

## **“One Medicine: the Continuum of Medicine, Veterinary Medicine and Biomedical Science”.**

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### **Introduction.**

Chancellor, Provost , Ladies and Gentlemen. Thank you , Provost, for your generous introduction. It is indeed an honour to be invited to give this years Bourne lecture in memory of Geoffrey Bourne . Geoffrey Bourne , your first Vice Chancellor who as an educator and scientist who had the vision to create here in this marvellous country of Grenada a most remarkable medical school which later evolved under the leadership of Keith Taylor, as Vice Chancellor, into what is today- a thriving and confident young University. St George’s University is an internationally recognised institution of higher education which has set a dynamic global perspective and can rightly claim to be a strategically important landmark of learning in the West Indies.

In this lecture I am going to address the topic of “ One Medicine”. I have chosen this as a topic because it seems appropriate to the St. George’s Medical School and the close relationship it has with the veterinary school. The development of the veterinary school owes much to the foresight and drive of Peter Bourne, who as Vice Chancellor, fostered the development of veterinary medicine. In the long history of both the Medical and the Veterinary Professions and the education of undergraduates in both there has always been a healthy interaction between medicine, veterinary medicine as well as biomedical science. The co-location of a medical school with a veterinary school which you have here is one way to promote this interaction .

I am a veterinarian and an immunologist and my exposure to one medicine has always been a feature of my entire career. I did my PhD with a very distinguished immunologist and veterinarian Professor Robin Coombs, one of the founding fathers of immunology and inventor of the Coombs test for haemolytic diseases of the newborn and much else. His Immunology Division in the Department of Pathology in Cambridge was a wonderful environment of medics vets and scientists without boundaries between them. In Robin Coomb’s laboratory it did not matter what species you worked on what mattered was the questions you asked. Robin would say “ask the right question and you have got half the answer.”

In a professional context medicine and veterinary medicine are separate and the veterinary and medical schools do have distinct educational goals essential to their respective missions. Veterinary medicine is concerned with such issues as farm and companion animal medicine, animal welfare and veterinary public health and medicine has of course its focus on human health. However there are many areas where there is no boundary between the two but considerable overlap especially in the fields of infectious diseases, genetic diseases, cancer and public health. It is a wide field and so in this lecture I am going to focus on prion diseases, genetic diseases of dogs and zoonotic infectious diseases. All illustrate the essential interplay between our respective disciplines.

## **Prion Diseases of Man and Animals.**

Prion Diseases of man and animals rank as a classical example of One Medicine. Before the advent of Bovine Spongiform Encephalopathy (BSE), prion diseases were well recognised in other species including man. In animals the prion diseases are scrapie of sheep, transmissible mink encephalopathy (TME ) and chronic wasting disease (CWD) in elk and deer in the USA. TME has occurred from time to time in mink farms in the USA where mink have been fed condemned carcasses of sheep or cattle which contain prions - an example of a food borne prion disease. In humans there are a range of well known prion diseases such as Kuru and Creutzfeldt Jakob Diseases (CJD) which includes both sporadic, familial and iatrogenic forms as well as the human form of BSE known as variant CJD (vCJD).

CWD deserves a mention as it is a well known transmissible spongiform encephalopathy (TSE) of wildlife. CWD is seen in rocky mountain elk and deer. These animals waste away, have difficulty in moving, are highly infectious for other deer and elk and secrete high levels of prions in saliva. At present there is no evidence that CWD transmits either to livestock or man.

The prion diseases of scrapie, kuru, CJD and BSE are all caused by novel infectious agents known as a prions. These have been the cause of not one but two TSE epidemics, one in cattle (BSE) and the other, tragically in man, of vCJD. In spreading through the animal and human food chain BSE had extensive consequences for animal health, many industries involved in animal and human food ranging from animal feed industries to supermarkets, public health and public trust in Government. Rarely in the history of veterinary medicine could an obscure and rare brain disease of ruminants come to have had such a huge impact on global aspects of agriculture, food, human health and public trust in Government and science.

I have always regarded BSE as a kind of animal health Chernobyl. It has drawn into its fall-out veterinarians, medics, scientists as well as a wide range of Government departments of Agriculture, Environment, Health, Treasury, Education and Science. A wide range of industries such as farming, food and health care as well as the animal feed industry, the pharmaceutical industry and even the cosmetics industry were all affected. The cost to the UK taxpayer has been in the region of £12 billion. The BSE crisis has spread out to involve the EU proving to be a bigger issue than the European single currency. The effects of the BSE crisis have been global involving many other countries such as Canada, the USA and Japan. It is therefore not surprising that the World Health Organisation has recommended that *“the eradication of BSE must remain the principle public health objective of national and international animal health control authorities.”*

What makes prions uniquely interesting is the fact that they represent a new type of infectious agent. Prions are infectious proteins--- they are not infectious organisms in the usual sense and are not killed by irradiation, UV light, heat and enzymes ( nucleases) that degrade nucleic acids. Infectivity is only reduced by enzymes that destroy proteins. Thus in terms of killing off infectious agents the rules have changed- and changed dramatically. Prions are relatively “bomb proof”.

Unlike conventional infectious agents there is no immune response to prions:

- There is no vaccine
- There are no antibiotics
- There are no therapeutics

At present all we can do for patients with prion diseases is good nursing and care until they die.

The hallmark of all the TSEs be they animal or human is the classic picture of spongiform encephalopathy where the the brain section is riddled with holes due to destruction of neuronal cells in the CNS. What is remarkable about this is that there is no reaction from the host to the prion agent. There is no immune response, there is no inflammation. Prions are class 1 killers- they kill silently and by stealth. That is why prion diseases are called “encephalopathies” and not encephalitis. In viral encephalitis, for example in AIDS or other viral encephalitides, there is a host immune response and inflammation in the brain and meninges. Richard Rhodes in his book *Deadly Feasts* aptly describes the neurodegeneration in the human form of BSE as “an atrocity of destruction” .

### **Scrapie of sheep.**

Sheep scrapie is the prototype prion disease which has been recognised since 1750 in European sheep breeds originating in the Merino breed in Spain. It is so called because the sheep scratch and nibble and tear at their fleece. They also show gait abnormalities, twitching, shivering and a range of limb paralysis.

It is a classical TSE with characteristic brain pathology and is 100% fatal within 16 months to two years after the onset of symptoms. Scrapie is endemic in many countries with the exception of Australia and New Zealand which are scrapie free. In sheep scrapie infection is sustained between ewe and lamb by perinatal infection and contamination of pastures. Scrapie has never been shown to cause any human CJD-like disease.

In the context of naturally occurring TSE diseases of animals it is instructive to look at what happens in endemic and naturally occurring scrapie. Although scrapie presents as a neurological disease infection begins very early on in the gut. Infectious prions can cross the gut epithelium through the specialised M cells and the first sign of prion replication can be detected in the Peyer’s patches of the gut associated lymphoid tissue. This is then followed by neuroinvasion via the parasympathetic and sympathetic nerves and ganglia to the brain and spinal cord. This replication in the gut associated lymphoid tissue and peripheral nervous system can be bypassed by direct inoculation of prions into the CNS as is frequently done experimentally

### **Kuru in man.**

Kuru , which means shivering, was a mysterious illness mainly affecting women and children and was first recognized in the Fore tribes in the Eastern Highlands of Papua New Guinea. . Clinically all cases had difficulty in standing, lacked co-ordination and

developed paralysis . Kuru was shown to be associated with the practice of ritualistic cannibalism and later shown to be experimentally transmissible to animals

Amongst the Fore tribe it was the commonest cause of death of women and young children at the height of the epidemic. These slides show some of the cases of Kuru where just as in sheep scrapie there are gait abnormalities, difficulty in standing, progressive paralysis a wide range of behavioural changes and eventually death. The kuru epidemic was brought to an end when the Australian Health Authorities persuaded the Fore people to end ritualistic cannibalism. The epidemic went into decline with no new cases after 1960 and died out in the younger age groups as the source of infection had been stopped. Those infected before 1960 continued to die and as the incubation period is very long, up to 50 years some cases, affected individuals are still being seen today.

The relevance of kuru to BSE is twofold

- It was the first example of a “food borne” TSE disease-albeit a highly unusual one.
- When ritualistic cannibalism, which was fuelling the epidemic stopped the epidemic went in to decline.

Kuru is a fascinating story of truly pioneering medical science by Dr. Carleton Gajdusek and his colleagues Joe Gibbs and Michael Alpers . Their research led to the understanding of this disease and its link to the practice of ritualistic cannibalism. The early studies that began to unravel the nature of Kuru as a disease also owe much to a veterinarian Dr Bill Hadlow who was so struck by the similarities between the pathology of kuru and scrapie that he published a very important paper in the Lancet wherein he concluded that

*“Thus it might be profitable, in view of veterinary experience with scrapie, to examine the possibility of the experimental induction of kuru in a laboratory primate, for one might surmise that the pathogenetic mechanisms involved in scrapie -however unusual they may be-are unlikely to be unique in the province of animal pathology”*

It was this observation, which captures the essence of One Medicine, that may well have influenced the subsequent attempts by Gajdusek and his colleagues to investigate kuru by attempting to transmit the disease to experimental primates.

### **Creutzfeld Jakob Disease (CJD) .**

CJD occurs sporadically affecting men and women in late middle age (65-75 years ) and has a worldwide incidence of 1.3 cases per million. It is rapidly progressive, always fatal and was shown to be transmissible to experimental animals by Hsiao and Prusiner. The first cases of CJD were recorded by two German physicians Creutzfeld and Jakob in the 1920s.

There are two other forms of CJD. Familial CJD accounts for about 15% of all CJD cases and is a genetic disease arising through point mutations in the PrP gene leading

to progressive dementias. Although a genetic disease, proof that familial CJD was a TSE comes from the work of Masters et al who showed that one of the forms of familial CJD was experimentally transmissible to primates. Iatrogenic CJD is passed on by the accidental transmission through medical or surgical procedures. This emphasises the transmissibility and health risks of human to human transmission of CJD and is a major issue for current handling of variant CJD. Iatrogenic CJD was a 'near miss' of an epidemic in man caused by the injection of human growth hormone to cure dwarfism in children. The human growth hormone used was contaminated by prions since it had been derived from a pool of pituitary tissue that contained CJD material. It was sheer luck that this was not a major medical catastrophe-genetically engineered growth hormone is now used instead to avoid this kind of medical mistake.

Kuru, Scrapie and CJD can all be regarded as a classic example of One Medicine in that they are all caused by the same mechanism. Prion proteins can be isolated from brain extracts from any of the prion diseases be it Kuru, scrapie or CJD and if inoculated into laboratory animals result in disease onset after a long incubation period of several months or years. The brain of the lab animal shows typical spongiform change but more importantly the infectivity can be recovered and repeatedly passed to more animals of either the same or different species. This is what defines such encephalopathies as "transmissible" and fulfils Koch's postulates for an apparently "infectious" disease. Transmission within a species is easier than transmission between species but this can be done. The relative resistance to transmission of prions between species is due to the effect of the species barrier and determined significantly by the polymorphisms in the PrP gene. Experimental transmission of TSEs opened up important new avenues for the study of prion diseases and was the key evidence that linked all three diseases together.

Until these groundbreaking experiments in animals were done these three diseases of Kuru, scrapie and CJD were regarded as quite separate:

- Scrapie was regarded as an obscure infectious disease of sheep of interest only to veterinarians and farmers.
- Kuru was a strange tropical disorder afflicting the Fore tribes in New Guinea whose rituals were bizarre.
- The human forms of CJD were puzzling but very rare disorders occurring worldwide at a level of 1 in a million people.
- Iatrogenic CJD was a medical risk.

A typical experiment to prove infectivity of prions is usually carried out in mice. The lifespan of a mouse is about 2 years and if inoculated with prions the mouse develops a TSE disease over varying periods. Rogue prions or PrP<sup>sc</sup> can be detected by antibody staining of the brain sections. This type of experimental approach has allowed the identification of the infectious agent in the brain extract.

What are prions at the level of proteins and genes.? Passage of infectivity from one mouse to another allowed the identification of the molecules involved and an understanding of the molecular basis of TSE diseases. The protein rich brain extract that contains infectivity contains a normal brain protein known as PrP<sup>c</sup> and an abnormal form of this normal protein known as PrP<sup>sc</sup> scrapie or PrP<sup>sc</sup> for short.

PrP<sup>c</sup> and PrP<sup>Sc</sup> are two forms of the same protein with characteristic molecular fingerprints. The gene for this protein was isolated, cloned and sequenced. PrP<sup>c</sup> is a normal gene and protein in all brain and other tissues. Since PrP<sup>Sc</sup> is an altered form of a self-protein it is therefore no surprise that the immune system does not recognise abnormal prions.

What is PrP<sup>c</sup> and how does it turn into the rogue prion-PrP<sup>Sc</sup>. The normal PrP<sup>c</sup> molecule is a GPI linked cell surface protein of about 230 amino acids, with one disulfide bond and 2 glycosylation sites. It can be destroyed by proteases such as proteinase K. The three dimensional structure of recombinant PrP<sup>c</sup> is characterised by three alpha helices where the protein is twisted into ribbon like structures and a short and flat beta pleated sheet. The abnormal prion protein, PrP<sup>Sc</sup>, arises from a conformational change in PrP<sup>c</sup> without a change in amino acid sequence to give a molecule which has a about 50% beta sheet. This form is largely resistant to proteinase K and can form protein aggregates in brain tissue leading to cell death and spongiform change.

How does an abnormal form of normal protein cause disease like scrapie, kuru and BSE? The answer to this comes from the prion hypothesis of Prusiner which provides part if not all of the answer to this challenging question. The prion hypothesis for which there is now ample experimental evidence is as follows. PrP<sup>c</sup> is converted into the abnormal shape and once formed catalyses more of itself by a type of feedback amplification loop. What causes PrP<sup>c</sup> to change to PrP<sup>Sc</sup> is exposure to either external rogue prions (e.g. the infected meat in Kuru, the infected placenta in sheep scrapie) coming into the gut and starting the process of PrP<sup>c</sup> to PrP<sup>Sc</sup> conversion in the gut lymphoid tissue with eventual spread to the brain. Mutations in the PrP gene as in familial CJD also predispose to this conformational change.

There may also be factors yet to be discovered since an important question is how is natural scrapie maintained as an endemic disease in sheep? Is it really all explained by the fact that PrP<sup>Sc</sup> is being transmitted from sheep to sheep or does something else trigger the conversion in the first place?. There seems little doubt that once PrP<sup>Sc</sup> is generated it acts as an autocatalyst. It is possible that in scrapie PrP<sup>c</sup> to PrP<sup>Sc</sup> conversion is the end stage of a more complex process. The vicious circle of PrP<sup>Sc</sup> amplifying more of itself leads to progressive accumulation of PrP<sup>Sc</sup> over time hence the long incubation periods of prion diseases. Eventually this results in death of nerve cells and spongiform encephalopathy. It is a kind of "molecular domino effect" where the rogue prion knocks the other normal copies of PrP into the abnormal shape. Aggregates of PrP<sup>Sc</sup> build up and in brain sections aggregates of PrP<sup>Sc</sup> can be seen microscopically as plaques or by using special stains such as Congo red as tangles of red stained fibres or in the electron microscope as stacks or rods of abnormal proteins. There is now overwhelming evidence for Prusiner's hypothesis.

Evidence that prions are the causative agent in TSEs is now overwhelming. In summary

- PrP<sup>Sc</sup> is the unique marker of a TSE in all species
- PrP<sup>c</sup> knock-out mice are not susceptible to TSEs
- Prions cannot be propagated in PrP<sup>c</sup> knock-out mice

- Species barrier is controlled by PrPc genotype
- Susceptibility to TSE related to PrPc polymorphisms
- Point mutations in PrPc result in familial CJD diseases
- Strain specific properties of PrPsc are encoded by conformational variants of the normal protein

### **The BSE and v CJD epidemics.**

The origin of BSE is not known but the mechanism that turned a rare disease into an epidemic is. The very first case may have occurred as early as 1975 either as a rare and sporadic case of BSE, or an unusual scrapie strain in a sheep but these slipped into the animal food chain. In an abattoir after the meat is removed the rest of the carcass is passed on to renderers. Animal carcasses can be rendered down by heat treatment and solvent extraction to provide two products—a protein residue and fat – the protein residue, known as meat and bone meal (MBM) is recycled as an animal feed supplement and the fat or tallow has many uses ranging from soaps to cosmetics.

Although rendering is carried out at high temperatures that destroy conventional infectious agents prions are not destroyed in this process. The use of MBM as an energy supplement in animal feed to boost production of milk and meat has been a long established and worldwide practice. At some stage in the UK –possibly as early as ten years before the onset of the epidemic in 1975—a TSE carrying animal carcass contaminated this process and the prion content of MBM was magnified exponentially. Like a chain letter once the bad news started it was amplified a million fold by the repeated cycles of rendering, feeding, infecting: rendering feeding infecting and so on.

The infectious dose for a cow is extremely small. 1 gram will certainly infect and infectivity can be detected as low as one milligram. A BSE infected cow is estimated to have as many as 100,000 infectious doses- that is one cow can potentially infect 100,000 others as there is no species barrier in cattle to cattle infection .

The point today for this process is that it doesn't take much to start this process of amplifying infectivity through the MBM feeding cycles. As was stated in the BSE Inquiry “The long fuse of a TSE may be lit by a few prion molecules” . This is why there is now a worldwide ban on feeding MBM to ruminants. In the UK and EU MBM feeding it is also banned for all farm animals- MBM derived from any animal cannot be fed to any other farmed animal. It is a kind of industrialised cannibalism and the bans are in place to stop any potential for recycling of prion infectivity within or between species through the feeding cycle.

The BSE epidemic gave rise of course to widespread fears about the outcome for the human v CJD epidemic. The vCJD epidemic peaked around the year 2000 and shows a decline in recent years. There is every sign of a downward trend but if vCJD turns

out to have an incubation period similar to Kuru of up to 40 years it is too early to say if the epidemic is over .

Because so little was known at the time of the appearance of vCJD many of the basic quantitative parameters regarding infection dynamics were unknown. These include lack of knowledge of the infectious dose for man, the attack rate, the route of infection and so on. The estimates for the numbers of people who might be infected and develop the disease ranged from anything between 80 and 500,000 cases of v CJD. Such wide band widths were predicted since at that time the infectious dose for humans was not known, the route and source of infection was not known and there were many potential variables. The press tended to focus on the upper limit and not the lower. Now thankfully such apocalyptic figures have not been realized and so far there have been only 159 cases of v CJD in the UK. In France there have been 14 cases so far. Genetic susceptibility is well known in prion diseases and these may represent only the most susceptible of individuals with others yet to follow.

### **The legacy of BSE.**

The jump of BSE to man through the food chain to cause the vCJD epidemic has resulted in many concerns about the iatrogenic transfer of vCJD between people. Whilst the species barrier may have had a major effect on limiting the scale of the v CJD epidemic in the transmission of BSE to man there is no such species barrier in vCJD transmission between individuals-hence the concern. Because of this the UK health authorities introduced a raft of public health measures during the vCJD epidemic as precautionary measures to limit the risk of iatrogenic spread. Such measures include

- White blood cell depletion from all blood packs
- Ban on use of UK plasma for therapeutic blood products
- Policies on the re-use and sterilisation of surgical instruments
- New practices for dental instrument sterilization
- Use of disposable instruments for tonsillectomy
- Ban on re-using trial contact lenses

Even as innocuous a practice as re-using trial contact lenses by opticians has been banned in the UK because of the potential risk of transmitting prions via the eye, which is well known route of experimental infection.

The legacy of BSE/vCJD for the human health care industries is considerable. This applies particularly in the safety of blood and blood products where there are many concerns.. At present there is no preclinical blood test for vCJD prions thus making it difficult to test for the presence of prions in blood or blood products. PrPsc is difficult to destroy by heat, UV light, irradiation and there is evidence from sheep experimentally inoculated BSE that PrPsc can be spread by blood transfusion. Thus the use of UK blood as a source of plasma products such as blood clotting factors is banned until methods can be developed that remove prions from manufactured blood products. It has led the National Blood Service in the UK to ban the donation of blood by those who have inadvertently received blood from any individual who has subsequently developed v CJD. As an example of the precautions that have been taken worldwide Australian citizens who were resident in the UK for more than six



months at the time of the UK BSE crisis are not allowed to be blood donors in Australia at the present moment.

It is now some 10 years since the vCJD epidemic began and 20 years since the cattle epidemic so what are the issues today and do the animal TSEs have any lessons for vCJD in man.?

The key issue today for v CJD is the question of the iatrogenic transfer of v CJD from human to human through surgical or medical procedures. Unlike the situation with AIDS there is no preclinical diagnostic test to detect potential carriers of vCJD nor do we know the potential size of the number of individuals who might be incubating the disease. Given the long incubation period of TSEs in man which with Kuru could be up to 50 years this is a very serious question of public health and safety of the blood supply.

A central issue concerns v CJD and blood transfusion. It is now well established that in both sheep scrapie and human vCJD that lymphoid tissue contains PrPsc concentrated on a specialised set of cells known as the follicular dendritic cells (FDC) which lie in the B cell area of the lymph node and spleen and other lymphoid organs. Studies in sheep scrapie by Brandner et al were the first to show that prions were detectable in lymphoid tissue during the preclinical phase. The same was then shown for humans with v CJD. This led to a large survey for PrPsc in lymphoid tissue in man by Hilton et al which showed that 3/14, 000 appendices were PrPsc positive. If this is regarded as a marker of preclinical infection then the extrapolation from this is that some 4000 people in the UK may be carriers of preclinical v CJD. The presence of prions in lymphoid tissue may well explain why this infectivity can be detected in the white blood cell fraction of blood as this contains the recirculating cells of the lymphoid system.

### **Sheep as a transfusion model for v CJD.**

What is needed in this difficult area is an animal model that allows us to try and understand some of the fundamental questions of what components in blood carry infectivity and obtain evidence which allows quantitation of risk. Thankfully this is possible by using natural scrapie or experimental BSE in sheep. Scrapie and experimental BSE in sheep may well prove to be enormously important to providing key answers to the difficult questions on blood safety and current work being carried out at the Institute of Animal Health in England by Fiona Houston and her colleagues is providing an animal blood transfusion model for studying prion infectivity in blood. The preclinical and clinical donors are either sheep experimentally challenged with BSE or naturally infected with scrapie and blood from these sheep is transfused to scrapie free recipients. There is clear evidence from this work that sheep blood contains infectivity in the white cell fraction and that both preclinical animals as well as clinical can transmit infectivity to naïve recipients. These studies are an excellent example of the value of a natural disease in sheep being used to provide fundamental information on what the nature of prion infectivity in sheep blood. Thus sheep with scrapie are certainly making their contribution to One Medicine.

### **The good legacy of BSE.**

Although BSE has been a story of tragedy it has also brought some considerable gains for scientific understanding of TSEs and a greater understanding of how to handle epidemics in animal health that affect public health. In summary the advantages have been

- Huge strides in understanding of prion diseases
- New scientific understanding of neurodegenerative and protein misfolding diseases (Alzheimer's Disease)
- Better understanding and control of zoonotic diseases
- improved TSE diagnostics for man and animals
- Recognition of the linkage between animal health, food safety and public health
- The importance of openness and transparency with the public to gain trust and confidence in matters of animal and public health

### **Canine Genetic Diseases.**

I now want to turn to another large area in veterinary medicine where the study of the naturally occurring diseases in their target species is opening up new avenues of understanding for human medicine. This is the area of genetic diseases of companion animals . This area is a goldmine for comparative medicine .

The domestication of the dog from its ancestor the wolf is one of the biggest genetic enterprises of a domestic animal going back for 1000s of years. Different dog phenotypes have existed for millennia and selective breeding of companion animals particularly dogs and cats for desirable traits has been a considerable development in the evolution of different breeds of companion animal. It is at its most advanced with dog breeding where there are now over 400 different breeds. Breeding for desirable traits is further telescoped by the 'breed barrier rule' which has led to different dog breeds being developed that are unique genetic "lineages" each one representing relatively closed gene pools.

However there is no gain without pain. The consequences of selective breeding for desired traits has resulted in the co-selection of a range of genetic diseases. There are about 430 inherited disorders many of them autosomal recessive conditions such as increased cancer susceptibilities, auto immune diseases, epilepsy, deafness and possibly behaviour.

What makes these diseases interesting in the context of One Medicine is that the selectively bred dogs share the environment with man and are exposed to a similarly wide range of microbiological and environmental challenges to health from very young to old age . This is in stark contrast to the inbred laboratory animal for genetic diseases research as these are kept in relatively sterile and non-challenging environments with short life spans.

Thus the genetic diseases of companion animals represent a unique and rich source of the "experiments of nature" which in human medicine have often revealed fundamental insights into biology and medicine.

What has given this field enormous significance has been the work on understanding the canine genome. From many studies it is now clear that there is considerable homology between dog and human chromosomes that is allowing the mapping of canine genes by the techniques of reciprocal chromosome painting. There is also now an extensive assembly and sequence of the entire canine genome based on the boxer dog and the poodle.

Genes which predispose to certain diseases are more common in some breeds and in others the disease is rare. One of the reasons for this is that there is a strong founder effect through the use of popular sires that may be a carrier for the disease allele. Many of the traits are due to the action of several genes but there are three conditions where the precise gene mutation is known and mapped and its mechanism of causing disease is known. These are hereditary renal cancer, narcolepsy and the genes involved in progressive retinal atrophies some of which are equivalent to early onset night blindness or retinitis pigmentosa in man.

Probably the best example at present which illustrates the One Medicine concept in the context of genetic diseases of man and dogs is seen in the recent advances in understanding narcolepsy. Narcolepsy in man is a well known genetic disease with an incidence in the population of about 1/2000. This was a poorly understood disease until recently characterized and is recognised clinically as a sleep-wake disorder. Patients show excessive day time sleepiness, sleep paralysis and the disease has a close association with MHC Class II genes. It is a disorder with a marked similarity to canine narcolepsy.

It was the studies of Lin et al on canine narcolepsy that really “woke up the entire field of medical research on narcolepsy” when they showed that canine narcolepsy recognized in dachshunds, poodles etc was a simplified genetic system where the defect was due to a mutation in the canine gene for the cell membrane receptor for a sleep modulating neuropeptide orexin or hypocretin .

This work was the first data to link the hypocretin gene family to sleep disorders and led directly to the identification of the defect in some forms of human narcolepsy which is a more complicated genetic system than in the dog - the defect in man is now known to be a mutation in the neurotransmitter which leads to defective synthesis. It is not an identical mechanism but all part of the function of the sleep modulating neurotransmitters in the CNS.

The canine narcolepsy story then is one of the classic examples of One Medicine. It also shows the remarkable speed of medical progress made possible by the genome revolution in man and animals resulting in the space of a few years of a new understanding of a puzzling human condition arising from the study of a rare canine disease.

Canine genetic diseases are also helping us to understand the complex aetiologies and pathogenesis of more complex polygenic disorders. A particularly good example comes from the studies of canine Diabetes Mellitus . Several studies have now shown that there is an increased risk of late onset diabetes in middle aged to old dogs in breeds such as the Samoyed, the Tibetan Terrier and the Yorkshire Terrier. This is in

contrast to other inbred dogs where Diabetes is either rarely seen ( e.g. the Boxer) or at very low frequencies ( German Shepherds). In mixed breed dogs the incidence of diabetes is about 0.36% but the Samoyed has about 15 times this risk.

Breed dispositions for cancer susceptibility are also well recognized. Histiocytic sarcoma which can present as a lymphoid cell tumour in dogs is seen at greatly increased incidence in certain breeds but most notably in Flat Coated Retrievers and Bernese Mountain dogs. This is an autosomal recessive condition and the familial distribution throughout many offspring generated from one dog emphasizes the popular sire effect where the spread of an autosomal recessive gene through many offspring occurs in the course of repeated breeding and inbreeding of offspring.

### **Zoonotic diseases.**

At the start of the 21<sup>st</sup> Century the global concern was about “millennium bug” i.e computer viruses. However millennium bugs turned out to be the real thing -viruses and bacteria. The global reach of such infectious agents is considerable. These range from the spread of flu , SARS and West Nile Fever virus and many other that can all be regarded as emerging infections. We urgently need to better understand these infectious diseases and to be better prepared for them. Infectious diseases do not respect geographical boundaries and our modern world makes the reach of such infections extensive and ever threatening. Recent epidemics of animal diseases including those that transmit to man are wake up calls.They are in stark contrast to the statement by the Surgeon General of the USA in 1967 that “It is time to close the book on infectious diseases and shift all national attention and dollars to the ‘New Dimensions’ of health: chronic diseases ( US Surgeon General William H.Stewart 1967)

- in reality we have simply turned to a fresh page.

The spread of zoonotic diseases is made possible by the close interaction of wildlife, domestic animals and humans. There are of course many causes for the rapid emergence of exotic diseases. These range from genetic changes in pathogens – and the repeated emergence of new flu strains is a good example of this-to the genetic changes in farmed animals through the inbreeding of selected lines of poultry that may be more susceptible to pathogens. Other causes include ecological changes resulting in destruction or changes to natural habitats for wildlife growth and high density housing. Practices in intensive agriculture are also contributory factors –no better example than the widespread practice of feeding high protein diets of MBM to enhance milk yield of dairy cows fuelling the BSE epidemic. Also contributing are global animal movements both legal and illegal .

Once the infectious agent has emerged or jumped species there are plenty of risk factors that promote spread. There is international trade in food products, long distance transport of livestock as we saw that with the extensive foot and mouth disease (FMD) outbreak in the UK. New reservoirs of WNF are now widespread in the mosquito populations of the USA. There are also political risk factors –eg the planned expansion of the EU to include such countries as Turkey brings with it the concern of further incursion of say FMD or Blue Tongue virus(BTV) in sheep.

We should not imagine for one minute that we shall ever escape the biological interaction between pathogens, animals and humans. To put it in the context of the war on bugs- there will always be new threats and containment and not conquest is the way forward.

Many health authorities are now fully aware the significance that global travel may play in the rapid spread of zoonotic diseases. The statistics of air travel are interesting in this regard in that no city on earth is more than 24 hours away from any other and the volume of air passenger traffic can accelerate such spread as we have seen with SARS and WNF. It remains a puzzle as to how WNF got in to the US-explanations are inadvertent passenger aircraft transport of mosquitoes from the middle east to the USA . The SARS epidemic dramatically illustrated the role of travel in rapid disease spread. The number of cases across the globe grew at an alarming rate until the application of strict public health strategies and isolation contained further spread.

Avian influenza, especially that caused by H5 N1 is highly infectious for birds and has to be regarded with utmost seriousness. Although H5N1 has not as yet become a major human flu pandemic -and one hopes never will- avian flu is an accomplished species jumper. Although human cases of H5N1 flu have been in the low hundreds ( in contrast to millions of bird cases) so far there have only been 185 deaths mainly through direct contact with infected birds. Nonetheless the mortality rate of those becoming infected is around 50% which is extremely high for a zoonotic flu virus .

Avian flu and its spread emphasizes the key issues for animal and human health authorities in the control of zoonotic diseases. Speed of clinical detection, rapid diagnosis and rapid action must be applied to outbreaks. Rapid diagnosis of infectious agents in the field using state of the art molecular diagnostic technologies are essential .

Preparedness can of course be at many levels. Preparedness based on huge stockpiles of vaccines and antiviral drugs is crucial but so also is awareness and biosecurity. In developing countries and in rural areas simple attention to limiting spread of infections through early reporting is essential.

There are many lessons that have been learned and many more yet to be learned. My conclusions on the key current issues for infectious diseases of man and animals can be summarized as

- Surveillance, vigilance and containment
- Medical and veterinary surveillance needs to be integrated
- Effective regional, national and global co-ordination
- Better understanding of animal and human demographics
- Oversight of the international trade in pets, livestock and wildlife
- International funding in support of disease control in developing countries
- Animal diseases recognized not only as of economic significance but as a matter of public health

## **Conclusion**

Thus I hope I have illustrated that across the wide spectrum of issues in animal health whether they be degenerative diseases, genetic diseases or zoonotic infections. They

all illustrate the continuum of medicine, veterinary medicine and basic biomedical science and the essential and fascinating interplay between them which can do more to advance knowledge in both medicine and veterinary medicine than either can achieve on their own .

