Institution:
University of Cambridge

Unit of Assessment:
UoA6

Title of case study:
Improving recognition and treatment of chronic pancreatitis in dogs

1. Summary of the impact (indicative maximum 100 words)

Research led by Dr Watson has demonstrated that chronic pancreatitis (CP) is more common and clinically significant in dogs than veterinary surgeons previously recognised, with strong breed predispositions. Prior to this work, the veterinary profession believed that dogs had a single attack of acute pancreatitis which did not result in the development of exocrine pancreatic insufficiency (EPI) and/or endocrine insufficiency (diabetes mellitus (DM)). The work by Watson has shown the importance of chronic disease and has altered the long term treatment of affected dogs across the profession. It has also prompted companies in the UK, Europe and the USA to increase their focus on low-fat dietary management, pancreatic enzyme supplementation and analgesia improving the quality of life of affected dogs.

2. Underpinning research (indicative maximum 500 words)

Research undertaken by Dr Watson (Clinical Resident October 1993; Lecturer January 1998; Senior Lecturer since August 2004) and colleagues in the Small Animal Medicine Department, Queen's Veterinary School Hospital (QVSH), from 2003 to 2013, focused on canine chronic hepatic and pancreatic diseases. Watson noticed an unexpectedly high prevalence of EPI due to end-stage CP in clinical cases and published a small retrospective series of histopathologically confirmed disease in 2003[1]. Prior to this, canine CP was believed to be rare: the major cause of EPI in this species was thought to be an inherited disease (pancreatic acinar atrophy) in young German Shepherd dogs. EPI in older dogs of other breeds was not recognised, diagnosed or treated, leading to profound cachexia and often humane euthanasia of affected patients, some of which had concurrent DM. Most cases of DM in dogs were believed to be autoimmune and DM due to end-stage CP was not recognised.

The retrospective case series provided the springboard for research to define the prevalence and clinical importance of CP in dogs. A major challenge in the non-invasive diagnosis of CP, (shared with human medicine), is that it requires histological examination of the pancreas. Watson designed and undertook a prospective pathology study in 2004 using post-mortem (PM) material from first-opinion practice to define the prevalence and breed association of canine CP. Professor Michael Herrtage helped with study design (QVSH Lecturer October 1980; Senior Lecturer October 2000; Reader October 2004; Professor since October 2008). PM sections of liver and pancreas from 200 dogs were collected at Glasgow Veterinary School and sent to Cambridge for interpretation by Watson and pathologists Dr Aude Roulois (University of Cambridge's Veterinary School (UCVS)) lecturer 1 July 2002 – Aug 2005; Wellcome Trust Fellow 2005-March 2008) and Dr Tim Scase (UCVS Lecturer 1 March 2006 – 31 July 2008). The results showed that the prevalence of CP in 200 old dogs (euthanased in first opinion practice for no specific reason) was remarkably high, at 34% [2]. In addition, this study showed a significantly increased relative risk in some breeds including Cavalier King Charles Spaniels (CKCS) and a difference in pathological appearance between pedigree dog breeds was noted, suggesting different aetiologies. Some breeds showed a duct-centred pattern typical of duct blockage or autoimmune disease, others an intra-acinar pattern typical of premature enzyme release in humans. They were the first and only group to describe these breed differences and the prevalence of CP in dogs.

Given these findings and to establish CP as a common clinically significant disease in dogs Watson and colleagues commenced a clinical study in 2004 recruiting cases from the QVSH with compatible clinical signs for a variety of imaging and blood tests, the interpretation of these tests being carried out by clinical pathologist Dr Joy Archer (UCVS Senior Lecturer since 2004). Pancreatic biopsy was performed if clinically justified or disease was confirmed at PM. Sixty-one dogs were recruited, with a strong clinical suspicion of CP. Nine of these cases were English cocker spaniels, four were CKCS, three were Border collies and many other breeds were represented by one or two cases. Results of the first 14 PM-confirmed clinical cases were published in 2010[3], confirming the breed relationships identified in the pathological studies,

particularly in CKCS (2 cases) and English cocker spaniels (5 cases) and also demonstrating that many cases have chronic pain and progress to end stage disease with EPI or DM or both which respond symptomatically to low fat diet and enzyme supplementation, together with insulin injections in diabetic dogs. Watson continued her investigations into breed-specific pathology from 2004 together with Aude Roulois, Michael Herrtage and Andrew Holloway (UCVSpart-time resident 2002, Clinical Radiologist October 2004-October 2006), focussing on the English Cocker spaniel. This study described the clinical and imaging appearance of the disease in 8 English cocker spaniels and compared histopathological sections with 59 dogs of 16 other breeds and crossbreeds with CP. Immunohistochemistry using anti-CD3, anti-CD79a, and anti-cytokeratin antibodies was used to evaluate distribution and type of lymphocytic inflammation and appearance of pancreatic ducts. The research demonstrated that the disease in cockers showed a predominance of T-lymphocytes targeting ducts and veins, very similar to human autoimmune CP and distinctively different histologically from the disease in most other dog breeds[4].

3. References to the research (indicative maximum of six references)

1. Watson PJ (2003) Exocrine pancreatic insufficiency as an end stage of pancreatitis in four dogs. *Journal of Small Animal Practice* 44, 306-312

2. Watson PJ, Roulois AJA, Scase T, Johnston PEJ, Thompson H and Herrtage ME. (2007) Prevalence and breed distribution of chronic pancreatitis at post mortem in first opinion dogs. Journal of Small Animal Practice 48 609-618

3. Watson PJ, Archer J, Roulois AJA, Scase T, Herrtage ME (2010) Observational study of 14 cases of chronic pancreatitis in dogs. Veterinary Record 167:968-76.

4. Watson, PJ, Roulois, A, Holloway, A. and Herrtage, ME. (2011) Characterization of chronic pancreatitis in cocker spaniels. Journal of Veterinary Internal Medicine 25; 797-804

Relevant sources of funding (All to Penny Watson as PI).

- £905 from the University Jowett Fund to pump-prime early research.
- *A study of the diagnosis and consequences of chronic, recurrent pancreatitis in the dog, focussing on its contribution to the aetiology of canine diabetes mellitus and exocrine pancreatic insufficiency* £5767 from the PetPlan Charitable Trust in February 2002 for one year
- *A prospective pathological study investigating the prevalence of chronic pancreatitis in dogs and its association with other diseases*. £6230 from BSAVA PetSavers awarded in January 2004 for 2 years.

Relevant prizes and invited reviews

BSAVA Petsavers prize for the best article in the Journal of Small Animal Practice 2008 ref 2
Marbocyl Departmental prize for Excellence in Clinical Research 2008 for reference 2

4. Details of the impact (indicative maximum 750 words)

(a) Impact on veterinary practitioners

This research has changed the way that veterinary practitioners across the world have recognised and treated CP in dogs over the past 5-10 years, improving the quality of life of affected dogs. Testimonials from veterinary surgeons in the UK, France and the USA (Refs 6 a, b and c in section 5) all corroborate the fact that this research has fundamentally changed their recognition and treatment of CP in dogs. Prior to our clinical study, detailed in section 2, CP was not recognised by practising veterinary surgeons as a common cause of chronic relapsing gastrointestinal disease, pain, EPI and DM. Watson's work has changed veterinary treatment of affected dogs – particularly the recognition of pain and consequent analgesia, changing to low fat diets and giving enzyme supplementation to dogs with EPI. This has profoundly improved their quality of life and in some cases has led to the avoidance of euthanasia on humane grounds. The managing director of Davies Veterinary Specialists, one of the largest veterinary referral centres in Europe, himself a

specialist in small animal medicine, has provided a testimonial and noted in November 2012 that: *'I can honestly say your work has changed how I think about the role of chronic pancreatic disease in older dogs and how I practice'.* This can be entirely attributed to the work of Watson and colleagues. There were no previous publications on CP in dogs apart from single case reports. The only other group working on canine CP in the world published their first paper on the disease in dogs in the Veterinary Journal in 2013. This supported the findings of Watson and colleagues and did not add anything new to impact disease treatment.

The results of the research have been disseminated by the authors, through many lectures to practising veterinary surgeons in the UK, USA and Europe, including annual lectures for two of the main continuing professional development providers in the UK (Improve CPD and the British Small Animal Veterinary Association (BSAVA)); invited lectures for: BSAVA Congress Birmingham 2010; BVA Congress London 2011; European College of Veterinary Internal Medicine Congress Ghent 2011; an abstract at the American College of Veterinary Internal Medicine congress in New Orleans in 2012 and lectures sponsored by major dog food companies: Royal Canin, in France and Brazil in 2010 and Eukanuba in Norway in September 2013. Over the impact period, Watson has made major contributions to small-animal medicine textbooks used by veterinary surgeons in first-opinion practice, updating the sections on pancreatitis since 2008 to stress breed relationships and the importance of CP as a cause of EPI in dogs. Watson contributed the entire section on liver and pancreas disease in Nelson and Couto's Small Animal Internal Medicine (4th edition, 2008), a leading textbook on Small Animal Medicine for veterinary students and practising veterinary surgeons. Watson also contributed sections on pancreatitis in the BSAVA Manual of Clinical Pathology (2nd edition; 2005) and the BSAVA Manual of Canine and Feline Rehabilitation, Supportive and Palliative Care (1st Edition 2010). An invited review in a popular USA Open Access, practitioner-focussed review journal has widened impact to veterinary practitioners in the USA (Watson PJ. Topical Review: Chronic pancreatitis in dogs. *Topics in Companion Animal Medicine* 27: 133-139).

(b) Impact on owners and breeders of affected dogs

This work has had far-reaching impact on owners and breeders of affected dogs, particularly in high-risk breeds (English Cocker Spaniel and CKCS). The results of the research have been disseminated by Watson, talking at breed society meetings and via internet sites. In October 2011, Dr Watson engaged with English Cocker Spaniel health co-ordinators at a large breed seminar to promote the research. The Cocker Spaniel Breed Council now lists Chronic Pancreatitis in the 'Health schemes and Research' section of their website (listed in section 5:5) directly as a result of this research and are asking for breeders to contact us if their dog suffers from CP. A Cocker Spaniel breeder has raised funds specifically for the research by producing a leaflet and selling home-made brooches ('Norbert's Ribbon'), demonstrating their commitment to helping.

CKCS breeders are increasingly recognizing CP in their dogs, allowing more effective treatment by their veterinary surgeons. References to CP appear on a number of CKCS health websites, referencing our work, and increasing awareness of the disease in the breed. For example, the website 'Cavalier Matters' has been written by breeders, demonstrating their engagement with the problem and their wish to advertise it further amongst breeders and owners (see link in section 5:5). The breeder who runs this web-site has also given a testimonial (section 5:6e) saying: '*We hope that Penny's research will one day elucidate the cause of this horrible disease in the breed….Meanwhile, just recognizing the disease goes a long way towards allowing treatment to improve the quality of life of these lovely little dogs and we can thank Penny for allowing this to happen'.* This breeder is helping Watson's research by developing a health questionnaire to be filled in by owners when they donate bodies of dead CKCSs for PM. We are coordinating this tissue collection scheme with other researchers investigating spinal cord and heart disease elsewhere in the UK (see website referenced in section 5:5).

Increased awareness in owners that their animals may suffer from CP has increased the likelihood that they will present to their veterinary surgeon when necessary. This is evidenced by the breeder testimonials and the large number of emails and phone calls for advice now received by Watson from veterinary surgeons in practice. Impact on owners in the USA is evidenced by Watson's

contribution to an American website for owners of dogs with EPI which has resulted in many emails from owners in the USA and UK. The owner forum demonstrates the reach of the impact and this is referenced in bullet 4, section 5.

(c) Impact on Industry: marketing of diets and nutraceuticals

The results of this research have changed the way that nutraceutical and veterinary nutrition companies market their products. VetPlus, a global leader in veterinary nutraceuticals and a major supplier of pancreatic enzyme supplements used to treat dogs with EPI in the UK, re-wrote their brochure to include end-stage CP as an important cause of EPI in addition to pancreatic acinar atrophy, as a direct result of Watson's work (section 5:1). They have produced a newsletter based on Watson's work to use in marketing their product to increase awareness amongst veterinary surgeons that EPI can occur as an end stage of CP and thus in older dogs of breeds other than German Shepherds (section 5:1). Eukanuba (Proctor & Gamble Pet Care), a major veterinary clinical diet manufacturer, has noted that Dr Watson's work has had a significant impact on the way they market their low fat diets. The Communications Manager for this company, based in Geneva, stated in October 2013: '*This work has definitely led to more emphasis in the marketing our intestinal diet for chronic pancreatitis. This diet, at only 10% fat, has been formulated to meet the recommendation of containing low fat. I have also used the data, both published and personal communication shared by Dr Watson at a number of European congresses and seminars, to help promote the usage of this diet with general practitioners for the optimal management of pancreatitis. Additionally, the prevalence of chronic pancreatitis in the canine population, as elucidated by Dr Watson's work, provides a strong impetus for our company to continue communicating to the veterinary profession about this important disease….'.* (Ref 5.7c). This company subsequently ran a lecture tour of day meetings in September 2013 in Norway for Veterinary Surgeons with Dr Watson as the keynote lecturer entitled: 'Chronic pancreatitis in the dog: the rediscovery of a forgotten disease'. The communications manager stated: '*We had a tremendous response from the veterinarians and the tour attracted a large number of delegates to each talk. The information shared by Dr Watson was of great clinical use to those attending and has been very influential in promoting the use of a low fat diet as part of the management protocol.'*

5. Sources to corroborate the impact (indicative maximum of 10 references)

1) VetPlus: http://www.vetplus.co.uk pancreatic enzyme supplement Lypex brochure attached. Newsletter based on Watson's work (VP Newsletter) also attached.
2) PDF of Eukanuba's Intestinal diet and product compendium showing this diet is recommended for use in acute and chronic pancreatitis. PDF of advertisement for lectures in Norway on chronic pancreatitis and introductory page from proceedings
3) Evidence that Nelson and Couto is a leading textbook for veterinary internal medicine (figures for new edition attached detailing place of the text book in the veterinary market)
4) American Website for owners of dogs with EPI epi4dogs.com. The owner forum: http://www.epi4dogs.com/apps/forums/topics/show/9204962-pancreatitis-to-epi-
5) Breed society web-sites: (a) Cockers http://www.thecockerspanielclub.co.uk/health.htm (b) References to CP appear on a number of cavalier health websites, referencing our work. For example: http://www.cavaliermatters.org/hereditary-diseases/chronic-pancreatitis-cp/ and the scheme coordinating collection of tissue is found at: http://www.thecavaliercollectionscheme.org/the-researchers/.
6) Leaflet helping fundraising for our research in cocker spaniels ('Norbert's Ribbon') enclosed
7) Testimonials from veterinary surgeons and breed health coordinators:
   a) Managing Director of Davies Veterinary Specialists, a Large Referral Centre in the UK (Veterinary Surgeon)
   b) Professor of a US Veterinary School and life-long researcher and author on pancreatic disease in dogs
   c) Communications Manager; Eukanuba, (of Proctor and Gamble Pet Care), Switzerland
   d) Breed Health Coordinator for the English Cocker Spaniel breed in the UK
   e) Coordinator of 'Cavalier Matters' which describes itself as a campaign for the future survival of the Cavalier King Charles Spaniel Supporting Research, Rescue and Reform