Multiple malignant meningiomas in a young cat

R G Lobetti[a], J W Nesbit[b] and D B Miller[a]

ABSTRACT

A 2-year-old cat was presented with generalised muscle tremors and progressive fore- and hindlimb ataxia, 5 months after the initiation of chemotherapy for thymic lymphoma. The lymphoma was treated with combination chemotherapy (cyclophosphamide, vincristine and prednisolone), which resulted in remission. The neurological signs progressed to paralysis and the cat subsequently died. On autopsy, multiple meningiomas were diagnosed, which is an unusual finding. It is possible that the lymphoma chemotherapy resulted in the development of the multiple meningiomas as secondary malignancies.

Key words: cat, chemotherapy, feline, lymphoma, meningioma, secondary malignancies.

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INTRODUCTION

Lymphoma is a common tumour in the cat and is responsive to chemotherapy[18]. Besides the commonly encountered side-effects associated with chemotherapy, the possibility of induction of secondary neoplasms exists. Although this phenomenon is well described in man[5,7,8,10,13], the induction of secondary malignancies in animals receiving chemotherapy has been alluded to[2,16], but never conclusively identified or well documented. This article reports development of multiple meningiomas following chemotherapy for a thymic lymphoma in a cat.

CASE HISTORY

A 2-year-old, castrated male oriental short-hair cat was initially presented with dyspnoea, left forelimb lameness and left-sided Horner's syndrome. The latter had been present since the cat was severely injured in a car accident approximately 1 year earlier. Clinical evaluation revealed inspiratory dyspnoea, tachycardia and confirmation of Horner's syndrome. Neurological examination revealed conscious proprioceptive deficit and reflex reduction in the left forelimb. Further neurological assessment was not performed on account of the history of neurological deficits following a traumatic injury. Complete blood count (Table 1), serum biochemistry profile, FIV and FeLV titres, and urine and faecal analyses were within normal limits. Survey thoracic radiographs showed a soft tissue density in the cranial thorax and thickening of the cranial mediastinum resulting in caudal displacement of the cranial lung lobes. Survey radiographs of the cervical spine, abdomen and left forelimb, as well as abdominal ultrasonography, revealed no significant abnormalities. On fine-needle aspirate cytology of the cranial thoracic mass, thymic lymphoma of intermediate grade was diagnosed. Owing to the anatomical location of the mass, a biopsy was not performed.

The cat was given chemotherapy utilising cyclophosphamide, vincristine and prednisolone (COP protocol[2,16,18]). The treatment regimen consists of induction therapy as follows: oral cyclophosphamide (Endoxan, Noristan Laboratories), 300 mg/m^2 at 3-weekly intervals; intravenous vincristine (Pericristine, Lennon Pharmaceuticals), 0.75 mg/m^2 weekly for 4 weeks and then at 3-weekly intervals; and oral prednisolone (Centaur Laboratories), 20 mg/m^2 once a day for 3 weeks, then every other day, to be given for 1 year, followed by maintenance therapy[2,16,18].

At the start of chemotherapy, a dose of 50 mg/m^2 of cyclophosphamide was inadvertently administered to the cat daily for 4 days instead of at the recommended dose of 300 mg/m^2 at 3-weekly intervals. This resulted in a sustained leukopaenia for a period of 13 days (Table 1). Over the following 3 months the chemotherapeutic regimen was well tolerated by the cat. The only side-effects were hair loss and transient nausea and diarrhoea. Vincristine and cyclophosphamide was not given on one occasion (Day 18) because of leukopaenia. Chemotherapy resulted in complete resolution of the dyspnoea and, according to the owner, the cat's appetite, behaviour and habitus normalised. The left forelimb lameness, however, never resolved.

Regular 3-weekly assessments of the cat showed no obvious abnormalities. Five months after the commencement of chemotherapy the cat suddenly developed anorexia, listlessness, and generalised muscle tremors. At this stage the cat was still on the induction phase of the chemotherapy. Lameness of the left forelimb and Horner's syndrome were still present. A complete blood count showed a mild leukopaenia (Table 1, Day 146) that was attributed to the chemotherapy. Serum biochemical profile revealed a mild elevation in alanine transaminase activity (52, normal < 23 U/ℓ). Urine analysis showed hypersthenuria (SG 1.060), and mild proteinuria and bilirubinuria; the last 2 findings were not considered significant, as the urine was very concentrated. Thoracic radiographs and abdominal ultrasonography showed no abnormalities. Fine-needle aspirate cytology of the liver revealed moderate fatty degeneration of the hepatocytes and bile stasis. These changes were attributed either to hepatic lipidosis, as the cat was anorexic, or the effects of the chemotherapy, or both. Over the next 2 days the cat developed progressive fore- and hindlimb ataxia and paresis. Paralysis and a vertical nystagmus developed shortly before the cat died.

Gross abnormalities on autopsy were limited to the brain and spinal cord. Although not as apparent in the fresh specimens, close inspection of the formalin-fixed central nervous system revealed the presence of numerous discrete, slightly translucent greyish-tan firm lobulated tissue masses of variable size scattered randomly over the surface of the brain and spinal cord. The lesions

[a]Department of Medicine, Faculty of Veterinary Science, University of Pretoria, Private Bag X04, Onderstepoort, 0110 South Africa.

[b]Department of Pathology, Faculty of Veterinary Science, University of Pretoria.

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Table 1: **Haematological data.**

	DAY 1	5	7	14	18	39	60	81	102	130	146	Normal values
Red cell count	8.68	6.57	6.23	6.53	5.93	8.68	8.35	8.41	7.48	7.94	8.08	$5.5–8.5 \times 10^{12}/\ell$
Haematocrit	43.9	34.1	32.1	34.7	31.8	44	41.9	41.4	37.6	40.1	40.2	24–45 %
White cell count	13.5	3.5	3.6	4.7	2.9	8.2	6.2	7.5	8.4	7.5	5.6	$7–20.5 \times 10^{9}/\ell$
Neutrophils	9.45	1.54	1.76	2.26	1.62	6.89	3.53	5.92	7.14	5.55	4.48	$2.5–12.5 \times 10^{9}/\ell$
Band cells	0	0.07	0.25	0.47	0.75	0.16	1.98	0.08	0	0.23	0	$0–0.3 \times 10^{9}/\ell$
Lymphocytes	2.97	1.68	0.9	1.6	0.17	0.74	0.25	0.9	0.42	0.9	0.67	$1.5–7 \times 10^{9}/\ell$
Monocytes	0.41	0.04	0.54	0.24	0.17	0.08	0.06	0	0.17	0.08	0.06	$0–0.8 \times 10^{9}/\ell$
Eosinophils	0.54	0.14	0.14	0.05	0.06	0.33	0.37	0.23	0.42	0.75	0.28	$0–1.5 \times 10^{9}/\ell$
Basophils	0.14	0.04	0	0.09	0.12	0	0	0.38	0.25	0	0.11	Rare
Platelets	244	89	123	259	175	343	221	219	180	283	116	$300–600 \times 10^{9}/\ell$

extended from the parietal lobes of the cerebral hemispheres cranially to the lumbar spinal cord caudally. The cerebellum was predominantly affected. On section the masses varied in size from less than 1 mm up to 6 mm in diameter. The larger masses occurred only in the brain and compressed the underlying parenchyma. Histological examination confirmed the presence of multiple masses of neoplastic tissue involving the meninges and underlying neural tissue in the brain; neoplastic involvement was restricted to the meninges in the spinal cord. The masses varied in size and comprised sheets of neoplastic cells arranged in a lobular pattern (Fig. 1). The lobules were separated by well vascularised fibrous connective tissue stroma. Growth characteristics were both expansile, resulting in compression (Fig. 2), and invasive, resulting in focal replacement of the subjacent neural tissue (Fig. 3). The reaction to the compressive and infiltrative processes was minimal and characterised by multifocal linear demyelination and astrocytosis of the surrounding neural tissue. The central regions of the lobules of the larger neoplasms were necrotic. The majority of the neoplastic cells were large, slightly pleomorphic with indistinct cell margins, abundant finely granular cytoplasm and central round to oval nuclei containing 1 or 2 inconspicuous nucleoli and dispersed chromatin (Fig. 4). The neoplasm was also constituted of large cells with a single large polymorphic nucleus (Fig. 4). Up to 5 mitoses per high-power field were present; atypical mitoses were also present. The neoplasms were classified as malignant meningotheliomatous meningiomas based on the histological criteria. The thymic remnant showed no overt abnormality on histological examination.

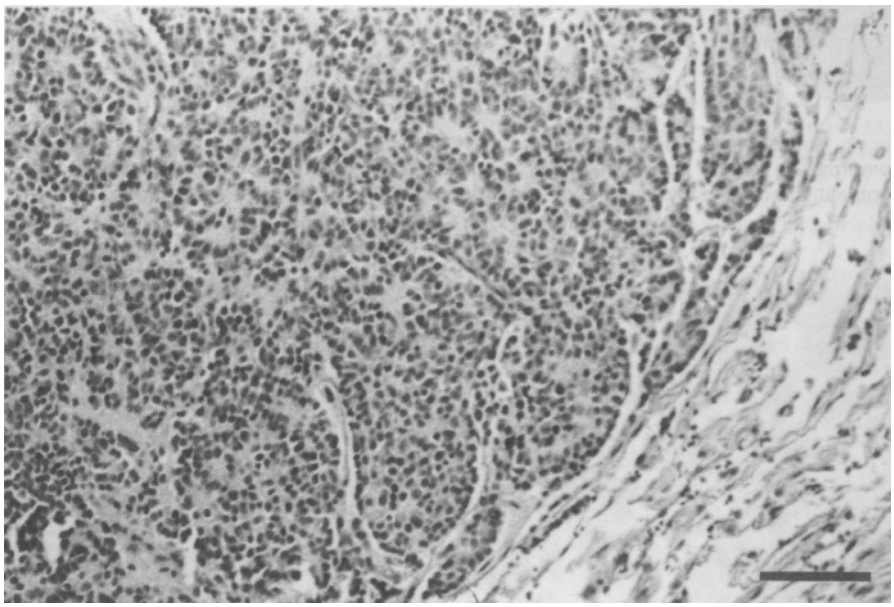

Fig. 1: **Meningotheliomatous meningioma. Sheets of neoplastic cells arranged in a lobular pattern.** Bar = 50 μm. Haematoxylin and eosin.

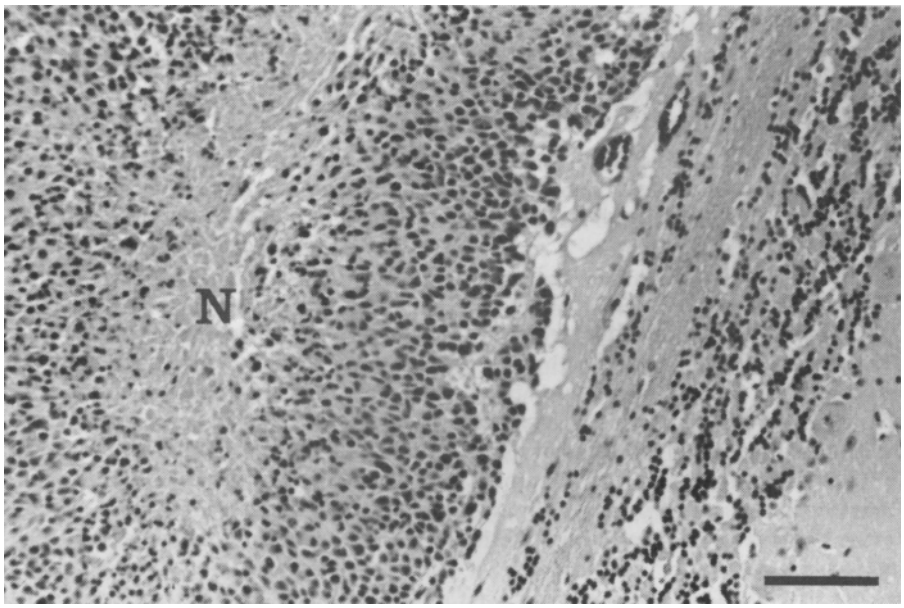

Fig. 2: **Meningotheliomatous meningioma. Cerebellum. Neoplasm with central necrosis** (N) **on the left compressing the adjacent molecular layer with consequent demyelination and astrocytosis.** Bar = 50 μm. Haematoxylin and eosin.

DISCUSSION

Meningiomas are tumours arising from mesodermal elements of the meninges,

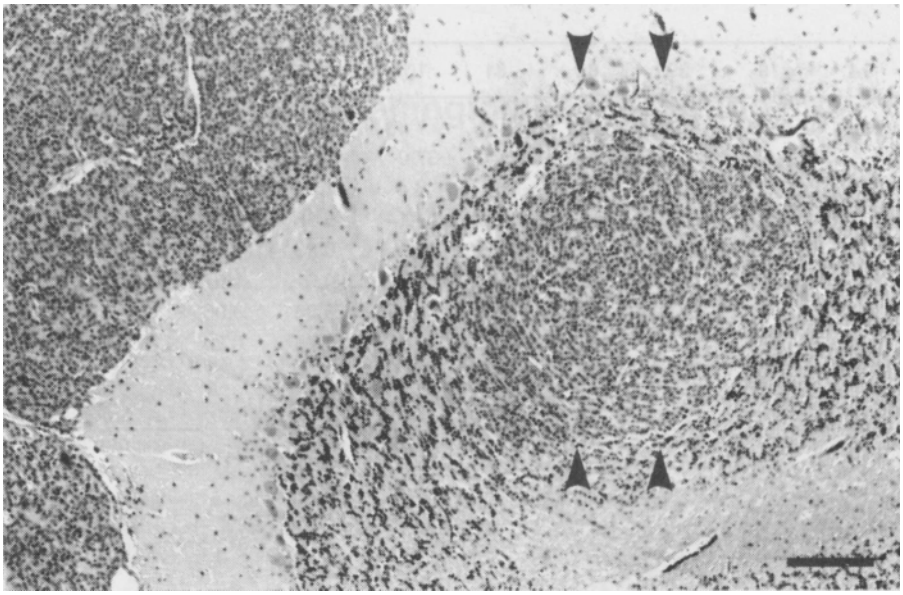

Fig. 3: **Meningotheliomatous meningioma. Cerebellum. Neoplasm on the left inducing compression of the adjacent molecular layer and with the presence of an invasive neoplastic nodule** (arrowheads) **in the granular layer.** Bar = 100 µm. Haematoxylin and eosin.

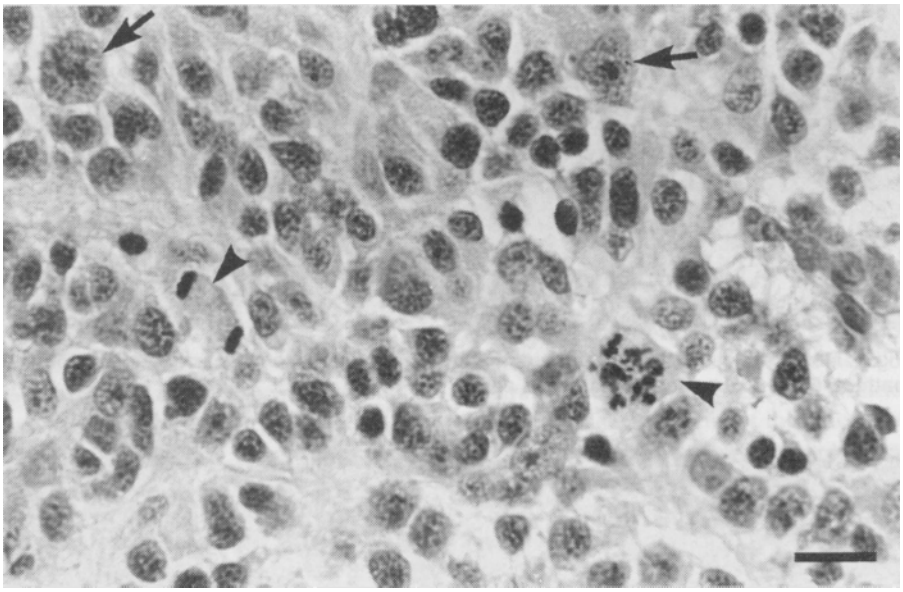

Fig. 4: **Meningotheliomatous meningioma. Mitotic figures; one bizarre** (arrowheads) **and occasional neoplastic cells with a single large pleomorphic nucleus** (arrows). Bar = 10 µm. Haematoxylin and eosin.

specifically from the arachnoid cells[15,17]. They are usually benign and slow-growing tumours[15]. Malignancy is rare and is characterised by cellular pleomorphism, infiltrative growth and increased mitosis[4]. In the cat, meningioma is the most common tumour of the central nervous system[4,11,15,19]. It is frequently multiple in this species and older male cats are at greater risk[11,15,19]. Thus, in this case, it was unusual, as the cat was only 2 years of age. Grossly, the tumour is well demarcated, variable in shape, firm, encapsulated, and grey-white in colour[17]. Most tumours are supratentorial, and occasionally infratentorial[4,15]. The presence of multiple meningiomas, both in the brain and spinal cord, in conjunction with focal necrosis, tissue invasion, cellular and nuclear atypia, and a high mitotic index signifies a distinct malignant tendency of the neoplasm in this case.

Neurological deficits reported with meningiomas in the cat include severe generalised and partial seizures, lethargy, mental impairment, circling, visual deficits, hemiparesis, tetraparesis, ataxia, and nystagmus. These deficits occur as a result of displacement or destruction of normal tissue[15]. Neurological signs that were evident in this cat were lethargy, tetraparesis, ataxia and nystagmus.

In man and in animals, the most commonly encountered side-effects associated with chemotherapy relate to toxic effects on the alimentary tract, bone marrow suppression and immunosuppression. It is ironic that many of the antineoplastic drugs are themselves carcinogenic and/or mutagenic[16]. Vincristine is a cell-cycle-specific agent that blocks mitosis and produces metaphase arrest. It has a relatively low toxicity for normal marrow and epithelial cells. Important side-effects are hair loss and neuromuscular abnormalities. The neuromuscular abnormalities are characterised by weakness, loss of reflexes, ataxia and muscle cramps. Other side-effects that have been reported include pancytopaenia, dysuria, fever, cardiac toxicosis and gastrointestinal disturbances[1,3]. Cyclophosphamide interferes with normal mitosis and cell division in all rapidly proliferating tissues. Thus, important side-effects are pancytopaenia and alopecia[1,3]. In the cat, dog and pig, administration of cyclophosphamide has been shown to cause severe and sustained leukopaenia within 2–3 days of administration[9,12,14]. This effect was apparent in this cat and was compounded by the daily administration of cyclophosphamide for 4 days. Sterile haemorrhagic cystitis and gastrointestinal disturbances are also common. Other reported side-effects are mucosal ulceration, skin hyperpigmentation, interstitial pulmonary fibrosis and hepatic toxicity[1,3].

Drugs that are commonly reported to have resulted in secondary malignancies in man include cyclophosphamide, chlorambucil, vincristine and methotrexate[6,10]. Polychemotherapy, with or without radiotherapy, for the treatment of a primary tumour is associated with an increased risk of development of a secondary malignancy[8]. In one study in man, the number of secondary tumours observed exceeded the number expected in an age and sex-matched control population[5]. Combination chemotherapy utilising cyclophosphamide, vincristine, procarbazine and prednisolone was evaluated in this study. The role of cyclophosphamide in tumorigenesis is due either to immunosuppression or direct cytotoxicity[7]. There is a greater tendency for renal and bladder carcinoma to develop in patients treated with a chemotherapeutic protocol including cyclophosphamide than those treated with protocols exclud-

ing cyclophosphamide[7,13]. Cyclophosphamide has resulted in solid tumour induction in man treated for non-Hodgkin's lymphoma[6].

As the cat had neurological signs (left-sided Horner's syndrome, conscious proprioceptive deficit and reflex reduction in the left forelimb) when first presented, it is possible that the meningiomas were already present, but this is unlikely because of the history of trauma and subsequent development of the neurological signs, the age of the cat, and the initial, non-progressive nature of the neurological signs.

In our opinion the chemotherapeutic protocol utilised in this case not only resulted in induction of secondary multiple meningiomas but also contributed to the malignant transformation of these neoplasms. The increased use of chemotherapy in animals may predispose to the development of secondary malignancies and this may be a more serious problem than is currently appreciated.

REFERENCES

1. Calabresi P, Chalbner B A 1990 Antineoplastic agents. In Goodman A G and Gilman L S (eds) *The pharmacological basis of therapeutics* (8th edn). Pergamon Press, New York: 1209–1263
2. Carter S K 1987 Principles of cancer chemotherapy. In Theilen G H, Madewell B R (eds) *Veterinary cancer medicine* (2nd edn). Lea & Febiger, Philadelphia: 345–470
3. Coppoc G L 1988 Chemotherapy of neoplastic disease. In Booth N H, McDonald C E (eds) *Veterinary pharmacology and therapeutics* (6th edn). Iowa State University Press, Iowa: 861–876
4. Cordy D R 1990 Tumors of the nervous system and eye. In Moulton J E (ed.) *Tumors in domestic animals* (3rd edn). University of California Press, Berkeley: 640–666
5. DeVita V T 1981 The consequences of the chemotherapy of Hodgkin's disease. *Cancer* 47: 1–13
6. Folb P I 1988 Cystostatic and immunosuppressive drugs. In Dukes M N G (ed.) *Meyler's side effects of drugs* (11th edn). Elsevier Science Publishers, Amsterdam: 928–960
7. Garvin D D, Ball T P 1981 Bladder malignancy in a patient receiving cyclophosphamide. *Urology* 18: 80–81
8. Henry-Amar M 1983 Second cancers after radiotherapy and chemotherapy. *Journal of the National Cancer Institute* 71: 911–916
9. Henry C J, Brewer W G, Royer N S 1994 Hematological and clinical responses to combined mitoxantrone and cyclophosphamide administration to normal cats. *Canadian Veterinary Journal* 35: 706–708
10. Kyle R A 1982 Second malignancies associated with chemotherapy. *Seminars in Oncology* 9: 131–142
11. Luginbuhl H 1961 Studies on meningiomas in cats. *American Journal of Veterinary Research* 22: 1030–1040
12. Mackie E J 1981 Immunosuppressive effects of cyclophosphamide in pigs. *American Journal of Veterinary Research* 41: 189–194
13. McDougal W S, Cramer S F, Muller R 1981 Invasive carcinoma of the renal pelvis following cyclophosphamide therapy. *Cancer* 48: 691–695
14. Medleau L, Dawe D L, Calvert C A 1983 Immunosuppressive effects of cyclophosphamide, vincristine, and L-asparaginase in dogs. *American Journal of Veterinary Research* 44: 176–180
15. Nafe L A 1979 Meningiomas in cats: a retrospective clinical study of 36 cases. *Journal of the American Veterinary Medical Association* 174: 1224–1227
16. Rosenthal R C 1995 Chemotherapy. In Ettinger S J, Feldman E C (eds) *Textbook of veterinary internal medicine* (4th edn). WB Saunders Company, Philadelphia: 473–484
17. Storty R W 1988 Central nervous system. In Thomson R G (ed.) *Special veterinary pathology.* DC Decker, Toronto: 509–564
18. Theilen G H, Madewell B R, Gardner M B 1987 Hematopoietic neoplasms, sarcomas, and related conditions. In Theilen G H, Madewell B R (eds) *Veterinary cancer medicine* (2nd edn). Lea & Febiger, Philadelphia: 345–470
19. Zaki F A, Hurvitz A I 1976 Spontaneous neoplasms of the central nervous system of the cat. *Journal of Small Animal Practice* 17: 773–782

Book review — Boekresensie

Wildlife resources — a global account of economic use

Edited by H H Roth and G Merz

1996. Springer, Berlin, Heidelberg, New York, 403 pp., hard cover. Price not stated. ISBN 3 540 61357 9.

The editors, together with a team of 31 contributors, have compiled an authoritative work on all aspects of the consumptive and non-consumptive use of wild animals and related aspects of domestication and conservation. The book is organised into 3 parts. The first deals with the concepts and principles of wildlife utilisation in general, the 2nd part addresses the utilisation of specific groups of reptiles, birds and mammals, while the 3rd part discusses wildlife products and the commodities derived from them.

The book is organised following the 1.1.1 system with literature references at the end of each chapter and an index of animal names at the end, while the finer details are presented in numerous tables. All this renders it a highly readable book.

One possible criticism is that the book follows the German tradition prominently adopted by Alfred Brehm, the original author of 'Das Tierleben', in giving preference or even exclusivity to the 'higher' vertebrates, as if the use of fish and non-vertebrate resources was not of at least equal importance, globally as well as particularly in our South African marine environment. Another is that the authors of the individual chapters are not named as such, which will make it more difficult to quote from this book in a scientific paper.

This very comprehensive and excellent text is highly recommended to all professionals involved in the conservation and utilisation of wildlife as well as to everybody else with an interest in this field.

F W Huchzermeyer
Pathology Section
Onderstepoort Veterinary Institute