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Aspects of the fatal malignant disease among the Tasmanian devil population (*Sarcophilus laniarius*)

Aspetti della malattia maligna mortale tra la popolazione dei diavoli di Tasmania (Sarcophilus laniarius)

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Summary

The world's largest remaining marsupial carnivore, the Tasmanian devil (*Sarcophilus laniarius*, formerly *harrisii*) has over the last ten years been found to be suffering from a previously unknown and invariably fatal malignancy, now known as Devil Facial Tumour (DFT), which results in disfiguring and debilitating tumours of the facial skin and within the oral cavity. The disease has caused high mortality by apparently infectious spread and, with its high prevalence, seriously affects the continuing viability of the species. In the face of this epizootic, the devil has now been listed on Tasmania's and on Australia's threatened species registers as "vulnerable", below "endangered", "rare" and only one more step before "extinct". This paper describes the research challenges and outlines some approaches to the investigation of DFT pathobiology and aetiology. The environment of Tasmania is widely contaminated by human activities, whose residual health effects on native wildlife are unknown. The Tasmanian devil is the major carnivore at the head of a diverse native animal food chain of grazing herbivorous marsupials. The rôle of bioaccumulated persistent organic pollutants and possibly genotoxic chemicals requires investigation as do conventional infectious pathogens such as exogenous and endoge-

Riassunto

Negli ultimi dieci anni si è scoperto che il più grande marsupiale carnivoro rimasto al mondo, il Diavolo di Tasmania (*Sarcophilus laniarius*, in passato *harrisii*) è colpito da un tumore maligno precedentemente sconosciuto ed invariabilmente fatale, oggi conosciuto come Tumore Facciale del Diavolo (*Devil Facial Tumour* = DFT), che comporta tumori sfiguranti e debilitanti localizzati nella cute del muso e all'interno del cavo orale. La patologia causa alta mortalità con andamento apparentemente infettivo e, con la sua alta prevalenza, mette seriamente in pericolo la sopravvivenza della specie. Di fronte a questa epizoozia, il diavolo è stato ora inserito nel registro delle specie minacciate in Tasmania e in Australia come "vulnerabile", sotto a "in pericolo", "raro" e solo un posto prima di "estinto". Questo articolo descrive le problematiche della ricerca e indica alcuni approcci di indagine sulla patobiologia ed eziologia del DFT. L'ambiente della Tasmania è fortemente inquinato dalle attività umane, i cui effetti sanitari sulla fauna selvatica indigena sono sconosciuti. Il diavolo di Tasmania è il principale carnivoro a capo di una catena alimentare indigena diversificata di marsupiali erbivori che brucano. Il ruolo di agenti inquinanti organici, bioaccumulati persistenti e forse anche di agenti chimici genotossici richiede un

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nous viruses (or their genomes). Several potentially analogous conditions of known viral origin are described and recently the likelihood of infective cellular transmission from devil to devil has been reported. The risks inherent in any disease of unknown origin with potential to spread to other species cannot be overstressed. Eur. J. Oncol., 11 (2), 95-102, 2006

Key words: **Tasmanian devil facial tumour, environmental toxins, endogenous and exogenous viruses**

approfondimento, così come i patogeni infettivi convenzionali quali virus esogeni ed endogeni (o i loro genomi). Vengono descritte molte condizioni potenzialmente analoghe di origine virale conosciuta e recentemente è stata riferita la possibilità di una trasmissione di cellule infette da diavolo a diavolo. I rischi legati a qualsiasi patologia di origine sconosciuta con la possibilità di diffondersi ad altre specie non possono essere sottovalutati. Eur. J. Oncol., 11 (2), 95-102, 2006

Parole chiave: **tumore facciale del diavolo di Tasmania, tossine ambientali, virus endogeni ed esogeni**

Introducing *Sarcophilus laniarius*

Since the opening of the Bass Strait between Tasmania and Australia by rising sea levels as a consequence of climatic change some 12,000-10,000 years ago, the world's only two large marsupial carnivores have found safe haven in the island state. The last known specimen of the thylacine (*Thylacinus cynocephalus*), colloquially known as the Tasmanian Tiger, died in a Hobart zoo in 1936. Despite extensive searches, the species is now widely thought to be extinct, bounty-hunted out of existence because of its believed predatory attacks upon livestock, particularly sheep and chickens[1].

Meanwhile, although the Tasmanian devil became extinct on the Australian mainland perhaps 450 years ago[2], it has survived, successfully adapting with the environment in Tasmania (fig. 1) and achieving large numbers - perhaps 150,000 in 1990[3] - and has reached an almost iconic status locally, widely contrasting with its Disney-esque characterisation abroad.

The devil is a powerfully built carnivore of up to 13 kg (males average 12 kg, females 7-8 kg) that is secretive and usually shy of people[4]. Fertility commences between one and two years of age and a female will usually rear only one litter of up to four cubs per year. Fertility decreases from the age of five and senescence and death occur by six years[5]. In any year and over her lifetime, a female will have had several sexual partners. Young are pouch-fed and incubated for about 25 weeks and become independent at about 40 weeks old. Mortality is high in the first year of independent life[5]. The devil in its environment performs services similar to those of the hyaena[6]. In one recent case in South Africa's Kruger National Park, a hyaena has been found with a spontaneous, highly anaplastic fibrosarcoma originating from the buccal mucosa (Bengis R., personal communication). The

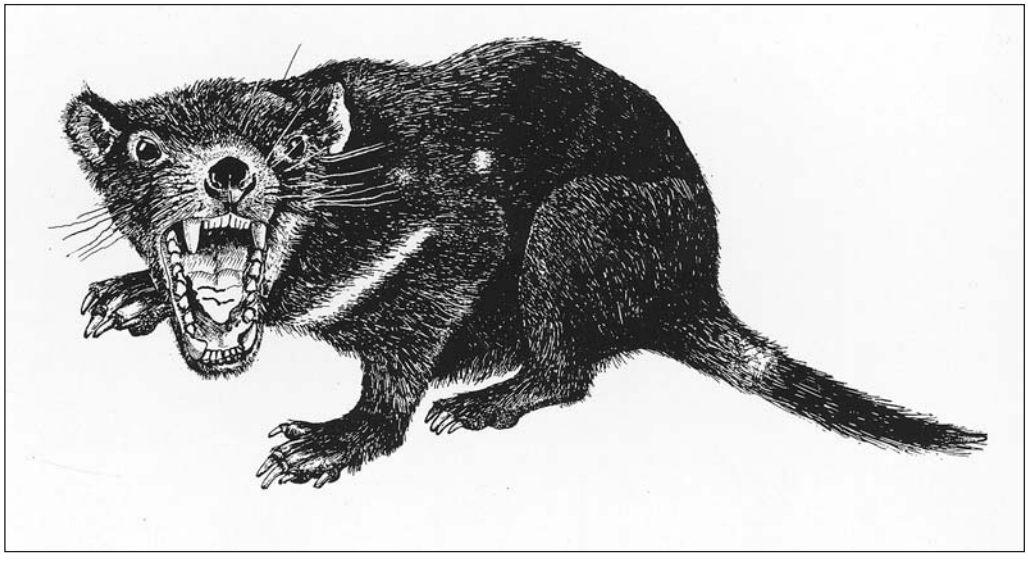

Fig. 1. *Sarcophilus laniarius,* acknowledgement Larry A. Belbin, 1983

Tasmanian devil and the African hyaena (*Crocuta crocuta*) are also both known to prey upon young and weak animals of their own species as well as carrying out useful and hygienic work by cleaning their habitats of road-kill, carcasses, carrion and the like. As a consequence of these cannibalistic and scavenging habits, devil carcasses are not generally found in the wild.

Like other dasyurid marsupials, the Tasmanian devil has six pairs of autosomal chromosomes and two sex chromosomes (XX/YY), with the Y chromosome being minute[7]. Very low genetic diversity, taken together with the known long-term history of major falls in population numbers, followed each time by recovery[8], supports the theory of a nucleus of population founders with a small genetic pool typified by low heterozygosity and low allelic diversity. These features may reflect island effects and repeated periods of fluctuations in the devil population numbers[9,10]. Some additional alleles, not represented in the dense eastern devil populations, occur in the lower-density western ones and this allelic variation may have important implications for the long-term survival of the species[9].

The Devil Facial Tumour (DFT)

Several types of neoplasia are known in the larger dasyurids, particularly among captive Tasmanian devil populations; skin and mammary adenomas or adenocarcinomas and squamous cell carcinomas with metastatic spread to the lungs are common[11-13]. In recent years the devil has fallen victim to a mysterious and fatal disease, previously unknown (figs. 2, 3), and first observed in 1996 among the high-density, contiguous populations of the far north-east of Tasmania[14]. DFT was described in February 2005, as "a unique disease with no diagnostic test or vaccine and no understanding of its cause, transmission, its lag time or potential to affect other species"[15]. At that date only adults had been found with the disease: by March 2006 juveniles (under two years old) were also affected[16].

The disease is characterised by disfiguring and eventually debilitating tumours involving the subcutaneous tissues of the face, muzzle and oral cavity[17]. The clinical signs and histopathology of DFT are now clear. Large, rapidly increasing tumours are erosive, fungating and ulcerating lesions with metastases to cervical and submandibular lymph nodes. Multi-focal secondary tumours occur; commonly in the lungs and, less commonly, in the spleen, kidney, heart, mammary gland and brain[16]. Tumours are almost certainly transmissible between devils[7] and are currently described as anaplastic, round cell sarcomas of neuroendocrine origin[17]. Such tumours are rarely seen in humans[18]. To date no basic morphological and pathological definition has been published, although the cancer shows constant gross anatomical, histological and structural properties[7]. In addition, the karyotype of neoplastic cells from eleven devils shows a consistent chromosomal anomaly including the presence of three marker chromosomes whether these cells are derived from different tumours in the same animal or between different animals[7]. The disease is progressive and invariably fatal, with no evidence of spontaneous remission or regression[14]. Animals usually die within a few months of the lesions appearing. Particularly in high-density populations, numbers may have been reduced by an estimated 50% in as little as three years[15]. By contrast, no incidence of DFT in the devil populations of the State's wildlife parks has been reported[15]. This may relate to absence of potential infectivity, differing environmental risks, social contacts among captive devils[19], or by possessing an immune system not compromised by toxic chemicals in their protected habitat.

The geographic distribution of DFT

As a means of determining the spatial distribution of DFT, field monitoring of the geographical spread is difficult and possibly unreliable. Mapping has had to proceed on only manifestational bases of where diseased animals have been captured. At present, diagnosis can only be based on the presence or absence of observed tumours on the skin of trapped devils whereas histology would provide a more specific test. A screening test for devils incubating DFT either by marker protein, antibody presence or genomic fingerprint is an urgent need. It is therefore not at present possible to ascertain where or when any population is totally clear of disease. Pre-clinical stages of DFT will not normally enter the record, although in one case a devil was found asymptomatic but believed to be positive for DFT[20]. Capture-release-recapture surveys prove that devils without visual DFT lesions may subsequently develop grossly obvious cancers in a matter of months[20]. Prevalence-by-area calculations are further hampered by loss of animals due to possible local variations in other causes of devil mortality, especially old age deaths and road-kills.

Accepting these difficulties, the Tasmanian Department of Primary Industries, Water and Environment (DPIWE) reports that DFT is widespread across some two-thirds of Tasmania's total area of 26,383 sq ml (68,331 sq km), predominantly in the east, centre and north-east[20]. Early results from trapping had quickly

Fig. 2. Healthy young adult male

Fig. 3. Diseased juvenile devil with tumour, aged approximately 13 months

distinguished between areas containing only healthy devils in the west from those with confirmed cases of DFT, broadly in the east (fig. 4).

A presumed spread of the pattern from an initial index region of occurrence in the far north-east of Tasmania, where devils were previously at high density, may be occurring into the west and north-west of the state where diseased animals have previously not been recognised[21]. New cases of DFT are being detected along the extreme western boundary of the current range. This has led to speculation that natural boundaries, such as major river courses or other environmentally adverse conditions for devils may delay or limit spread[21] (fig. 4). Lower densities of devil populations in western Tasmanian habitats may reduce direct animal to animal contact and hence slow the progress of cancer in these areas.

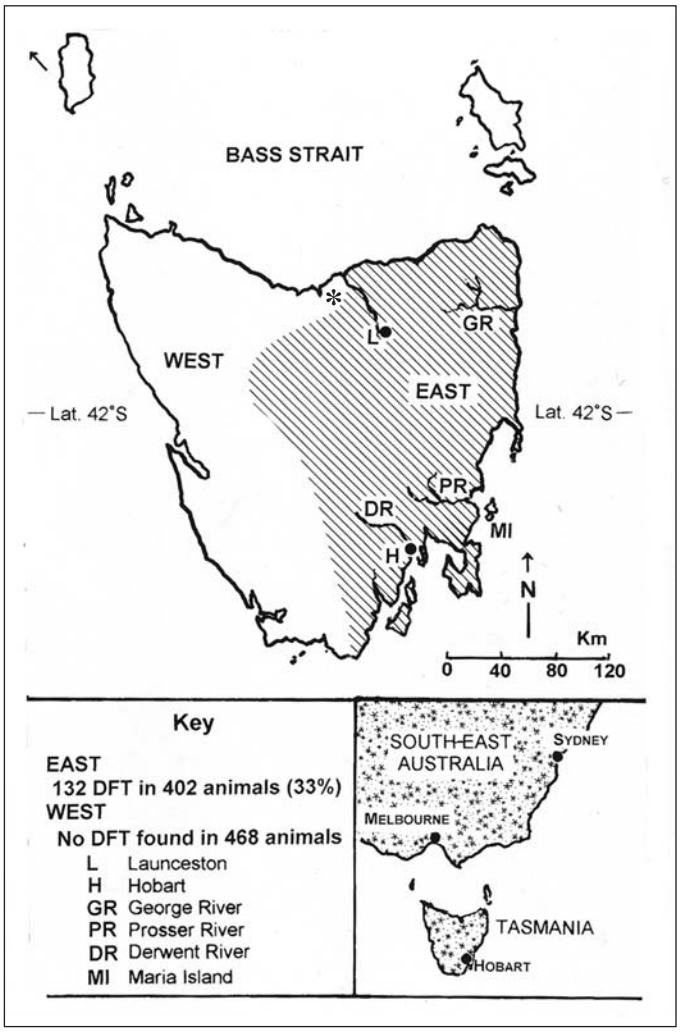

Fig. 4. Occurrence of DFT in Tasmania up to 31 December 2004 (From DPIWE[20])
* A diseased devil was found in January 2006 as a road-kill north-west of Launceston in a previously disease-free area

Ensuring species survival?

The serious threat of extinction posed by DFT, with an estimated 75,000 dead animals in eight years, has caused concern regarding how best to protect and save the species. The task of researching and protecting the Tasmanian devil has been largely controlled by the DPIWE, in conjunction with the University of Tasmania's Zoology Department and other authorities[20]. Major effort by the DPIWE has gone into monitoring the progress of the disease in wild populations of devils and in developing a more detailed understanding of the natural demographics of these animals[5].

One response by the DPIWE has been to isolate "insurance" populations of DFT-free healthy devils (based on visual assessment of trapped animals) from their wild kin[19]. Captive holding pens at an urban quarantine facility and on an offshore island (Maria Island, see fig. 4) are currently being utilised. From a total of 25 apparently unaffected post-weaning juveniles derived from a population considered DFT-free, two female devils selected as healthy in one such "Noah's Ark" population had developed facial tumours within three and ten months of capture. In the absence of a pre-clinical diagnostic test or any firm understanding of routes of transmission, the disease status and infectivity of progeny reared from these females would be questionable. The selection of animals for insurance purposes requires isolation facilities for each animal. Risk is also sharply increased if such animals are selected from devil populations known to be affected by DFT. Facilities in other Australian states are loath to receive Tasmanian devils without lengthy quarantine because, as this scenario has demonstrated, "… rapid development of lesions can occur in previously visually-free animals"[19]. Any captive insurance population is subject to the additional long-term burden that "… the genetic diversity of devils is not large enough to maintain an isolated population for longer than about five years"[19].

A second response centres on the multiple peninsula character of Tasmania's coastal outline. The objective has been to create peninsular zones artificially freed of infection by re-doubling culling efforts locally in the Forestier and Tasman peninsulas until no infective animals can be found to remain. A single road bridge connects these areas to mainland Tasmania and diseased animals trapped beyond it are being euthanased (Hamilton J., personal communication) although viral-contaminated faeces would remain. The trial will assess the effect of culling diseased devils from defined peninsular areas and preventing the ingress of devils from the mainland of Tasmania. If this method is successful, other areas may be selected for similar treatment but, again, the lack of a pre-symptomatic diagnostic test will become a significant limitation on assessing the effectiveness of this approach.

Unlike other neoplasms of Tasmanian devils[11-13], the spontaneous appearance and high prevalence of DFT suggests an unusual aetiology which remains only partially elucidated[7]. With limited scientific literature on DFT to date, defining the pathobiology and aetiology has been protracted and has focussed on collecting field data in free-ranging populations and on laboratory studies of histopathology and cytology. Two main hypotheses are now suggested here[22]: an initiating environmental trigger for the presence of viral infections, or activated oncoviral gene sequences, or both.

Environmental hypotheses

One aetiological contender, either as a primary, triggering or contributory factor, is pollution in Tasmania, where a wide variety of potentially noxious and cumulative chemicals has been used as herbicides, insecticides and animal poisons[23]. The highly toxic sodium monofluoroacetate (commonly known as 1080) has been used for some 50 years and is now in widespread use by forestry companies and agriculturalists to protect young plantation trees and farmlands from herbivorous wildlife. Widespread use of poisons has particular implications for top-order scavenging species such as devils, and poisoned native herbivores have ensured a constant supply of carcasses to support artificially high devil populations as well as introducing highly toxic agents into their habitat. While dogs and foxes are known to be very susceptible to secondary 1080 poisoning (indeed, they can die outright[24]), it is not known whether this poison causes any sub-lethal effect on devils, such as lowering their immunity to infection.

Meanwhile, due to their perceived habit of preying on weak livestock, devils themselves have been targeted for poisoning. Mevinphos (Phosdrin®), which causes high mortality, especially among dispersing juveniles in early summer[25] is suspected of being genotoxic[26] and was in wide use in north-east Tasmania in the early to mid-1990s, specifically to kill devils (Cronin S. personal communication), before being withdrawn from commercial sale in 1997. This period and location would therefore cover the first recognised sighting of a devil with DFT in 1996. Moreover, while scavenging, the devil's facial tissues would be the first point of contact with toxins in carrion. The actual mechanism whereby devils survive acute exposure to an index event and then go on to develop neoplastic cells is unclear. Pollutants and other compounds that become long-lived environmental contaminants are known to affect the normal function of mammalian genes, even at extremely low exposure levels, and can also lead to the bioaccumulation of lipophilic organic pesticides. The toxicological effects of both 1080 and mevinphos as well as some eight other agricultural chemicals on the devils' health and procreation are not clear. All these need unequivocal definition.

Infective transmission of DFT: cellular and viral

Two actions are compatible with the presence of primary tumours on the head, either or both of which suggest direct transmission of infectious material by facial biting[7,14]. The first could be the direct transfer of infected malignant cells and the second could be viral transmission, with neither of these being necessarily incompatible with the other.

Endogenous cellular transmission

Pearse and Swift[7] have recently shown that the chromosomes in the tumours have undergone a rearrangement identical in each animal studied (n=11). In the light of this and of the known fighting behaviour of the devils[25], these authors propose that the disease is transmitted by allograft, whereby infectious cells are directly passed between the animals by facial biting.

The only known analogue with this process is canine transmissible venereal tumour or sarcoma (CTVT)[27] (which also occurs in other *Canidae* such as foxes, coyotes and wolves). The cells are easily transplanted and, moreover, are known to respond well to chemotherapy. Both naturally-occurring and experimental transplants of CTVT show an initial stage of rapid tumour growth followed by spontaneous regression and remission[28], whereas no such regression is seen in DFT.

The hypothesis therefore states that, in devils, the direct transfer of viable neoplastic cells from facial sarcomas could implant as infective cells or allografts between affected and unaffected animals[7]. This could account for the apparently contagious or infectious pattern of spread observed, but would necessarily assume that these xenograft cells have the capacity to evade the recipient's major histocompatibility complex (MHC) and are not recognised as "non-self".

In vitro cultures of cells from DFT cases showing consistent chromosomal alteration[7] imply that this unique cancer epizootic was derived from a single source origin of a particular tumour cell clone with viable cells transformed from infected (and infectious) devils to others through direct bite inoculation. Confirmation of this direct transmission of DFT cells to "uninfected" devils will lie in successful laboratory or field transplantation of infected cells from donor to recipient devils.

Evidence that these xenograft cells evade immunosurveillance by cell-mediated and humoral immune function in their new hosts would be a further significant discovery. Such a theory might be supported by the generally low heterozygosity recorded in Tasmanian devils across their range and by the ability of cancer cells to evade the MHC within the whole population. If neoplastic cells, experimentally inoculated, are to establish and proliferate in recipient disease-free devils – as in natural DFT cases – then proof of this means of transmission would assist substantially in understanding DFT in devil populations.

Conventional exogenous oncoviruses

A second causative hypothesis suggests that transmissible oncogenic viruses could well be the primary infective agents of DFT; transmission of CTVT with cell-free filtrates was mentioned as long ago as 1960[28] and C-type particles were reported in 1970 to be associated with CTVT[29], implying that the agent of DFT may also be a C-type retrovirus. Clearly, a fresh look at this possibility produced by old evidence is indicated. Similarly, DFT might represent the resurgence of an ancient virus such as that responsible for the transmissible infection of seven species of marine turtle[30, 31], including some in Australia[32].

The transfer of an oncogenic virus, perhaps encoding an active oncogene infection, should not be ruled out. There are now numerous examples of viruses successfully crossing from one species to another[13]. Human-induced changes to natural ecologies, new intensive animal husbandry systems or dietary regimes, global movements of live or processed animal products, unusual wild animal migrations or overpopulations are among the recognised catalysts for the emergence of new pathogens or disease syndromes which may lead to serious epizootics or epidemics.

By analogy with other cryptic virus with ability to cross species boundaries[33, 34], even a mutation from a known virus or viral gene may yet be found to be the underlying cause of DFT. At least two retroviruses known to occur in the domestic cat (*Felis catus*) population[35], and presumably also in feral cats common in the Tasmanian bush, offer another cross-species retroviral possibility. The danger in this case would extend to other Tasmanian dasyurids, such as the Spotted-tail and Eastern Quoll (*Dasyurus maculatus* and *D. viverrinus*) populations, or even to other mammalian species.

If DFT were due to a conventional exogenous oncovirus, this could produce cryptic oncogenic insertions into the host genome. Many known oncogenes have now been isolated from RNA viruses and would be comparable with gamma retroviruses such as Feline Leukaemia Virus (FeLV) and Koala (*Phascolarctos cinereus*) Retrovirus (KoRV), both of which lead to immunosuppression and high prevalences of lymphoreticular tumours. KoRV is unusual in that it is a truly endogenous, yet highly active, retrovirus that is transmitted vertically from parents to offspring *via* the gametes. KoRV is present in virtually all koala populations in Australia[36] and is closely related to the exogenous, horizontally transmitted Gibbon Ape Leukaemia virus. In some host species, for example cats, FeLV disease results from recombination of exogenous with endogenous strains[35] and immunosuppression by chemical pollutants, or Kaposi sarcoma-type tumours, as in AIDS in which KSHV (human herpesvirus 8) is the causative agent[22].

Infection, possibly by haematogenous blood-feeding insects, with a fibropapillomavirus (PV) or with Epstein-Barr virus (as in Burkitt's sarcoma in which mosquitoes are a co-factor), should also be considered. PV infection is ubiquitous, difficult to miss and has been recognised in humans, non-human primates, cattle, and other species[37]. In such cases, electron microscopy has proved equivocal[38]. Lesions similar to PV-induced ones have been reported in over a score of animals including in Tasmanian devils[11, 39]. Electron microscopy has revealed no virus particles in any tissues from devils affected with DFT but a cryptic viral instigator for the condition may yet exist. Indeed, all or part of the viral genome may persist in the transformed cell and there is often no production of infectious progeny virus. In addition, animals may inherit viral genes.

The research effort to date has been largely conducted within the Tasmanian Government's veterinary laboratory in Launceston. The need now is for these questions to be opened up far more broadly to wider avenues of multidisciplinary enquiry. Research institutions with expertise in molecular technology, gene probes and retroviral sequencing should be given access to a range of devil tissues.

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