Review

Tasmanian devil facial tumour disease: lessons for conservation biology

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Tasmanian devil facial tumour disease is an infectious cancer that threatens the largest surviving marsupial carnivore with extinction. After emerging in 1996, it has spread across most of the range of the species, leading to a population decline of more than 60%. This bizarre disease, in which the cancer cells themselves are the infective agent, illustrates some important general principles about disease and conservation biology, including the threat posed by loss of genetic diversity and the potential of pathogens with frequency-dependent transmission to cause extinction.

Introduction: host-specific pathogens and extinction

Since Anderson and May [1,2] first drew ecologists' attention to the significance of parasites and pathogens in the population dynamics of their hosts, the importance of infectious disease in conservation biology has been widely discussed [3–7]. In only one case to date [8] (the Polynesian snail *Partula turgida*) can extinction be unequivocally attributed to a parasite, although there is very strong evidence that the fungal pathogen *Batrachochytrium dendrobatidis*, the causative agent of chytridiomycosis, has been responsible for the extinction of several frog species in both Australia [9,10] and Central America [11] and that avian malaria and bird pox caused the extinction of up to 13 species of Hawaiian land birds [4,12,13]. It seems that the Tasmanian devil *Sarcophilus harrisii*, the largest surviving marsupial carnivore, might be added to this list in the near future. An infectious cancer, devil facial tumour disease (hereafter DFTD), has spread throughout most of the range of the species, leading to a population decline of at least 60% [14]. As a consequence of this disease, the species was formally listed as endangered by the Australian state of Tasmania in May 2008.

In the cases of frog and Hawaiian land bird extinctions, the pathogens thought to be responsible have a range of host species. Extinction was able to occur because one or more of the host species was relatively unaffected by the pathogen and therefore functioned as a reservoir, maintaining a high force of infection on the species threatened by extinction [6]. However, DFTD is entirely host specific. The tumour has never been detected in the other five members of the Tasmanian devil's family (Dasyuridae) present in Tasmania, and its biological nature (discussed below) makes it almost inconceivable that it could infect any other species.

In this review, I show that this unusual disease provides some important lessons for conservation biologists concerning detecting and managing threats posed by emerging disease. This case cautions that species-specific infectious diseases can pose an extinction risk, provided their transmission is frequency dependent. DFTD is an excellent example of how loss of genetic diversity within populations increases threats from pathogens. Finally, it is an ideal case study with which to evaluate the management options available to conservation biologists faced by an emerging disease threat.

The Tasmanian devil and its tumour

With the extinction of the thylacine or Tasmanian tiger *Thylacinus cynocephalus* in the 1930s, the Tasmanian devil became the largest extant marsupial carnivore. Male devils can be up to 13 kg in weight, with females being somewhat smaller [15]. Until the appearance of Tasmanian devil facial tumour disease in 1996, devils were common and widespread across most of Tasmania, with estimates of the population size ranging up to 150 000 [16].

Since European settlement, there is anecdotal evidence that Tasmanian devil populations might have been through a series of substantial fluctuations [17]. It has been proposed that these fluctuations might have been related to the influence of density-dependent infectious disease [18]. In particular, it was suggested that an increase in devil numbers between the mid-1900s and 1990 might have been a recovery following a disease epidemic. However, there is no concrete evidence of any epidemic of infectious disease being observed in devil populations before the appearance of Tasmanian DFTD in 1996, and the external signs of the disease are so gross (see Figure 1) that it is inconceivable that this disease could have been present at high prevalence much before it was first observed. As predators of lambs and domestic poultry, devils were extensively persecuted until at least the middle of the 20th century [15], and the apparent increase in population size since the 1960s until the appearance of Tasmanian devil facial tumour disease might have been related to a reduction in this persecution.

In 1996, a devil with an unusual facial tumour was photographed at Mt William (Figure 2) in the northeast of Tasmania [15]. Although this attracted some interest, the marsupial carnivore family Dasyuridae to which the devil belongs is well known in zoos to be prone to development of tumours [19,20], so the threat that the tumour would prove to pose to Tasmanian devil populations was not immediately apparent. However, over the next five or so years, more individuals were observed with the cancer, with records spreading south and west from the original point

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Figure 1. Tasmanian devil facial tumour disease **(a)** Early tumour on the lower lip. **(b)** Late-stage tumour. Note displacement of teeth. Photographs by Rodrigo Hamede, School of Zoology, University of Tasmania.

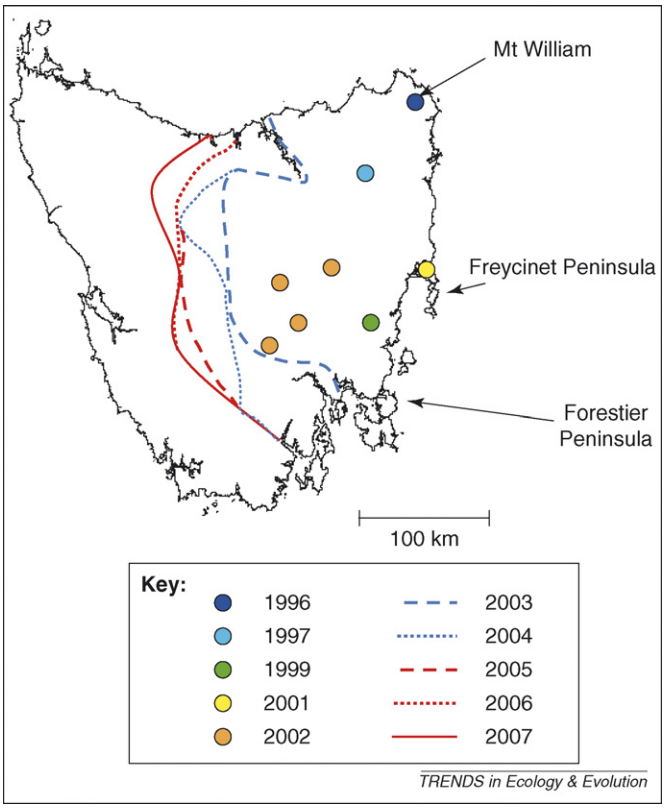

Figure 2. Spread of DFTD since 1996. Data to 2005 inclusive are from Hawkins *et al.* [16], updated with information from McCallum *et al.* [22] and Tasmanian Department of Primary Industries and Water [14] Individual locations where disease was reported are shown until 2002. After 2002, reports at new locations became more frequent (37 in 2003, 57 in 2004) and so envelopes drawn by hand around the distribution of records up to and including that year are shown for 2003 onward.

of discovery (Figure 2), and substantial population declines and changes in age structure of Tasmanian devil populations began to be observed [16,21,22].

Devil facial tumour disease is a very unusual infectious cancer. Karyotypes [23] and molecular genetic evidence [24] show that all tumours are a single clone, derived from one individual devil. Tumours are genetically different from their hosts [24]. This means that the tumour cells themselves are the infective agent and the tumour is an infectious cell line: essentially a clonally reproducing mammal that is an obligate parasite. Primary tumours occur on the face or in the oral cavity, but metastases elsewhere are common [25]; death is thought to occur from a combination of factors, including inability to feed, secondary infections and metastases [26].

It likely that the tumour will occur across the entire range of the devil within five to ten years [22]. In areas where disease has been present for some time, mark-recapture methods have estimated declines of up to 90%, with almost complete disappearance of animals older than two years [21,27]. This is especially alarming because devils usually do not begin to reproduce until two years of age and normally live up to six years in the wild [21].

Over the total range of the species, the population decline, as estimated by broadscale spotlighting surveys, exceeds 60% [14]. Once clinical signs of the tumour have been detected, there is almost 100% mortality within six months. In affected populations, prevalence among two-year-old animals exceeds 50% (H.McC., unpublished data). Given this information, it is not surprising that mechanistic models and rates of decline estimated from mark-recapture data from the best-studied site at Freycinet National Park (see Figure 3) both project extinction within five years [22].

When does a host-specific pathogen cause extinction?

Epidemiological theory suggests that a host-specific pathogen is unlikely to cause extinction. Most infectious diseases have a threshold host density below which the basic reproductive number R_0 is less than one, meaning that each case of infection is replaced by less than one case in the next disease generation. This threshold means that the pathogen should disappear from the population before extinction occurs [6].

There are some important exceptions to this generalisation, however. A threshold host density exists only if the contact rate between susceptible and infected hosts depends on host density. However, if the rate at which hosts contact each other is independent of population density, the transmission rate depends on the proportion of those contacts that are with an infected host. This is

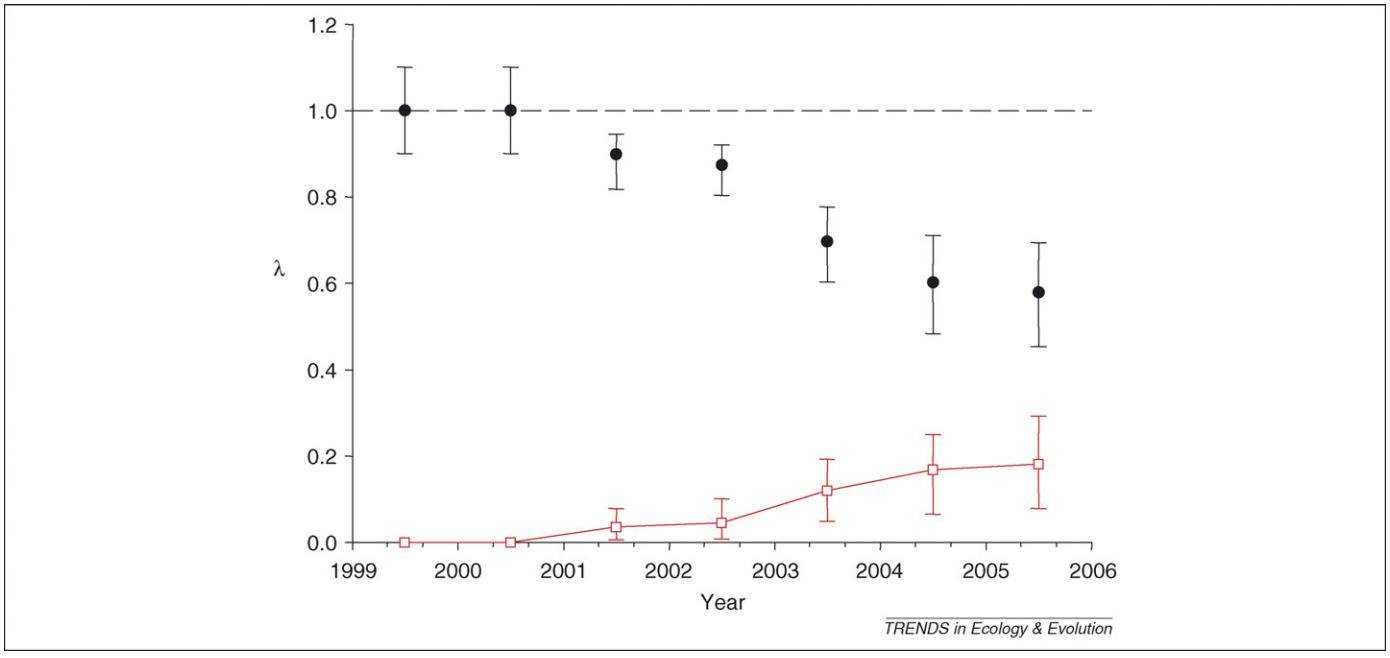

Figure 3. Effect of DFTD on the growth rate of the devil population on the Freycinet Peninsula, Tasmania. The finite rate of increase of the adult (two years and older) portion of the Tasmanian devil population on the Freycinet Peninsula, estimated from Pradel mark-recapture methods [71], is shown in black, with solid symbols. Before the disease arrived in 2001, the adult population was stable, with a finite rate of increase very close to 1. The value of λ of 0.6 means that the adult population is now declining by ~40% per year. The prevalence of DFTD in the total devil population over the same period is shown with red open symbols. This prevalence includes subadults (one- to two-year-olds), which have much lower levels of disease than adults. From data in Lachish *et al.* [27].

known as frequency-dependent transmission [28]. In this situation, there is no threshold density and extinction of a sole host is therefore a possible outcome [29]. Frequency-dependent transmission is often associated with sexually transmitted diseases, because the number of sexual partners per unit of time is determined by the mating system of the species rather than population density [28]. Once a population has declined sufficiently that the frequency of mating is reduced, the species is subject to an Allee effect [30,31] and thus might be unable to maintain its numbers.

There is limited direct evidence concerning the mechanism of DFTD transmission in the wild. The tumour cells are thought to be spread between individuals by biting, which occurs frequently during sexual encounters and during aggressive interactions over food [22]. Rates of biting, particularly bites to the head, are especially high in the mating season [32]. Further, DFTD is very rare among sexually immature animals [16]. It therefore appears that DFTD might have many of the characteristics of a sexually transmitted disease and might be expected to have frequency-dependent transmission. Another line of evidence supporting this is that disease prevalence has remained very high in infected populations, even as density has been reduced by up to 90% [22]. The disease is therefore one of the first examples in which it appears that an infectious disease with frequency-dependent transmission is likely to cause extinction.

Consequences of low genetic diversity

Conservation biology textbooks emphasise the possible negative consequences of loss of genetic diversity within populations [33], and management strategies, particularly of captive populations, have concentrated on maintaining genetic diversity [34]. The long-term consequence of loss of genetic diversity is lack of evolutionary potential to respond to novel challenges such as environmental change. In the short term, in addition to inbreeding depression [34], inability to respond to pathogen infection has been suggested as one of the problems posed by loss of genetic diversity [35].

In particular, diversity in the major histocompatibility complex (MHC) region is critical [36]. The MHC is the most polymorphic part of the mammalian genome [24]. It is important in discrimination between 'self' and 'non-self' and is therefore associated both with transplant rejection and resistance to infectious diseases [37]. Whereas it is the latter function that has usually been considered of most importance in conservation biology [38], DFTD is analogous to a tissue transplant, so it is the former function that is probably of more significance in this case. Genes encoding the MHC are divided into two broad classes. Class I loci present peptides derived from within the host cell and are therefore important in transplant rejection and immune responses to intracellular pathogens such as viruses, whereas class II loci are associated with immune responses to extracellular parasites such as most bacteria [39]. In eutherian mammals, classes I and II are physically separated, but it appears in marsupials that they are intermixed [37]. Whether dealing with class I or II, the higher the heterozygosity in the individual host, the more likely it is that a given immune insult will be recognised, and the greater the genetic diversity in the host population as a whole, the more likely it is that the population will be able to respond to an infectious disease threat.

Direct empirical evidence of an association between MHC heterozygosity and resistance to parasitic infection has only been found in a limited number of cases [40], with several studies failing to detect any relationship [41]. Some

endangered species have passed through extremely tight population bottlenecks, with no obvious increase in susceptibility to infectious disease [42].

In the case of the devil, there is very clear evidence [24] that it is loss of MHC diversity that is allowing DFTD to spread throughout the population in the east of Tasmania, with the threat of overall extinction of the species. Devil populations in Tasmania have extremely low genetic diversity, as measured by microsatellites, with both lower heterozygosity and allelic diversity than either other Australian marsupials or most other carnivores [43]. This suggests that the population passed through a bottleneck at some point in the recent past, possibly around the time of the last ice age, after which rising sea levels isolated the island of Tasmania from the remainder of Australia. At MHC class I loci, all Tasmanian devils in the eastern part of the state (which is the main area currently affected by the disease; see Figure 2) are so similar genetically that they have been described as having 'functionally identical' MHC types [24]. Despite devils possessing a competent immune system [44], tumours are therefore not recognised as foreign by the host devil's MHC [24].

Why are cancers of this kind so rare?

There is only one other infectious cancer similar to DFTD currently known in the wild, canine transmissible venereal tumour (CTVT; Box 1). In addition, there is a transmissible cancer of golden hamsters, but it is known only from inbred laboratory populations [45,46]. The existence of the two tumours in wild populations demonstrates that such transmissible cell lines have the potential to arise. It appears that low genetic diversity in the host population is a precondition: although domestic dog populations have high genetic diversity, it is hypothesised that CTVT first appeared in an inbred population and only subsequently evolved the ability to 'hide' from the host immune system [47]. There are certainly many highly inbred populations of numerous species, and it is perhaps surprising that there are no other known incidences of similar tumours. One possibility is that such host–cancer associations might be evolutionarily unstable. Given that the tumour is a single clone, and that cancers are notoriously genetically unstable [48], the clonal line could be expected to accumulate deleterious mutations, which, following the principle of Muller's ratchet, could not be eliminated, leading to a progressive deterioration in fitness [49]. It might therefore be the case that such tumours appear with some frequency in inbred populations but disappear before they can be detected. Alternately, if tumours of this type are often as lethal as Tasmanian devil facial tumour disease, they might rapidly drive their local host population to extinction, with the consequent disappearance of the tumour itself. Both CTVT and DFTD appear to be transmitted in a frequency-dependent fashion: given that transfer of live cells between hosts is required for tumour transmission, intimate contact, such as occurs in sexual contacts, is required.

Managing DFTD

The tools available for managing any infectious disease in free-living wildlife are limited [50,51]. One possibility is to isolate uninfected individuals, and a second possibility is suppression of disease by culling. A third option is to try to identify or select for resistant animals, which could then be released into the wild. Finally, there is the possibility of developing a vaccine.

Isolation

Bringing uninfected animals into captivity where they can be isolated from the threat of infectious disease is an obvious first step, which has already been undertaken

Box 1. Canine transmissible venereal tumour

Canine transmissible venereal tumour has been well known to veterinarians as a transmissible cancer since the 19th century and is found on all continents except Antarctica [70]. As its name suggests, primary tumours occur on the genitalia of dogs, although metastases can occur elsewhere. Tumours are spread between individuals by the direct transfer of cells during sexual intercourse. Although it has been known for some time that transmission occurs only by transfer of viable tumour cells [70], it was only with recent molecular work [47] that it was conclusively shown that all tumours are members of a single clone and that the tumour is not of viral origin. The tumour is the 'oldest known somatic mammalian cell in continuous propagation' [47]. It has very low microsatellite variability and it is estimated that the clone is somewhere between 200 and 2500 years old. Unlike DFTD, which appears to be only able to propagate because of very low MHC variation in the host population, CTVT is able to establish on hosts with a variety of MHC types (even including other canids such as jackals and foxes) by down-regulating MHC expression on the tumour's cell surface, thus 'hiding' from the host immune system [47]. Figure I shows a neighbour-joining tree based on 21 microsatellite loci of 11 dogs (A–M, top) and their tumours [47]. It is clear that the tumours are closely related to each other and different genetically from their hosts.

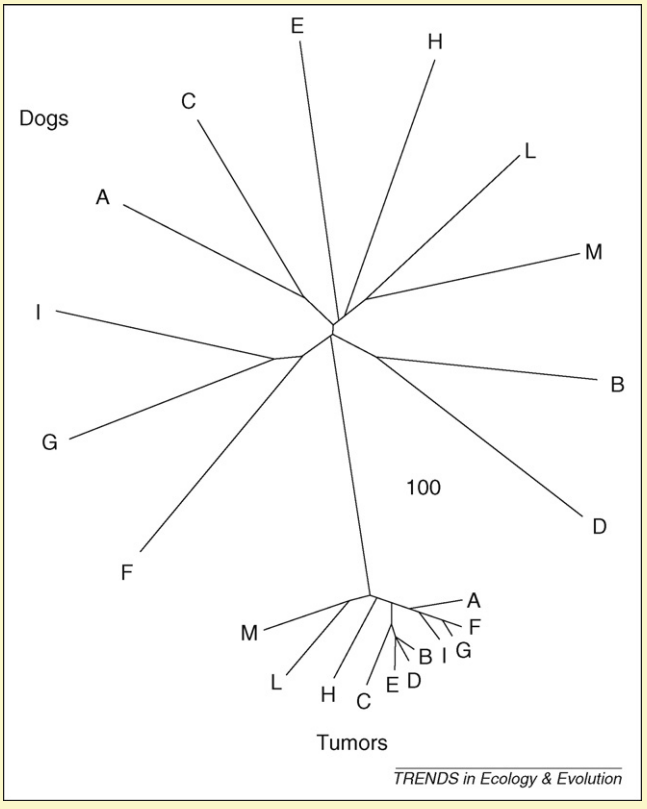

Figure I. Neighbour-joining tree based on 21 microsatellite loci of 11 dogs (A–M, top) and their tumours (A–M, below). Reprinted from Ref. [47] with permission.

[52]. However, whereas close-order captive management theoretically enables matings to be controlled so as to maintain genetic diversity, evolutionary changes and selection for animals that are most able to reproduce in captivity will inevitably occur if not all matings are successful [53]. This might not ensure maintenance of genetic characteristics most suitable for survival in the wild. Further, behavioural changes in captivity are almost inevitable and the history of reintroductions to the wild from captivity is chequered at best [54,55].

Another option for the Tasmanian devil is to introduce the animals to offshore islands. This raises a variety of issues related to impact on other species that are present on the islands. The introduction of predators to islands in the Southern Hemisphere has produced a wide range of problems [56], although in every case these have been predators to which the island fauna have had no previous evolutionary exposure [57]. Several islands off the Tasmanian coast might potentially be suitable for devil introductions. None has supported a devil population in historic times, but all the species present on these islands coexist with devils on main island of Tasmania. The debate as to whether it is legitimate for conservation purposes to introduce species to locations outside their historic range has parallels with the debate surrounding 'assisted migration,' which is suggested as a response to climate change [58].

Protecting uninfected populations *in situ* with some form of barrier is an attractive option, as it would maintain the ecological function of the devils as the top predator in the ecosystem. However, despite the success in South Africa of fencing (in association with vaccination) to prevent foot and mouth disease incursion [59], fencing out an infectious disease is likely to be an expensive and difficult option. In conclusion, any sensible isolation strategy needs to cover a variety of options rather than placing all eggs in one basket.

Disease suppression

'Stamping out' by culling is the standard response to an exotic disease incursion in livestock. With hindsight, culling all devils in the region of northeastern Tasmania where the disease first occurred could have removed the disease threat to the entire species. However, with the knowledge that existed at the time, mass extermination of an iconic native species could not have been justified. Another problem with culling in wildlife is that the increase in movements and dispersal that can occur following removal of substantial proportions of an existing population might cause the rate of disease spread to increase, as has been the case with badger removal to suppress bovine tuberculosis in the United Kingdom [60]. There are preliminary indications that a concerted attempt to remove all infected individuals might have slowed the rate of DFTD progression in the semi-isolated Forestier Peninsula in southeastern Tasmania [52]. Whether euthanasia of all infected devils trapped in routine monitoring is desirable has been quite controversial. In an open population, culling is unlikely to have any major impact on disease prevalence at a population level and clearly will limit knowledge of disease progression and spread in unmanipulated populations.

Selection for disease resistance

This is potentially a long-term solution to the threat posed by DFTD. However, there is currently no firm evidence that any animals are either totally or partially resistant to disease. Populations in the west of Tasmania (which is currently uninfected, although the disease is moving steadily westward) are weakly genetically differentiated from those from the east coast [43]. Whether the observed differences in microsatellites reflect functional MHC differences and whether such differences would be sufficient to make some west coast animals resistant is still unknown. Further, it is possible that the tumour itself might evolve in an adaptive fashion (as appears to have happened with canine venereal transmissible tumour: see Box 1), so that even if some west coast genotypes are currently resistant to disease, this might not be the case in the future.

Vaccination

Finally, there is the possibility of developing a vaccine. Very few vaccines have been developed against any cancer. The fact that all DFTD cells are virtually identical genetically might make developing a vaccine possible [44]. A counterargument is that, given that the disease is able to transmit because it is not recognised by the host immune system, it is unlikely to be a suitable target for a vaccine (which relies on stimulating an immune response). Even if a vaccine were to be developed, there would be the challenge of distributing it in a wild population on a broad scale. This has been done for rabies vaccination in foxes in Europe and raccoons in the United States [61], but only after considerable research effort and expense.

What we have learned: implications for conservation biology

An obvious lesson from DFTD is the importance of early action in addressing emerging disease threats. Because its infective nature was not recognised early, DFTD already occupies the majority of the range of the devil, which makes eradication of the disease with any form of culling, whether of all animals or infected animals only, almost impossible. Most disease threats to endangered species are from known pathogens, for example rabies [62,63], distemper [64,65] or avian malaria [13]. Surveillance can therefore follow normal veterinary practices such as serological testing. This is not possible for an as yet unidentified pathogen. In the cases of DFTD and chytridiomycosis, the lag between disease emergence and recognition of the actual threat posed was substantial because these were entirely new infectious agents. Large-scale frog declines first occurred in Australia as early as 1979, but it was not until 1996 that disease was suggested as the cause of decline [66] and the infectious agent *Batrachochytrium dendrobatidis* was not identified until 1998 [10]. The delay between the first appearance of DFTD in 1996, the general recognition that it was an infectious agent (around 2004 [67]) and its identification in 2006 [23] was somewhat shorter, but earlier recognition of its infectious nature would have greatly assisted in its control.

Identification of the causative agent of a disease is not crucial for many management strategies, but early recognition that the disease is infectious is critical [51]. To detect

future emerging disease threats in other species, it is important to establish syndromic surveillance [68], so that wildlife biologists witnessing unusual declines can share information about common features that might indicate the action of an unidentified infective agent.

A second lesson is that not only multihost pathogens with reservoir species are important in conservation biology. Host-specific pathogens such as DFTD can pose major extinction risks if their transmission is frequency dependent. Determining whether and how a pathogen's transmission depends on host density remains difficult from field data [28,69]. However, transmission associated with sexual contact, vector-borne transmission and prevalence remaining high even after population crashes are all warning signs that transmission might well be frequency dependent.

Finally, DFTD is the clearest example to date of loss of genetic diversity in a species leading to the emergence of a pathogen that threatens to cause the extinction of the entire species. With the loss of genetic diversity within populations becoming increasingly common because of habitat loss and fragmentation, it remains to be seen whether cancers transmitted as infectious cell lines will remain bizarre oddities, or whether they will become increasingly common. Certainly, wildlife biologists need to vigilantly investigate unusual cancers in inbred populations or species with low genetic diversity.

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