The Koala and its Retroviruses:
Implications for Sustainability and Survival

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Disease in Wild Koalas *(Phascolarctos cinereus)* with Possible Koala Retrovirus Involvement

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Abstract. A wide range of serious, and oftentimes fatal, conditions has been observed in both free-living and captive populations of koalas *(Phascolarctos cinereus)* and are attributed, perhaps prematurely, to the koala retrovirus (KoRV). These maladies include lymphoma, leukaemia, and other bone marrow conditions, and the so-called koala AIDS. A variety of other conditions that involve disordered growth of cells and tissues, altered or inappropriate immune responses, and degenerative conditions may also be consequences of insertional mutagenesis, or other pathogenic mechanisms associated with KoRV infection. The list of potential KoRV-associated pathologies continues to grow, as more thorough and consistent approaches to clinical assessment and diagnosis are applied to wild and captive koalas.

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This paper aims to briefly describe a selection of well-recognized and newly-observed conditions that may have KoRV as a contributing factor. For most, however, the link with KoRV is evidentially non-existent, and its role in those diseases purely speculative. However, they are listed here to give KoRV researchers, particularly those based in laboratories, a fuller picture of the clinical spectrum of disorders afflicting koalas, and perhaps some guidance on future research directions. Some of these conditions, in the fullness of time, may have their definitive aetiologies and pathogenesis better illuminated as a result.

The evidence for the involvement of a retrovirus in leukaemia in koalas began building with the discovery and reporting of virus particles in the bone marrow of a leukaemic koala in 1988 (Canfield *et al.,* 1988), and the recognition of a spectrum of conditions in koalas similar to that observed in FeLV-infected cats (Hanger, 2009). A full-length KoRV genome sequence was reported in 2000 (Hanger *et al.*, 2000). While it is tempting to conclude that KoRV is responsible for leukaemia, lymphoma, and related diseases in koalas, causation has not yet been proven. Certainly KoRV has characteristics found in pathogenic gammaretroviruses, including the immunosuppressive domain of the transmembrane portion of the envelope protein (Fiebig *et al.,* 2006). The evidence for KoRV pathogenicity in koalas is building, but not unequivocal.

This paper describes a wide range of diseases and syndromes observed in wild koalas, mainly in Queensland, which may be caused by disruption of normal cellular function and regulation by KoRV. It is important to remember that none has been conclusively causally linked to KoRV infection. These diseases have been included because they represent disordered growth of tissues, either as neoplasia, or benign conditions, or they are associated with putative disruption to normal cellular function, for example, the koala "AIDS" condition. Also included are some immune-mediated conditions, which may be associated with immune dysfunction or dysregulation by KoRV, or perhaps other factors.

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Figure 1. Cranial osteochondroma.

Disorders of growth—Neoplasia

Leukaemia

The leukaemias are a group of conditions that include the haematopoietic malignancies and, by definition, arise in the bone marrow. The classical forms of leukaemia are associated with the presence of malignant cells in the bloodstream, but non-leukaemic (aleukaemic) forms occur, in which there are no, or minimal, malignant cells in the circulation. Leukaemias may arise from abnormal early multipotential progenitor cells or from more differentiated progenitor cells, but the phenotype of the cells will depend upon their ability to undergo further differentiation or, in the case of unipotential stem cell transformation, the lineage. Leukaemias may be of lymphoid or myeloid origin; and within the myeloid group may be further characterized as erythroid, granulocytic, megakaryocytic, or monocytic, depending upon the recognition of lineage (Robbins, 1974). Occasionally, leukaemias are encountered that are biphenotypic, in which leukaemic cells may express myeloid and/or lymphoid markers, but are derived from the same abnormal progenitor cell clone, or more rarely from separate clones (Ganesan, 1995; Lichtman, 1995).

A variety of types of leukaemia have been observed in koalas. Lymphoid leukaemia appears to be the most common, and is, as often as not, associated with solid tumours of lymphoid origin. Myeloid and erythroid lineage leukaemias have also been seen, although definitive identification of cell lineage (using cytochemical or immuno-cytological techniques) has not been attempted for most. A leukaemia of megakaryocyte-like morphology was noted

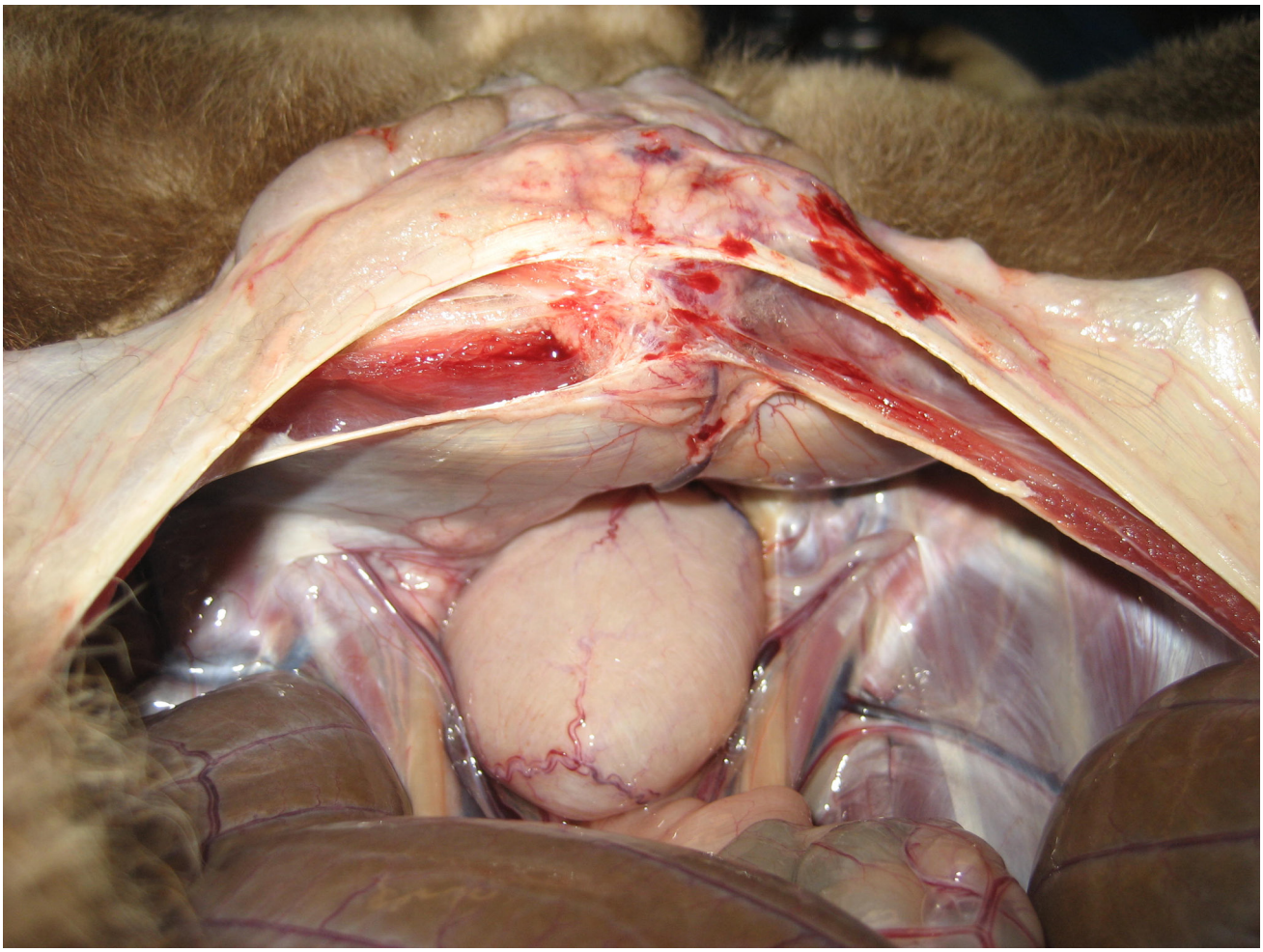

Figure 2. Pelvic osteochondroma.

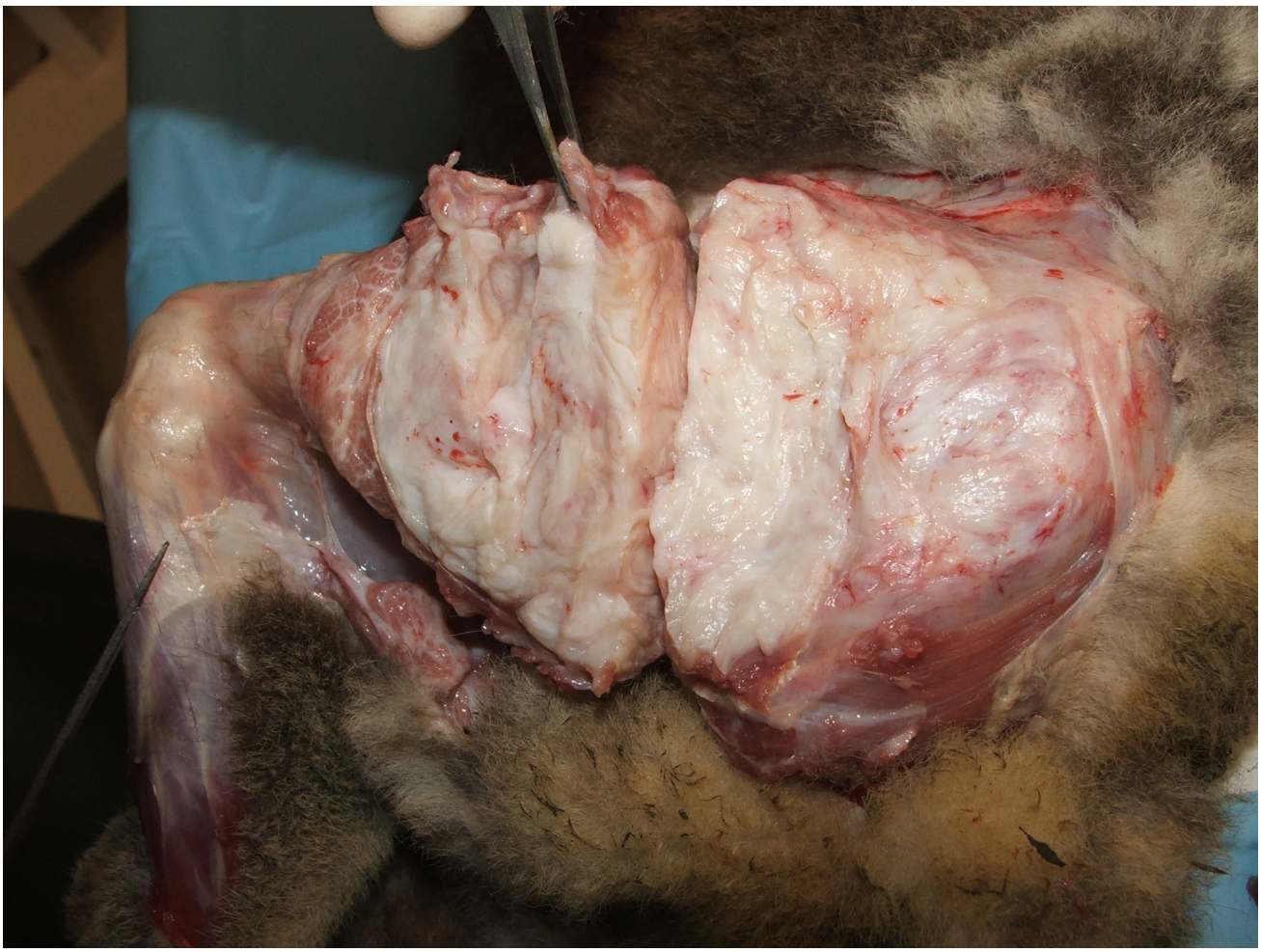

Figure 3. Fibrosarcoma on the thigh of a koala.

in a wild koala from the Gold Coast, which was euthanized because of paralysis associated with spinal infarction. Cells resembling immature megakaryocytes were observed in a wide range of tissues. Some leukaemias are quite obvious on blood smears, others (the "aleukaemic" forms) are not. In these cases, some white cells may appear atypical and the diagnosis must be based on bone marrow cytology. Leukaemias are often associated with infiltration of a wide range of organs and tissues, including brain and spinal cord.

Lymphoma

The term *lymphoma* refers to a malignant proliferation of cells of the lymphoid lineage, and may also be referred to as *lymphosarcoma*. The distinction between lymphoid leukaemia and lymphoma is one of definition: the lymphoid leukaemias arise from clonal expansion of a progenitor cell in the marrow, whereas the lymphomas arise from cells in the other lymphoid tissues. However, in both animals and humans, lymphoma may have a leukaemic phase, and the distinction does not necessarily or consistently define separate clinical entities (Magrath, 1995).

Lymphomas may be singular or multiple solid tumours affecting all lymphoid tissues, or specific subsets, for example: abdominal lymphoid tissues only, peripheral lymph nodes only. Isolated tumours of the thymus have been observed. The tumours are generally firm, pale, off-white tumours, often with areas of haemorrhage and necrosis. Grossly the tumours are often well demarcated, but histologically the margins show invasion into surrounding tissues. Abdominal lymphoma is often not associated with enlargement of peripheral lymph nodes. Ascites is usually present and the fluid contains high numbers of neoplastic lymphoid cells, and is often blood-tinged. Serosal surfaces may be variably affected by a coating of nodular tumour.

Osteochondroma

Osteochondromas are large, usually single, tumours of mixed cartilage and bone that most commonly in koalas affect the bones of the head (Fig. 1) (Blanshard, 1994; Canfield *et al.*, 1987; Sutton, 1986). However, they also occur in the pelvis, ribs, clavicles, and long bones (Hanger *et al.*, 2003). Histologically, these tumours are quite variable, with areas of quite orderly growth of cartilage and bone and other areas with disorderly growth and characteristics of malignancy. Some cases of osteochondroma have crossed the acetabular joint, causing growths on both the pelvic bones and proximal femur. The tumours tend to be expansive, rather than infiltrative, and cause clinical signs referable to displacement, compression, and impingement on organs, tissues, and their functions (Ladds, 2009). The tumours are relatively slow-growing, with one tumour affecting the pelvis of a koala expanding by 10–15% (diameter) every two weeks (Fig. 2).

Fibrosarcoma

One fibrosarcoma was observed in a captive koala at, or close to, a site of vaccination for *Bordetella*. The poorly demarcated and infiltrative tumour affected the skin and subcutis in the interscapular region, and contained cavities containing viscous myxomatous fluid. It was diagnosed histologically as a malignant fibrous tumour, but resolved spontaneously in the koala. The formation of vaccination-

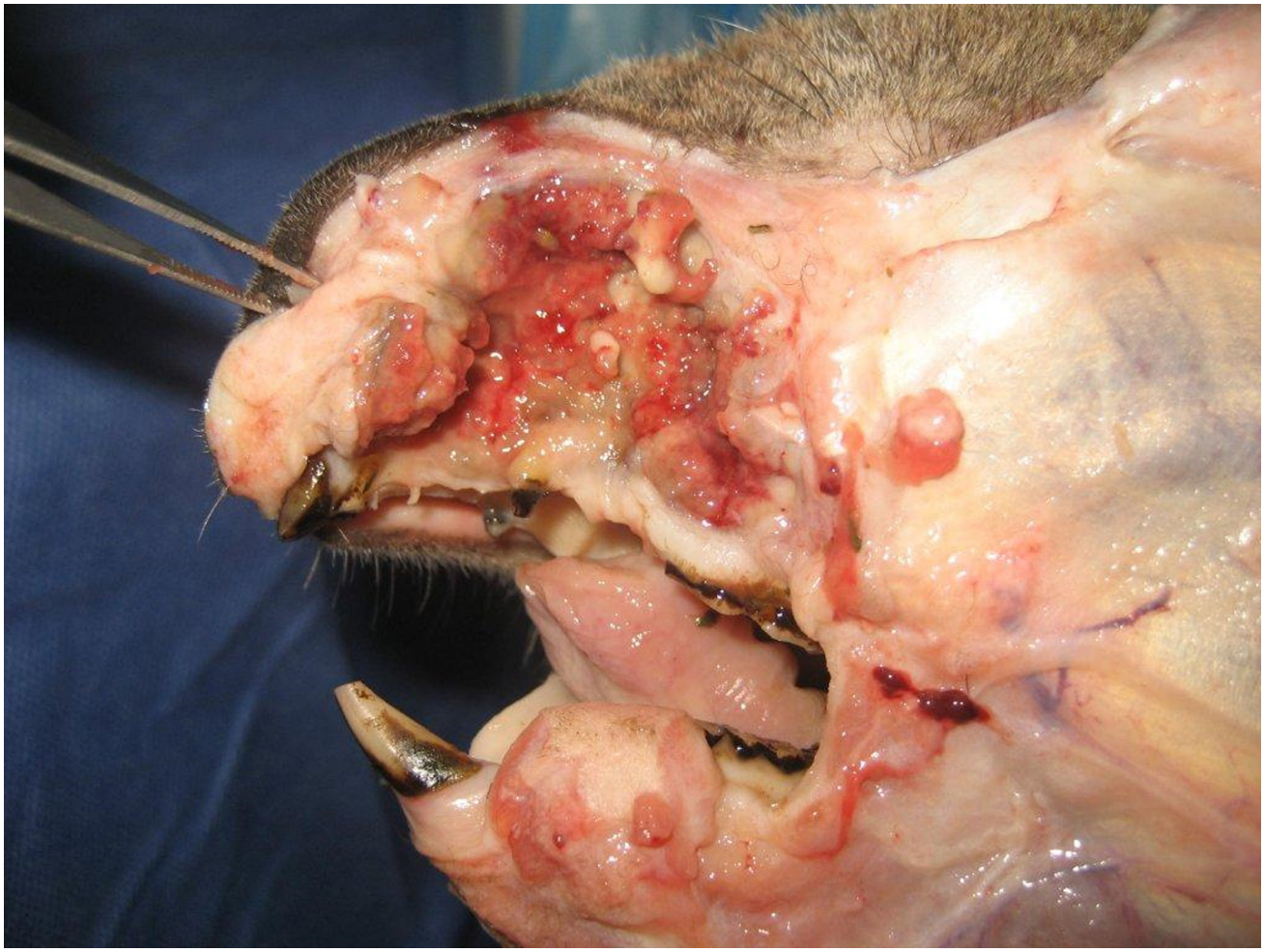

Figure 4. Maxillary fibrosarcoma.

site fibrosarcomas is a well-recognised phenomenon in cats (Kitchell, 2005). In most other cases observed in koalas, the tumour has arisen spontaneously or from an unknown trigger. These tumours tend to be aggressive, rapidly-growing, and infiltrative; affecting a wide range of organs and tissues (Figs. 3 and 4).

Mesothelioma

Mesothelioma in koalas is most commonly a diffuse malignant nodular tumour affecting the abdominal surfaces (e.g., peritoneum, mesentery, and gastro-splenic ligament) or pleura. It results in massive ascites with thick, blood-tinged, viscous fluid, with a consistency similar to joint fluid. Affected koalas present with gross distension of the abdomen, often in poor body condition, and sometimes with dyspnoea. Grossly, both the parietal and visceral peritoneum (serosal surfaces) is covered in small, red nodules with a glistening, slimy surface. Ante-mortem diagnosis is based on the finding of viscous, blood-tinged pleural or abdominal fluid, which strings out significantly when dripped from the tip of a needle or hub of a syringe (Fig. 5). Cytologically, the cells resemble large, atypical, and pleiomorphic mesothelial cells, often with characteristic eosinophilic material apparent in cell clusters (Fig. 6).

Other tumours

A variety of other tumours has been observed in koalas, including squamous cell, renal and sebaceous carcinomas, mammary adeno-carcinomas, and poorly defined neoplastic-like conditions (Blanshard, 1994; Ladds, 2009). One particularly interesting case occurred in a captive koala at the site of a healed fight wound to the right shoulder. The tumour developed in, or near, the periosteum of the proximal humerus and, at the time of euthanasia of the koala, had evolved into a poorly differentiated, pleiomorphic sarcoma containing numerous anaplastic spindle-shaped cells and frequent giant cells. The original lesion radiographically resembled a minor periosteal reaction, presumably in response to injury from the bite wound from another male koala. As the tumour developed, biopsy and cytology submissions to a veterinary pathology laboratory returned diagnoses of “non-suppurative fibrosing cellulitis”, “pyogranulomatous panniculitis”, “granulomatous osteomyelitis”, “anaplastic neoplasm” and, at necropsy, “probable sarcoma” of indeterminate lineage. A 4-cm diameter tumour of similar gross and histological morphology had also developed in the thigh, where the koala had received numerous antibiotic and analgesic injections. This interesting tumour certainly had features of chronic, granulomatous, and fibrosing inflammation and also sarcomatous malignancy, but never received the benefit of a consensus on its definitive histological diagnosis amongst the pathologists examining it. Whether it was a true neoplasm, arising from clonal expansion of a single abnormal cell, or a non-clonal, but unregulated/dysregulated, inflammatory response made little difference to the koala. The tumour acted clinically like a malignant neoplasm and caused sufficient pain and debility to the koala to warrant eventual euthanasia (Cumming, 2008).

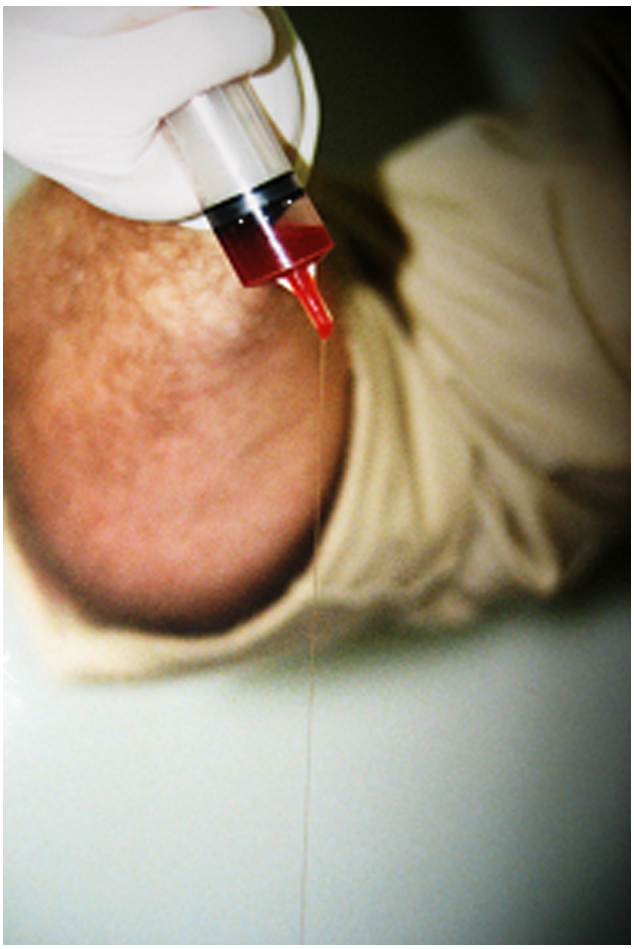

Figure 5. Viscous mesothelioma ascites fluid.

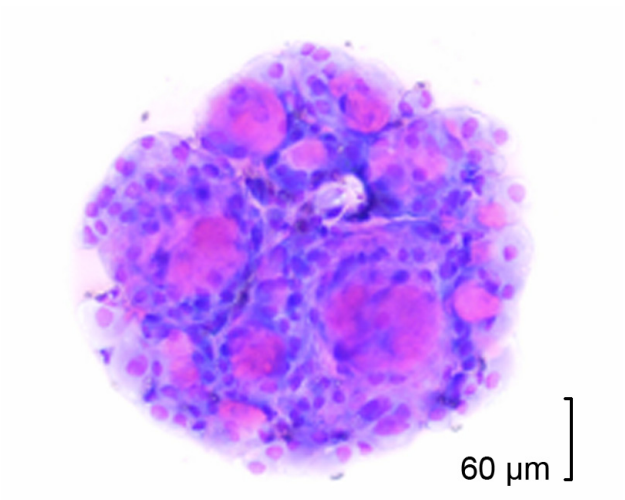

Figure 6. Mesothelioma cytology—showing distinctive eosinophilic material.

Myelodysplasia

Myelodysplastic conditions and myeloid leukaemias are seen occasionally in koalas, but at a lower frequency than lymphoid leukaemia. These cases may be detected by the finding of slightly unusual white cells in blood smears and cytopaenias. However, blood smears may be essentially normal, or have subtle cytopaenias. Anaemia associated with chronic inflammatory disease, and other causes of bone marrow suppression should be ruled out prior to making a diagnosis of primary marrow disease or myelodysplasia. Examination of bone marrow smears, collected from the iliac crest, may reveal hyper, or hypocellularity of the marrow, with atypical cells present or abnormal maturation of haematopoietic cells. In koalas, the distinction between myeloid leukaemia and myelodysplasia is possibly arbitrary, as both conditions are part of a spectrum of disorders that are probably causally and mechanistically linked. Abnormal blood cells may or may not be present in the circulation, and it is likely that myelodysplasia, in cases that survive long enough, may progress to leukaemia.

Benign growth disorders

Sebaceous hyperplasia/adenomatosis, causing generalised and widespread, greasy, multilobular, cutaneous nodules mainly in the ventral skin and pouch (Fig. 7), has been observed in a number of koalas. These small nodules are benign growths of sebaceous gland tissue, the cause of which is unknown.

Plantar and palmar hyperkeratosis, and focal papillary hyperkeratosis

Horn-like, hard, cutaneous growths of the plantar and palmar skin (Fig. 8) have been observed occasionally in koalas and, in some cases, the koalas were concurrently affected by lymphoma or other bone marrow conditions (Canfield *et al.*, 1992; Hanger, 2000). The pathogenesis in koalas may be similar to that occurring in FeLV-affected cats (Muller *et al.*, 1989). A less severe, focal papillary hyperkeratosis has been observed in other koalas: one at the interscapular region, the others on the palmar/plantar skin. It is possible that the newly-discovered koala papillomaviruses are involved in the pathogenesis of these lesions and perhaps KoRV interferes with the normal immune response, allowing more severe lesions to develop. One study found a prevalence of papillomavirus of 10/72 (14%) of koalas swabbed (Antonsson & McMillan, 2006).

Polycystic kidney disease

Unilateral polycystic kidney disease has been observed in one koala, whose other kidney was sonographically and grossly normal. The affected kidney was extensively affected by tubular hyperplasia and cyst formation, which replaced the normal architecture almost to the point of completeness (Fig. 9). Histologically, there were occasional small wedges of normal renal tissue between the large areas of tubular hyperplasia and cysts. There were also occasional foci of mononuclear infiltration and frequent accumulations of what appeared to be neutrophils in and around hyperplastic tubules. The histological changes were entirely consistent with the diagnosis of polycystic kidney disease. The causes of this condition in other species (including humans and cats) commonly have a genetic basis, with 90% of human cases caused by an autosomal dominant genetic defect. Unilateral renal cystic disease in humans is a recognised, but rare disease, in which the affected kidney shows changes histologically indistinguishable from autosomal-dominant polycystic kidney disease (Wilson, 2004).

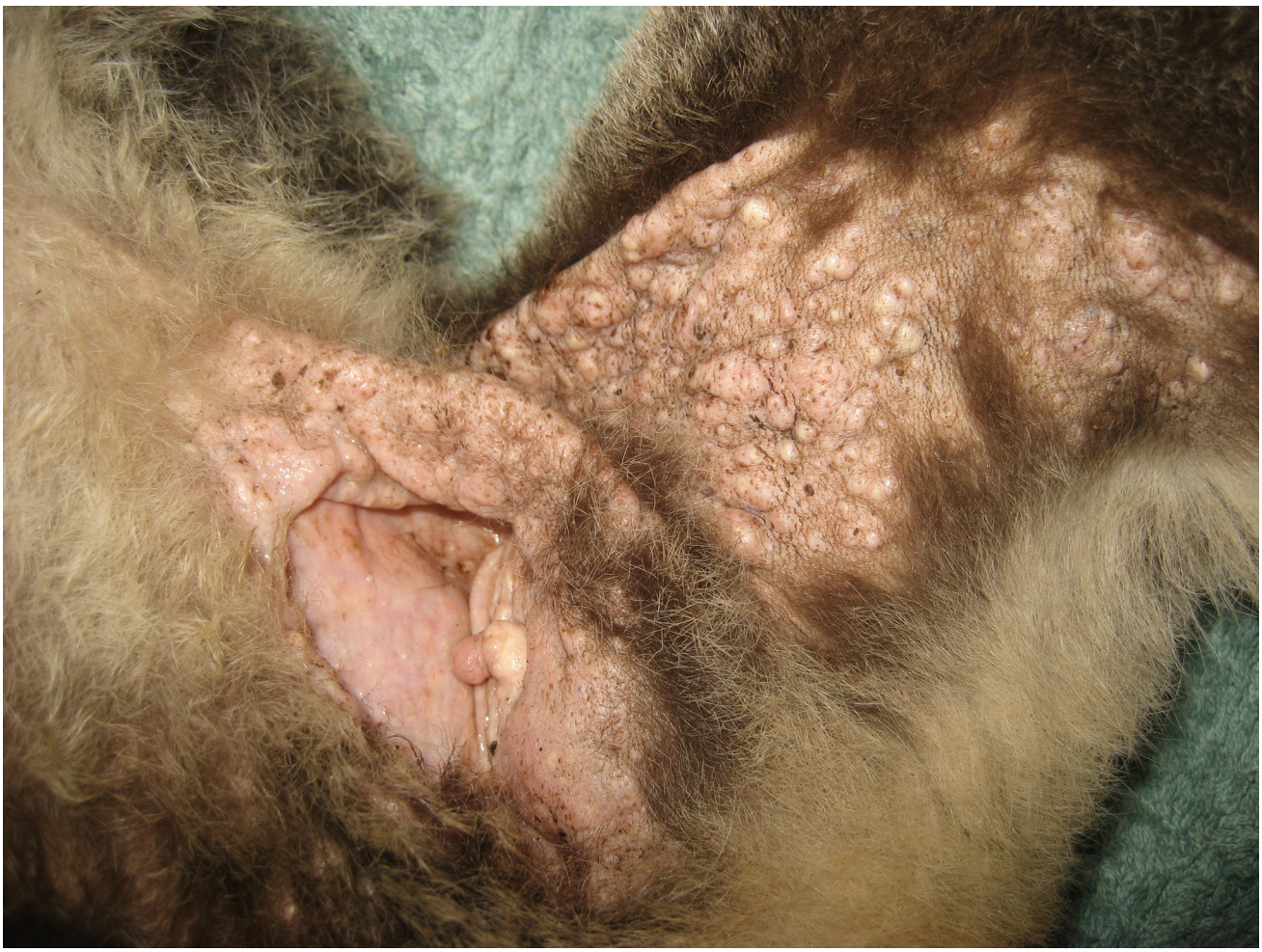

Figure 7. Sebaceous adenomata.

Immunological conditions

Koala "AIDS"

The koala "AIDS" condition remains a relatively poorly defined syndrome, characterised by chronic illthrift and a variety of clinical signs and syndromes consistent with immune incompetence, suppression or dysfunction. These clinical signs and syndromes include stomatitis (ulcerative and non-ulcerative) (Fig. 10); severe, extensive dermatitides; extensive or serious fungal infections, including cryptococcosis, candidiasis, and filamentous fungal dermatopathies; caeco-colic dysbiosis and typhlocolitis syndrome; severe, chronic chlamydiosis; severe periodontal disease, "opportunistic" and recurrent or treatment-refractive infections, and poor body and coat condition of undefined cause (Figs. 11–13). Because immune function tests are not generally available to the clinician, the diagnosis is presumptive, and based on the finding of two or more of the conditions listed above (A. Gillett, pers. comm.). These koalas may show haematologic changes consistent with immuno-suppression, such as profound lymphopaenia, but whether these findings are associated with causation, or consequent to the major disease process, is impossible to say in most cases.

Immune-mediated conditions

Thyroiditis

Interstitial, non-suppurative thyroiditis was detected incidentally in a koala that had succumbed to the koala "AIDS" condition, with concurrent chronic illthrift, typhlocolitis, and gastro-intestinal candidiasis. Histologically, there was depletion of thyroid glandular secretion and intense interstitial mononuclear inflammation, oedema and fibrosis. The cause of the inflammation was not apparent.

Plasmacytic enteritis

Plasmacytic enteritis in koalas is characterised by mild to intense lamina proprial and submucosal plasma cell infiltrates and other mononuclear cell infiltrates to a lesser degree, affecting any part of the gastro-intestinal tract from the stomach to the rectum. Many of the koalas with more severe lesions detected histologically were affected by chronic illthrift and poor body and coat condition. The plasmacyte-dominated infiltrates are reminiscent of those found in *Chlamydia*-infected organs and tissues, and it is possible that the condition is caused by chlamydial infection. At the time of writing, some of these cases were being subjected to PCR and immuno-histochemistry in an attempt to illuminate the aetiology.

Figure 8. Plantar hyperkeratosis.

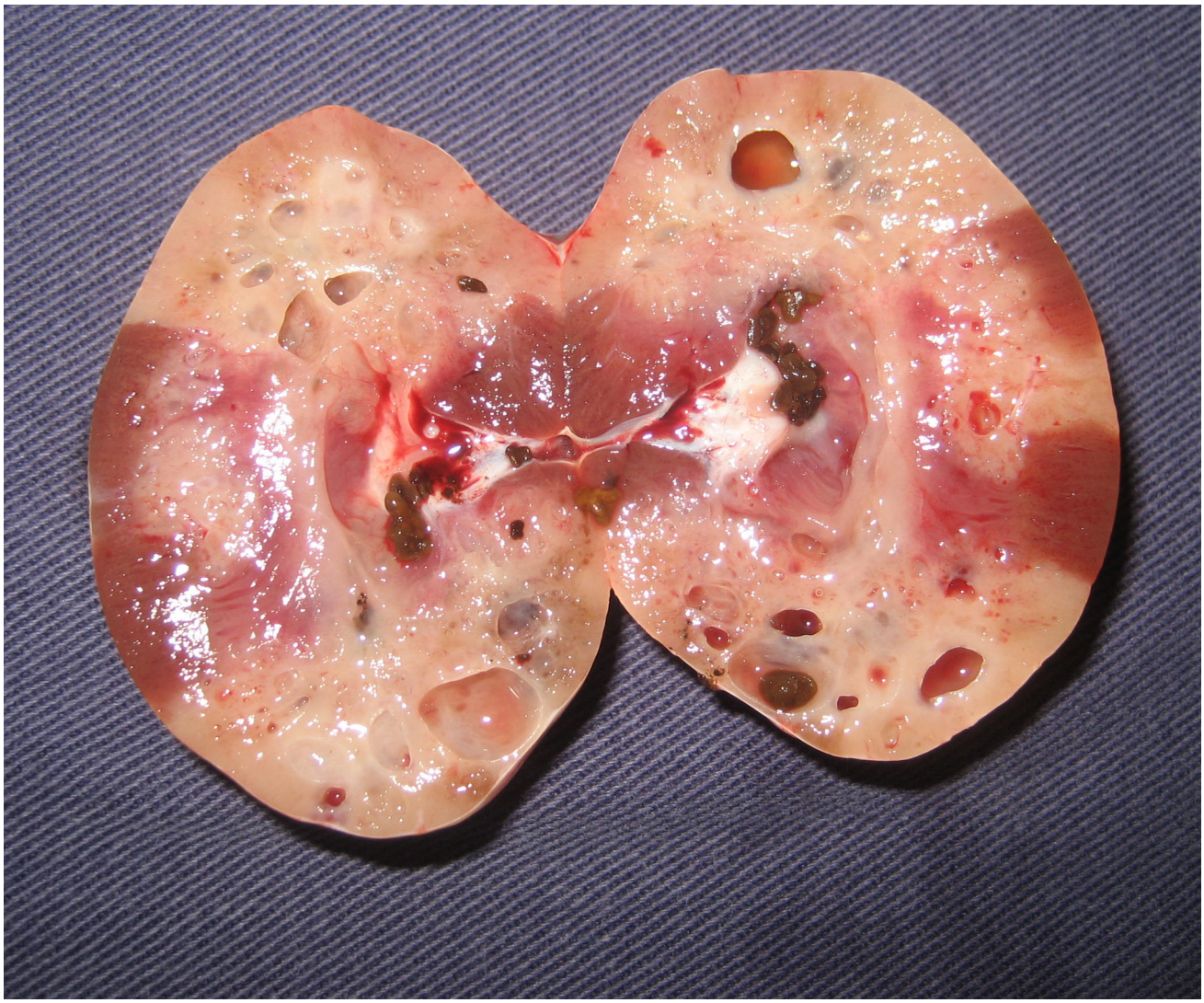

Figure 9. Polycystic kidney.

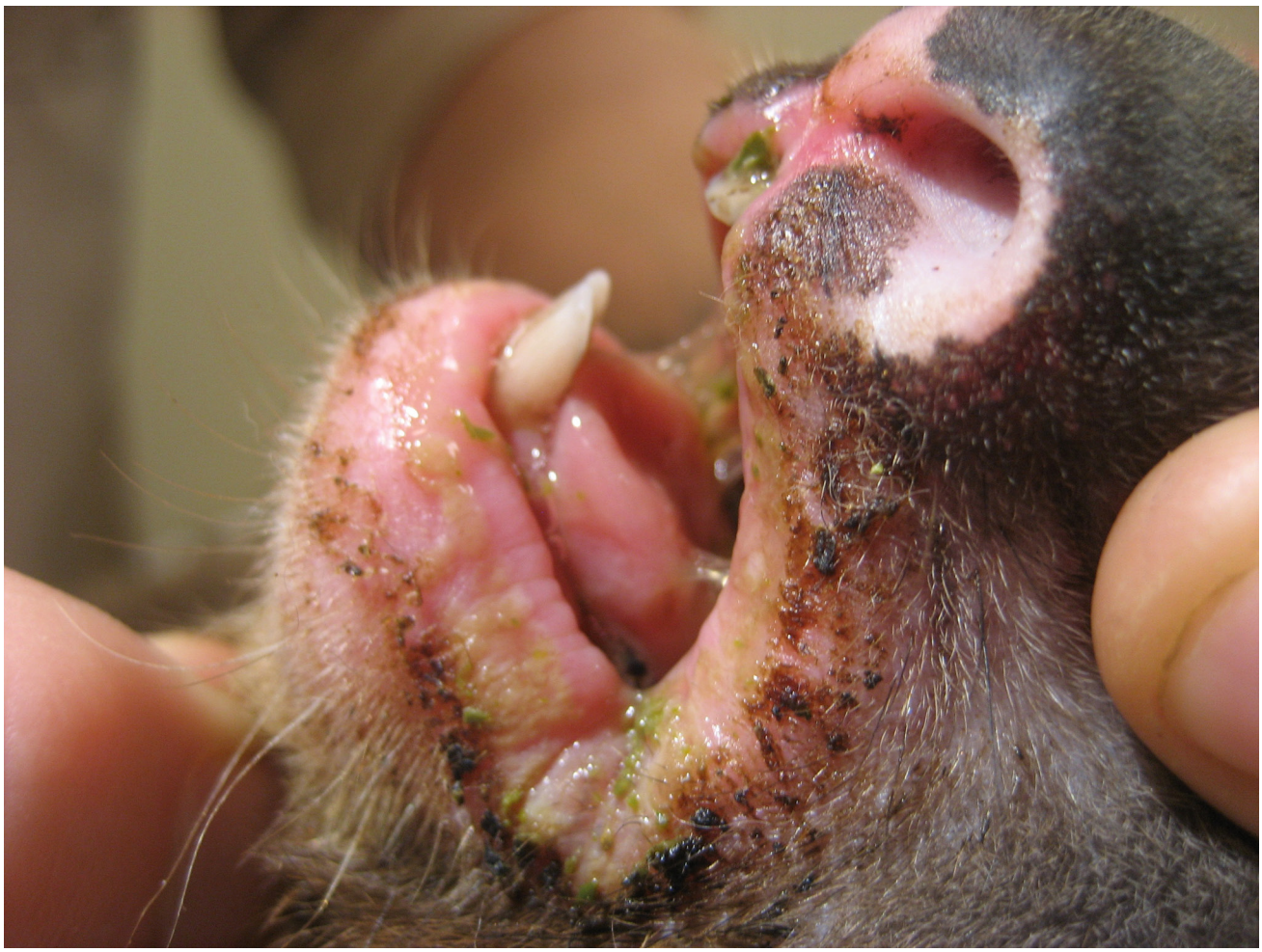

Figure 10. Stomatitis.

Figure 11. Typhlo-colitis.

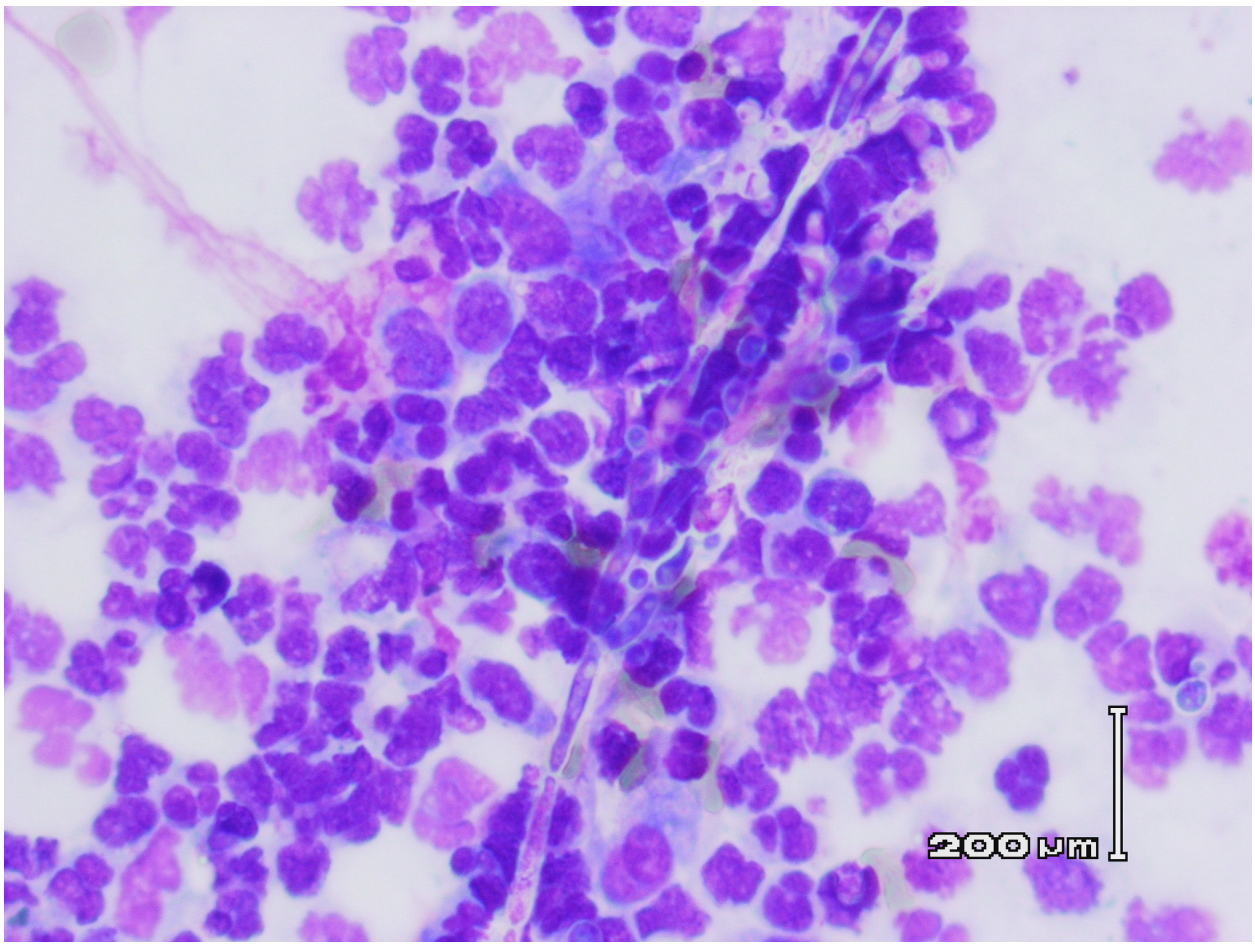

Figure 12. Candidal pseudohyphae—myocardial abscess.

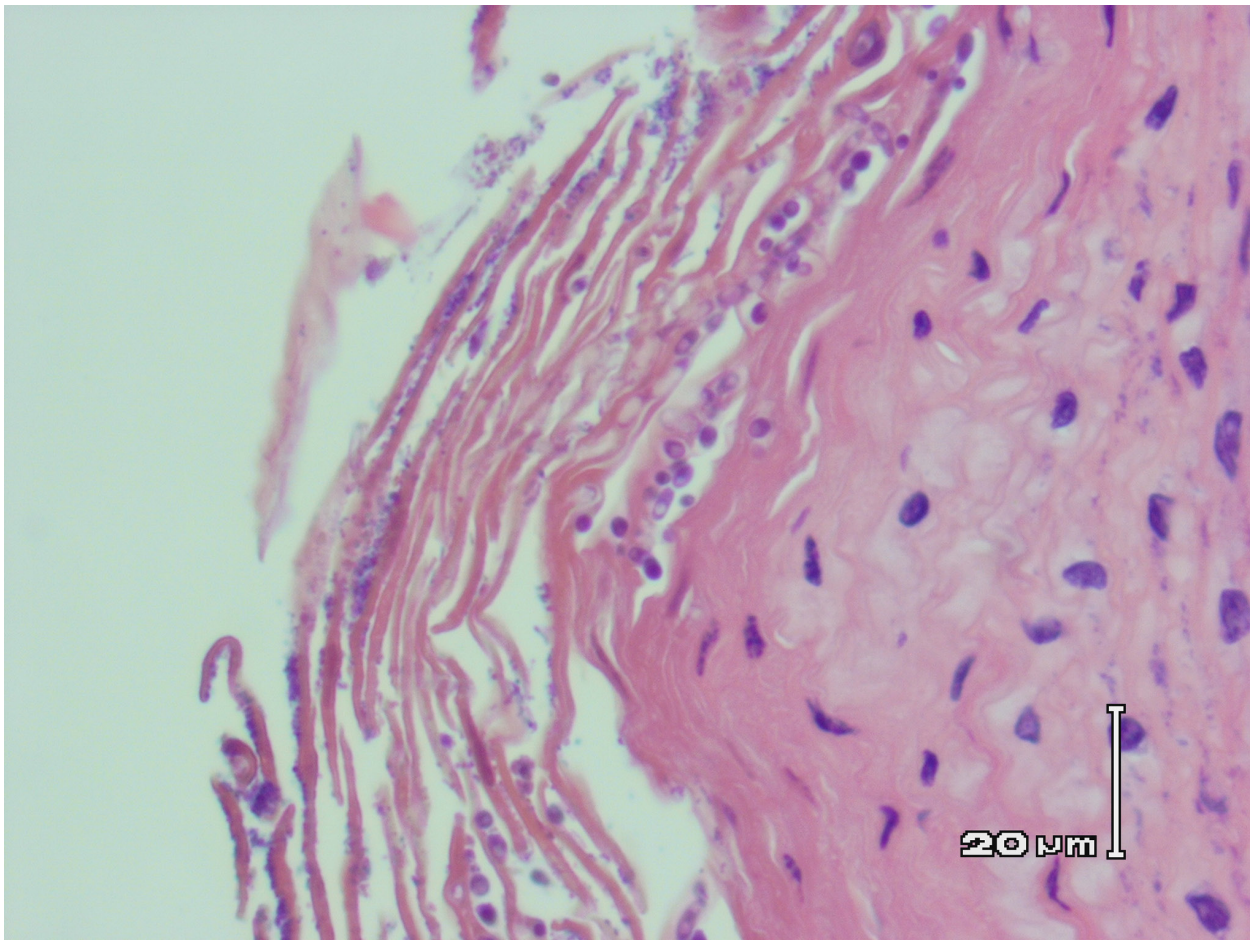

Figure 13. Candida invading oesophagus.

Chlamydiosis

While koalas with mild, self-limiting, chlamydial infections could hardly be accused of having poor or inappropriate immune responses, certainly another group of koalas—those that develop very severe, debilitating and sometimes fatal chlamydial disease—could be. In such cases, the immunological response to the infection appears to be entirely out of proportion to the inherent pathogenic risk, and consequently severe and permanent organ and tissue damage occurs because of the immune response. Whether severe, debilitating chlamydiosis is caused by highly pathogenic strains of the organism, environmental factors or KoRV-associated immune modulation or dysfunction, is a question needing urgent investigation.

Other conditions

A number of other conditions are worth considering in the case against KoRV, but are either beyond the scope of this paper to deal with, or have been adequately described by other authors. They include: pouch death of joeys; chronic illthrift (without concurrent AIDS indicators); cryptococcosis and systemic candidiasis; severe cutaneous and pox-type lesions; severe, fatal trypanosomiasis; and non-suppurative meningo-encephalitis. Undoubtedly, this list will continue to grow over time.

Prevalence and incidence of KoRV-associated disease in free-ranging koala populations

Veterinary examinations and sampling of 296 koalas from wild populations in south-east Queensland were conducted between July 2008 and March 2013. At the time of their initial examination, 23 (8%) of these koalas had disease lesions or syndromes that might be associated with the koala retrovirus. Disease lesions/syndromes found in the population included:

1 AIDS-like condition/immunodeficiency disorder (8 koalas)
2 Polycystic kidney disease (1 koala)
3 Myelodysplasia (2 koalas)
4 Neoplasia (3 koalas): 1 had renal lymphoma, 2 had leukaemia
5 Generalised sebaceous adenoma (2 koalas)
6 Severe chlamydiosis (7 koalas)

Of the 296 koalas, 126 were monitored longitudinally (for an average of 416 days per koala) and were subjected to one or more follow-up veterinary examinations (between December 2008 and March 2013). The incidence of new KoRV-associated disease lesions/illness diagnosed in the population since the initial veterinary examinations was 12.5% (in other words, each koala in the population had a 12.5% chance each year of becoming ill, or developing a new lesion). KoRV-associated disease that was detected in the population included:

1 AIDS-like syndrome/immunodeficiency disorder (8 koalas)
2 Chronic ill-thrift (unexplained poor body condition, brown, clumped coat) (5 koalas)
3 Cryptococcosis (1 koala)
4 Cancer (1 koala had a pelvic osteochondroma, 1 koala had a maxillary fibrosarcoma)
5 Severe chlamydiosis (3 koalas)

Prevalence of KoRV-associated disease—Australia Zoo Wildlife Hospital

The following table shows figures, based on 6001 koala admissions to the Australia Zoo Wildlife Hospital over the past 9 years, of possible KoRV-associated diseases. It is important to note that hospital admissions are a biased group, and figures do not necessarily represent true prevalence in free-living populations. Nevertheless, they demonstrate the relatively high rates of occurrence of these so-called KoRV-associated diseases.

A survey of wildlife veterinarians and facilities around Australia revealed that, other than dermatitis and mixed neoplasms generally in old animals, KoRV-associated disease was not observed in Victorian and South Australian koala populations, but was common in Queensland and New South Wales populations (A. Gillett, pers. comm.).

Table 1. Prevalence of KoRV-associated disease in koala admissions to the Australia Zoo Wildlife Hospital (AZWH).

AZWH category/disease	number out of 6001 cases	%
anaemia/myelodysplasia	54	0.9
myelodysplasia	42	0.7
osteochondroma	19	0.3
KoRV–AIDS	143	2.4
other Neoplasia	60	1.0
dermatitis	50	0.8
cryptococcosis	11	0.2
lymphoma (without leukaemia)	8	0.1
leukaemia	49	0.8
lymphoma + leukaemia	55	0.9
total	494	8.2

Conclusions

The genetic similarity of KoRV with other pathogenic gammaretroviruses and the occurrence of a spectrum of clinical conditions in koalas similar to those in other species is circumstantial evidence for its role in causation. However, convincing proof of its role in these diseases has not been elucidated. Further analysis of solid tumours, particularly relating to unique KoRV integration sites, and recent research efforts attempting to link particular KoRV genotypes with disease, may be productive in this regard, or at least provide further evidence for KoRV pathogenicity.

The importance of KoRV in the epidemiology and pathogenesis of chlamydial disease is still poorly understood, and therefore its role in population dynamics and local extinction is unknown. Certainly chlamydial disease has profound effects on fecundity and population persistence in some areas, but less so in other areas, with the causes of these differential impacts open to speculation. Whether KoRV has an important impact on koalas and their conservation remains an unanswered question, and certainly a topic worthy of further research efforts.

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