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Moredun's Centenary Science Stories

Volume 3

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introduction

This, the third volume of Moredun's Centenary Stories, is published around the time of easing of the lockdown due to the COVID-19 pandemic. The success of the vaccine roll-out for SARS-Cov-2 in recent months has been truly remarkable across the UK, but less so in global reach especially to poorer countries.
The commercial vaccines available include those based on mRNA, viral-vectored and recombinant antigen approaches, all of which have been used previously for animal vaccine development, demonstrating the inter-connections between animal and human product development. Moredun's current vaccine programme also focuses on viral-vectored and recombinant antigens for some of the most important endemic and zoonotic pathogens of livestock species.

It has been a very difficult task to choose the topics to include and then what to cover in each story. I asked the scientists currently working on the topics of the stories to give me 3-4 scientific papers which they felt were the 'principal milestones' in developing the research and leading to different impacts for farmers, vets, landowners, scientists and all who benefit from our work. The stories, therefore, are far from comprehensive and are designed to tell some of the ups and downs of the scientific process along the way, using language that hopefully is accessible to most readers.

In some stories, I have referred to previous scientists employed at Moredun, while some names are mentioned in the references; in other stories I have mentioned a small number of current staff and students. In all cases, the success of Moredun's science throughout the last 100 years is almost entirely down to the vision, skills, and sense of purpose of all the many staff who have contributed across the Moredun Group. I would also like to acknowledge the financial support from the Scottish Government in particular (via its many acronyms) RESAS, for their ongoing commitment to longer-term strategic research which is the essence of our work.

In each story I have tried to show why the subject matter is contemporary and where it fits with the current Global Grand Challenges we all face: emerging infectious and zoonotic diseases, exemplified by the current COVID-19 crisis; endemic diseases adversely affecting welfare and reducing production efficiency, in turn impacting on Climate Change targets; food safety and security; and finding solutions to these problems including diagnostics, vaccines and disease control programmes.

Moredun has been involved in collaborative research endeavors over the many decades as you will read in some of the stories in this volume and others. These have included working with colleagues at the University of Glasgow with a particular focus on parasitology, and with the Roslin Institute and the University of Edinburgh in genetic and genomics of multiple animal species.

Moredun scientists have collaborated with numerous universities across the UK and further afield, in attracting external funding from UK and EU funding bodies. This has resulted in very significant income generation which has increased over recent years, and which adds to the financial support gained via RESAS and the Scottish Government.

Moredun Research Institute is one of the partner organisations for SEFARI (the Scottish Environment, Food and Agriculture Research Institutes), which also includes Scotland's Rural College (SRUC), The Rowett Research Institute for Human Nutrition at the University of Aberdeen, The James Hutton Institute, Biomathematics & Statistics Scotland (BioSS), and the Royal Botanic Gardens of Edinburgh. This has allowed Moredun scientists to engage in cross-cutting research which is based on inter- and multi-disciplinary scientific activities. This integrated approach has resulted in Moredun's contribution to a wide variety of policy-relevant impacts including those relating to adaptation and mitigation of climate change, addressing land reform and the biodiversity crisis. This is in addition to the benefit of Moredun's work on livestock production in Scotland which is essential in order to support sustainable agriculture with high health and welfare through disease prevention and control.

Moredun is renowned internationally for its expertise in infectious diseases of livestock. Collaborations have taken place across all continents of the world – including the Arctic, but not Antarctica – indicating the importance of pathogens and pests globally. Worthy of particular mention include links with east Africa, Australia, South America and numerous European countries.

Scotland and Moredun may be of modest size, but they have a big impact in delivering the science agenda. I hope some of the stories to follow provide support for this statement.

Professor Julie Fitzpatrick
Scientific Director and Chief Executive

A Tale of Two Squirrels

Photo: Neil Inglis

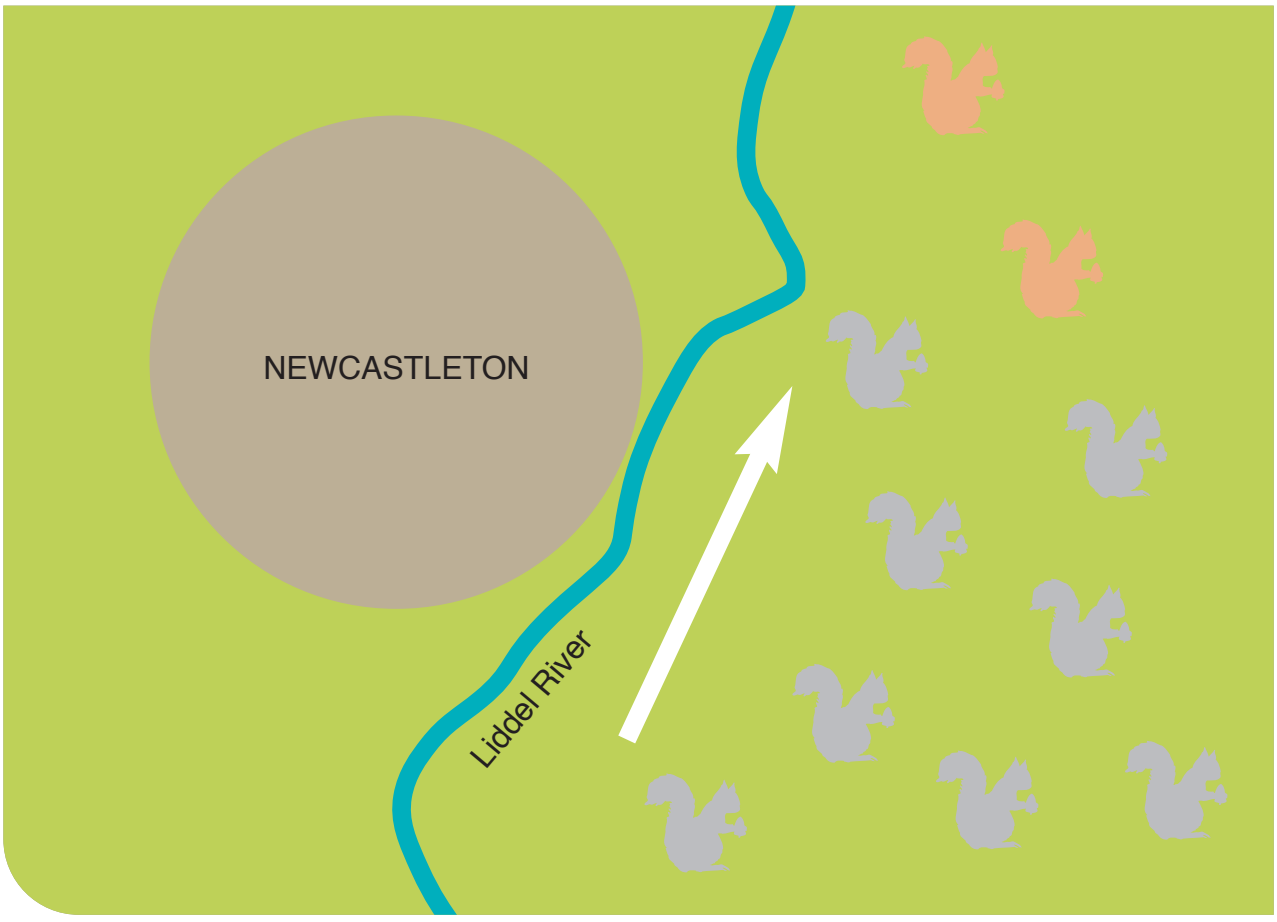
Above: Sciurus vulgaris. Opposite: Sciurus carolinensis.

The decline in the red squirrel (*Sciurus vulgaris*) population in the UK was first recognised in the early 20th century when many different theories as to the cause were explored. These included competition with the grey squirrels (*Sciurus carolinensis*) which had been introduced from the USA in the last few decades of the 19th century, predation by other wildlife species, and finally the possibility of emerging infectious disease.
Affected red squirrels were usually found dead with severe ulcers affecting their skins and especially the lower limbs and paws, supporting the infectious disease theory. Red squirrels also had ulcers in their mouths, preventing feeding and resulting in high mortality within populations. A virus, originally called squirrel parapox virus was identified in lesions.

Moredun virologists became involved in the investigations when it became clear that when red squirrel populations died out, they were replaced by grey squirrels. This was observed in the Borders region between Scotland and England where the course of disease moved north up the principal river valleys, home to the indigenous red squirrels and invading greys.
An ELISA test was developed to detect antibodies to the parapox virus. Blood samples from squirrels showed that more than 60% of apparently healthy grey squirrels had antibodies, indicating that they had been exposed to the parapox virus and had survived. In contrast, less than 3% of red squirrels had antibodies, three of which from the sample had evidence of parapox-associated disease ([1]Sainsbury et al, 2000). This provided evidence that backed up the epidemiological observations that the grey squirrels might act as a reservoir of the parapox virus for the red squirrels.

The cause of the disease affecting red squirrels was originally identified as a parapox by electron microscopy which allows visualisation of the shape and size of viruses. Use of molecular techniques to identify the genetic code of viruses showed that three of the genes known to be always present in parapox viruses were not detectable in samples from the squirrels. This led to the re-classification of the virus as squirrelpox virus (SQPV; [2]Thomas et al, 2003).

Studies on a small number of red squirrels challenged with SQPV followed disease progression using a polymerase chain reaction (PCR) test, which detects viral DNA. Results showed that the squirrels had developed antibody responses and that there was a rapid progression of lesions affecting the skin and mouth within 10 days of infection. The internal organs of the squirrels were unaffected with very low levels of virus detected. This provided evidence that the source of virus for transmission to other squirrels, both red and grey, was from secretions from skin lesions and from the mouth via saliva ([3]Fiegna et al, 2016).



A map of Newcastleton and the river Liddel which follows the line of the Scottish-English Border. As grey squirrels moved north up the valley (white arrow), red squirrels began to die out.

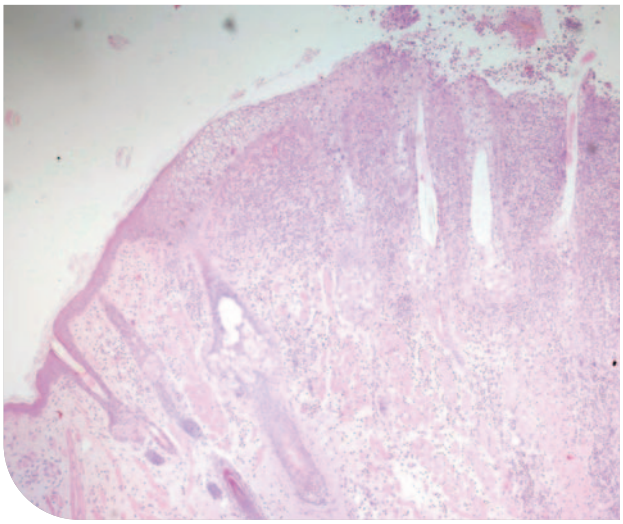
Photo: www.shutterstock.com

In addition to providing information on the progression of disease, this study, among others, indicated that an important aspect of control and prevention of disease transmission was to minimise contact points among squirrels – something that is easier said than done.

Efforts continue in a variety of ways to prevent SQPV from devastating the UK's iconic red squirrel. This includes favouring red squirrels by implementing forest and woodland planting schemes, and targeting grey squirrels through trapping and euthanasia, plus biological interventions to induce infertility. Moredun continues to work towards development of a vaccine against SQPV which would be used in red squirrels to protect them from infection. Challenges include identifying protective forms of the virus for vaccine development and finding ways of delivering the vaccine, ideally orally so that the vaccine could be incorporated into food sources. Although oral vaccines currently exist for some wildlife species, for example rabies vaccines for foxes in the EU, vaccines for oral delivery pose many biological and logistical challenges.

Moredun's work on SQPV arose due to the expertise of the virology team in investigating Orf in sheep, caused by an ovine parapoxvirus (this virus does not transmit to squirrels) over many years. This is a great example of transferable skills which allow investigation of diseases affecting different species and demonstrates Moredun's role in protection of wildlife and biodiversity. Dr Colin McInnes is the leading scientist in the UK with his expertise of SQPV and more of this "Tale of Two Squirrels" can be found in a book chapter authored by him ([4]McInnes et al, 2015). He is also the only Moredun staff member to be invited to discuss protection of red squirrels by HRH The Prince of Wales, a strong supporter of this work.

I would like to thank Dr Colin McInnes for his help in producing this story.



This is a microscopic image of a lesion on the eyelid of a red squirrel with SQPV. The left side of the picture shows the normal thick layer of epithelial cells which protect the tissues. To the right of the picture tip this layer is missing, resulting in a painful ulcer which makes eating difficult often results in the eyelid closing. This presumably makes it difficult for the squirrel to move around and forage, quite apart from it undoubtedly being painful

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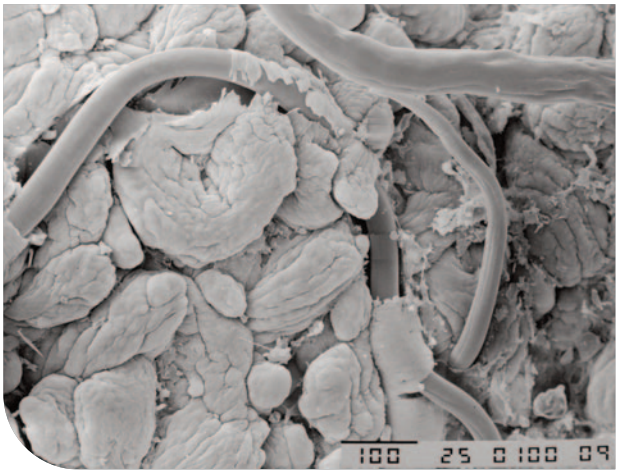
Anthelmintic Resistance - The Worms Are Turning!

The Moredun Research Institute has retained its internationally renowned position as a leader in many aspects of livestock parasite research. The development of highly safe and effective broad-spectrum drugs for treating worms (anthelmintics), between the 1960s and 1990s were significant breakthroughs, resulting in substantial improvements in livestock health and productivity, and leading to some believing that the disease threat from worms had been resolved. This period saw a reduction in global research investment for endemic parasites generally, but especially for worms. While other laboratories changed direction, Moredun continued to expand its capacity for those traditional parasitological methodologies important for diagnostic taxonomy (identification of species by visual observation), while also developing novel approaches to the application of molecular biology, genomics, and proteomics, to worms. Diversification also included a change in the host species; initially, Moredun's work related mainly to sheep worms, but more recently studies have also included worms of most livestock including cows, pigs and deer.

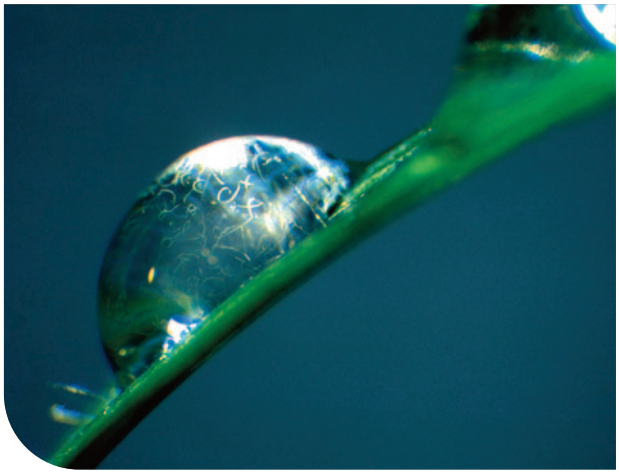
'Anthelmintic resistance' occurs when worms become unaffected by the drugs used to treat livestock, and it has long been recognised as a serious problem. Resistance was first identified in the southern hemisphere where parasite lifecycles are more extended seasonally, and thus require more frequent treatments for disease. This was followed by recognition of similar patterns in the northern hemisphere. Timing and frequency of treatments are just two of the important drivers for genetic selection of worms resistant to anthelmintics. Stimulated by the observation that anthelmintic resistance had been identified in worms, mainly *Teladorsagia circumcincta* (the brown stomach worm of sheep) from farms in Scotland, Moredun scientists conducted a survey of anthelmintic resistance in nematode parasites in Scottish sheep in 2003 ([1]Bartley et al). Of more than 90 farms under the management of members of the Moredun Foundation, 64% were found to have resistance to thiabendazole, one of the benzimidazole (or white wormer) family of drugs. There were farm locality and regional differences in the percentage of farms demonstrating resistant worms, but the survey did not identify any specific farm management practices which were associated with resistance. Interestingly, no resistance was found to the levamisole or ivermectin groups of drugs in this early study. Resistance to almost all of the five different anthelmintic classes licensed for use in sheep, including ivermectin, has been identified in UK flocks in later studies (Table 1).

Table 1

Anthelmintic Class & Colour		Date of Introduction in UK	Date of First Case of Resistance Reported in UK
1-BZ	White benzimidazoles	1960s	1984
2-LV	Yellow, levamisoles	1970s	1996
3-ML	Clear (ivermectin)	1980s	2002
3-ML	Clear (moxidectin)	1990s	2007
4-AD	Orange, monepantel	2010	2018
5-SI	Purple, derquantel (includes 3-ML)	2012	Currently unreported



Electron microscopic image of Teladorsagia circumcincta invading and damaging the tissues lining the abomasum (real stomach) of a sheep, causing reduced absorption of food and weight loss.



Water droplet on a grass stem showing multiple, white-coloured parasitic larvae. This will be consumed by a sheep to continue the parasite lifecycle.

Studies were subsequently conducted at Moredun which involved backcrossing worms (mating a worm to one of its parents) of *Haemonchus contortus* strains resistant to the drug, ivermectin, with worms which were susceptible to the drug ([2]Redman et al, 2012). Worms replicate by sexual interactions and the study involved allowing drug-resistant individual female worms to mate with susceptible individual male worms – it was certainly fiddly work to pair them up! The progeny (or offspring) of these worms were then mated to either resistant or susceptible worms for four generations. This project demonstrated that it was possible to introduce ivermectin-resistance genes from two independent worm strains into an ivermectin-susceptible worm strain of *H. contortus*.

This approach allowed investigation of the mechanisms that worms use to develop resistance and identified a genetic marker which showed evidence of genetic linkage to ivermectin resistance. This was a novel approach that provided a powerful adjunct to both candidate gene and whole genome analysis aimed at identifying anthelmintic drug resistance genetic loci for following studies. Sequencing of the *H. contortus* genome, the first for a parasitic livestock roundworm, was published in 2013 ([3]Laing et al.) led by colleagues at the University of Glasgow and including contribution from Moredun's Frank Jackson, Dave Bartley and Alison Morrison.

More recently, [4]Melville et al. (2020) conducted a study which used classical parasitology and two genomic sequencing techniques to investigate benzimidazole resistance in *Nematodirus battus*, a roundworm causing diarrhoea and death mainly in young lambs in spring and early summer. Analysis of many *N. battus* populations in the UK identified two mutations (single nucleotide polymorphisms, SNPs) previously associated with benzimidazole-resistance in other roundworms. The SNP, called F200Y, was identified at a low frequency in approximately a quarter of the populations tested. Four out of the five farms with a high frequency were in the northwest of England, possibly indicating an early emergence of resistance in that region of the country. The other SNP, called F167Y, was also identified but only at an extremely low frequency, suggesting that this mutation is at an even earlier stage of development. This work provided a benchmark of resistance in *N. battus*, currently indicating that the prevalence is still extremely low and at an early stage but that farmers need to keep an eye on the ongoing situation. Available tools will enable monitoring strategies, thus providing a unique opportunity to follow the progress of benzimidazole-resistance in the future. Both sequencing techniques employed in the 2020 study showed comparable results, suggesting they can both be utilised to monitor the development and dissemination of resistance SNPs in *N. battus* and help confirm benzimidazole-resistance in cases of suspected clinical drug failure.

Understanding mechanisms of resistance is a priority for animal health companies developing new anthelmintic molecules and drugs, including the newest classes (monepantel and derquantel/abamectin). While roundworm resistance to anthelmintics will inevitably develop, management decisions can slow the pace of resistance development and extend the duration of efficacy of drugs for treatment of livestock parasites (See Moredun's Centenary Science Story on "Smart Sheep for Smarter Farming"). Continued efforts are required as the worms seem to turn many situations to their advantage!

The work on anthelmintic resistance at Moredun has only been possible due to funding from the Scottish Government which supports underpinning capacity to ensure maintenance of facilities, databases and biobanks. The Moredun collection of parasites is very extensive and includes many species which are used as reference strains by collaborators worldwide. Of particular interest is that some of the individual worms and larvae were collected prior to the development of different drug families, which provides a unique resource to compare genomes and proteomes of parasites pre- and post-drug use in livestock. Dr Dave Bartley and many "para team" members are in constant demand for their practical knowledge exchange events – a reflection of Moredun's longstanding contribution to livestock farming communities.

I would like to thank Dr Dave Bartley for his help in developing this story.

Practical parasitology demonstrations at one of Moredun's UK Roadshow events.

Adult Nematodirus battus female with characteristic corkscrew shape

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A Novel Vaccine for Pasteurellosis Pneumonia in Ruminants

Professor Willie Donachie was awarded the Honorary Moredun Foundation Fellowship from Chairman, Ian Duncan Millar, for his longstanding contribution to Moredun's research and development.

I have very much enjoyed writing this story as this must be the most successful output from the Moredun Research Institute over the decades. Vaccines are the 'green' solution to disease threats as they prevent initial infection of the animal and reduce or remove the requirement for treatments with antibiotics and other drugs. The process of vaccine development for pasteurellosis pneumonia has contributed fundamental scientific observations on bacterial structure and function, resulting in scientific publications, patents and commercial contracts leading to significant royalty income. And of course, the vaccines have reduced disease and improved welfare for millions of sheep and cattle. The novel vaccines for pasteurellosis pneumonia developed at Moredun were real win-wins for both the livestock themselves, and for farmers worldwide who gained from the improved health and productivity of their livestock.

As with the other stories in the Centenary Science Stories volumes, the choice of the key scientific highlights was provided by Professor Willie Donachie, the principal inventor of the *Pasteurella haemolytica* components for the Heptavac P Plus group of vaccines. Willie was previously Deputy Director at Moredun for many years, and John Jeffrey, previous Chair of the Moredun Research Institute, dubbed him "The Mr Moredun."

It is notable that a good number of the Moredun Centenary Science Stories start with a publication in Nature, a high impact journal. This story is one of those. *Pasteurella haemolytica* was shown to have two variants, recognisable by observation of the bacterial colonies growing in the laboratory and by biochemical tests. This distinguished A strains, restricted to cases of pneumonia in sheep, while T strains were isolated from cases of septicaemia in lambs ([1]Smith, 1959).

Heptavac-P, the combined vaccine against clostridial diseases and pasteurellosis in sheep. This vaccine is still marketed today and encompassed the ground-breaking technology developed by Willie and the Moredun team.

The Gram-negative bacterium *Pasteurella haemolytica*, reclassified as *Mannheimia haemolytica* in 1999, is the most common cause of pneumonia in lambs and calves worldwide. Young lambs and calves can suffer from septicaemia due to infection, while severe signs of pneumonia with coughing, difficulty breathing and dullness are recognised mainly in animals over 3 months in age and in adults. Flock or herd outbreaks are common, resulting in around a 2% death rate of affected individuals. Early vaccines produced against *P. haemolytica* were simple, inactivated bacteria and there was no scientific evidence of their efficacy.

Moredun scientists found that *P. haemolytica* serotype A2 cells, recovered from the lungs of sheep with pneumonic pasteurellosis, contained different combinations of proteins when compared with *P. haemolytica* serotype A2 bacteria grown in the laboratory in conventional bacterial growth media. This experimental approach was explored as it was known that bacteria require access to iron, a micromineral essential for cell growth and function. One group of proteins, termed the Iron Regulated Proteins (IRP) was found to be present only when *P. haemolytica* were grown in the absence of iron. The bacterial envelope which surrounds the cells was shown to be recognised by antibodies from the blood and lung fluids of lambs recovering from pasteurellosis, indicating that the bacterial proteins, including the IRPs, were readily accessible to the immune system and hence provided a novel approach for vaccination ([2]Donachie and Gilmour, 1988).

This work led to an important publication which showed that an experimental vaccine comprising IRP given to lambs as two doses four weeks apart, and then challenged experimentally with an aerosol of live *P. haemolytica* serotype A2, provided a high degree of protection from both death and disease compared to unvaccinated lambs. These studies were performed on lambs which were derived by hysterectomy and thus deemed 'specific pathogen free', in order to identify the specific impact of an experimental challenge with a single pathogen ([3]Hart et al, 1971). The lambs vaccinated with the IRP produced high levels of IgG antibodies in the blood and the pattern of antibodies induced was similar to that from a lamb which had recovered from natural pasteurellosis. Another group of lambs was also studied which had been vaccinated with *P. haemolytica* proteins that had been produced in the presence of iron. This group of lambs had similar death and disease scores as the unvaccinated lambs, providing definitive evidence that the IRPs were the protective components of the vaccine ([4]Gilmour et al, 1991). Heptavac P Plus was the lead vaccine produced commercially by Hoechst Animal Health in 1997, and was a combination of seven antigens from clostridial species plus killed cells from nine *Pasteurella* serotypes expressing IRPs.

The development of a *P. haemolytica* IRP vaccine for cattle followed on directly from the success of the sheep vaccine, but here the *P. haemolytica* serotype A1 cells were combined with two viral antigens – Respiratory Syncytial virus (RSV) and parainfluenza virus type 3 (PI3) – in the Bovipast RSP vaccine, launched in 1999. As with the results found with the sheep vaccine, the cattle vaccine was effective against disease caused by serotypes not included in the vaccine, demonstrating once again the cross-protectiveness of the IRP components ([5]Crouch et al, 2012).

Consistent results on the protective effect of Heptavac P Plus and the Bovipast RSP vaccines provided the pathway to commercialisation of what was to become two of the most successful livestock vaccines ever produced. Over the years, Hoechst Animal Health became in turn Hoechst Rousell Vet, Intervet, Schering Plough and eventually MSD. The patent and product for the IRP-based vaccines went along the chain. Usually, the patents and know-how relating to a new vaccine are passed on smoothly from the inventor and institute to the commercial company. However, this was not to be for the IRP vaccines. Disputes about prior art relating to the IRPs resulted in Willie Donachie being called as an expert witness to the United States Patent and Trademark Office (USPTO) in Alexandria, Virginia in 2008 to defend the patent, then owned by Schering-Plough, against objections by a competitor animal health company in the USA. The USPTO found the case in favour of Schering-Plough.

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Professor Willie Donachie received this medal on behalf of the Pasteurella Project Team at Moredun. It was awarded by the Royal Agricultural Society of England on 22 February 2002 in recognition of Moredun's discovery and development of Pasteurella vaccines for sheep and cattle.

The royalties from this work benefitted the inventor who filed the patent and the two main scientists whose innovative work underpinned subsequent vaccine development. The royalties also provided valuable income to Moredun Research Institute which was in turn invested into ongoing research projects and programmes. The knock-on benefit to all Institute staff during the years of royalty payments came in the form of a very welcome, yet modest, Christmas bonus.

The success of the Moredun IRP vaccines was recognised nationally in 2002, when Willie Donachie was awarded the Royal Agricultural Society of England Technology Award – the first time it was ever awarded for a vaccine.

This story epitomises the concept of "prevention being better than cure," which is a key aspect of Moredun's ambition for animal health and welfare research and development. It has always proved impossible to obtain the numbers of vaccines sold and animals protected by the pasteurellosis vaccines for a variety of reasons, some outlined above. What is clear is that ruminants across the world have benefitted from protection against a particularly severe form of infectious disease through novel vaccine development.

I would like to thank Professor Willie Donachie for help in developing this story.

Photo: www.pixabay.com

Transmissible Spongiform Encephalopathies

The term 'Transmissible Spongiform Encephalopathies', or TSEs, was introduced into the scientific literature and general press in the 1990s as a result of the recognition of a new condition affecting cattle, descriptively called 'Mad Cow Disease'. 'Scrapie', a chronic, progressive, neurodegenerative (damaging to the brain) disease of sheep which is invariably fatal, was another manifestation of a TSE and it was recognised as having been around for many hundreds of years or longer.

There is a fascinating historical account of scrapie in the book "Social Construction of Disease - From Scrapie to Prion" written by [1]Kiheung Kim in 2007. This book recounts that scrapie in sheep was first described by [2]Comber in 1772 where the disease was called 'shakings' and was characterised by "sensitive reactions, dizziness, itchiness and paralysis of the body". Comber believed the disease to have a genetic origin, rather than infectious, and it was recognised that sheep "at length, died".

The Moredun Research Institute and the Agricultural Research Council joined the field of scrapie research in the 1930s. This was stimulated, in part, due to the unintentional introduction of scrapie as a contaminant of a novel louping-ill vaccine, resulting in the unexpected opportunity to understand more about the physical and chemical properties of the possible "infectious agent". Significant progress was made over the decades on the microbiological and microscopic aspects of scrapie by scientists at both the Moredun Research Institute and by the Institute for Animal Disease at Compton. The Director of the Moredun Research Institute at the time, Dr John Stamp, joined forces with the Animal Breeding Research Organisation to conduct extensive breeding studies, as some scientists believed that scrapie was a genetically inherited disease. This project was led by Moredun geneticist, Dr Alan Dickinson, and resulted in the understanding that host susceptibility to scrapie is genetically determined; in other words, different genetic strains of sheep exhibit differential susceptibility to disease. However, the "necessary cause" of disease is a transmissible agent.

Scrapie is now referred to as a 'prion disease', one which is characterised by conversion of the normal cellular prion protein found in cells of the tissues, (PrPc), into aggregates of a misfolded 'disease-associated form' (PrPd). This change is stimulated by exposure to an external source of PrPd, and as such is a transmissible disease. Other examples of prion diseases include Bovine Spongiform Encephalopathy (BSE) in cattle (Mad Cow Disease), Chronic Wasting Disease (CWD) in deer, and Creutzfeldt-Jakob Disease in humans. Along with scrapie, these diseases are termed TSEs, and no conventional infectious agents carrying DNA or RNA (such as bacteria, viruses or protozoa) have ever been isolated from affected individuals or groups of animals.

An early key finding about scrapie was described by [3]Zlotnik and Rennie in 1963. They showed that when brain or spleen tissues from scrapie-infected sheep were either injected into the brains of mice, or fed orally to them, no disease could be identified. However when tissues were taken from these mice and then injected or fed into another group in a process called 'passaging', a fatal neurological disease resulted in the following 5-9 months. This indicated that experimental transmission of scrapie material from sheep to mice was possible, one of the important indicators of an infectious causal agent for scrapie.

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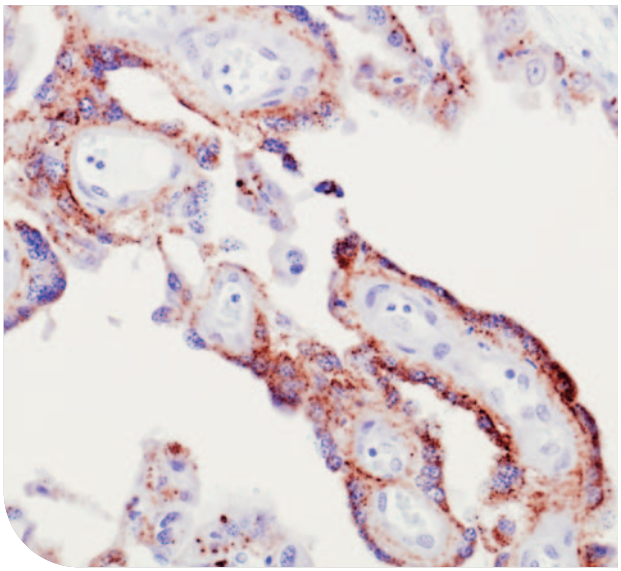


A microscope image of a PrPd positive placenta.

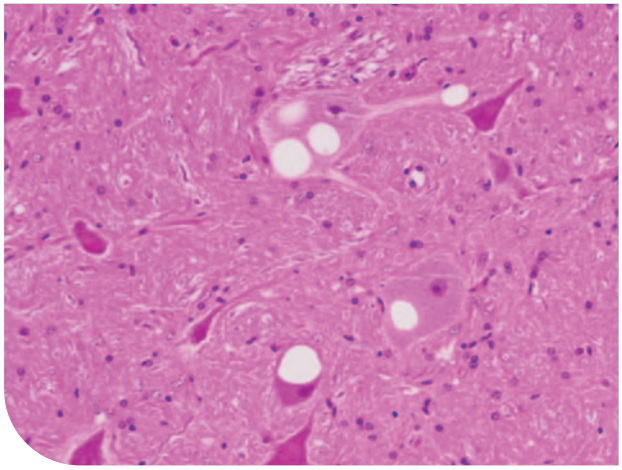
A scrapie-positive ram showing wool loss from excessive scratching.

The work on sheep scrapie was subsequently developed into the 'Scrapie Plan'. This was based on genotyping sheep: sequencing the gene encoding the cellular prion protein and identifying which PrP genotype (the animal's genes) made sheep more or less resistant to scrapie. The occurrence of scrapie was then reduced by breeding from resistant sheep. This was pioneering work by Dr Nora Hunter and colleagues at The Institute for Animal Health and Roslin Institute, and the success of this plan is clear from the reduction in number of reported cases of classical scrapie to almost zero in the UK in recent years.

More recent research on the TSEs at the Moredun Research Institute was conducted between the mid-1990s and 2008, principally through collaborations with the Veterinary Laboratory Agency (now APHA). Several large-scale studies focused on the susceptibility of sheep, cattle and deer to BSE and scrapie. Detection of PrPd in tissues from these animals informed food safety, disease mechanisms and surveillance, and furthered understanding about the significance of the interaction of host genetics and source of infection.

Original work identified the disease-associated prion proteins in the kidney tissues of scrapie-affected sheep. Studies using immunohistochemistry (where antibodies identify different protein targets in tissues) showed PrPd in the kidneys of 44% and 51% of naturally infected sheep and experimentally infected sheep, respectively ([4]Siso et al, 2008). The location of the PrPd suggested a blood-borne route of infection and provided the possible route of environmental contamination via voided urine onto pasture or pens.

Scrapie exists as several strains and these were demonstrated from the introduction (passage) of original sheep isolates containing prions in experimental mice. Four strains from these experiments, including the Moredun strain ME7, were then re-introduced into sheep by either the oral route or by injection into the brain and under the skin (the combined route). These studies showed that the incubation period of the disease was slower when scrapie tissue was fed orally than when the combined route was used, and that only about 50% of the sheep exhibited pathological signs of scrapie when the oral route was used. This study also showed that scrapie strains cloned in mice produced different pathological and biochemical signatures depending on the PrP genotype of the sheep ([5]Siso et al, 2012).



This image is of sheep brain affected by scrapie. The white holes in the tissue are abnormal and result in the "spongy" appearance which led to the name of the TSEs.

Some of the red deer that formed part of the BSE experiment.

BSE suddenly appeared as a clinical disease in the mid-1990s, and evidence suggests resulted from feeding cattle with meat and bone meal unknowingly contaminated with prion-infected brain material. However, both wild and captive deer had also been offered the same feedstuffs. Research was then undertaken at Moredun to investigate if red deer could be experimentally infected with BSE brain material via two experimental routes: injection into the brain and orally via a stomach tube. Of the 6 deer that had this material injected into their brains, all 6 developed clinical disease approximately 1000 days post-injection and had pathological signs of BSE in their brains. However, only 1 out of the 6 deer that were given the BSE brain material orally developed clinical signs around day 1700. This highlighted that BSE in red deer more resembled natural infection in cattle, characterised by lack of PrPd accumulation in the tissues of the lymphatic system, unlike experimental BSE infection in sheep or CWD in deer. Importantly, it was demonstrated that BSE in red deer could be differentiated from CWD by using detailed examination of brain tissues and identification of different forms of the PrPd in the two diseases ([6]Martin et al, 2009). Fortunately, this study provided some reassurance that a species transmission barrier for introduction of BSE to deer via feed existed, even if not completely so.

It is generally considered that while some animal species are susceptible to scrapie, others are not - including horses, dogs and rabbits. Dr Francesca Chianini and the Moredun team, in collaboration with Dr Joaquín Castilla (CIC bioGUNE, Spain) showed that it was possible to overcome the species transmission barrier in rabbits. They used an in vitro technique which amplifies PrPd to a high level and showed that rabbit brains produced de novo (new) prions which could then, in turn, produce pathological and clinical signs of a 'typical' TSE in rabbits which had been injected in the brain with these de novo prions ([7]Chianini et al, 2012). The experimental approach adopted does not mimic the more likely oral route of infection for scrapie. However, this study was important as it demonstrated that a species previously classified as resistant was both susceptible to, and capable of, developing clinically transmissible prion disease.

Across much of its centenary of endeavour, Moredun has had a clear and important impact in this research area, in collaboration with numerous researchers and organisations around the world.

I would like to thank Dr Francesca Chianini, Philip Steele and Scott Hamilton for their help in developing this story.

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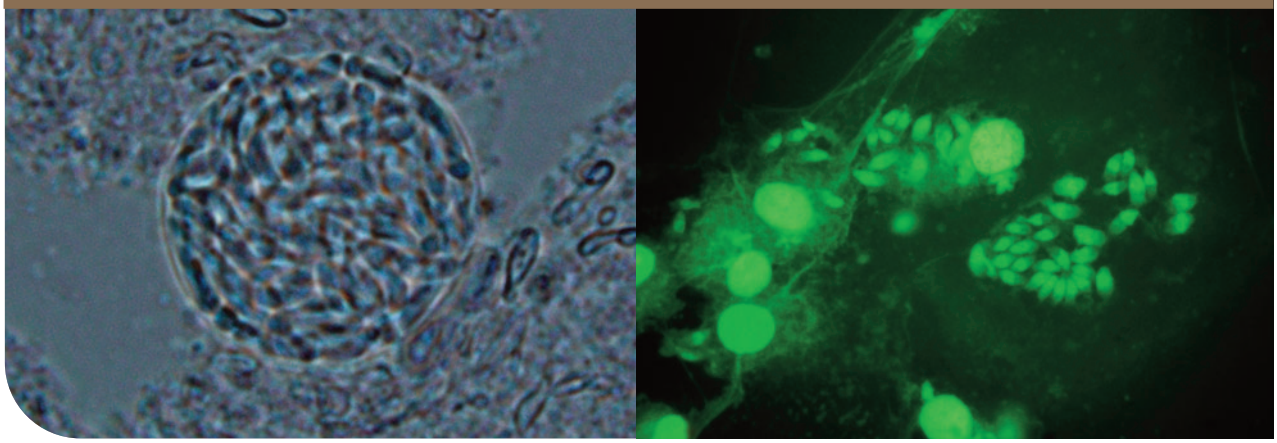
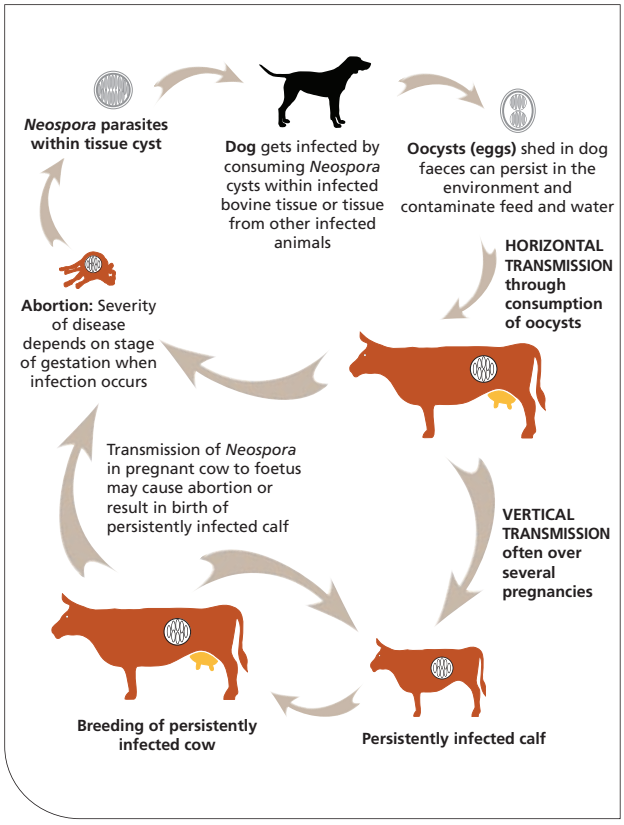
Neosporosis - A Major Cause of Abortion in Cattle



Neospora parasites exist in two different forms in cattle, the tachyzoite stage that multiplies rapidly inside cells during acute infection (above right) and the bradyzoite stage that multiplies very slowly and are contained within tissue cysts (above left), allowing the parasite to persist in cattle.

For many years, vets and farmers have known that there must be another cause of abortion over and above the well-recognised pathogens associated with this problem, which include *Brucella, Salmonella, Campylobacter, Leptospira, Listeria* and *Coxiella* species. The missing link was *Neospora caninum*, a protozoan parasite with a complex lifecycle, which resulted in high levels of infection in both beef and dairy cattle, and which proved difficult to diagnose and a challenge to prevent.

Primary infection with *N. caninum* originates with the infective stage of the parasite, oocysts, which are found in the faeces of infected dogs. The oocysts are then transmitted to cattle via contaminated food or water. When infected heifers become pregnant, or pregnant cattle are infected during gestation, this may result in abortion. For the parasite cycle to complete, aborted materials or fluids have to be consumed by a dog, and the process repeats. This has led to advice being given to dog owners to help control neosporosis infection - dogs should not be allowed to deposit faeces on pasture or on feedstuffs for cattle, and dogs should be kept well away from aborting cows. This part of the lifecycle is known as the 'horizontal transmission route' which involves spread of *N. caninum* via oocysts in the environment, and is considered to be minor in comparison to the principal route of infection. This principal route occurs when pregnant cows become infected and then go on to produce a live calf, which is also infected. This is known as the 'vertical transmission route' and is made even more impactful as these persistently infected female calves may remain in the breeding herd and then go on to produce more infected calves in subsequent pregnancies.



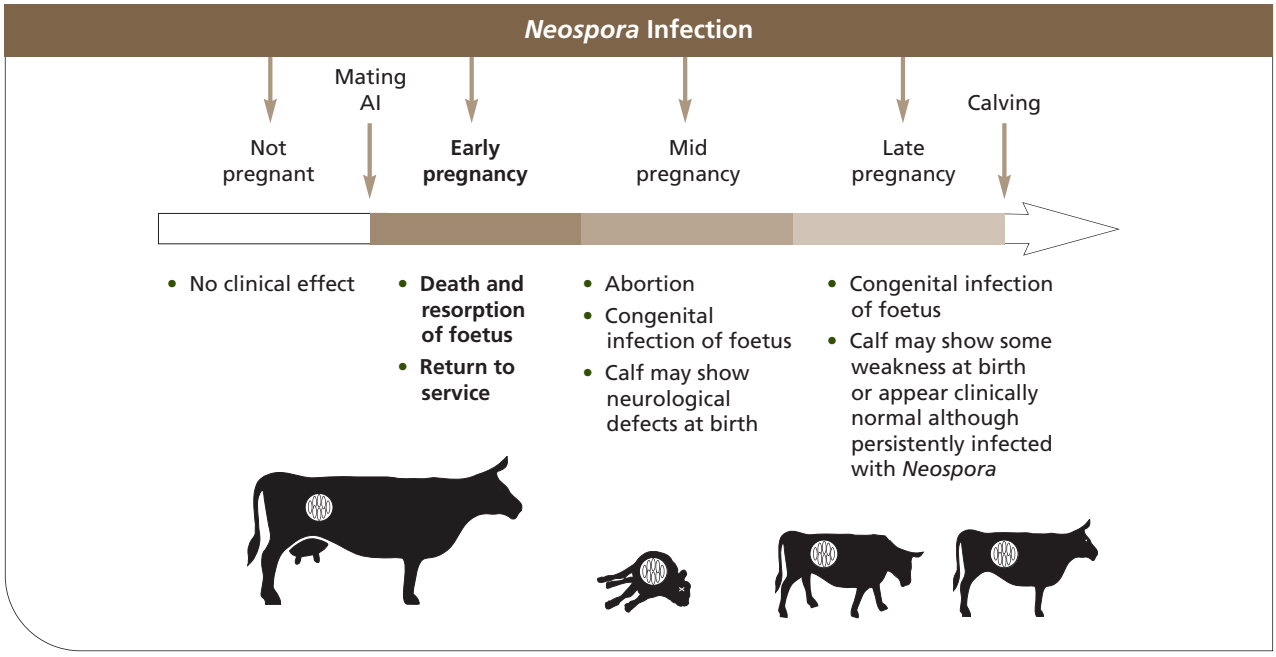
Lifecycle diagram for Neospora caninum showing the horizontal and vertical transmission routes.

Moredun has conducted many different types of investigations into the cause of abortion in cattle over the years. One study by [1]Buxton et al in 1997 was based on blood samples taken from 456 aborting cows and 547 aborted foetuses, most of which were paired mother (dam)-foetus (a stage after an embryo, 42 days or longer after conception). This indicated that 16% of aborted foetuses had antibodies for *N. caninum* while a lower percentage of dams had developed antibodies. This suggested that *N. caninum* is a relatively common cause of foetal loss in cattle in Scotland, and that a main route of transmission was likely to be vertical from dam to foetus. Twenty years later, and with the development of Polymerase Chain Reaction (PCR) tests, which detect the DNA of *N. caninum*, a new study showed that 18% of aborted bovine foetuses in Scotland were positive by PCR with either the brain, heart or placenta showing evidence of presence of the parasite ([2]Bartley et al, 2019).

Some fundamental work conducted by Moredun scientists focused on disease pathogenesis – how *N. caninum* interacted with the bovine host to cause disease and abortion. This involved large, time-consuming and expensive studies on cows at various stages of pregnancy. When *N. caninum* was introduced into cows by injection either intravenously or subcutaneously (under the skin) during early pregnancy, the result was rapid death of the foetus with evidence of damage to both the placenta and the foetus ([3]Macaldowie et al, 2004). In contrast, when cows in mid-pregnancy were challenged experimentally with *N. caninum*, some of the tissue damage resolved and a proportion of the pregnancies were maintained ([4]Maley et al, 2003). This is despite the fact that parasite DNA could be detected in the placenta and the foetus, and a strong inflammatory response was detected in placental tissues on both the maternal and the foetal side of the placenta. Together, these studies provided evidence that the stage of pregnancy at which infection occurs is an important factor in determining the disease severity and the outcome of infection – foetal loss and abortion, or persistent infection of the offspring. This work also demonstrated that the inflammatory and immune responses induced by *N. caninum* could be either beneficial or detrimental; some patterns of responses protected the host animal while some protected the parasite, and yet others played a role in disease pathology.

Antibodies are an important and well understood arm of the immune response of animals. However, the cellular or cell-mediated immune response is more complex. This involves T cells, which can be divided into two main types based on function and on the cytokines (small-sized and short-lived proteins), which they produce in order to interact with other cells. Studies at Moredun with *N. caninum* infected cattle showed that TH1 cells (a subset of T cells) produced the inflammatory cytokines IL-12, IFN-α and TNF-α in cells of the placenta in early pregnancy. These TH1 cells were found to be less frequent and less concentrated in tissues of the placenta later in pregnancy, partially explaining the less severe clinical outcome in cows in late pregnancy, compared to early or mid-pregnancy ([5]Canton et al, 2014).

More recently, novel diagnostic approaches involved the identification of molecular markers which were used to identify diversity in the genes of *N. caninum*. This showed that there is a very high level of diversity with 96 genotypes identified from 108 *N. caninum* samples from four countries and two continents ([6]Redigor-Cerrillo et al, 2013). Close relationships between the Spanish and Argentinian genotypes suggested that the Spanish genotypes might have been introduced to the South American continent as a result of transportation of cattle. This is a good example of pathogens and disease finding ways of travelling across the globe!



So, where does this leave neosporosis for now? There is currently no vaccine, however Moredun scientists continue to develop options for biological protection with emerging vaccine technologies coming to the fore for complex pathogens. Early work at Moredun has shown that it is possible to induce protective immunity against vertical transmission of *N. caninum* through immunisation of live parasites prior to mating ([7]Innes et al, 2001). The Cattle Health Certification Standards (CHeCs) provides advice on testing herds for infection (http://www.checs.co.uk). The dilemma is that farmers ideally might choose to cull cows which are antibody positive as these are more likely to abort; however, if many cows in a herd are antibody positive this may not be cost-effective or practical. It is important therefore to only source heifers or cows for breeding which are antibody negative as this is the most common route of introducing infection into herds.

As is often quoted at the end of published scientific papers: more research is required…

I would like to thank Dr Frank Katzer and Professor Lee Innes for their help in developing this story.

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Smart Sheep for Smarter Farming

Global livestock farming systems can involve high numbers of animals, extensive grazing areas and restricted availability of on-farm labour. Finding ways of automatically identifying sick sheep and then applying relevant treatments and preventive actions is therefore a very attractive prospect. Moredun scientists, led by Dr Frank Jackson and, more recently by Dr Fiona Kenyon, have combined forces with sheep farming communities to find practical ways to address these problems.

Classical veterinary and farming text books will tell the reader that when it comes to worm control in sheep, the best option is to treat the whole grazing group with an effective wormer (anthelmintic) and then to move the treated lambs to clean pasture. For many years, this has NOT been the recommendation. Sheep worms develop resistance to all anthelmintics (see the story 'Anthelmintic Resistance - The Worms Are Turning!' in this Volume for more information), and thus a proportion of the worms will survive drug treatment. If lambs are moved to clean pasture after treatment, then the eggs deposited on pasture will be from worms which have survived the drug. Therefore, when the eggs hatch into larvae they will all be derived from resistant worm populations. This has the effect of concentrating drug-resistant worms on pasture.

The technique of "Targeted Selective Treatment" (TST) is by far the better option. In this scenario only the lambs which require treatment for worms receive anthelmintic, and those that don't are left untreated. When these different lamb groups are returned to pasture after treatment, the eggs deposited are from a mix of susceptible and resistant worms. This results in a reduced selection pressure' for anthelmintic resistance. So, how does a farmer identify the lambs which do need treatment for worms? This is, in some ways, rather obvious - it is those lambs which gain weight slowly, due to the damage of the worms in their gastro-intestinal tract affecting absorption of food, which need treatment. However, it is not quite as simple as that as mathematical algorithms based on production efficiency calculations and threshold values for timing of treatments (the 'Happy Factor') are required for TST decisions ([1]Greer et al, 2009). Published work has shown that if farmers take a TST approach to worming their sheep, they treat fewer animals (therefore saving costs of drugs), reduce the onwards transmission of resistant worms for other sheep populations following, and importantly, reduce the emergence of anthelmintic resistance genes in the worms meaning the drugs will work effectively for longer ([2]Kenyon et al, 2013). Farm performance across several financial outcomes has also been demonstrated by the use of precision livestock systems, including in mountain sheep flocks ([3]Morgan-Davies et al, 2018). This is a "win-win-win" in terms of economics, environments and evolution!

A ewe and Dr Fi Kenyon in action on farm!

Lambs line up in the race for Targeted Selective Treatment

To achieve this, farmers need to have lambs wearing Electronic Identification (EID) tags and facilities for handling and weighing. It is also useful if the equipment can 'shed' lambs automatically into those which require treatment and those which do not. Larger farms can do this, but labour time and costs in weighing all livestock can be prohibitive. What if it is not necessary to weigh all lambs - would detailed examination of a sample or a proportion of the lambs work just as well? The good news is that the answer is "yes"! Recent studies using a 'sentinel group' approach as a novel monitoring strategy for grazing lambs, was designed to target whole-group anthelmintic treatment based on weight gain of only a proportion the flock. Monitoring as few as 20% of lambs was sufficient to identify when the larger co-grazing group required treatment. The sentinel approach minimises the labour requirements, providing a more accessible monitoring method for targeting anthelmintic treatment ([4]Melville et al, 2021). Another encouraging result was that TST approaches are transferable from one farm to another using a "Standard Efficiency Threshold". This means that there is no need to tailor the threshold for decision making calculations on when to time and target use of anthelmintics for individual farm conditions ([5]McBean et al, 2021).

The 'Smart Sheep for Smarter Farming' approach is currently being extended through multiple research programmes supported by UK and EU funding bodies. Moredun is a partner in a number of networks which bring interdisciplinary skills together to tackle the problems of disease and poor welfare in small ruminants with relevant experts in digital technology, engineering, data science, and socio-economics, as well as veterinary and biological sciences. The vision is to integrate Precision Livestock Farming (PLF) to a sector which has yet to exploit compulsory EID of sheep with improved management on farms. Real-time information will be collected from a range of sources, including radar data from satellites for estimating the mass of grass growth on pastures. Cloud-based, online tools will be used to monitor lamb performance, optimise treatments for disease and measure the response of lambs to those treatments. Financial and carbon footprint information will be incorporated into the resultant models. In terms of welfare, assessments will be conducted on 'Digifarms' to cover the major endemic diseases of sheep, with equipment such as 'Walk Over Weighing' (WOW).
This project is truly collaborative and results from close working with colleagues from SRUC, several sheep-farming focused businesses and newer collaborations with many EU research institutions. Dr Andy Greer of the University of Lincoln, New Zealand, played an important early role in calculating the Happy Factor. Moredun's role, and that of Dr Fiona Kenyon in particular, is to ensure that reducing endemic disease while optimising the health and welfare of sheep and lambs underpins future sustainable ruminant farming in Scotland.

I would like to thank Dr Fiona Kenyon for help in developing this story.

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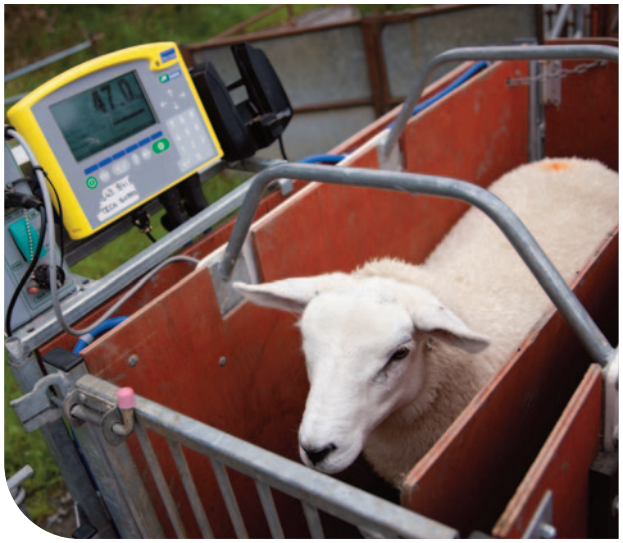

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1 SINGLE DOSE VIAL 0.5mL
COVID-19
VACCINE

Moredun's Role in the Past, Present and Future of Livestock Disease Control

The thoughts of Tom McNeilly, Head of Department, Disease Control

As a result of the recent COVID-19 pandemic, control of infectious disease has become one of the most pressing issues of our time. Due to the amazing efforts of the global scientific community in rapidly developing effective vaccines and diagnostic tests for SARS-CoV-2, we now have the tools with which to control Covid-19, reducing deaths associated with the disease and returning our lives back to something approaching normality. However, having the tools is not enough – it is the way that these tools are applied that matters, for example who to vaccinate first, and how to use the diagnostic tests in the most effective way to identify infections and stop spread of the virus.

Moredun has a long history of developing tools to control livestock diseases – vaccines, diagnostics and drugs – but an equally long history of working out how best to use these tools to maximize their impact, and importantly to communicate this to farmers and vets. This holistic approach to disease control is key for Moredun's strategic vision to improve the health and welfare of our farmed animals, and there are many examples of this throughout Moredun's history. Indeed, Moredun (as the Animal Diseases Research Association) first started by visiting agricultural shows and farms in the Moredun van, diagnosing diseases on-site and immediately advising the farmers how to best to control these diseases. This legacy continues through regular farmer and vet training events and Moredun's legendary disease "fact sheets". There is also the new mark II version of the Moredun bus which is kitted out with a state-of-the art laboratory and will soon be travelling around the country once COVID-19 restrictions ease!

So what has Moredun achieved in terms of disease control to date? This would be a long list, but some notable examples would be the identification of clostridial diseases and their control by vaccination, determining calcium deficiency as the cause of milk fever and advising on the best use of anthelmintic drugs to control parasites while avoiding development of drug-resistant parasites. This latter work exemplifies an important concept in disease control – that blanket treatment of livestock with drugs (e.g. ant-parasitic drugs, antimicrobials) leads to drug resistance, and that treatments should be limited to animals that will most benefit from the treatment. This rather difficult concept (that short term benefits may lead to longer term problems) also highlights the importance of good communication in order to make sure the latest thinking in terms of disease control is understood by farmers and vets.

In terms of the future direction in disease control at Moredun, we are in a time of significant challenges to the livestock industry including climate change, Brexit-related changes to trade, and a reducing agricultural workforce. However, this is also a time where exciting new technologies are now available with the potential to revolutionise our approach to disease control. One of the biggest developments in recent years is the digital revolution where computer-based record keeping is now becoming second nature on the farm (genetics, health, nutrition and treatment records) and within abattoirs (carcass quality and disease records). Importantly, this information can be linked to individual animals via their electronic ear tags. These records contain highly valuable information and the challenge is now to link these data together to identify the factors associated with more efficient and healthy livestock (leading to improved animal welfare and reduced environmental impact), and better product quality (to improve the competitiveness of the UK livestock industry). A second exciting development is the rapid expansion of farm equipment and sensors for Precision Livestock Farming (PLF) – automated real-time monitoring of individual or groups of animals in order to identify and improve traits associated with health, welfare and productivity. An added benefit of PLF is that it allows high-level monitoring of livestock with less labor input, something that is particularly important given the reduced agricultural workforce in the UK.

Regardless of the new approaches to disease control, the future still requires continued engagement with farmer and vets in order to identify key issues, test new control strategies, and communicate our latest research findings. While COVID-19 has undoubtedly improved our ability to communicate digitally (webinars, video-calls) and will continue to play a role in the future, we look forward to the time when we can meet in person again!

Please Pick Up Your Dog Waste

Did you know that dog faeces can **carry *Neospora* parasites** that cause cows to abort their calves?

BAG IT, TIE IT, BIN IT!

For more information about *Neospora* visit **www.moredun.org.uk/research/diseases/neosporosis**

Moredun

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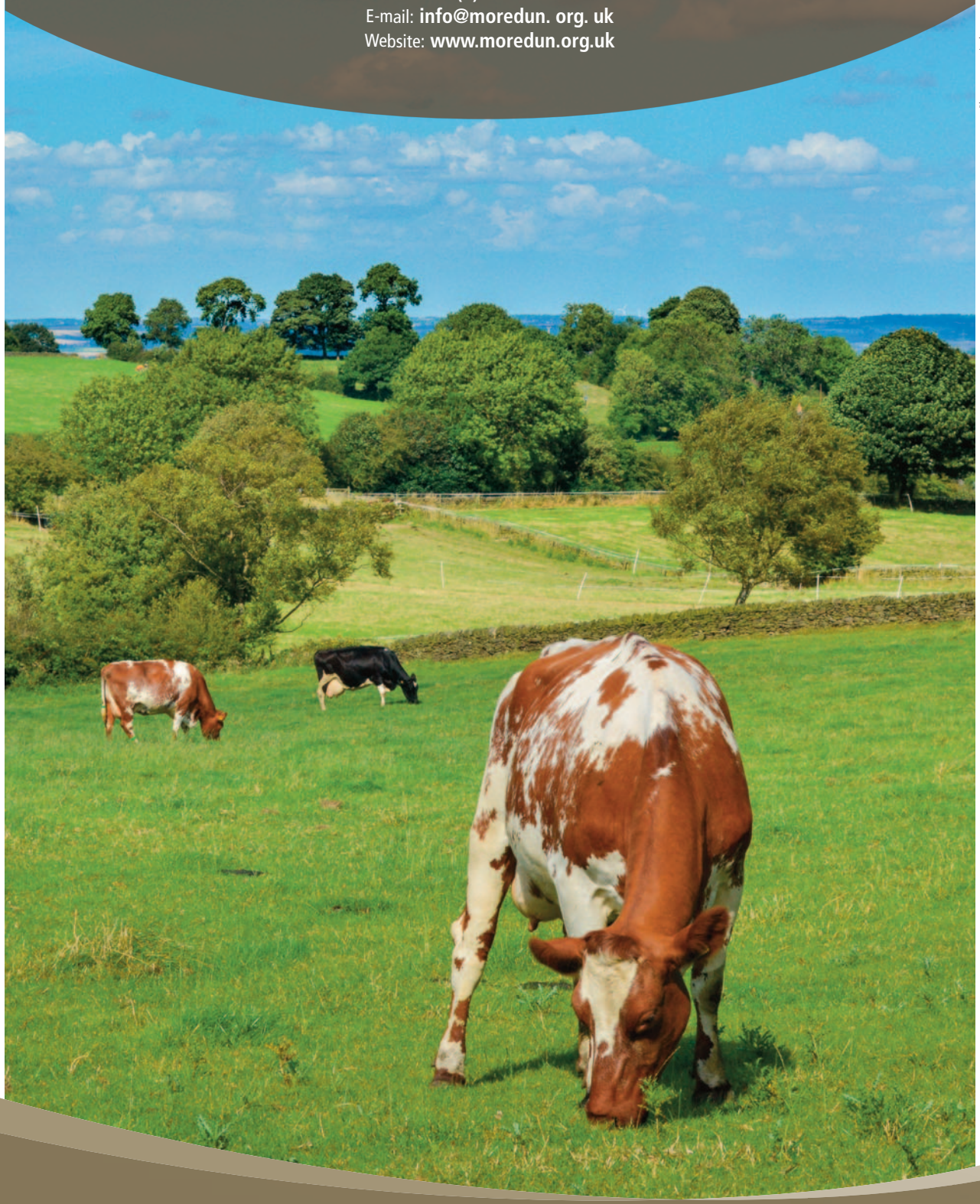

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