cords of the reticular zone. Some foci, nodular, were seen about bronchioles of the lungs but they were not a common or striking lesion. Mesenteric lymph nodes would be very hyperplastic, with cells similar to those seen in the spleen and other organs.

HEPATOMAS AND OTHER LIVER TUMORS - No hepato-carcinoma were observed.

A bile duct tumor was found in one female. It was characterized by clearly defined atypical bile duct cells forming bizarre ducts. No evidence of cirrhosis was detected. Three vascular tumors were found, one in a males, and two in females. These were described as hamangiomas.

Hepatomas were seen in 11% of the males and in 15% of the females. These tumors were too infrequent to be associated with any caging pattern. They were present as delineated nodules of atypical large hepatocytes which could easily be differentiated from the normal hepatocytes with a regular architectural organization. No capsule was seen except as a false one consisting of a zone of compressed hepatocytes. Usually, the hepatomas could be detected grossly but sometimes they were not and small tumor masses would be found in situ. It is quite possible that early hepatomas of this size may have been missed.

STOMACH TUMORS - Adenomatous tumors were the most common seen and also were the most common of all tumors found in the mastomys. The tumors were observed in 19% of the males and 15% of the females. No attempt will be made to separate those thought to be non-malignant from the malignant. It is quite likely that even those considered to be benign were not and the diagnosis arrived at was so-made because an adequate sampling of the tumor was not done. The frequency of the various types of stomach cancer cannot be stated except in general terms. The most common was in the form of adenomatous polyps. They occurred in almost all areas of the fundic glandular stomach but more often near the junction of the squamous lined forestomach and the fundic glandular stomach. In several instances a confused intermixing of severely hyperkeratotic material from the forestomach and dilated hyperplastic glandular structure at the junction gave the appearance of a neoplasm. These possibly should have been considered to be adenoma but were not. Such lesions were most common in the female mastomys.

Included with the more common polyps were a few papillary tumors. These tumors may be of a different origin, but they were located in the same general part of the stomach. The polyoid tumors bulged from the glandular stomach surface into the lumen and the papillary type was pedunculated with branching fronds, but probably arose from the nearby squamous epithelium. It was quite difficult to determine the origin because of the peculiarity of the tissue distribution at the junction of the two types of stomach epithelium. For convenience they are both tabulated as adenomas of the stomach.

Fungating adenocarcinoma, which may have arisen from the polyps noted above, were the usual type. They were unquestionably invasive, sometimes involving the serosa. Ulceration of tumor surfaces were occasionally observed. No distant metastases were ever found from these obviously malignant neoplasms.

An unusual neoplasm of the stomach in the mastomys is the carcinoid tumor. In man, this tumor is found, usually, in the small intestine. In the mastomys it is found in the glandular stomach. In man, there are peculiar fibrous tissue deposits on the pulmonary and tricuspid valves of the heart which is believed to be derived from the serotonin produced by the carcinoid cells. The valvulitis seen in the mastomys hearts does not resemble the carcinoid associated lesion in man. Microscopically, the tumor is found in the glandular area and is composed of polyhedral cells nested in a fibrous matrix. With appropriate stains, the cells are argentophilic. No special stains were used in this study since the tumor is so easily identified. The carcinoid tumor of the stomach was seen in 1.6% of the males and 0.7% of the females. This is further support for the notion that this rather uncommon tumor could not be related to the very common valvulitis observed in the hearts of mastomys.

It is recognized that Snell has found that even the adenomatous tumors of the stomach in this species is actually a carcinoid tumor with glandular hyperplasia and metaplasia. It is planned to test this observation with additional staining techniques.

Mention was made earlier of a lesion that was called a squamous cell tumor of the stomach of the mastomys; out of desperation. It occurred in 2.0% of the males and in 6.8% of the females. There is some serious doubt about such a diagnosis. The lesion is wildly bizarre, but does not invade the deeper structures of the epithelium of the forestomach. Mention was also made before of the presence of hyperkeratosis, almost without exception, in this species. The female of the species has the more severe manifestation. It was noted that the squamous cell tumor also occurred more frequently in the female. Possibly what was seen was simply an even more severe manifestation of the hyperkeratosis observed.

ADRENAL TUMORS - Cortical adenomas of the adrenal were found in 7.8% of the males and 1.6% of the females. The more frequent occurrence of the tumor in males suggested that there might be some relationship with the very common occurrence of hypertrophy of the cortex also seen in the males (see tables 5 and 6). There is no evidence, however, to support the suggestion other than this casual relationship. The cortical adenomas were encapsulated masses of cells of cortical origin. Cells were regular in size, with small nuclei, uniform in staining quality, and arranged in cords along vascular sinuses. The larger adenomas were easily seen at autopsy. No malignant tumors were seen.

Pheochromocytomas of the adrenal were seen in two males and one female, a frequency of 0.8% in each sex. They were encapsulated and were composed of uniform polyhedral cells in nests. No effort was made to stain for the chromaffin reaction in the cytoplasmic granules.

No metastatic tumors were seen in the adrenals.

PITUITARY TUMORS - The problem of diagnosis of adenomas of the pituitary was discussed earlier. It has been decided to classify the hyperplasias collectively with adenomas. There were 4.8% of the males with the lesion and 1.8% of the females. The nature of these hyperplasia-adenomatous manifestations were described under lesions of the pituitary. It will not be repeated here. Histologic studies are now being conducted to determine the cell types.

Chromophobe adenomas of the pituitary in aging rodents is a troublesome diagnostic problem. It is not that the tumor is in itself unique, but that it is impossible to determine whether or not it is really an hyperplasia frequently observed in aging rodents. No further discussion will be made other than to point out that 1.6% of the males displayed lesion and 0.9% of the females. Ordinarily, one would expect a greater frequency in the aged females than the males.

PULMONARY ADENOMAS - These tumors were much less frequent than other rodents, most particularly the mouse. Only 1.7% were seen in males and 0.8 % in females. Of the five tumors this represents, four were clearly of the alveologenic type and one might be considered adenomatosis by some. If so classified, it would reduce the rate of occurrence in the male to 1.3%.

No metastatic tumors were observed.

OTHER TUMORS - The benign adenomas of the urinary bladder were of the papillary type. The transitional cell tumor was obviously malignant and probably was of papillary origin.

The adenoma of the pancreas was a large connective tissue encapsulated autonomous growth of the exocrine pancreas. Such a tumor is rare in man, but is seen occasionally in rats and mice.

The miscellaneous sarcomas were all fibromas or fibrosarcomas of

the skin with one exception. That was an undifferentiated tumor of the base of the heart. The carotid body tumor was also associated with the vessels at the base of the heart.

Testicular tumors of all types were not common. Ovarian tumors of all types were seen in 13.2% of the females. This is somewhat less than expected on the basis of experience with other rodents.

Prostatic adenomas combined with seminal vesicle adenomas were seen in 3.7% of the males. This is probably an underestimate since only tissues showing gross anomalies were chosen for microscopic studies.

Other tumors were encountered infrequently and will not be discussed.

Table 1

Comparison of occurrence of
CHRONIC INTERSTITIAL MYOCARDITIS
 among male mastomys with different caging patterns

Animals	Gamma Cage	Mouse Cage	B-20 Cage	B-35 Cage	Rat Cage	B-60 Cage
	N %	N %	N %	N %	N %	N %
♂	18 <u>5.6</u>	—	—	15 <u>37</u>	—	20 <u>20</u>
2 ♂ ♂	—	22 <u>15</u>	35 <u>11</u>	—	—	—
3 ♂ ♂	—	25 <u>24</u>	—	—	25 <u>8.0</u>	13 <u>23</u>
6 ♂ ♂	—	15 <u>6.6</u>	—	—	—	—
(♂♀)♂	—	13 <u>15</u>	27 <u>15</u>	—	11 <u>9.1</u>	—
ALL MALES CAGED WITH SAME SEX WITHOUT RESPECT TO TYPE OF CAGE				199 <u>15</u>		
ALL MALES CAGED WITH FEMALES WITHOUT RESPECT TO TYPE OF CAGE				40 <u>15</u>		
ALL MALES AND ALL CAGING AND ALL TYPES OF CAGES				239 <u>15</u>		

Table 2

Comparison of occurrence of CHRONIC INTERSTITIAL MYOCARDITIS
in mastomys between sexes with different and similar caging patterns

		♂♂		♀♀	
		N	%	N	%
Animals	Cage				
(♂ ♀)	Mouse	13	<u>15</u>	11	<u>27</u>
2	Mouse	22	<u>15</u>	29	<u>21</u>
6	Mouse	15	<u>6.6</u>	19	<u>16</u>
(♂ ♀)	B-20	27	<u>15</u>	23	<u>26</u>
2	B-20	35	<u>11</u>	47	<u>26</u>
All		112	<u>13</u>	129	<u>24</u>

Table 3

Comparison of occurrence and severity of KIDNEY DISEASE
in male mastomys with different caging patterns; chronic
interstitial nephritis - A and glomerulosclerosis - B.

Gamma Cage A B N %(sev)%(sev)		Mouse Cage A B N %(sev)%(sev)		B-20 Cage A B N %(sev)%(sev)		B-35 Cage A B N %(sev)%(sev)		Rat Cage A B N %(sev)%(sev)		B-60 Cage A B N %(sev)%(sev)	
♂	19 68(1.8)68(1.6)	—	—	—	—	17 100(2.2)94(2.0)	—	—	—	20 95(2.5)100(1.9)	—
2♂♂	—	23 91(1.0)78(1.4)	37 78(1.1)92(1.1)	—	—	—	—	—	—	—	—
3♂♂	—	27 93(2.0)93(1.9)	—	—	—	—	—	25 80(2.4)64(2.0)	12 100(1.8)100(1.6)	—	—
6♂♂	—	15 80(1.3)73(1.1)	—	—	—	—	—	14 86(2.1)100(1.8)	—	—	—
(♂ ♀) ♂	—	11 82(2.1)64(2.1)	28 86(2.2)79(1.8)	—	—	—	—	—	—	—	—
ALL	19 68(1.8)68(1.6)	76 87(1.6)77(1.6)	65 82(1.7)86(1.5)	17 100(2.2)94(2.0)	39 83(2.3)82(1.9)	32 97(2.2)100(1.8)					
ALL MALES CAGED WITH SAME SEX WITHOUT RESPECT TO TYPE OF CAGE			N 209	A%(severity) 87 (1.8)			B%(severity) 86 (1.6)				
ALL MALES CAGED WITH FEMALE WITHOUT RESPECT TO TYPE OF CAGE			39	84 (2.2)			72 (2.0)				
ALL MALES AND ALL CAGING AND ALL TYPES OF CAGES			248	86 (1.9)			84 (1.7)				

Table 4

Comparison of occurrence and severity of KIDNEY DISEASE
in mastomys between and among sexes with different and similar caging
patterns; chronic interstitial nephritis - A and glomerulosclerosis - B.

Animals	Cage	♂♂				♀♀			
		N	A%(severity)	B%(severity)		N	A%(severity)	B%(severity)	
(♂ ♀)	mouse	11	<u>82</u> (2.1)	<u>64</u> (2.1)		11	<u>73</u> (1.8)	<u>36</u> (1.0)	
2	mouse	23	<u>91</u> (1.0)	<u>78</u> (1.4)		25	<u>52</u> (1.8)	<u>40</u> (1.8)	
6	mouse	15	<u>80</u> (1.3)	<u>73</u> (1.1)		22	<u>59</u> (1.6)	<u>36</u> (1.7)	
(♂ ♀)	B-20	28	<u>86</u> (2.2)	<u>79</u> (1.8)		27	<u>78</u> (1.6)	<u>70</u> (1.7)	
2	B-20	37	<u>78</u> (1.1)	<u>92</u> (1.1)		53	<u>53</u> (1.3)	<u>40</u> (1.3)	
ALL		114	83 (1.5)	<u>77</u> (1.5)		138	<u>63</u> (1.6)	<u>44</u> (1.5)	

Table 5
Comparison of occurrence and severity of
THYROIDITIS
among male mastomys with different caging patterns

Animals	Gamma cage	Mouse cage	B-20 cage	B-35 cage	Rat cage	B-60 cage
	N % severity	N % severity	N % severity	N % severity	N % severity	N % severity
♂	14 78 2.9	—	—	15 73 2.6	—	19 79 2.9
2 ♂♂	—	20 80 2.4	26 81 2.2	—	—	—
3 ♂♂	—	21 81 2.0	—	—	21 81 2.2	13 69 2.6
6 ♂♂	—	14 71 2.0	—	—	14 64 3.1	—
(♂ ♀) ♂	—	12 83 3.0	24 66 2.3	—	—	—
ALL MALES CAGED WITH SAME SEX WITHOUT RESPECT TO TYPE OF CAGE				177 78 2.5		
ALL MALES CAGED WITH FEMALES WITHOUT RESPECT TO TYPE OF CAGE				36 72 2.7		
ALL MALES AND ALL CAGING AND ALL TYPES OF CAGES				213 77 2.4		

Table 6
Comparison of occurrence and severity of
THYROIDITIS
in mastomys between and among sexes with
different and similar caging patterns

		♂♂		♀♀		
Animals	Cage	N % severity		N % severity		
(♂ ♀)	Mouse	12 <u>83</u> 3.0		8 <u>40</u> 3.3		
2	Mouse	20 <u>85</u> 2.4		25 <u>96</u> 2.7		
6	Mouse	14 <u>71</u> 2.0		19 <u>94</u> 3.4		
(♂ ♀)	B-20	24 <u>66</u> 2.3		24 <u>69</u> 3.4		
2	B-20	26 <u>81</u> 2.2		45 <u>87</u> 3.2		
ALL	—	96 77 2.4		119 91 3.2		

Comparison of occurrence of ADRENAL change
in male mastomys with different caging patterns;
cortical hypertrophy - A, cortical adenoma - B.

cortical hypertrophy - A, cortical adenoma - B.

Animals	Gamma Cage		Mouse Cage		B-20 Cage		B-35 Cage		Rat Cage		B-60 Cage							
	A	B	A	B	A	B	A	B	A	B	A	B						
	N	%	N	%	N	%	N	%	N	%	N	%						
♂	17	100	5.9	—	—	18	<u>100</u>	0	—	—	10	<u>100</u>	10.0					
2 ♂♂	—	—	21	<u>100</u>	9.0	34	88	2.9	—	—	—	—	—					
3 ♂♂	—	—	24	<u>79</u>	8.3	—	—	—	24	<u>100</u>	33	11	<u>82</u>	0				
6 ♂♂	—	—	15	<u>100</u>	6.7	—	—	—	14	<u>79</u>	0	—	—					
(♂ ♀ ♂)	—	—	11	<u>100</u>	0	28	<u>61</u>	3.6	—	—	—	—	—					
ALL	17	<u>100</u>	5.9	71	<u>95</u>	6.0	62	<u>75</u>	3.3	18	<u>100</u>	0	38	<u>90</u>	17	31	<u>91</u>	5.0
ALL MALES CAGED WITH SAME SEX WITHOUT RESPECT TO TYPE OF CAGE					198 <u>93</u> 7.6													
ALL MALES CAGED WITH FEMALE WITHOUT RESPECT TO TYPE OF CAGE					36 <u>81</u> 2.7													
ALL MALES AND ALL CAGING AND ALL TYPES OF CAGES					234 <u>91</u> 6.6													

Table 8

Comparison of occurrence of ADRENAL change in mastomys
between and among sexes with different and similar caging patterns;
cortical degeneration -A for females, cortical hypertrophy-A for
males and cortical adenoma-B for both sexes.

Animals	Cage	♂ ♂			♀ ♀		
		N	A%	B%	N	A%	B%
(♂ ♀)	Mouse	11	<u>100</u>	0	11	<u>100</u>	9.1
2	Mouse	21	<u>100</u>	9.0	21	<u>52</u>	4.8
6	Mouse	15	<u>100</u>	6.7	17	<u>47</u>	0
(♂ ♀)	B-20	28	<u>61</u>	3.6	25	<u>68</u>	0
2	B-20	34	<u>88</u>	2.9	50	<u>98</u>	0
ALL	—	109	<u>90</u>	4.4	124	<u>73</u>	2.8

Table 2

Frequency of tumors by sexes, pooled
without respect to type of caging

TYPE	♂ ♂			♀ ♀		
	No. Tumors	No. Tissues	%	No. Tumors	No. Tissues	%
Thymoma	24	269	8.9	17	147	12
Lymphosarcoma	9	238	3.8	5	136	3.7
Hepatoma	23	218	11	19	128	15
Vascular tumor liver	1	218	0.5	2	128	1.6
Bile duct tumor	0	218	0	1	128	0.8
Stomach, adenoma	48	249	19	21	136	15
Stomach, carcinoid	4	249	1.6	1	136	0.7
Stomach, squamous cell	5	247	2.0	9	132	6.8
Adrenal, cortical adenoma	19	243	7.8	2	129	1.6
Pheochromocytoma	2	243	0.8	1	129	0.8
Pituitary adenoma	9	190	4.8	2	113	1.8
Chromophobe adenoma	3	190	1.6	1	113	0.9
Pulmonary adenoma	4	234	1.7	1	130	0.8
Urinary bladder, adenoma	1	269	0.4	1	147	0.7
Transition cell tumor, bladder	0	269	0	1	147	0.7
Pancreas, adenoma	0	269	0	1	147	0.7
Carotid body tumor	1	269	0.0	0	147	0
Adenoma, large intestine	1	269	0.4	0	147	0
Sarcoma, various	5	269	1.9	0	147	0
Seminoma, testes	1	244	0.4	-	-	-
Sertoli Cell tumor	1	244	0.4	-	-	-
Leydig Cell tumor	1	244	0.4	-	-	-
Spermatocele	1	244	0.4	-	-	-
Seminal Vesicle, adenoma	7	269	2.6	-	-	-
Prostate, adenoma	3	269	1.1	-	-	-
Granulosa cell tumor	-	-	-	13	125	10
Luteoma	-	-	-	3	125	2.4
Arrhenoblastoma	-	-	-	1	125	0.8
Leiomyoma, uterus	-	-	-	5	147	3.4
Ovarian atrophy	-	-	-	61	125	49
Ovarian Cyst	-	-	-	13	125	10

The discussion at this time will be brief, and limited to a summary of some observation. Quite possibly there will be modified by later studies, as were noted in the report.

Some observations,

1. The ubiquitous chronic cardiac valvulites; it was so common that caging experiences could not have been a factor.
2. The non-specific chronic interstitial myocarditis that was observed in 24% of the females and 15% of the males. It was not related to the caging experience.

3. The relatively moderate chronic interstitial nephritis which was seen in 86% of the males and 63% of the females. Glomerulosclerosis was observed in 77% of the males and 44% of the females. It, too, was a relatively moderate manifestation. The caging experience did not appear to be an influence.

4. The hyperkeratosis of the forestomach was seen in almost all animals. It was somewhat more severe in females. It could not be associated with the caging experience.
5. About 21% of the males and 16% of the females had either an adenoma or carcinoid of the fundic glandular stomach. In this report, they are reported separately, although it may well be that they are all a carcinoid tumor. No evidence of a serotorin effect was noted in the heart. No evidence of a caging effect could be seen.

6. A thyroiditis, almost always of the struma lymphomatosa type (Hashimoto's disease), was observed in 91% of the thyroids of females examined and in 77% of the males. In the females it was more severe than in the males.

7. In over 90% of the males there was a marked cortical hypertrophy, quite possibly of the reticular zone. A few cases of a cortical degeneration were seen. They were far less common than in the females. In that sex, 73% had either a hydropic degeneration or "brown-degeneration", of the cortex, sometimes with a collar of unique cells in the juxta-medullary region. No caging related trend could be detected.
8. The pituitary in 4.8% of the males and 1.8% of the females displayed a hyperplasia-adenomatoid lesion that was easily seen at autopsy. The exact cell type involved has not been determined.
9. Thymomas were seen in about 9% of the males and 12% of the females. It is likely that this is not a significant biological difference. It was not treatment related. It is an unusual entity in the mastomys in that it resembles a lymphoma with clear areas of histiocytes giving a "starry-sky" appearance.
10. Lymphosarcomas were equally common in females and males, ie., 3.7 and 3.8% respectively. These reticular tumors were much less common than in most other rodents. They too were unique in that the primary lesion arose among the cords of the red pulp and never involved the malpighian corpuscle, even though distant metastases were severe. No caging experience dependency was noted.
11. Pulmonary tumors were uncommon. Only 1.7% were seen in males and 0.7% in the females. Of the 5 tumors this represents, 4 were alveologenic and 1 was likely an adenomatosis.
12. No amyloidosis was seen.
13. Mammary tumors were rarely seen so there could be no correlation with adrenal cortical adenomas such as is sometimes seen in mice.