Spontaneous diseases in a closed colony of *Praomys (Mastomys) natalensis*

K. C. SNELL [1] & H. L. STEWART [2]

In comparison with other rodents, the mastomys is unique as regards the patterns of neoplastic and non-neoplastic diseases that it develops, some of which may constitute suitable animal models for corresponding diseases of man. Among the spontaneous diseases commonly encountered in necropsies of 600 mastomys maintained in a closed colony were: (1) degenerative joint disease of diarthroses and interventricular disks, which develops regularly in the second year of life; (2) renal disease, a type of immune-complex glomerulonephritis, affecting approximately 80% of mastomys in the age bracket 18–36 months; (3) thymomas and thymic hyperplasia affecting 30% of mastomys by the time they are 2 years old or older; (4) a combination of thymoma and polymyositis in a mastomys showing serum-globulin reactivity, presumably auto-antibody against striated muscle; (5) beginning before the age of 1 year, replacement of the normal cell population of the lymphoid tissues by plasma cells, and intense plasma cell infiltration at many other organ and tissue sites; (6) haematopoietic neoplasms, without leukaemic blood, in 10% of mastomys; and (7) histamine-producing argyrophilic carcinoid tumours of the glandular stomach in approximately 60% of old male and 30% of old female mastomys. Additionally, other neoplasms not infrequently encountered in mastomys rarely occur in other rodent species; conversely some neoplasms commonly found in other rodents, including especially tumours of the lung and mammary gland and leukaemia, are rare or absent in mastomys.

The purpose of this presentation is to describe briefly some of the pathological processes that we have observed in our colony of mastomys [*Praomys (Mastomys) natalensis*]. Breeding stock was obtained from the Walter Reed Army Medical Center, Washington, DC on two occasions, in 1954 and in 1959 (1). The Walter Reed stock, we understand, was built up by the late Dr Joseph E. Smadel from animals obtained from the South African Institute for Medical Research, Johannesburg. We originally obtained these animals for the purpose of studying the neoplasm that the late Dr A. G. Oettlé had diagnosed as adenocarcinoma of the glandular stomach and that we subsequently demonstrated to be an argyrophilic carcinoid (2).

Our untreated mastomys were kept in animal rooms that housed other rodents and were given Purina Laboratory Chow and water. Some were segregated by sex and others were allowed to breed. They lived their full lifespan unless they became ill or developed a palpable tumour, at which time they were killed and necropsied. A few died accidentally. An average of 60 pieces of tissue were taken from each animal for subsequent histologic study. The necropsies now number approximately 600.

Mastomys differ in their disease pattern from other rodents in the development of spontaneous neoplastic and non-neoplastic diseases far in excess in number per animal and variety and much less rare than those we commonly encounter in mice and rats. Some of these diseases are unique to mastomys and others have been seen only rarely in other rodents. The converse of this is that certain diseases common to other rodents rarely or never occur in mastomys. Certain of the diseases of mastomys may be of an immunological nature and caused by a virus or viruses. Some may constitute suitable animal models for corresponding human diseases.

NEOPLASTIC DISEASES

Glandular stomach

Argyrophilic carcinoid tumours of the glandular stomach develop in approximately two-thirds of old

[1] Medical Officer, Laboratory of Pathology, National Cancer Institute, Bethesda, MD 20014, USA.

[2] Consultant, Registry of Experimental Cancers, National Cancer Institute, Bethesda, MD 20014, USA.

male and one-third of old female mastomys (2). The Sevier-Munger and Azzopardi silver methods applied to formalin-fixed tissues reveal the diagnostic coal-black granules in the cytoplasm of the carcinoid cells. The neoplasm originates as proliferations of argyrophil cells within the gastric glandular mucosa in the body or fundus. The foci enlarge, coalesce, and infiltrate the muscularis mucosa and submucosa. The submucosal deposit comes to constitute the main mass of the neoplasm. There is early invasion of lymphatic and blood vessels followed by penetration through the entire wall of the stomach onto the peritoneum and metastasis to regional lymph nodes, pancreas, liver, and lungs. Some carcinoids have been successfully transplanted to the thigh muscles of other mastomys and have been carried for several generations. They retain the identical histologic pattern and reaction to silver salts found in the primary tumours. Many host animals in which the transplant has attained a diameter of 1.0 cm or more develop multiple ulcers of the stomach, duodenum, and upper jejunum. The animals die from intestinal haemorrhage, perforating ulcers, or peritonitis.

Chemical examination of such transplantable argyrophilic gastric carcinoids revealed that they contained appreciable amounts of histamine, and that the dialysed microsome-free supernatant of the tumour tissue produced significant amounts of histamine in the presence of L-histidine and pyridoxal phosphate (3). These findings evidently account for hypersecretion of gastric acid and the alimentary tract ulcers. The transplanted carcinoids contain appreciable activities of specific histidine decarboxylase and aromatic L-amino acid decarboxylase, which may relate to the inherent properties of the cell of origin, the histamine-containing argyrophilic cell, which in normal mastomys is found distributed in the gastric mucosa (4).

From their ultrastructural observations, Capella et al. (5) attributed the histamine-dependent hyperchlorhydria of tumour-bearing animals to the function of the carcinoid cells, which resemble the enterochromaffin-like cells and round granule cells of the acid-secreting portion of the glandular stomach. We have not seen the characteristic right-sided cardiac fibrosis that occurs in some patients with massive carcinoid deposits in the liver because the carcinoids of mastomys do not elaborate 5-hydroxyindoles.

Liver

Hepatomas develop in about one-third of untreated animals over the age of 18 months, and the number and size increase with age. The spontaneous hepatomas have many of the morphological features common to the hepatoma of the mouse. Hepatomas have not metastasized in our mastomys. However, a colleague, Dr C. F. Hollander of the Institute for Experimental Gerontology, Rijswijk, The Netherlands, has shown us sections from a dozen or so mastomys from his colony in which the hepatic tumour did metastasize, chiefly to the lung. We have induced hepatic carcinomas in large numbers in our mastomys, 16 months of age or younger, by feeding *N,N'*-2,7-fluorenylenebisacetamide (2,7-FAA).

Thymus

About one-third of our mastomys develop thymic hyperplasia or thymoma by the time they are 2 years old, and many more when they are older (6). The male-female ratio is 2 : 1. The thymomas may attain a width of 3 cm, compromising the space in the thoracic cavity. The histologic pattern of the thymoma corresponds closely to that of man in whom the normal relationship of cortex to medulla is effaced and the different thymic cellular and structural components appear in abnormal relationship to each other. In the hyperplastic thymus, the pattern of cortical and medullary markings is reproduced, although lacking somewhat the regularity seen in the non-involuted thymus of young animals. Thymomas and the hyperplastic lesions arise from the involuted thymus. In some mastomys, the remnant of involuted thymus may still be seen attached to a globular nodule of hyperplastic thymic tissue. This indicates to us that the usual process of thymic involution proceeds uninterruptedly until late in life when something happens that calls forth a new formation of thymic tissue. The reasons for this phenomenon are mysterious. One might suspect that this thymic overgrowth is in response to a slowly developing cellular immune defectiveness that requires immune surveillance. Perhaps it is more than coincidental that the age distribution of the animals with thymic hyperplasia and thymoma and with chronic glomerulonephritis closely correspond.

Haematopoietic tissues

Interrelated neoplastic, reactive, and inflammatory diseases of the haematopoietic tissues are found in about 10% of our necropsy series. We have classified about a quarter of the cases as either nodular-follicular lymphosarcoma or diffuse lymphosarcoma. Slightly more than one-half of the cases are reticulum cell sarcomas, well-differentiated, anaplastic, or

mixtures of well-differentiated and anaplastic reticulum cell sarcoma with lymphosarcoma. There is one example each of solitary plasma-cell myeloma of the cervical spine and " pseudolymphoma ". The remaining cases comprise atypical reticulum cell hyperplasia and inflammation. None of the animals has had leukaemic blood. No haematopoietic neoplasm originated in the thymus. The plasma cell myeloma readily transplanted to other mastomys, but attempts to transplant 3 other neoplasms were unsuccessful. All the reticulum cell sarcomas were classifiable as the Type B neoplasm of Dunn (7). We have speculated whether there is, in mastomys, a relationship between an autoimmune state and the occurrence of the reticulum cell sarcomas, hyperplastic lesions, and the inflammatory processes so often associated with an abundance of plasma cells, some of which contain intracytoplasmic and intranuclear PAS-positive inclusions.

Ovary

Proliferative foci of granulosa cells and genuine granulosa cell neoplasms are commonly encountered. Some of the neoplasms metastasize. Most of them must be non-functional because mammary gland hyperplasia and carcinoma (8) are exceedingly rare lesions. Despite the rarity of mammary carcinoma in untreated animals, highly malignant carcinomas could readily be induced, when 2,7-FAA was fed to females.

Miscellaneous neoplasms

Other common neoplasms are leiomyomas of the uterus and adenomas of the adrenal gland cortex, pituitary gland, pancreatic parenchyma and islets and parotid gland; equally common perhaps are adenomatous polyps of the uterus and at the ileocecal junction, none of which metastasizes. Most common of all are haemangiomas of many different sites. Neoplasms of mastomys that are rarely, and in one or two instances have never been, encountered in untreated mice or rats are chordoma, meningioma, synovial sarcoma, carcinoma of the nasopharyngeal tube, papilloma of the lacrimal sac, carcinoma of the extrahepatic bile duct, teratoma of the mediastinum, carcinoma of the female prostate, granular cell tumour of the uterine horn, seminoma of the testis, carcinoma of the rete testis, and carcinosarcoma of the seminal vesicles. Conversely, tumours that are common in mice but rare in mastomys are leukaemia, alveologenic tumours of the lung, osteosarcoma, and mammary gland tumours.

NON-NEOPLASTIC DISEASES

Degenerative joint disease

Severe degenerative joint disease of diarthroses and intervertebral disks develops regularly during the second year of life (9). Virtually all peripheral articulations, with the exception of the hips, shoulders, and sacroiliacs are affected, but the elbows and the knees most severely. In the diarthrodial joints, there is extensive erosion of articular cartilage and sclerosis of epiphyseal bone, and in some animals proliferative synovitis and periarticular mucoid cystic change are prominent. Fibrillation of the costal joints, both at the sternal and the vertebral ends of the ribs is frequent.The cartilage is disrupted, leaving round islands of necrotic chondrocytes within amorphous and hyaline material. The subchondral portions of the vertebral bodies become deformed in advance of the lesions; erosion and eburnation extend into the epiphyses and even penetrate them deeply. Marginal osteophyte formation of mild degree is frequently present on both the ventral and dorsal edges. Aseptic necrosis of the secondary centres of ossification of the vertebrae is a common finding.

Degeneration of intervertebral disks results in gross narrowing of the spaces between the vertebral bodies. Portions of degenerated disks protrude dorsally into the spinal canal in many segments of the spine. This usually elevates and occasionally disrupts the dura mater and exerts pressure leading to degeneration in different segments of the spinal cord and the cauda equina. Massive myelomalacia occasionally follows; more often, focal areas of demyelination, infiltration by Gitter cells, and clusters of cholesterol crystal clefts are present in the cauda equina. Clinically, after 2 years of age, most mastomys are disinclined to use the hind legs and about 10% become paraplegic.

Glomerulonephritis

Approximately 80% of mastomys of our colony develop one or more of 3 forms of glomerulonephritis: membranous, proliferative, and severe chronic (1).

The severe chronic form has been diagnosed in a few young animals, but is largely found in animals in the age bracket 18–36 months. Grossly, the kidneys may appear unremarkable, or the surface finely or coarsely granular and the tissue pale or grayish tan.

Histologically, all portions of the nephron and the interstitial tissue are involved, while the extraglomerular blood vessels remain normal. Within the tuft, however, the capillaries become thickened and the lumen reduced, and some may appear telangiectatic. Adhesions and crescents are often present, and many glomerular tufts contain inflammatory cells. Occasional glomeruli are obliterated. Tubular segments of the nephron show progressive alterations of hypertrophy, atrophy, and flattening of the lining cells, desquamation of epithelial cells, and casts. The interstitial tissue becomes thickened, hyperaemic, and infiltrated with lymphocytes, plasma cells, and granulocytes.

We think that we can trace transition stages and progression from early membranous glomerulonephritis to the proliferative form and from either or both of these lesions to the severe chronic form. With membranous glomerulonephritis, 10% or more of the glomeruli may be involved, while the tubules, interstitial tissue, and extraglomerular vascular system remain virtually intact. Later, nearly all the capillary tufts show hyaline thickening of the glomerular loops and basement membrane of Bowman's capsule, producing the wire-loop appearance. With the lesion of proliferative glomerulonephritis the glomeruli show, in addition to these changes, hypercellularity. In a few specimens, an occasional glomerulus shows an acute degenerative lesion characterized by intracapillary hyaline thrombi, narrowing sometimes to the point of occlusion of the capillaries, and swelling and thickening of their walls by fibrinoid. This resembles the glomeruli of patients with disseminated lupus erythematosus, which is thought to reflect an autoimmune disease or hypersensitivity mechanism.

Van Noord et al. (10) described the development of the glomerular alterations of mastomys as revealed by electron microscopy. The earliest alterations consist of diffuse thickening of the basement membrane of the peripheral capillary loops, loss of the three-layered structure, and the appearance of small nodules on the epithelial aspect of the membrane. Subsequently, swollen visceral epithelial cells with bizarrely formed nuclei appear, and the glomerular basement membrane shows diffuse thickening with subepithelial nodules. In many, the mesangial region is expanded, with a noteworthy increase of cellularity. Collagen fibrils are commonly observed in the mesangial matrix, as are lipofuscin bodies in the cytoplasm and inclusions in the nuclei of mesangial cells. Free cells and many microvilli originating from the visceral epithelial cells are commonly seen in Bowman's space. The capillaries occasionally contain polymorphonuclear leucocytes and aggregates of thrombocytes. Immunofluorescence studies using rabbit antimastomys immunoglobulins have initially shown fluorescence in the mesangial region. With aging, the fluorescence increases and a granular deposition of the globulins becomes evident along the peripheral capillary loops. This suggests that the renal disease that mastomys develop is a type of immune-complex glomerulonephritis (11–12).

Myasthenia gravis

Myositis and atrophy of skeletal muscle are present in approximately one-fifth of the animals with thymoma. Other lesions that seem to be associated are severe myocarditis and chronic inflammation, often with degeneration and atrophy of the extraorbital and intraorbital lacrimal, Harderian, and one or more of the salivary glands. In one 17-month-old female mastomys with the combination of thymoma, polymyositis and myocarditis, serum-globulin reactivity, presumably autoantibody against striated muscle, was found in high titre (13). The sera from thirteen mastomys, used as age- and sex-matched controls, all reacted to produce striational staining in low titre (up to 1 : 10), whereas sera from younger animals failed to react. There is a possibility that the myositis, myocarditis, inflammatory lesions of other sites, thymomas, and thymic hyperplasias of mastomys may have some relationship to myasthenia gravis of man believed by some to be associated with autoimmunity.

Ubiquity of the plasma cell

When mastomys are well under 1 year of age, plasma cells begin to populate the spleen, lymph nodes, and lymph nodules of the intestine, and thereafter they may account for a high proportion of the cells at these sites. Plasma cell and lymphocytic thyroiditis is exceedingly common, and it is by no means unusual to find collections of plasma cells in the salivary and orbital glands, in other viscera including the heart, and in the mesenteries. This suggests a relationship to the tissue changes associated with Sjögren's syndrome. We have applied the term " pseudolymphoma " to an unusual disease in one mastomys, in the sense that this term was used by Talal and associates (14) for tumour-like aggregates of lymphoid cells of dubious malignancy that they found in various organs of patients with

Sjögren's syndrome. The association of polymyositis and autoantibodies to striated muscle in mastomys with thymomas and the development of membranous glomerulonephritis suggestive of an immune-complex disease contributes to the possibility that the haematopoietic diseases also have an autoimmune basis. From studies in man and animals, including SJL/J and (NZB × CFW)F_1 mice (15–16), a body of information has developed that may shed light on the interrelationships between neoplasia and hypergammaglobulinaemia, dysproteinaemia, and autoimmune diseases.

Adrenal gland

A conspicuous lesion of all old female mastomys is brown degeneration.

RÉSUMÉ

MALADIES SPONTANÉES OBSERVÉES DANS UNE COLONIE FERMÉE DE *PRAOMYS (MASTOMYS) NATALENSIS*

Comparé à d'autres rongeurs, le mastomys se comporte de façon remarquable face aux maladies néoplasiques et non-néoplasiques qui se déclarent chez lui et dont certaines peuvent constituer un modèle animal de la maladie correspondante chez l'homme. Parmi les maladies spontanées que l'on a rencontrées couramment lors de l'autopsie de 600 mastomys maintenus en colonie fermée, figuraient notamment: 1) la maladie dégénérative des articulations (diarthroses et disques intervertébraux) au cours de la deuxième année de vie; 2) une néphropathie du type glomérulo-néphrite à immun-complexe, qui affecte environ 80% des mastomys âgés de 18 à 36 mois; 3) thymome et hyperplasie thymique affectant 30% des mastomys âgés de 2 ans et plus; 4) une combinaison de thymome et de polymyosite chez un mastomys qui présentait des globulines sériques agissant probablement comme auto-anticorps contre les muscles striés; 5) remplacement, avant l'âge d'un an, des cellules normales des tissus lymphoïdes par des plasmocytes, avec infiltration intense de plasmocytes dans de nombreux autres organes et tissus; 6) des néoplasmes hématopoïétiques, avec absence de sang leucémique chez 10% des mastomys; 7) des tumeurs carcinoïdes argyrophiliques de l'estomac glandulaire, produisant des histamines, chez environ 60% des vieux mâles et 30% des vieilles femelles de mastomys. D'autres néoplasmes que l'on rencontre parfois chez les mastomys sont rares chez d'autres espèces de rongeurs; l'inverse est vrai aussi: certains néoplasmes que l'on rencontre habituellement chez d'autres rongeurs (notamment tumeurs du poumon et de la glande mammaire, et leucémie) sont rares ou inexistants chez le mastomys.

REFERENCES

1. SNELL, K. C. & STEWART, H. L. Neoplastic and non-neoplastic renal disease in *Praomys* (*Mastomys*) *natalensis*. *J. nat. Cancer Inst.*, **39**: 95-117 (1967).
2. SNELL, K. C. & STEWART, H. L. Histology of primary and transplanted argyrophilic carcinoids of the glandular stomach of *Praomys* (*Mastomys*) *natalensis* and their physiologic effects on the host. *In:* Proceedings of the US-Japan Symposium on Experimental Carcinoma of the Glandular Stomach, Hakone, Japan, June 10-13, 1969 (Gann Monograph No. 8), Tokyo, Japanese Cancer Association, 1969, pp. 39-55.
3. HOSODA, S. ET AL. Histamine production by transplantable argyrophilic gastric carcinoid of *Praomys* (*Mastomys*) *natalensis*. *Science*, **170**: 454-455 (1970).
4. HOSODA, S. ET AL. Histidine decarboxylase in the transplantable argyrophilic gastric carcinoid of *Praomys* (*Mastomys*) *natalensis*. *Biochem. Pharmacol.*, **20**: 2671-2674 (1971).
5. CAPELLA, C. ET AL. Ultrastructure of endocrine cells and argyrophil carcinoids of the stomach of *Praomys* (*Mastomys*) *natalensis*. *J. nat. Cancer Inst.*, **50**: 1471-1485 (1973).
6. STEWART, H. L. & SNELL, K. C. Thymomas and thymic hyperplasia in *Praomys* (*Mastomys*) *natalensis*. Concomitant myositis, myocarditis and sialodacryoadenitis. *J. nat. Cancer Inst.* **40**: 1135-1146 (1968).
7. DUNN, T. B. & DERINGER, M. K. Reticulum cell neoplasm, Type B, or the " Hodgkins-like " lesion of the mouse. *J. nat. Cancer Inst.*, **40**: 771-821 (1968).
8. SNELL, K. C. & STEWART, H. L. Adenocarcinoma and proliferative hyperplasia of the prostate gland in female *Rattus* (*Mastomys*) *natalensis*. *J. nat. Cancer Inst.*, **35**: 7-14 (1965).
9. SOKOLOFF, L. ET AL. Degenerative joint disease in *Praomys* (*Mastomys*) *natalensis*. *Ann. rheum. Dis.*, **26**: 146-154 (1967).
10. VAN NOORD, M. J. ET AL. The development of ultrastructural glomerular alterations in *Praomys* (*Mastomys*) *natalensis*. *Lab. Invest.*, **26**: 364-375 (1972).

11. OLDSTONE, M. B. A. & DIXON, F. T. Immune complex disease in chronic viral infections. *J. exp. Med.*, **134**: 32s-40s (1971).
12. NOTKINS, A. L. Infectious virus-antibody complexes: interaction with anti-immunoglobulins, complement and rheumatoid factor. *J. exp. Med.*, **134**: 41s-51s (1971).
13. STRAUSS, A. J. L. ET AL. Spontaneous thymona, polymyositis, and serum autoantibodies to striated muscle in the rodent, subgenus *Praomys* (*Mastomys*) *natalensis*. Similarities to thymoma with myasthenia gravis in man. *Lancet*, **1**: 1126-1129 (1968).
14. TALAL, N. ET AL. Extrasalivary lymphoid abnormalities in Sjögren's syndrome (reticulum cell sarcoma, "pseudolymphoma," macroglobulinemia). *Amer. J. Med.*, **43**: 50-65 (1967).
15. MCINTIRE, K. R. & LAW, L. W. Abnormal serum immunoglobulins occurring with reticular neoplasms in an inbred strain of mouse. *J. nat. Cancer Inst.*, **39**: 1197-1211 (1967).
16. BARNES, R. D. ET AL. Auto-immune disease in (NZB × CFW)F_1 mice. *J. Pathol. Bact.*, **95**: 391-403 (1968).

DISCUSSION

EDDY: Has anyone attempted to isolate viruses from these *Mastomys*?

COETZEE: Dr Oettlé was intrigued by the differential occurrence of cancer in animals from the same original stock and we considered that food might be an important factor. The same type of cancer was found in another colony at the SAIMIR, namely, a pink-eyed agouti colony which I inbred from a red-eyed normal colour female (wild caught, Pretoria).

STEWART: The frequency of the gastric carcinoid cancer varies considerably in different colonies. In the colonies in the Netherlands and in Japan, the frequency of gastric carcinoid is low.

WALKER: Has this animal species been used for any infectious disease or immunology experiment? Is anything known about the immunological response to an infectious disease?

STEWART: Not to my knowledge.