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EDITORIAL

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Do dogs develop autoimmune diabetes?

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Humans have obvious disadvantages for the study of diabetes. A domesticated yet outbred species, their breeding behaviour is casual and unregulated. They cannot identify their own fathers with >95% confidence, and few can trace their descent for more than five generations. Their lifespan is inconveniently long, experimental conditions such as diet and housing are difficult to standardise, and ethical and legal constraints limit the range of experiments that can be performed upon them, let alone their sacrifice and dissection at the conclusion of research studies. This species readily develops spontaneous diabetes when provided with a suitable environment, but the disorder is heterogeneous and phenotypic characterisation can be challenging. It therefore comes as no surprise that most experimental research in diabetes is performed in other animals, and tends to be published in more exclusive journals [1].

There are plenty of animal species to study, for all mammals secrete insulin and develop hyperglycaemia if the pancreatic islets are removed. Spontaneous diabetes has been reported in, for example, apes, pigs, sheep, horses and cats, with isolated case reports in the fox, dolphin and hippopotamus. Naturally occurring animal diabetes should therefore provide an endless source of insight into the human disorder. In reality, it does not. Mordes and Rossini commented in 1985 that 'the data gathered from the larger mammals are so inchoate as to be of limited value' [2], and investigators have largely restricted themselves to inbred rodent strains, the convenience species of diabetes research, with very occasional forays into primates and other large species.

Although spontaneous diabetes has been little studied in outbred animals, dogs were long favoured for the study of experimentally induced diabetes. Early investigators operated with bare hands upon unanaesthetised animals. One contemporary described Claude Bernard '...with his tall hat on, from beneath which escaped long locks of greying hair: around his neck was a muffler which he scarcely ever took off... his fingers were nonchalantly thrust into the open abdomen of a large dog which howled mournfully. He turned towards his visitor with a benevolent glance, asking him to wait a moment, and went on with his experiment' [3]. The dog was the obvious choice for Minkowski when he challenged von Mering's contention that an animal could not survive pancreatectomy [4]. Banting and Best were on occasion reduced to buying dogs on the streets of Toronto, and Banting once led a victim back to the laboratory with his tie attached to its collar. Dogs are generally anxious to please, and it is with a sense of deep shame that we learn that one of their animals would jump on the operating table in its eagerness to do what its new owners wanted [5]. Mann and Magath performed the first successful animal hepatectomy in a dog—successful in that the victim did not promptly expire due to pooling of blood in the gut—and thus discovered a model of spontaneous hypoglycaemia [6]. Soskin and Levine pursued their studies of glucose metabolism in dogs entirely gutted by removal of liver and abdominal contents yet kept alive for days by human ingenuity [7]. Engermann and Bloodworth studied diabetic retinopathy in the dog, and came up with some of the first convincing evidence that metabolic control influences its rate of progression [8]. Dogs are still used in diabetes research, but—thankfully so—much more rarely. Yet dogs too develop spontaneous diabetes, and we know surprisingly little about it. In this issue of *Diabetologia* Brian Catchpole and his colleagues tell us about the spectrum of diabetes in the dog, and argue that this includes a form of immune-mediated diabetes [9].

Dogs have lived and worked with humans since remote prehistoric times; their social instincts and deference to authority make them good companions. The archaeological record indicates that they were first tamed in the Middle East 14,000 years ago, but genetic analysis suggests that they first diverged from a wolf ancestor some 135,000 years ago, with multiple interbreeding events since then

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[10]. They have evolved long legs, sharp teeth and large brains, but are otherwise structurally primitive. Dogs show extraordinary genetic plasticity, and are unique among mammals in their range of size and shape, not to mention the astounding number of varieties that have been developed by selective breeding [11]. The cat, by way of contrast, is much less plastic in the hands of breeders. Most canine breeds are of recent origin and show considerable genetic overlap with other varieties; their distinctive morphology is thought to arise from variation in key genes that accelerate or retard development. Inbreeding has inevitably thrown up a number of genetic disorders, some of which have thrown light upon human disease [12], but only one genetic form of diabetes has as yet been identified [13].

Modern dogs are relatively inactive and consume more food than their ancestors, much of it in the form of vegetable chow for which evolution left them unprepared. Many are overweight. Dogs are more likely to become obese when they are owned by people over 40 years of age and when these owners are themselves overweight. One survey found obesity in 44% of dogs owned by the overweight as against 25% of dogs with owners of normal weight. Genetic influences can be ruled out with some confidence in this situation, and it is notable that 31% of obese dogs were judged to be of normal weight by their owners [14]. It is a curious fact that obesity in dogs is either unrelated to diabetes [15] or only weakly so, suggesting that dogs are better able than ourselves to compensate for excess adipose tissue by increased insulin production. There is therefore no obvious canine equivalent of human type 2 diabetes.

The way we classify diabetes in humans is not helpful to veterinarians, who prefer a more empirical division into insulin deficiency diabetes and insulin resistance diabetes. Insulin resistance diabetes is usually secondary to hormonal antagonism to the actions of insulin, as seen in acromegaly or corticosteroid excess. A more common hormonally mediated form is related to the sexual cycle of bitches, who are sexually receptive when they go into oestrus and then enter a phase of dioestrus during which they undergo hormonal changes similar to those of pregnancy—even if not actually pregnant. This repeated metabolic challenge can give rise to the canine equivalent of gestational diabetes. Early surveys showed a clear excess of diabetes in older females, but this has declined as more bitches are neutered. It is interesting to note that a similar female preponderance of diabetes was seen in humans in the first half of the twentieth century, when women had more children and men were less fat [16, 17]. The contraceptive pill saved women from endless pregnancies, thus reducing their risk of diabetes in later life. Neutering did the same for dogs.

Insulin deficiency diabetes is much more common, and usually develops from 5–9 years of age, the canine equivalent of middle age. It does not respond to oral agents, and ketoacidosis develops if the diagnosis of diabetes is delayed. Secondary referral centres see an increasing number of dogs with this form of diabetes, but this may reflect greater willingness to keep such animals alive with insulin rather than a genuine rise in incidence. Insulin deficiency diabetes has a variety of causes. One rare form is secondary to islet hypoplasia, and presents in the first year of life [13]. Late-onset diabetes is often a consequence of acute or chronic pancreatitis. Subclinical exocrine pancreatic deficiency has been noted in others, but is not easy to diagnose and may be a consequence rather than a cause of beta cell failure [9]. For example, the exocrine pancreas shrinks in long-duration human type 1 diabetes, presumably because the trophic effect of insulin upon the exocrine pancreas is lost [18]. And, last but not least, some dogs may have a form of spontaneous immune-mediated diabetes that resembles our own type 1 diabetes. If confirmed, this would be a remarkable observation, for the only other outbred species in which this occurs is our own. Let us review the evidence.

The discovery of human type 1 diabetes was aided by the clear-cut difference in phenotype between children, almost all of whom (at that period) suffered from type 1 diabetes, and overweight adults, who mostly had type 2. No such distinction can be made in canine insulin deficiency diabetes, and careful phenotypic dissection will therefore be needed. A number of clinical and pathological features first drew attention to the existence of type 1 diabetes in humans [19], and it may be helpful to consider these in relation to the dog.

Human type 1 diabetes is associated with other autoimmune disorders. Dogs may develop similar conditions (e.g. lymphocytic thyroiditis [20]), and there is some evidence for an association between canine diabetes and hypothyroidism or Addison's disease [21]. The HLA associations of human type 1 diabetes were key to our understanding of the disease, and Catchpole and colleagues have produced the first evidence that diabetes in dogs is associated with dog leucocyte antigen (DLA) genes. Screening an admittedly heterogeneous pool of animals, they picked up an association with the haplotype DLA DRB1*009, DQA1*001 and DQB1*008, as compared with breed-matched controls, together with DLA DQA1 alleles coding for arginine at position 55 (Arg55) in hypervariable region 2, possibly equivalent to HLA DQA1 Arg52 in humans. A number of earlier studies have reported islet autoantibodies in canine diabetes, but methodological concerns and lack of standardisation or appropriate controls plagues this field, much as it did in the early days of human type 1 diabetes. Catchpole et al. have, however, cloned and expressed recombinant full-length canine GAD65 and the C-terminal region of canine islet antigen-2, and demonstrated the presence of autoantibodies to these in a proportion of newly diagnosed dogs. Cell-mediated immunity, meanwhile, has yet to be examined. The remaining link in the chain is the demonstration of insulitis. Willy Gepts looked for this in vain [22, 23], but the few dogs he was able to examine mostly had long-duration diabetes. In contrast, insulitis was reported by other investigators in six of 13 dogs who developed diabetes in the absence of extensive exocrine pancreatic damage [24].

In summary, there is emerging but incomplete evidence that some dogs develop a spontaneous immune-mediated form of diabetes. The condition affects mature animals, and is more like latent autoimmune diabetes of the adult than classic type 1 diabetes. These observations surely deserve our attention. It is a curious reflection on the way we do research that countless millions of dollars have been poured into the rodent holocaust, yet the possibility that the species that shares our lives most closely also develops spontaneous autoimmune diabetes has scarcely been considered. Mice can tell us about mechanisms, but they cannot, despite the quaint belief of many investigators, tell us much about a complex disorder that affects outbred creatures in the real world. Dogs, just possibly, can.

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