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INTERNATIONAL SYMPOSIUM ON CHRONIC CARDIAC VALVE DISEASE (CVD) IN THE CAVALIER KING CHARLES SPANIEL

MAY 16, 1998

This transcript is a service of the Cavalier King Charles Spaniel Club, USA

INTRODUCTION

The Cavalier King Charles Spaniel Club, U.S.A., Inc (CKCSC, USA) has, for a long time, been aware of the high incidence of chronic cardiac valve disease in the Cavalier King Charles Spaniel, just as have Cavalier clubs in other countries, particularly the United Kingdom and Sweden.

Our membership has continuously been appraised of the findings and suggestions have been made to breeders of means of curtailing the incidence and perhaps reducing the severity of the disease.

In this "The Year of the Heart" in which the CKCSC, USA is instituting a number of programs geared toward the study and control of chronic cardiac valve disease, this symposium was organized in order to bring together international experts to present data and provide guidelines for breeders.

We urge our members to follow their recommendations, and hope that we will attain our goal of bringing the prevalence, the age of onset, and the severity of the disease to the levels seen in other breeds of dogs.

The original transcript of the audiotapes was forwarded to the speakers for review, and the document has been edited accordingly. Dr. Swenson also kindly submitted a previously published document, and pertinent parts of this are included.

CAVALIER KING CHARLES SPANIEL CLUB, U.S.A., INC.

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MAY 16, 1998

Andrew Beardow, BVM&S, MRCVS
Veterinary Referral Center, Little Falls, NJ

James W. Buchanan, DVM, M Med Sci
School of Veterinary Medicine
University of Pennsylvania

Virginia Luis Fuentes, MA VetMB DVC MRCVS
College of Veterinary Medicine
University of Missouri

Bruce Keene, D.V.M., MSC
College of Veterinary Medicine
University of North Carolina

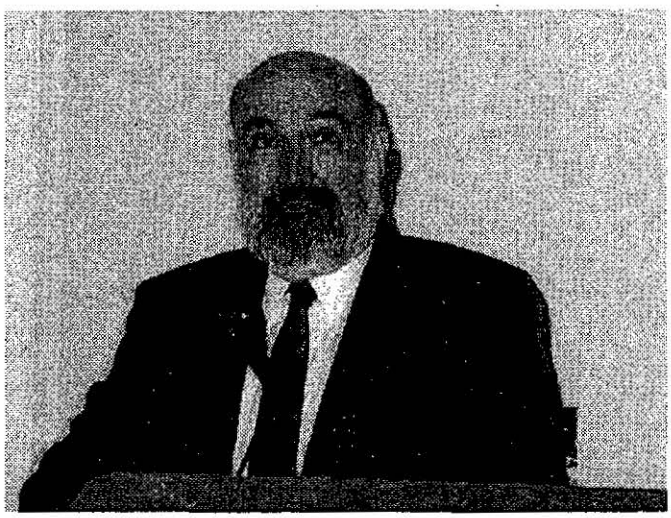
Lennart Swenson, MSC
Department of Animal Breeding and Genetics
Swedish University of Agricultural Sciences
Uppsala, Sweden

Andrew Beardow BVM&S, MRCVS

Andy graduated from the Royal (Dick) School of Veterinary Studies in Edinburg, Scotland in 1987.

Following an internship at the University of Liverpool he crossed the Atlantic to complete a residency in Cardiology at the University of Pennsylvania. He stayed on at Penn as lecturer before moving to Cardiopet in 1993. Andy is currently vice president of Cardiopet and president of Cardiopet Veterinary Associates, an independent company that operates the Veterinary Referral Center in Little Falls NJ. Andy has published many articles and textbook chapters and has lectured around the world.

While at the University of Pennsylvania Andy worked with Dr. James Buchanan on a project to evaluate the prevalence of heart valve disease in American Cavalier King Charles Spaniels and maintains an active interest in this problem.



James W. Buchanan, DVM, M Med Sci.

Dr. Buchanan is a graduate of Michigan State University School of Veterinary Medicine where he obtained his DVM degree in 1960, and of University of Pennsylvania School of Medicine Division of Graduate Medicine where he earned a Master of Medical Science (Cardiology) degree in 1967. He is qualified by the American Board of Veterinary Internal Medicine as Veterinary Internist and Veterinary Cardiologist. He has been associated with the University of Pennsylvania, School of Veterinary Medicine since 1960, is currently Professor of Cardiology and was Chief, Section of Cardiology from 1989 to 1991. He has done extensive research on heart disease and is the author of many books and scientific articles. Dr. Buchanan is best known to us as the principal investigator of heart valve disease in the Cavalier King Charles Spaniel in the U.S.A.

Bruce W. Keene, D.V.M.

Doctor Keene graduated from the Ohio State University dual degree program in Veterinary Medicine and Physiology/ Pharmacology in 1979. After an internship at the Animal Medical Center and completion of a cardiology residency at Ohio State he became ACVIM board certified in cardiology in 1983. He spent 2 post-doctoral years following clinical residency, one at the University of Zurich, Switzerland, and one as a research fellow of the American Heart Association at Ohio State. He spent 5 years on the faculty of the School of Veterinary Medicine at the University of Wisconsin-Madison before joining the North Carolina Sate University College of Veterinary medicine in 1990. He is currently on scholarly leave from NCSU at the University of Oxford's National Health Service Center for Evidence-Based Medicine. Dr. Keene's research interests include the therapy of heart failure, as well as the pathogenesis and cause of acquired heart disease in dogs and cats.

Virginia Luis Fuentes, MA VetMB DVC MRCVS

Dr. Fuentes qualified from Cambridge University in 1984, and spent 5 years in small animal practice before joining the Edinburgh Veterinary School as a Lecturer in Veterinary Cardiology. She obtained the Diploma in Veterinary Cardiology in 1992, and was recognized as a Specialist in Veterinary Cardiology by the Royal College of Veterinary Surgeons in 1994. She moved to the University of Missouri-Columbia in 1997 as an Assistant Professor in Veterinary Cardiology. Dr. Fuentes has been involved in breed schemes for the control of canine heart disease since 1991, working with the British Boxer Breed Council on aortic stenosis, and as advisor on heart problems to the British Cavalier King Charles Club from 1994-1997.

Lennart Swenson M Sc.

Genetic consultant for the Swedish Kennel Club; member of the Breeding Committee and member of the Scientific Committee of the Union of Kennel Clubs in the Nordic countries.

He started his career as a dog breeder in 1972 with his first litter of Skye Terriers. He started his research at the University in 1978. The aim of his research is to improve the dog's physical and mental health. His first project was hip dysplasia in German Shepherd dogs at the Swedish Dog Training Center. They began with a prevalence of 50% hip dysplasia and reached a level of 5% in 10 years. Later the work included other diseases and studies of the genetic variation of mental capacities. Today his main work consists of studies on the inheritance of a number of diseases in the dog population registered by the Swedish Kennel Club. He also participates in the development of various performance tests such as herding tests for Border Collies, tests for young dogs of Retriever breeds and German Pointers. He participates in and develops educational programs for dog breeders and national breed club representatives for the Swedish Kennel Club.

Anne Eckersley-Robins, President:
Good afternoon.

It is very exciting to have so many people here at this first-time symposium where the experts will help us figure out what to do about heart valve disease in Cavaliers. Before I came here I read a joke on the Internet that I wish to share with you. A mother, father and son came to the U.S. from an obscure country. On their itinerary was visiting a shopping mall. At the mall they stopped at some large, shiny doors that would open and shut, open and shut. They could not figure out their purpose. The father and son sat and watched a long time. Along came an old lady. She hobbled through one of the doors, the door shut and then they saw little bright lights go all the way to the ceiling, and then the lights came all the way down again. The door opened and out came this gorgeous blonde. The father said: "Oh, my goodness. Quick, son, go get your mother!" I thought about that for a while. It would be nice if we could take the Cavaliers with heart valve disease and put them in that elevator, send them up, bring them back down, and **boom**!, they would have normal hearts. Well, it is not quite as easy as that. Our guest speakers today are not miracle workers, but they are here to guide us as to which elevator to use. In other words, which protocols we should follow in order to decrease the incidence of chronic cardiac valve disease in Cavaliers.

Dr. Beardow is our moderator today. He is going to introduce our speakers. At the end of their talks we will have about an hour of questions and answers. Please jot down your questions on the note-pads provided on your desk, and ask them at that session.

Dr. Beardow:

Thank you very much for that introduction. I don't know if I can follow that. As a foreigner in America I can appreciate the elevator story. I am still looking for something like that.

It is a great honor and privilege to be here today, in the Year of the Heart, as this year has been labeled by the Cavalier King Charles Spaniel Club, U.S.A. The purpose of the symposium is to bring together the leaders in the cardiology world who have established models in other parts of the world and who have done a lot of research related to chronic heart valve disease. We want to make the presentations first. This gives us a good overview not only of the problem, but approaches to the problem. Please save your questions for the discussion at the end.

Our speakers this afternoon are Dr. James Buchanan, Emeritus Professor of Cardiology, the University of Pennsylvania; Dr. Virginia Luis Fuentes, Visiting Lecturer in Cardiology, University of Missouri, formerly of England; Dr. Lennart Swenson, a geneticist, the University of Agriculture and Sciences, Uppsala, Sweden; Dr. Bruce Keene, Associate Professor of Cardiology, University of North Carolina and Visiting Professor in England.

The goal of this symposium is to develop a pragmatic approach to chronic heart valve disease in the Cavalier. Dr. Buchanan is going to talk about the Unites States experience, and he is also going to give an overview of the pathology of the disease and how it fits in with other problems that we see in Cavaliers. Dr. Luis Fuentes is going to talk about the experience in the United Kingdom, where they have actually looked at different models to control the problem. Dr. Swenson is going to talk about the Swedish experience with specific breeding studies. Dr. Keene is going to give us some insight into what it means to develop a screening program. Hopefully, at the end of this afternoon we will have a good perspective of the problem and its prevalence, and ways in which we might deal with it.

First, a brief overview.

The heart is divided into two halves, the right and the left. The right heart pumps blood from the body to the lungs. The left heart pumps blood from the lungs to the body. For a pump to work efficiently, it must be primed. Each side has a priming chamber, the atrium, and a pumping chamber, the ventricle. The tricuspid valve controls how the blood flows through the right heart, and the mitral valve controls the flow *in the left heart. Any problem with these valves is going to* interfere with proper pumping function.

A tricuspid valve leak causes back-flow of blood into the body, resulting in right heart failure with fluid accumulation in the abdomen (ascites) and tissues. A mitral valve leak causes back-flow and fluid accumulation in the lungs (pulmonary edema), with the characteristic cough and breathlessness.

We will talk mostly about the mitral valve. Mitral valve disease is not a problem just for the Cavalier, it is a problem in many different small breed dogs. The difference in the Cavalier are that it occurs with a higher frequency than we see in other breeds, and Cavaliers develop the disease in early middle age, whereas in most other breeds it is a problem of late middle to old age.

The tests we use to evaluate hearts are listed in Figure 1. Auscultation is the use of a stethoscope to listen to heart sounds. Radiography is chest x-ray that is used to look at the heart size and fluid in the lungs. Echocardiography is the use of ultra-sound to study the heart movements and the structure and function of the valves. Each of these gives pieces of information that can be put together to obtain an overall picture of the state of the heart. Doppler analysis is another technique. When sound waves are fired at an object, and that object is moving, the reflected sound waves will have a different frequency. A common example is a train going by with the whistle blowing. As it comes toward you it seems that the pitch gets higher, and as it goes away it gets lower. That's a Doppler shift. Doppler is used to measure blood flow through the heart. A very sophisticated form of Doppler is called Color Flow Doppler. With this the changes in frequency are color-coded, and you can get a good view of how the blood flows.

Mitral valve disease is significant in Cavaliers. The presentation of chronic valve disease occurs between ages of 10 and 15 for most breeds. In miniature poodles it appears at 12 ½ to 13 years. It is a disease of old age. Cavaliers, however present much earlier than other breeds. The consequences of the disease may be devastating. If a dog develops pulmonary edema, and we don't treat that appropriately, it will cause death.

In the left heart we have a primer, the left atrium and a pump, the left ventricle. Blood comes from the lungs into the

atrium, then into the ventricle. Between the atrium and the ventricle is the mitral valve which, when open, allows the blood to flow into the ventricle and, when closed, keeps the blood moving from the left ventricle to the aorta and out to the body. The normal valve is thin, almost invisible on echocardiographs. The abnormal valve is thickened and irregular and may show up as a huge blob of tissue. A damaged mitral valve will not close properly, and blood will flow back through the valve into the atrium. With color Doppler one can actually see the abnormal flow. The atrium dilates, and gets bigger and bigger (Figure 2). Ultimately, pulmonary edema will develop.
Built-in struts, called the chordae tendineae hold the normal valve leaflets in place. In this disease the struts thicken, and become distorted. Sometimes they break, compromising the integrity of the valve and with disastrous consequences.

Now I would like to introduce Dr. Buchanan who is going to talk about the experience with the disease in the U.S., and some more of the pathology.

Dr. Buchanan:

Thank you, Dr. Beardow. I will begin with a photograph of former president Reagan with his Cavalier. I learned this morning that Frank Sinatra also was a Cavalier aficionado, and I would like to get a picture of him and his Cavalier if any one has one.

I was asked to speak on "Cardiac pathology in the Cavalier". In addition to our concern with valvular disease I want to mention two other cardiovascular conditions. **Patent ductus arteriosus (PDA)** is a congenital heart defect that is more common in Cavaliers than in most other breeds. **Femoral artery thrombosis** is an arterial change that we have not observed in other breeds.

Fetuses have a blood vessel (ductus arteriosus) that connects the pulmonary artery and the aorta. This allows pulmonary artery blood to bypass the lungs and go directly into the aorta. This is true in people as well. All of you had this structure and fetal circulation before you were born.

The ductus is a muscular tube that normally constricts and closes soon after birth, and blood no longer flows through it. When it stays open (patent), the blood continues to flow through it and that causes a characteristic heart murmur. We know that patent ductus can be inherited in poodles and other breeds, and it is no reason to think it is not inherited in the Cavalier. About ½ % to 1 % of dogs have congenital heart disease. About ¼ of dogs with congenital heart disease have PDA. This abnormality occurs about 6 times more frequently in Cavaliers than in other dogs.

PDA is easily corrected. We go into the chest, dissect around the ductus and tie it off. The dog usually will live a normal life span, but it should not be used for breeding.

At the heart clinics many of you have seen us palpating the groin areas inside of the hind-legs. We are feeling for pulses in the femoral arteries. We discovered that some Cavaliers have no pulse or a weak pulse in one or both of these arteries. None of the affected dogs showed any signs of lameness. In all probability this is because dogs have other arteries that supply blood to the lower leg. The absent femoral pulse was a surprising finding, because in 5,000 other dogs we had never seen one occluded femoral artery. There were 22 (2.3%) Cavaliers out of 954 examined that had no detectable pulse in one or the other femoral artery. In addition we found 40 other dogs that had weak pulses. The total of abnormal pulses was 62 (6.5%). Half of the dogs with absent pulses were under 3 years of age, and several were closely related.

Microscopic examination of occluded femoral arteries in two Cavaliers showed a form of arteriosclerosis and thrombosis as the cause of the occlusion. We do not have evidence that this is an early sign of cardiovascular problems throughout the body. They do not seem to have other arteries that are affected. Thus far we have not seen a correlation with heart disease. But remember, ½ of these dogs were less than 3 years of age. We need to examine these dogs at 5 or 6 years of age and see how many of those with weak or absent pulses now have murmurs.

Cavaliers are **20 times** more prone to have mitral valve disease than other breeds. First I will review some clinical aspects of the disorder and some of the stethoscopic and radiographic methods we use to assess the severity. Other speakers will review echocardiography and electrocardiography. An angiocardiogram is a radiograph made after injecting contrast material into the heart. When we assess the mitral valve, we inject the material through a catheter inserted into the left ventricle. When the ventricle contracts (systole) a diseased heart valve allows some blood (and contrast material) to leak back into the left atrium. This is referred to as valvular insufficiency or regurgitation. Over time, usually months to years, the left atrium and left ventricle become enlarged. This can be seen in plain radiographs and indicates that there is substantial mitral regurgitation. Normally you would not expect any blood to leak into the atrium. When it does, it causes a heart murmur between the first and second heart sound.

The loudness of heart murmurs are graded from 1 to 6 (Figure 3). Grade 1 murmurs are very faint and often not heard initially. But if you have a really quiet room and listen hard all over the chest you may detect a little faint murmur. Sometimes you may not be able to convince another person that there really is a murmur there. The grade 2 murmur is also soft, but once it is localized there is no problem going back to the spot and picking it up. Another person directed to that spot would also hear it. A grade 3 murmur can be heard as soon as you put the stethoscope to the chest, but there is no vibration (thrill) on the chest wall that you can feel with your hand. When you feel a vibration it is at least a grade 4 murmur. A grade 5 murmur is very loud and causes a vibration, but you cannot hear the murmur with the stethoscope away from the chest wall. A grade 6 murmur is also associated with vibration, and it can be heard even with the stethoscope slightly removed from the chest.

Now I would like to review our study of the frequency of murmurs in Cavaliers.

The study began in 1990 and our report on the first 2 years included 394 dogs. The frequencies of murmurs in this group of dogs are shown in Figure 4. There was a steady increase in murmur frequency from 9% in dogs under a year of age to 100% in dogs 10 years or older.

The total number of dogs examined by 1997 was 990.

The age specific frequencies did not change significantly when comparing the 394 dogs to the subsequent group of 596 dogs. The frequency of murmurs in various age groups was similar to those reported in Sweden and Great Britain.

In Figure 5 we have distinguished grade 1 murmurs from the louder murmurs. Most cardiologists are reluctant to fault an animal that has a grade 1 murmur that may be an "innocent flow" murmur. Half of the murmurs in dogs less than 4 years old were grade 1, and of questionable significance. Most of the murmurs heard in 4years and older dogs were grade 2-6. We did not see a sex difference in the frequency or severity of murmurs, which is in contrast to the opinion expressed by others.

There is one more stethoscopic finding I want to mention. A large number of Cavaliers had systolic clicks with or without a murmur. We used to think that a systolic click did not mean anything, but there were 100 Cavaliers (11%) with systolic clicks out of 904 dogs examined. This is about 25 times more frequent than we find in other breeds. The frequency of clicks in dogs with murmurs (22%) was greater than in those without murmurs (6%). Some of the dogs had clicks for 2 or 3 years before they had murmurs. Once in a while the clicks go away. We are not yet ready to say that a dog has a bad valve because it has clicks, but it raises my level of suspicion.

Now I will review the structure of the mitral valve. It is located between the left atrium (upper chamber) and the left ventricle (main pumping chamber). There are two major leaflets that cover about 70% of the valve opening. The remainder of the opening is occluded by similar leaflet tissue in the commissural zones.

Normal valve leaflets are quite thin, and almost transparent. They are attached to the papillary muscles of the left ventricle by small white tendons (chordae tendineae). The valve functions like two barn doors that shut when the ventricle contracts (systole). The chordae tendineae keep the valve from closing too far.

The tricuspid valve apparatus is located between the right atrium and right ventricle. It is basically similar to the mitral valve but works under lower pressure and is less severely affected by chronic valve disease.

The pathology of mitral valve disease can be grouped into primary and secondary changes. Primary pathology of the valve includes thickening, prolapse, and elongation and rupture of the chordae tendineae. Valve thickening has been proposed as a criterion of disease that could be useful in echocardiographic screening, but I have seen dogs with ruptured chordae tendineae, mitral insufficiency, and congestive failure, that did not have very thick valves. If you see valve thickening, it is real. If you do not see thickening it does not necessarily mean it is a normal valve.

A normal mitral valve contains two principle layers, the thicker fibrosa and the thinner spongiosa. The fibrosa is a dense collagen layer that is continuous with the chordae tendineae. It provides most of the strength of the valve. The spongiosa is a loose connective tissue layer that is relatively pliable and weak. It allows the opposing valve edges to adapt to each other and form a tight seal. In chronically diseased canine valves the fibrous layer is thin and its collagen fibers are dispersed and separated by increased amounts of spongiosa-like material. This process is called myxomatous transformation. It causes variable amount of thickening, initially at the points of insertion of the chordae tendineae and later through the valve. The myxomatous change weakens the valve and allows portions of it to bulge upward toward the left atrium giving the valve a knobby appearance. Lengthening or stretching of the chordae tendineae also occurs and allows further upward bulging (prolapse) of the valve leaflet. Often one or more of the chordae tendineae break and cause the tip of the leaflet to flip upward resulting in worsening of the valve leak.

Secondary pathology of mitral valve disease includes cardiac dilatation and hypertrophy, left atrial jet lesions and left atrial rupture. As a consequence of a leaky mitral valve, an excessive amount of blood goes back and forth between the left ventricle and left atrium, causing both chambers to enlarge (dilate). The enlargement puts greater tension on the walls of these chambers and the heart muscle gets thicker (hypertrophy) in order to compensate for the increased workload. The area where the valve attaches (the annulus) also may dilate and this will increase the severity of the valve leak.

"Jet lesions" are raised white fibrous ridges on the endocardium of the left atrium that result from regurgitant jets of blood striking the endocardium each time the heart contracts. The repeated trauma to the left atrium also can lead to myocardial damage and arrhythmias that, coupled with a rise in atrial pressure, results in atrial enlargement and rupture in some cases. In a significant number of Cavaliers, more so than in other breeds, the left atrium ruptures in one or more places. This rupture may extend through part of the thickness of the atrial wall, or it may completely penetrate and bleed into the pericardial sac, causing cardiac tamponade and cardiac arrest. This is a unique complication that does not occur in other species, including humans. It suggests that there is a specific weakness of the atrial wall that occurs in dogs, particularly in Cavaliers.

I want to describe a radiographic method that we use for evaluating heart size. We call it the vertebral heart size (VHS). On a lateral radiograph we place over the heart a piece of paper, with one corner of the paper at the lower edge of the trachea. The length of the heart (long axis), from the base of the atrium to the tip of the apex, is marked on the paper. We then turn the paper, place the same corner on the front edge of the heart and mark the width of the heart (short axis). The paper corner is then placed at the front of the 4th thoracic vertebra, and the lengths of the long and short axes are recorded as the number of vertebrae between the corner and the marked axes. The VHS is the sum of the two measurements. A heart that measures 5.8 vertebrae in the long axis and 4.4 vertebrae in the short axis would be designated as having a VHS of 10.2v.

In 100 normal dogs the average VHS was 9.7v, with a range of 8.5 to 10.6v. In 12 Cavaliers without heart disease the average VHS was 9.9, with a range of 8.8 to 10.8v. That is slightly larger than other breeds, but the difference is not significant.

I think any heart measuring over 11v is beginning to enlarge. We also use this system to monitor progressive en-

largement. An example is Cavalier that came in at 6 years of age with a grade 3 systolic murmur and a 10.5v heart. When it came back six months later, his heart had increased to 11.7v, and the left atrium was prominent. Six months later the heart measured 13.3v, and both the atrium and ventricle were quite large. Two months after that he had a huge 13.6v heart. At this point the dog was only 7 years old. Our radiologists now routinely write the VHS in their reports. Any one who receives a report of a 9.5v heart will know that the heart is not enlarged. But if the VHS is 12 or 13v there is cardiac enlargement.

The Cavaliers have been an interesting group for us to look at, but we would like very much to look at them because they are nice dogs, rather than just being heart disease cases. Thank you.

Dr. Beardow:

Thank you, Dr. Buchanan. Our next speaker is Dr. Luis Fuentes, who is going to present studies from the U.K. and the U.K. approach to tackling this disease.

Dr. Luis Fuentes:

Thank you very much. I am here to represent the British perspective, even though I am now working in Missouri. Before I moved to Missouri I was in Edinburgh for seven years, working with Dr. Darke. Any British veterinarian, never mind British cardiologists, is going to be very familiar with mitral valve disease in Cavaliers. Cavaliers are very popular dogs in the U.K. They have the same problem with mitral valve disease that they have in other parts of the world.

First a quick look at mitral valve disease, summing up what doctors Beardow and Buchanan have presented. We have a thickening of the mitral valve leaflets. The valve becomes leaky. When the heart contracts, some blood goes the way it supposed to do into the aorta, but some will also go back into the left atrium (Fig 2). This is mitral regurgitation that creates increased pressure and distention of the atrium. Blood from the lungs, that normally empties into the atrium, will back up into the blood vessels in the lungs. Mitral regurgitation through a knobby damaged valve is a turbulent blood flow, and this creates the sound that we hear on auscultation as a murmur. With normal smooth valves, all we hear is the closing sound.

When you study serial x-rays of a Cavalier with fairly severe mitral valve disease, you can see the heart enlarging over time. Later you may see the effects of the blood backing up into the lungs, pulmonary edema. This may also happen suddenly. That is a sign of a ruptured chorda tendinea, the valve strut. The valve has now lost its support, and there is sudden catastrophic mitral regurgitation. The pressure in the left atrium goes up very rapidly, and fluid fills the lungs. The dog will cough up pink frothy pulmonary fluid, and death may ensue very rapidly.

Mitral valve disease in Cavaliers has been known for some years in Britain. Dr. Darke and his colleagues in Edinburgh did an early study of over 16,000 dogs. There were 250 Cavaliers and, of those, 45 had mitral valve disease. This singled the Cavalier out as the one breed that had a specifically high prevalence of the disease when compared to other breeds. At one of our first shows Dr. Darke did a survey of the prevalence of murmurs in Cavaliers in different age groups (Figure 6). There was quite a high prevalence of murmurs in the 2, 3 and 4 year old dogs; in 5 year old dogs over 50% had murmurs; by the time they got to 11,12 and 13, all of them had murmurs.

This was alarming news. The Cavalier King Charles Spaniel Club [U.K] (Cavalier Club)thought some action should be taken, and rightly so. It was decided that a study was to be undertaken based on annual testing carried out by the dog owner's own veterinarian. Forms were designed and distributed to owners. The owner was to keep one copy of the completed form, and submit one to the Cavalier Club where the information would be collated. The only advice given regarding breeding at this time was to only breed from "as old as possible, murmur free dogs". Things did not run smoothly. People became disillusioned, because they would have the dogs tested and send in the forms, they were seeing no results of the data and they did not know how to interpret their test results. One problem was that different vets interpreted their findings differently. If you wanted a dog to be murmur-free, you could go to the old guy up the road whose hearing was a bit dodgy, and you might get a clear certificate. The other problem was that it was up to the owners to send in the forms. If they did not want to send in the forms, we did not get any results. The database was cumbersome and unwieldy, and it was difficult to get any useful analysis out of the data. It was difficult to know what to do with the results and to make a sensible interpretation. If you were a breeder and had your animals tested, what did the results mean? What did it mean if you had a promising young bitch, 3 years old, no murmur – do you breed her this year? - do you wait another year? – do you wait two more years to see if you can get the best possible result and wait and see what happens? Meanwhile, she might develop a murmur, and then you would be kicking yourself that you did not breed her.

A few years ago there was another big push to try to do something about the scheme. We now had access to the excellent new Swedish studies that had been done, and that made a big difference. The Cavalier Club appointed a new subcommittee charged with establishing a workable protocol. A new database has been set up together with the British Kennel Club (Kennel Club). All results are being combined with the pedigree database of the Kennel Club, and we now are able to accumulate information on several generations of affected dogs. The information is confidential. The Kennel Club does not know the results of the testing, but the Cavalier Club has access to the results and can extract useful information.

Another new step was that we started publishing a list of Cavaliers who are murmur-free at age 5 or older. The information includes the dog's name and sex, dam and sire, date of birth, and the last date tested and found murmur-free. This list is distributed to all Cavalier Club members. Breeders can know which stud dogs or brood bitches have been tested and found murmur free. There is an added incentive in the public knowledge of murmur-free dogs: KUDOS to the owner and breeder! It is probably important that this booklet contains not just the dogs that are 5 years or older and murmur-

free. It should also contain dogs that were murmur-free at 5 years, but who developed a murmur at 6 years or later. Even if a dog developed a murmur at 6 years, that is better than the one who developed one before the age of 5. In last year's [British] booklet there were 81 male dogs listed that were murmur-free at the age of 5 years. Breeders now have this information available.

Just in the last few weeks James Wood, an epidemiologist at the British National Health Trust, has taken over the database and is studying the results. He has now produced a preliminary breakdown of some of the results. An epidemiologist is someone who studies the pattern of disease. It is important for us that we get input from epidemiologists who can help decide appropriate cut-off points for breeding. Dr. Wood has kindly provided new graphs of the most current data.

We now have over 7,000 examinations included in the database, and that number is going up every year. We see an increasing number of dogs being tested, because we have an aim and direction of the scheme.

When we break down the number of dogs into age-groups we see that we have 1500 dogs up to age 2 years, but far fewer in the 10,11,12 and 13 year groups (Figure 7). We need to have more dogs tested in the older age groups. Most dogs have had only one examination done (Figure 8), but, as the new protocol continues, we will get more and more information on dogs that have been tested repeatedly over a number of years

When we look at the age of examination and the percentage of dogs with murmurs at each age, we find a relative small number of dogs under the age of 2 years that have murmurs. Some of these may be due to congenital defects and not mitral valve disease. Some of these dogs may have a patent ductus arteriosus, but most cardiologists will be able to distinguish this type murmur from that of mitral valve insufficiency. As the age goes up, the prevalence of murmurs increases. The current studies are a bit different than Dr. Darke's. It appears as if the prevalence has gone down now when, more likely, this is because of the small number of older dogs. When we look at the murmur prevalence according to the type of examiner we also find a difference. Cardiologists find more murmurs in the younger dogs, than do general practitioners (Figure 9).

The guidelines for breeding are now better defined than previously.

We now recommend that you breed only from murmur-free dogs at least 2 ½ years old, whose parents were murmur-free at age 5 years.

We are using the parental status as an indicator of whether a dog can pass on mitral valve disease. Dr. Swenson will discuss the studies that led to these guidelines.

We know that the early scheme was fraught with problems. We now have a golden opportunity to take advantage of all the mistakes we made. We learned from those mistakes. The new scheme is going much, much better than the old one. There is a sense of purpose about it. The published list of dogs has provided a new focus. We still have predominantly young dogs tested. This is related to the fact that we carry out our studies at shows, and most exhibitors bring only their young dogs to the shows. There is a move in the U.S. to schedule health days separate from shows. That is an excellent idea. Perhaps here we can see the older dogs and include them in the database.

While there have been problems in the past, the studies done in Sweden enable us to establish good protocols. This is a long-term project, let us not fool ourselves. We are not going to change anything overnight. But at least we think that we have the means to start making breeding decisions that will have some effects. The more years we have this new database and scheme going, the more dogs will be included, and the list of murmur-free dogs will grow, and the breeders will have more choices. We will be able to use the database to provide detailed breakdown of the data, and find information on changes with time as the breeding guidelines are implemented. It will be very interesting to hear your comments at the end of the afternoon and see if we can dispel some of your concerns about adopting the new guidelines. Thank you for your time.

Dr. Beardow:

Thank you Dr. Luis Fuentes. Some very interesting data. Our next speaker is Lennart Swenson of the University of Agriculture and Sciences in Uppsala, Sweden. He has been the one primarily responsible for the data that guided the British Cavalier Club in their decision. So now we are going to hear it right from the horse's mouth.

Dr. Swenson:

I wish to thank you all for inviting me here. The other presenters here are veterinarians, I am a geneticist, and I will give you a geneticist's view. I am a former breeder of Skye Terriers, so I know what breeding dogs means. I am a genetic consultant for the Swedish Kennel Club, and I will be representing Sweden in the FCI breeding committee. I will have an opportunity to influence even FCI to think more about health.

It is not easy to gather information on health status in dogs, or to convince breeders of the necessity to consider a particular health problem in their breeding plans. Without knowledge of the impact of a disease, this is nearly impossible. The control of inherited diseases by breeding measures must be based on valid information. This could be obtained by medical examination of the right animals in sufficient numbers at an appropriate age, and disseminating the information to breeders. An example is what happened in another breed in Sweden. In 1976 36% of Rottweilers had hip dysplasia. This was down to 11% in 1994. How did we accomplish this? The Swedish Kennel Club required that every dog used for breeding must have hips examined. All results were made available to all breeders. Originally there was no ban against using dogs with hip dysplasia for breeding, but breeders eventually chose not to use them. Now the Swedish Kennel Club has ruled that dogs with hip dysplasia are not to be used for breeding.

The breeders choose which dogs to use for breeding, and in what mating combinations. That is the reason why breeder motivation is essential for the success of breeding programs aimed to control inherited diseases. Sometimes I think we do not stress this enough. We invest a lot of time and effort in constructing good methods for evaluating disease,

but we do not make enough effort to motivate breeders to participate in our programs. One way to motivate breeders is to show them the results of the programs. For example, in a German Shepherds hip dysplasia study, when you mated "unaffected hip" to "unaffected hip", 28% of offspring had hip dysplasia. If the mating was "unaffected" to "Grade I dysplasia", the incidence increased to 38%, and "Grade I" to "Grade I" resulted in 44% hip dysplasia. It is obvious what the choice of mating should be. This kind of data will motivate breeders to participate in selective breeding protocols.

There are a lot of questions about chronic valvular disease (CVD) that need an answer. I cannot answer all of them. What is the relevance of the disease, compared to other problems? What is the prevalence? How does CVD affect the dogs and their owners? Is the disease progressive? Is it inherited? If so, how? Does it affect males and females differently? Can CVD be altered or eliminated by selective breeding? I will try to touch on some of these questions.

A trustworthy model of inheritance is essential. If the disease were regulated by additive gene action, an estimate of inheritability would improve our chances of controlling the disease. We do not, at the present time, have an estimate of inheritability, but we do believe that the disease is regulated by additive gene interaction.

There is a difference between diagnosing a disease and defining a disease. In a genetic program we need a well described definition of the disease and a good description of the measuring character used to achieve the a goal. The goal would be to decrease suffering in the dog, but that is not something we can measure. We have to measure something else, and in Cavaliers we measure heart murmurs.

In 1978 I evaluated a protocol that had been in effect for 20 years, where we looked at parental hip dysplasia status in German Shepherds and found that 50% of German Shepherds born that year had at least one affected parent. We had an old protocol in effect of just recording the diagnosis, and we had not changed it in years. Under these circumstances one cannot expect to make any progress in reducing the incidence of hip dysplasia. Just examining the dogs is not enough. We need also to look at the results, and take some action.

The implementation of a genetic health program is very important. In Sweden we are very stubborn, and we have the support of the Swedish Kennel Club. A program was instituted where it was mandatory to have the hip status on record with the Swedish Kennel Club, if you were going to produce puppies and register them with the club. In the German Shepherd we now have information on all the litters and, in 1996, 92% were from non-affected parents.

There are now 111 breeds in which registration of the hip status is required.

This is a direct result of the involvement of the Swedish Kennel Club. In Sweden all national breed clubs associated with the Swedish Kennel Club have a breeding committee responsible for spreading information on health programs and breeding policies. In some clubs the committees gather the evaluations of mental ability and health status, as well as show results, and the breeding information on individual dogs.

The Swedish Kennel Club offers educational programs to breeding committee members and board members and in 1998 a program will be started for breeders.

Sweden regulates dog breeding by law. Animals may not be used for breeding if they pass on by heredity

1) any malformations or other characteristics that causes suffering

2) anything that negatively affects the natural functions of the offspring

3) a high frequency disposition for serious diseases

4) delivery difficulties or lack of the ability to breed naturally

This new law has been of great help to the breeding committees.

Changing the prevalence of a disease by selective breeding is often a slow process. This is not necessarily a result of a low correlation between what we measure (the measuring character) and what we are trying to achieve (the goal character), but more often a result of a failure in implementation and poor participation in the program.

n the absence of an open registry, where health records can be related to family records, we have limited opportunity to evaluate the implementation of a health program and the impact on the program on the disease.

Often effective, simple and relatively inexpensive methods of disease control can be abandoned for the wrong reasons. There is confusion between clinical diagnostic methods and definitions used in a genetic program and the program fails. Different countries have different measuring methods and definitions, and the breeder is confused and does not participate. We fail to implement the program, and therefore we are not successful. We leave one program and go on to another. There might be nothing wrong with the program, but the participation in a program using a specific method is not adequate.

If we were to agree that CVD is relevant in Cavaliers, and we could convince you that CVD is influenced by gender, age and family history of the disease, then together we could define the problem and decide on the breeding strategies needed to reduce CVD. If our problem is simply that too many young Cavaliers get CVD, then our breeding goal would be to reduce the prevalence of CVD and raise the age of onset in dogs that still get the disease.

It is not realistic to eliminate the underlying causes of CVD (the genes) by breeding measures, at least not until we know the reason for the high prevalence in Cavaliers. The high prevalence could be the result of an unfortunate **founder effect**, that is, the first dogs that formed the breed carried the genetic liability to develop the disease. Or it could be that some characteristics of **winning show dogs** correlate with CVD. Or, by bad luck, some of the **dominating stud dogs** carried the unfavorable genes.

But a realistic breeding goal would be to reduce the prevalence of CVD to a "normal" level (that seen in other breeds) in a few generations. This is a realistic goal, if you will agree to participate in an effective breeding strategy based on record of cardiac murmurs detected by auscultation.

In our study of the relationship between cardiac status in Cavalier King Charles Spaniels and prevalence and severity

of chronic valvular disease in offspring., the goal was to determine the effects of parental CVD status, and age and gender on the cardiac status in the offspring. We thought that the diagnostic test for screening for the disease would be auscultation. We did not know how many dogs were affected, age of onset, progression or whether it was inherited. I will discuss inheritance. The other speakers have covered most of the other issues.

This is how we designed the study:

We decided that a suitable age for screening for heart murmurs was 5 years, because at this age many dogs would be expected to have murmurs. From the computer files of the Swedish Kennel Club we chose all Cavaliers that were born in 1978 and now were 5 years old. We listed their sires and separated them into two groups. "Very good" were those that stayed healthy for a long time, and did not develop CVD until late in life or never did. "Very bad" were those that developed CVD at an early age. We ended up with 7 sires. We found all the dams of the litters and they were separated into 3 groups: early, medium, and late onset CVD. "Late" also included those that did not develop CVD. We located and examined the offspring and classified them according to the intensity of heart murmur (Figure 10). We also did DNA analysis of blood samples, hoping to find a marker. This was not successful, but we did find four puppies in one litter and one puppy in another litter that we excluded from the study because of incorrect pedigree!

We located 112 of the 120 offspring. Of the 112 offspring examined, 59 did not have murmurs, 29 had low intensity murmurs, 19 had moderate intensity murmurs, and none had high intensity murmurs (Figure 11).

We also noted a big difference in the incidence of heart murmurs in male and female offspring. There were 45% unaffected males, and 65% unaffected females (Figure 12). The study showed that males and females differ in severity of disease as well as in frequency. This finding can, in part, be attributed to sex-related differences in which the disease progresses.

This could be the result of different thresholds at which males and females develop CVD. Males and females should have the same genes, except for those on the sex chromosome. Male/female differences in age of onset and severity of CVD could be explained by a direct effect of the genes involved on the sex chromosome, or by secondary sex-characters regulated by the sex hormones. The differences in CVD phenotypes in the two sexes implies that males and females should be considered as two different groups. The female has a greater ability to suppress the manifestations of CVD. In the words of geneticists the female is of "inferior genetic quality" when compared to the male, in the expression of the manifestations of CVD. The potential for manifestation is there, but is not expressed. This may lead to the incorrect speculation that unknown environmental factors in the dam are responsible for CVD manifestation in the offspring. That would be underestimating the hereditary component passed on by the dams to the offspring.

And herein lies the reason for considering murmur-free females suspect if they come from a litter that has males with murmurs.]

The parents that were most affected had more affected offspring than did parents less affected. This evaluation was made by averaging the quality (murmur grade)of the parents and plotting this against the percentage of offspring without murmurs, and with murmurs of different grades. If both parents were grade 1, then the mean parental quality was 1+1 ÷2 =1. If one parent was grade 1 and the other 2, then the mean parental quality was 1+2 ÷2=1.5. We found that the higher the mean parental quality, the greater number of offspring had murmurs, and the severity of the murmurs also increased. (Figure 13). That indicated **that this is an inherited disease, and that measuring heart murmurs would be an efficient and reliable way of identifying the dogs likely to produce less affected offspring.**

The breeding goal is to reduce the incidence of heart failure in the Cavalier, and to delay the age of onset in the dogs that develop the disease. It is not realistic to expect that we can get rid of the disease entirely, but we would like for Cavaliers to have the same or better chances at long life as other breeds.

Here are some sources of information we use to assess the breeding value of a dog:

1) Any information on disease history is valuable.

2) Breeding dogs free of disease is valuable, but if we had information from those who stayed healthy, that would be better.

3) If breeding dogs have healthy parents, that is advantageous, and if the parents remained healthy that would indicate that we had chosen the right dogs.

4) If we have official records of if and when parents developed CVD, then we would have extremely valuable information.

Here are some examples:

1. A Cavalier female, 2 years old, no heart murmur. Is this information of high, low or medium value as a source of information for making a decision about breeding? It is low, because this is what you expect in a 2 year-old female. There is not enough information for a decision.

2. Another Cavalier female, 2 years old, but she has a cardiac murmur. Here the information value is high. You would make a decision here, you would **not** breed a 2 year old that has a murmur.

3. A Cavalier male, 5 years old, without a cardiac murmur: medium to high value information. You would consider using for breeding. Same with a female.

4. A Cavalier female, or male, 7 years old, no murmur: high value, you would make a decision to breed.

5. A Cavalier, age 2 ½ years, no murmur, with parents 5 years, no murmur: high value.

I want to point out that, from a genetic point of view, this would be exactly the same as if one waited until the dogs were at least 5 years old and murmur-free before breeding them.

As you see, if you as a breeder can obtain information on affected dogs, that would be valuable to you. We all have the same type of dogs, but some are murmur-free and others are not. This is valuable information. The time of onset [of

murmurs] is even more valuable information. You should be sharing this information with other breeders.

Our recommendation for breeding Cavaliers is: **Breed dogs that are at least 2 ½ years old and murmur-free that have parents that were murmur-free at age 5 years.**

In our data up until 1997, we found that 40% of Cavaliers had at least one parent under the age of 2 ½ years. It appears that some breeders took their last chances to use young dogs [for breeding]. When I deleted the litters that were produced early that year, we ended up with six litters in which the rules for breeding were not followed. These six litters were deleted from our study. The Swedish Kennel Club is writing a letter to the breeders of those litters, telling them that they have violated the rules, and if they do it again, something will happen.

Conclusions:

• At any given age, CVD in Cavaliers is more prevalent in males than in females

• Parental CVD status mas a major effect on the probability of the offspring developing a heart murmur, and the intensity of that murmur.

• Differences between the sexes in age at onset of a murmur and progression of the disease may be due to an age-related threshold that is approached more rapidly in males.

• The occurrence of CVD and its response to selection suggests that this disease is a multi-factorial, polygenic trait.

• Due to the lower degree of manifestation of CVD in females, they should be considered "genetically inferior" compared with males, in that they may be unable to express the effects of the genes that are present.

Thank you.

Dr. Beardow:

Thank you for this interesting presentation and for emphasizing the validity of information and recommending what we should be doing in our screening programs. I now introduce Dr. Bruce Keene, Associate Professor of Cardiology, North Carolina State University who will discuss the use of diagnostic tests.

Dr. Keene:

Thank you, Andy. It is a special pleasure to be here in Atlanta.

I will be presenting to you some of my thoughts, and give you something to think about regarding how you should allocate your resources when you are screening your dogs for CVD. Actually, the comments that I make could be appropriate for screening for any disease. What I would like to help you do is to use the current best knowledge to establish a rational screening strategy. To start we will review some of what has already been covered today. Then we will evaluate the best available screening tests, and touch on the cost and strategy.

We should prioritize our goals. Where do we want to spend our time and money? How can we do that most effectively? We certainly can agree that reducing the prevalence of chronic heart valve disease is very important. How feasible is it to do that? How quickly can we expect to see results? What kind of results can we expect? What is it going to cost? Can we increase the life expectancy for Cavaliers and, at the same time increase the quality of the dogs you now have, even those who have mitral valve disease? As we heard from Drs Luis Fuentes and Dr. Swenson, it will probably take years to achieve desired results. CVD is going to be with you for a couple of generations, at best.

We have already heard from the experts who generated the data that the prevalence of CVD in Cavaliers is quite high, much higher than in other breeds. It increases with age. Males manifest the disease sooner than females. CVD is an important cause of death. It is not just that a bunch of cardiologists hear heart murmurs. The dogs die of the disease and they do it in much greater numbers and at a much earlier age than we would like. There seems to be a 3-4 year development lag between the time the first murmur is heard and the time symptoms of heart failure occur. We know from the Dr. Swenson's work that CVD appears to be a multi-factorial polygenic threshold trait, much like hip dysplasia. He demonstrated dramatic and encouraging results of selected breeding in hip dysplasia.

At this time no candidate gene has been identified for CVD, that could be used for quantitative genetic studies. We know there are multiple genes involved, and probably non-genetic factors as well. If we could identify one gene that is responsible for, lets say, 30-40% of the trait, then we might be able to make faster progress by either manipulating that gene or concentrating on it. Alas, we do not have it.

Current genetic diversity and numbers of dogs limit the number of animals that can be realistically excluded from breeding. In a disease where the prevalence is high, and there is not a huge number of individuals in the population, you need to keep in mind that you may not be able to exclude all animals with the disease from the breeding population, even if you wanted to. What we need is a very reliable way to identify animals with the disease, and then decide how many of them we want to exclude from our breeding program.

The ideal diagnostic test should identify affected individuals at a very young pre-breeding age with 100% accuracy. It would be great if we could draw blood and do a polymerase based chain reaction (PCR), screening test and let it tell us that this dog has this form of whatever gene controls his collagen problem. We would know that we should not breed him or any dog that has this genetic code. Unfortunately, we can not do that. Not only can't we do it, we don't know of a gene that influences the trait, that might help us develop such a test.

We would like the test to be inexpensive, safe, non-invasive and widely available, so that everyone who wants to could participate in a screening program. None of our current tests qualify, as the ideal test should be all of these things.

The accuracy of our ideal test should not be operator-dependent. We do not have such a test, either. All the tests we have are very operator-dependent. This is the reason I believe we should make recommendations regarding the qualifications and expertise of the person doing the test. You say "well, how elitist of you!". It is not meant as an elitist comment, I am not trying to drum up business for cardiologists. It is a simple fact, if you have someone who does one thing day in and day

out eight hours a day, that person is going to be better at it than someone who does something that constitutes 5 or 10% of their daily activities.

The gold standard test is the examination of the gross pathology of the heart. You heard Dr. Buchanan say that some dogs have thin valves, but still have CVD. That is a problem if you are using echocardiography as the gold standard for measuring valve thickness. *You will miss it.* Obviously dogs who have undergone a pathologic examination of the whole heart are no longer good candidates for breeding. That really throws a wrench in the works.

Radiographs and, to a lesser degree electrocardiographs, provide extremely useful information on the progress of the disease and help make treatment decisions. Unfortunately, they do not provide information about the status of the valve, about whether or not a defect is present.

High quality two-dimensional color flow Doppler images allow us to see the valve itself, as well as leakage of blood through the valve. The accuracy of echocardiography when the valve is not leaking badly, has not been determined. There is really nothing that suggests echocardiography is better than auscultation for detecting CVD.

So we are stuck with the murmurs that develop long before there is significant valve leakage that has progressed to congestive heart failure. The only study of which I am aware, that evaluated the intensity of the murmur as a screening test, was done in Sweden. Murmurs in 79 Cavaliers of moderate or loud intensity were *indicative of disease*, and absence of murmur, or a low intensity murmur indicated that no disease was present. There were 43 dogs with murmurs louder than grade 2/6, all of these were around 5 years of age, and 36 dogs tested negative. Not all the dogs with a positive test had CVD. Fortunately, they did not kill the dogs to look at their hearts. What they did was use color flow Doppler and two dimensional left atrial size to evaluate the hearts. The disease was present in 39 of the 43 screening-positive dogs, and 4 were normal. That means 4 dogs would have been excluded from the breeding program because of a false positive test. The negative test was also wrong. Only 35 of the screening test negative dogs were free of disease, and one diseased dog snuck through (Figure 14).

There are terms we use to try to apply numbers to this sort of thing. **Sensitivity** is the term used to describe the proportion or fraction of those having the disease, those that are correctly identified by the screening test. In this study the sensitivity was about 97%, and that is quite good (Figure 15). **Specificity** is the proportion or fraction that does not have the disease and that are correctly identified as negative by the screening test. This was about 90%, which is also quite good (Figure 16). The **Prevalence** is the proportion of the whole population that is truly affected. In this study of 5 year old dogs the prevalence was 40/79, or about 50% (Figure 17). That seems to correlate with other studies. The prevalence would be influenced by who is supplying the data. If it is breeders who send in data you may have a selection bias. A breeder may get 5 dogs analyzed and send in only the good ones. There goes the accuracy of a study. Unfortunately, the prevalence is high in 5,6,7 year old dogs. It might not be 50%, but probably somewhere between 30 and 50%. The reason we are concerned about prevalence is that we really want to know how well a positive screening test can predict whether the animal actually has the disease. That is the **Positive Predictive Value**. For this study that would be 90% (Figure 18).

The **Negative Predictive Value** is the proportion that tests negative, that do not have the disease. Here that was 97% (Figure 19). If we set the point right where we have it, soft murmurs or no murmurs are o.k., we get a *profile* that approximates about 90%. In other words, about 90% of the time we would make the same decision, based on auscultation alone, as we make with the most sophisticated two dimensional measurements of left atrial size and color flow Doppler. We might be able to tweak that if we want to identify more dogs with the disease. We could lower the **threshold** so that only the softest of murmurs and no murmur would be negative, and those with grades 2, 3, 4, 5 and 6 are all positive (Figure 20). But when we pick up more true positives we also wind up making mistakes by classifying truly negative dogs as positive for significant CVD. The bottom line is how a test really changes our ability to predict whether a dog has the disease or not. If you have a group of 5 year-olds, half of the dogs will have CVD. You could be right half of the time if you just guessed, instead of listened to their hearts. If you listen carefully, you will be correct 90% of the time.

With any screening strategy you will be unhappy with the fact that you are going to make mistakes. Decisions based on auscultation alone will be the same as those based on echocardiography about *90% of the time.* I believe auscultation is more sensitive than echocardiography in predicting which dogs will develop CVD. Auscultation is also a lot cheaper. An estimated cost is $20-$60, the nice guy conducting the heart clinic today only charges $15. The echo-based screening test would cost at least 4 or 5 times as much as auscultation.

The effect of screening tests on compliance must be considered. For those who have many dogs we are better off with a screening test that is 90% accurate, but that 100% of breeders can afford. You must ask yourself what price you are willing to pay to get that little 10% more accuracy, if it indeed is 10% more accurate. If you save 4/5 of your screening budget by using auscultation alone, you will have money to either pursue the identification of a candidate gene, or clinical trials that will help in the treatment of your dogs or those that will be affected in the future, or do some other things.

Dr. Beardow:
Thank you, Dr. Keene.

I would like to clarify one point that was made in the previous presentation. We don't guess very often, probably about 25% of the time.

My job now is to summarize what has been presented, that we might wish to take up in the question and answer session. We have tried to integrate the experiences from the United States, the United Kingdom and Sweden, and presented the tools available to us to develop a pragmatic approach to the disease. Dr. Buchanan mentioned that systolic clicks are prevalent in Cavaliers and may be a sign we should consider.

Thrombosis of the femoral artery is another sign that might be indicative of more generalized disease. At any age CVD is more prevalent in males than in females. Parental disease status seems to have a major effect on the probability and progression of CVD in the offspring. CVD is probably a multifactorial polygenic threshold trait, more like hip dysplasia, and more complex than just influenced by a single gene. Females in litters where males have developed CVD should be considered suspect. Breeding values based on parental status, and perhaps earlier generations status may allow young dogs who are murmur-free to breed.

The test we use to screen for CVD must be easy to do and widely available, and not cost prohibitive. If it is not, then it is not going to be used. The test should be specific enough to identify dogs affected, but not so sensitive that we eliminate all of the breeding stock. It is better to use an inexpensive test with a relative high sensitivity, rather an expensive test that will allow just a few more percentage points. The established program should be strongly supported and uniformly implemented (Figure 21). To accomplish this is to present it well, so that it can be well understood. That is what we have tried to do today.

We now will open the topics for discussion. Please use the microphones available, state your name and where you are from, and state your question. This session is recorded, and a report will be generated.

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Q. Courtney Carter, Pennsylvania.

This question is for Dr. Luis Fuentes. You made a comment in your presentation that in the U.K. list 81 dogs were tested clear over the age of 5. That was 81 dogs out of how many that had papers submitted?

Dr. Luis Fuentes.

I do not have the information on the numbers that were submitted. One of the difficulties is that obviously there are issues of confidentiality, and the results of animals that have tested positive for murmurs are not made available. That information is in the database, and it will be extractable, but I am afraid I don't have the numbers right now to tell you how many dogs were tested to get the 81 dogs that were clear. I just received these results from Dr. James Wood. He prepared a preliminary analysis at the end of March. We are hoping to get a lot of questions answered.

Ms. Carter.

Will the general public be able to query, I guess the English Cavalier King Charles Spaniel Club, for information regarding the data? Would I be able to write to someone and ask how many dogs were actually tested to come up with the 81 that were clear?

Dr. Luis Fuentes.

We are hoping that the information booklet will, in the future, not just have the list of animals that are clear, but a more detailed breakdown of the numbers tested, numbers testing clear, number of males versus females, and so on. It is set up so that sort of information should be readily available. I am not sure of who will be handling specific queries, but they will certainly want to make the broad overview and analysis available to people.

Q. Suzanne Brown, Kentucky.

When a vet hears a murmur, the dog is often referred to a cardiologist. If a young dog has no symptoms of CVD, what further tests, if any, should be done? I have had several people who bought my puppies call and tell me a vet found a murmur in a young dog, under age 4, and they were immediately sent to a cardiologist, and were presented with a $500.00 bill. They were not thrilled, and I can't blame them. What should we be saying? Do they really need to go to the cardiologist, in the first place? Secondly, what should you do to do justice to the dog but still be reasonable to your pocket book?

Dr. Keene.

I would like to say something, then everyone can argue with me. You probably need to do something. If it is not a question of breeding, and there is not question in the veterinarian's mind that it is the typical murmur of mitral insufficiency, I feel that chest x-ray provides the best information about staging and possible need for treatment of the disease. Depending on what we see on the chest x-ray, that is probably the only thing that needs to be done.

Ms. Brown.

Can my vet do the chest x-ray, or must I go to a cardiologist?

Dr. Keene.

Certainly there are lots of general practices that take high quality chest films. Cavaliers are a bit barrel-chested, and oftentimes I think cardiomegaly is over-interpreted by general practitioners. I think you would have fewer false alarms if you had chest x-rays done by cardiologist, or taken by the general practitioner but read by a cardiologist or radiologist. Someone who has seen a lot of them should read the chest x-rays, and interpret the heart size using the vertebral score.

Q. Bob Sims, Pennsylvania.

"Aging heart" is a term that has crept into our terminology, and it has been said that a dog that has a murmur due to "aging heart" can be bred. Is that a medical term, or a breeder's term?

Dr. Beardow.

I certainly have not come across that term. Seeing the shaking of the heads of those on the panel, I don't think anyone else has, either. It is probably a breeder's term. Many small breed dogs get age-related degeneration of the mitral valve. It is not uncommon. The concern in the Cavalier is that this disease, which we usually see in older dogs, is occurring at a significantly younger age.

Q. Karen Ostman, Nebraska.

I have a concern addressed to the Club [CKCSC,USA]. Everything we do in regards to detection of heart murmurs is centered along the east coast, and some along the west coast. We have a problem in the mid-west. We need a list of available cardiologists, but no one provides this information. How do we get our test results analyzed? I usually get this answer:

"Oh, well, you don't have a lot of dogs out there, so it is not a big deal." But to me, my breeding program is an extremely big deal. The club centers its activities in the east. People who live in other areas do not have the same opportunities as those who live there.

Dr. Keene.

Have you ever seen the New Yorker cartoon, where the end of the world drops off outside New York City? I can't answer your concerns about the east coast centricity of your club. There is a list of board certified cardiologists available on the Internet at the American College of Veterinary Internal Medicine web site.

Q. Ms. Ostman. Do you have the address?

Dr. Keene.

www ACVIM com

Ms. Anne Eckersely-Robins.

I would like to answer your concern, Karen. CKCSC,USA is starting a Health Registry. Perhaps you do not know that. It was published in my President's message in the Bulletin. In the next Bulletin you will find the form used to enter the registry, and there will be a list of certified cardiologists. We are working on it.

Q. Unknown.

Can the patent ductus murmur be confused with that of CVD?

Dr. Buchanan.

No. The murmur is very characteristic of PDA. It is continuous, instead of the pulsating systolic murmur associated with mitral regurgitation. It is usually detected in dogs that are under a year old, at the time of puppy vaccinations. However, we have seen some Cavaliers with a variant of the murmur heard very high in the shoulder. The PDA can be very small, medium or quite large and the associated murmur can be heard all over the chest, or it may be localized. But it is seldom confused with the mitral murmur.

Another point I wish to make concerns the lack of experts in some areas. Some veterinarians now are able to take good quality radiographs and send them by mail or wire to a radiologist. You can get a second opinion evaluation by a radiologist or cardiologist even though he or she is not in your area.

Dr. Beardow.

There are a number of different ways that can be done. Your veterinarian can send the films overnight to a number of radiologists around the country. There are several companies that sell devices that can scan radiographs, convert them into a digital form, and transmit them to radiologists. A number of companies who have board certified radiologists on staff provide this service. Your veterinarian has many resources. You can always get a second opinion. We can provide the club with a list of consultants if you need one.

Q. Anne Shapiro, California.

My question is about the progression of heart disease. We saw the dramatic x-rays of a dog who had incredibly fast progression from fairly normal looking heart to one so huge, I assume the poor dog is no longer with us. I have had the experience of having a dog die from mitral valve disease that was symptomless until the day she keeled over, and another dog that developed a murmur at the age 3 and lived until two days short of his 13th birthday. Heart disease may have taken some of his lifespan, but certainly not a great deal of it. If he were what we see all the time, that would be lovely. Are these various rates of progression inherited? I would love to hear from the representatives of the U.S., U.K., and Sweden.

Dr. Swenson.

In general, if a dog gets the disease early in life, it progresses rapidly. That indicates a higher liability in that dog. He will have offspring that develop CVD early in life, and it will progress rapidly. In general, this type of polygenic inheritance and disease threshold functions that way.

Dr. Luis Fuentes.

That question was asked at the U.K. seminar in November 1996. There are plenty of anecdotal reports from owners who have had Cavaliers with murmurs that lived for a number of years without developing heart failure, as well as some that progressed very rapidly. We do not know if there are different forms of disease, but that is a question we hope to address with our current U.K. database. If dogs have annual tests and the results are submitted, we may be able to provide this information in the future. We cannot answer your question at present.

Dr. Keene.

There are a couple of prospective clinical trials in progress, not specifically for Cavaliers, that are looking at the effect of drugs on onset of heart failure. For example, will angiotensive converting enzyme inhibitor delay the onset of heart failure and keep a dog healthier longer?

The lag time between the time a murmur appears and the average time clinical signs appear is somewhere around 3-4 years. There is a great deal of individual variability. Some progress very rapidly, some take along time, and some do not progress at all. There may be different forms of the disease. Certain families or individuals may have more aggressive form of the underlying collagen problem.

Dr. Beardow.

We have seen a number of complicating factors that significantly influence the way the disease progresses. For example, if a critical chorda tendinea breaks, or the atrium ruptures, the dog is likely to deteriorate rather rapidly, and there may be sudden death. The process is very complex, and we do not have many apple-to-apple comparisons. It is important that we conduct prospective studies that include many dogs so that we can average out some of the variabilities to see if we truly have some trends.

Q. Beth Bales, Tennessee.

How is the information captured in the English study? This is related to Karen's concerns. I am fortunate to live in a university town that has a vet school. If you do not live near a vet school, the chance of having a board certified cardiologist listen to your dog is nil. They are not in private practice; there is a lot of money to be made elsewhere. How do you, in the study, consider the consistency of one cardiologist to another

when grading murmurs? One may call it a grade 2, another a grade 3.

Dr. Luis Fuentes.

There is a box on the U.K. form to check for murmur grade. The details of the murmur grade are entered into the database only if a cardiologist had done the examination. If a general practitioner enters a grade, that is not included in the database.

You have a big country, and not that many cardiologists. Your breed clubs can solve the difficulties you have with access to board certified cardiologists. They can arrange Heath Days or Health Clinics where a cardiologist can examine a large number of dogs. I understand you have one clinic going on right now. This is the only way that people who live far from a vet school area are going to get their dogs tested by a cardiologist. I hope that you eventually will have enough cardiologists to go around.

Dr. Beardow.

It has been historically true that the cardiologists are located at the main universities. More and more they are now spreading beyond the ivory tower. I, for one, am a cardiologist in private practice. It is true that most are in the big cities along the coast, more so than in the mid west. Nebraska? (Laughter).

Q. Cindy Beebe, Connecticut.

Dr. Swenson, why you did not use cardiologists for your study, since all the rest of it is so controlled?

Dr. Swenson.

The answer is, we did.

Dr. Beardow.

Dr. Swenson works with a group of cardiologists at his university. When he said he sent two people out to do the studies, they were both cardiologists. There were only two that did the whole study.

Q. Patricia Powers, South Carolina.

Dr. Swenson, you mentioned that the Swedish Kennel Club requires everyone to test yearly. How long did it take the Kennel Club to adopt this policy? What are the repercussions if a breeder does not chose to do this?

Dr. Swenson.

We have a tradition, established many years ago, of working with the Swedish Kennel Club in various health programs. All that we have to show is that a disease has a genetic component, and that it is of some relevance, and the Swedish Kennel Club will start a Registry. A breeder who does not comply with the Registry's requirements will first get a letter stating that s/he has violated the rules. If the violation is repeated, s/he will be reported to a disciplinary board of the Kennel Club. The penalty may be that s/he is suspended from registering puppies for 3 years, or something like that.

Q. Pat Winters, Virginia.

I think what Cindy meant to ask was: in Sweden, you have to submit a cardiology report in order to register puppies. These reports do not have to come from cardiologists?

Dr. Swenson:

Correct.

Ms. Winters:

Why?

Dr. Swenson.

We cannot call a veterinarian a cardiologist. All veterinarians claim they have the right to make this examination.

Ms. Winters.

So you are not allowed to specify this particular restriction?

Dr. Swenson.

No. We cannot make a list of veterinarians according to education. But the Swedish Kennel Club can specify a group of veterinarians accepted for its Registry. For the moment we are using 150 veterinarians who have had special training in small animals, including dogs and cats.

Dr. Keene.

Their situation is a bit different than ours. We have the American College of Veterinary Internal Medicine, whose regulatory purpose is to identify specialists.

Q. Cathy Gish, Kentucky.

You said that in the U.K. study, a dog that was clear at 5 would remain on the list of clear heart?

Dr. Luis Fuentes.

I would need to check on this, because there was some disagreement when the list was first started. The ideal situation would be to include on the list the dogs that were free of murmur at the age five, and to keep them on the list after that, even if they developed a murmur after the age of 5, say 6 or 7, provided that the date of the last murmur-free examination was listed. You would know that he either was not tested, or he had developed a murmur after the age of 5 years.

Ms Gish.

Are you saying, if a dog is clear at 5, but developed a murmur later, he could be used for breeding?

Dr. Luis Fuentes.

This is where we get back to cut-off points. If you exclude, say, the worst 30% of affected animals from breeding, so that you have 2/3 of the population to breed from, you are not restricting the gene pool excessively, but you avoid breeding from the worst. If the cut-off point is going to be 5 years, and that excludes 30% of the worst affected, then fine. You can use other characteristics to choose which stud dog you go to. If you want the fastest results possible, then you might want to choose a stud dog that did not get a murmur until he was 9 or 10. It depends on what criteria you prioritize for making your decision.

Ms. Gish.

But then you are better off breeding to a dog who developed a heart murmur at the age of 6, than to a 2 year old dog.

Dr. Luis Fuentes.

Exactly.

Q. Phyllis Lasser, New Jersey.

I would like your opinion on the benefits of Vitamin E

in dogs of mature ages and bitches that receive vitamin E when they conceive, and the incidence of heart murmur in their offspring.

Dr. Keene.

There is no evidence for or against the efficacy of Vitamin E influencing the incidence and progression of CVD in dogs. I just think nobody knows.

Q. Cecelia McNamara, Alabama.

Phyllis stole my question in part. Are there any environmental factors that have been identified, either nutrition or exercise, anything that can slow or increase the progression of CVD?

Dr. Beardow.

The simple answer to that one is that no one has proven this. There is a lot of anecdotal discussion about various supplements and of different approaches to exercise, etc. None of it has been tested and none of it has been proven. The only controlled study is the one Dr. Keene mentioned where they are studying whether drugs given to asymptomatic dogs would affect the progression of the disease.

Dr. Luis Fuentes

When considering environmental factors as contributors to CVD, one has to ask what is so different about environmental factors for Cavaliers, compared to other small breed dogs that develop this disease when they are much older. If there were something overwhelmingly different in the Cavalier environment, we might consider looking at it. At this time we do not know of a possible factor, so there is no reason to pursue a study.

Dr. Beardow:

Unless we consider being owned by Presidents and singers!

Q. Norman Schell, New York.

What is the status of mitral valve replacement in these dogs?

Dr. Buchanan.

A few veterinarians are doing cardiopulmonary bypass surgery but, because of the size and cost of artificial valves, most mitral valve surgery has involved repair rather than replacement.

One veterinarian in Texas will be reporting next week on cross-stitching of the valve in a few dogs, including at least one Cavalier.

My experience with placing a purse string suture around the mitral annulus includes two Cavaliers. In one, the atrium just fell apart when I put a clamp on it. Then I put another clamp behind that, and another behind that. Then there was no more to clamp. In the second the purse string procedure went well, but the dog had end stage pulmonary hypertension and could not ventilate adequately after the surgery. Keep in mind that we were doing end stage cases, which is what you have to start with when you are developing a procedure. If we could get to these dogs earlier, we would have a better chance of doing successful surgery.

The Cavaliers are relatively small for usual cardiopulmonary bypass techniques. When dealing with a 15-20 pound dog one must use small priming volume and other features. The artificial valves that are available for people are just too big to fit the mitral annulus of a Cavalier. Although less expensive than human surgery, the costs are still substantial. A veterinarian in Colorado doing bypass surgery figures that the minimum charge has to be at least $4000.00 to try it, and thus far no one has had a lot of success with it.

Q. Unknown.

I am involved with another breed. We have been fighting cataracts and hip dysplasia, and testing for many years. One of my veterinarian breeder friends' favorite phrase is "Genes never go away". Do you have any hypothesis, or data, or just a good gut feeling about this? If we do all this testing and are real diligent, what might we expect?

Dr. Swenson.

I have said before, we can not estimate heritabilities from our studies. But if we look at the regression of offspring status on parental heart status, a very high heritability is indicated. That means that you can make a big difference in the first generation, if you pick dogs at least 2 ½ years old and murmur-free and whose parents also were murmur-free. The problem is, you will not know the results of the breeding until the dogs are 7, 8, 9 years old, way into the next century. If you adopt and actually follow the recommended protocol, you will make a change in the first generation. In two or three generations you will make a major impact. What I am most afraid of is that you will not adopt and implement the recommended protocol.

Q. Pat Wells, California.

Cavaliers were bred from the English Toy Spaniel, the King Charles. Why is it that CVD is not as prevalent in that breed?

Dr. Swenson.

They have the same situation, at least in Sweden.

Ms. Wells.

The veterinary cardiologist I use balks at anything holistic or preventive. About 7 years ago I adopted a 9½-year-old English Toy Spaniel who had a grade 6+ murmur. He predicted that she might live one more year, if we were lucky. I put her on a holistic medicine regimen of, vitamin E, garlic, and a whole list of things I use with my Cavaliers and other animals that are predisposed to CVD. She lasted for about 4 years after that. I currently have an 8 or 9 year old Cavalier who is clear, and a 12 year old with grade 2 murmur. For years they have been on an exercise regime, holistic medication and raw food diet. I say there is something we could look at, in terms of prevention, something that would forestall the onset.

Dr. Keene.

I think that is right. If you decide to embark on a program of controlled clinical prevention trials, and you randomize the dogs, that is put half of them on Vitamin E, garlic, fox urine, whatever, and use the other half as controls, then you could test anything you want. The problem is deciding what to test. There should be a reasonable physiologic basis for the mechanism of action of the substance tested. If someone were to look at collagen degeneration with the aim of reducing free

radical injury, then Vitamin E might be a good candidate in a clinical trial. One reason for skepticism about trials is that people are closed-minded to the idea that what you are doing might actually be working. It is very difficult to sort out the efficacy of a substance when you are doing a half dozen or dozen thing at the same time. If there is not a good sound basis for its efficacy, that is a good reason for not embarking on a study of that substance. It may seem second nature to you to prepare and feed raw foods and buy vitamin E, and all this other stuff. Without having a proven benefit, it is difficult to convince others to do the same.

Dr. Beardow.

I agree with Bruce completely. If I heard the question correctly, you are talking about dogs that have murmurs. What we are trying to do with the breeding programs is to eliminate the problem.

I hear many people saying I use this holistic medicine, I use that one, and I really believe it to work. My creed is the first law of medicine: "Above all, do no harm". As long as you are not doing harm, I have no objection. It is not a matter of poo-pooing the holistic approach. If someone comes to me as a client I must, in good consciousness, feel convinced that what I do is appropriate. If I were to take a holistic approach to the exclusion of that with which I am comfortable, I would not be doing my client a service. I do not have any issues with the holistic approach. If a holistic method were studied and proven to work, I could tell my clients that it has been shown to work, and that they could go ahead and try it. Lacking that, we need to work within our "comfort" zone, and not make judgements about something that we do not understand. Maybe one day we will understand.

Q. Andrea Vest, North Carolina.

Do you have any recommendations for treating a dog with CVD? Do we wait until he develops symptoms? Can we postpone symptoms for 2-3 years by starting medication before that?

Dr. Keene.

Experimental canine studies have been done to evaluate when people should have mitral valve repair or replacement, and whether the time before surgery could be prolonged. It is not an ideal model for the Cavaliers' problem, but the data is out there and I think we should use it. The data suggests that angiotensive converting enzyme inhibitors, which work to control congestive heart failure, also work to prolong the interval until heart failure develops in persons who have significant regurgitation. Beta-blockers have not been looked at in CVD, but have been shown to work well in artificially induced mitral valve disease in the dog.

Right now there is a clinical trial in progress where animals, not all Cavaliers, have been randomized in a study of angiotensive converting enzyme inhibitor. One half is on the drug, the other half on a placebo. This trial is awaiting the results. We should have the answer to that question in the next year, hopefully.

If your group wanted to sponsor a clinical trial, there are lots of opportunities. You could look at beta-blockers, holistic approaches, anything you can think of. The ticket is to have something that everyone is willing to support and say yes, I am willing to try to answer this question.

Dr. Buchanan.

I want to comment about aspects of disease progression and when to start treatment. I do not think we have seen cardiac enlargement in a Cavalier less than 5 years of age, except in those with congenital heart disease. Although many dogs develop mitral murmurs earlier, it usually takes months and sometimes years before cardiac enlargement begins. This pertains to the question about what to recommend for a 3 year-old dog with a grade 3 murmur. If the client has lots of money and is aggressive, I would get a chest x-ray when the murmur is first heard. If not, I would be too concerned about getting a baseline radiograph until they are 4 or 5 years old. Then I would get a yearly x-ray to monitor the development of cardiac enlargement and use heart size as a guide. If the heart in a baseline x-ray measures 9.5v, and subsequently 10.5v, that indicates cardiac enlargement and the effects of mitral regurgitation. A heart over 11v in any Cavalier indicates mild cardiac enlargement and may be a useful starting point for a therapeutic trial when baseline radiographs are not available.

Dr. Keene.

I am sure, Jim, that you have seen lots more Cavaliers than I have. I can't think of a specific heart like that. (Well, there was old Charlie who was 2 ½ and had a big heart!). I would have thought that we did see Cavaliers at younger ages with big hearts. I am curious to know what everyone else thinks.

Dr. Luis Fuentes.

I can't think of specific examples, either. My impression is that in the U.K. we used to see dogs of 4 that had cardiomegaly, who were not in congestive heart failure. If you use a vertebral heart score of 11 as the cutoff point, I have definitely seen Cavaliers under the age 4 who had cardiomegaly.

Dr. Beardow.

On that point I can't give a specific example, but we have seen Cavaliers at 6 in heart failure. Not having radiographed them before that, I can only speculate whether they had cardiomegaly earlier.

Q. Karen Ostman, Nebraska.

I have a little problem with the term "free". This breed goes back to a gene pool of 4 dogs, and we have bred from those four dogs that were related, more or less. Are we really going to be free of this disease, even if we find the gene or whatever?

Dr. Swenson.

We will never get rid of the genes that cause CVD. Our goal is that all Cavaliers will die a natural death before they get CVD. Then we no longer have a problem.

Q. Patty Fensterwald, California.

Is someone in this country working on isolating the gene or genes? If so, how can we help?

Dr. Keene.

The problem is that a single gene does not control this trait. The best you can hope for in a multi-factorial polygenic threshold trait is that there might be a dominant gene that you can work on.

Dr. Swenson.

If there is a major gene that causes 30% of cases, then this is the gene that will disappear from the population first, if you start selective breeding. That way you will take away the possibility of finding it and that, of course, is a good thing.

Q. Bob Hochberg, Maryland.

Dr, Keene, you said a few minutes ago that it would be wonderful if we could all get behind a program and get things moving. Therein lies one of our biggest problems, the diversity in this country, with many claiming they know what the problem and the solutions are. Dr. Luis Fuentes, to what extent was the English Cavalier Club able to require responses from the members, how did they do it and to what extent?

Dr. Luis Fuentes.

I am not sure that I can answer what proportion of breeders is actively involved in the British Cavalier King Charles Club scheme at the moment. With any new breeding scheme there tends to be a core of active committed people who often have had first hand experience with the disease, and that has helped the motivation wonderfully. There will always be, at the periphery, people who don't want to have to confront the problem and would rather hide it under the carpet. There has been a change in the opinion about the mitral valve disease scheme in the U.K. over the last five years or so. There has been a growing acceptance that there is a problem, and more active involvement in the scheme. Things have definitely improved since more concrete guidelines were established. In breed schemes for other heart problems in which I have been involved, such as aortic stenosis in Boxers, we have seen a big shift from participation by only a few breeders with others not wanting to know, to everyone taking part because no one wanted to be left out. No one wanted to use stud dogs that were not tested. Having a list, and having an incentive to list the animals can be very helpful. Eventually, those who do not list their dogs will be marginalized. Sweden is very lucky in that their Kennel Club has a lot of clout. The Swedish attitudes of openness have helped. The U.K. Kennel Club and U.K. breed clubs do not operate the same way. There are issues of confidentiality, and reluctance to face up to what is a big problem. I think things will change once we have public lists. If enough people use the lists, then those who don't will be left out.

Q. Anne Eckersley-Robins.

Getting back to the 6 year-old with a murmur, opposed to the murmur-free 2½ year old. I assume you mean grade 1 murmur as opposed to 2, 3, 4, 5, or 6?

Dr. Luis Fuentes.

At the moment we have not made a distinction between low-grade murmurs and high grade murmurs. The recommendation is to breed from a murmur-free dog 2½ years or older with parents that were clear at 5 years, even if one parent developed a murmur at 6 years.

Ms. Eckersley-Robins.

I don't think I understood that. Did you mean a parent clear at 5 that came up with a grade 1 murmur at 6? They don't automatically come up with grade 2, 3, or 4 murmurs, do they?

Dr. Luis Fuentes.

It can vary.

Dr. Keene.

That is interesting. Until the Swedish studies were published, only a few people like Drs. Buchanan and Beardow actually knew that the intensity of murmur in mitral regurgitation in Cavaliers was related to heart size. Am I wrong?

Dr. Beardow.

Only in general terms.

Dr. Keene.

What actually makes a murmur louder is not necessarily increased turbulence of blood flow through the valve. In Cavaliers the heart is better coupled to the chest wall, and as the heart gets bigger the intensity of the murmur gets greater. But there is not 100% correlation. We have all seen dogs with grade 6/6 murmurs that have essentially normal left atria. Likewise, at the end of the dog's life, oftentimes a murmur gets softer.

Dr. Beardow.

We have looked at the shift of intensity of heart murmurs and have found dogs that were clear one year and had a grade 3 murmur the next.

Q. Unidentified.

And should we be breeding from the 6 year old who was clear at 5, but now has a grade 3 murmur?

Dr. Beardow.

You have to draw up your criteria and stick by them. If you add other confounders, we no longer have good guidelines. If the guideline says "clear at 5" then you never mind what happens after that. That is certainly proven by the Swedish study.

Q. Anne Eckersley-Robins.

Is the reality of the protocol that uses the 2½ year-old with parents that are 5 and clear that 50% of the dogs that we are breeding do not have parents clear at 5?

Dr. Beardow.

That is perfectly right. As I understand it there are two separate criteria. The dog itself is clear at 5, and you can breed it or the dog is clear at 2½ and both parents are clear at 5.

Q. Pat Winters.

Are you saying that if you have a clear 2½ year old, and one or both parents are not clear, then keep it until it is 5, and if it is then clear you can use it for breeding?

Dr. Swenson.

That is not my idea of how this program should be working. I recommend that we try to find dogs that are 2½ years old and free of heart murmur, that have parents free of murmur at age 5.

Sometimes you think you cannot afford to cut out that much of the breeding population. You forget that you already are doing this. You do not use more than perhaps 10% of the males as sires. You do not think this is too tough. You are willing to make a hard selection based on conformation, and delete a lot of dogs from the breeding population. But when

we talk about doing that to control CVD, you seem to balk. That seems a little peculiar to me.

Q. Unidentified.

Suppose the parents are clear at 5, but the siblings of the parents are not clear at 5? Do you still breed the offspring of the clear parents?

Dr. Swenson.

When we include more and more criteria it will be more difficult to reach the goals. It would be enough to find the dogs that are free themselves at age 2 1/2, and have parents that were free at 5.

Q. Unidentified.

Is there a relationship between juvenile-onset and adult-onset disease? Would you breed a dog with adult-onset disease rather than a juvenile-onset disease?

Dr. Swenson.

The reason why we chose 5 year-old dogs in our study is that we wanted to have a sufficient number of dogs with disease. Five years is a good place to start. 2½ is, of course, half of 5 which means that if you use only 2½ year olds, their parents must be at least 5.

Unidentified, same.

Is there enough data to know what happens when you use one clear at 5, but that at age 6 had a grade 3 or 4 murmur? Is he or she a better candidate for breeding?

Dr. Swenson.

Are we now talking about using that dog that developed a murmur at 6 for breeding? I would not use that animal for breeding.

Unidentified, same.

I am concerned because we have such a small gene pool. Someone said we started from 4 dogs.

Dr. Swenson.

Actually, many breeds started that way. I am not convinced it was 4, the number was probably greater. The Clumber Spaniel started from 6 or 8 dogs, the Sussex Spaniel from just a few. They also have problems. I do not think the situation is hopeless.

Dr. Beardow.

I think we are getting hung up on a number. When you start this type of program you have to be willing to look at the data, go to epidemiologists, go to geneticists and ask where do we start. It does not mean that you stick with it forever. In the U.K. they are constantly collecting and evaluating data, and re-evaluating the program. You want to hone in on perfection, hone in on dogs free of disease. You are not going to do that in one cut. The deeper the cut, the faster you will get there. But you may find that you have to eliminate ¾ of your breeding stock. Then you have to reach a compromise. If you get too hung up on numbers you lose the ability to compromise, to bring in reasons for discussion.

I may have garbled on a bit, but I don't *think* you should get hung up on the shift from 5 years to 6 years in one particular dog. You should be looking at the global picture.

President Anne Eckersley-Robins.

I wish to thank the five speakers who have come so far to conduct this symposium. It has been very, very interesting. A lot of our questions were answered.

I want to remind the members of our other projects for this "Year of the Heart". Our Heart Registry will be starting soon. Look for the forms in the Bulletin. The Cavalier Health Foundation is well on its way. Its aim is to support projects related to the health of the Cavalier. You can read about all of this in the Bulletin. This is our main means of communication, so *please read* it.

Last I wish to thank Bob Sims and Randi Rosvoll who have been working over a year to put together this symposium. It took a tremendous amount of work to line up speakers, plan the sequence of talks, provide the facilities, and to get everyone here at the same time. All of this is much appreciated.

DIAGNOSTIC TESTS FOR MITRAL VALVE DISEASE

AUSCULTATION listening with a stethoscope

RADIOGRAPHY chest x-ray

ECHOCARDIOGRAPHY ultrasound evaluation of the heart

DOPPLER ANALYSIS ultrasound measure of blood flow

Figure 1. Diagnostic tests used to evaluate the heart and its blood flow.

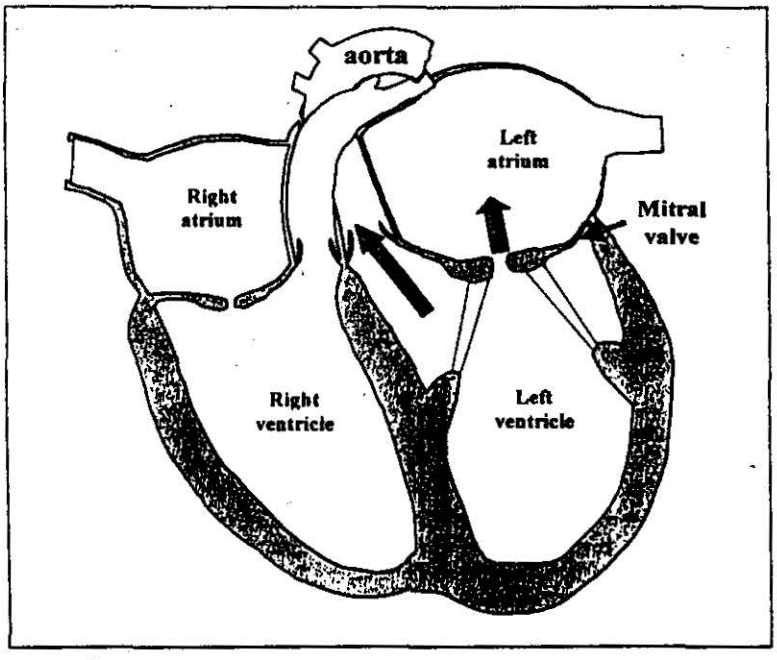

Figure 2. Chambers of the heart. If the mitral valve were normal, as is seen in the right heart, it would close during systole, and blood would flow only into the aorta. In CMV the mitral valve leaflets thicken and cannot close. Blood regurgitates through this abnormal mitral valve during systole. The left atrium is enlarged.

CLASSIFICATION OF HEART MURMURS

LOW INTENSITY MURMURS

Grade 1	Very faint and soft, audible only after several minutes of auscultation in a quiet room
Grade 2	Soft, but easily localized and readily heard

MODERATE INTENSITY MURMURS

Grade 3	Heard immediately on auscultation. No thrill.
Grade 4	Heard immediately, may be accompanied by thrill

HIGH INTENSITY MURMURS

Grade 5	Very prominent, accompanied by thrill
Grade 6	May be heard with the stethoscope barely touching, or with the ear alone. Accompanied by thrill.

Figure 3. Classification of heart murmurs. (Roman numerals I, II, III, IV, V, VI are sometimes used to designate heart murmur grade.)

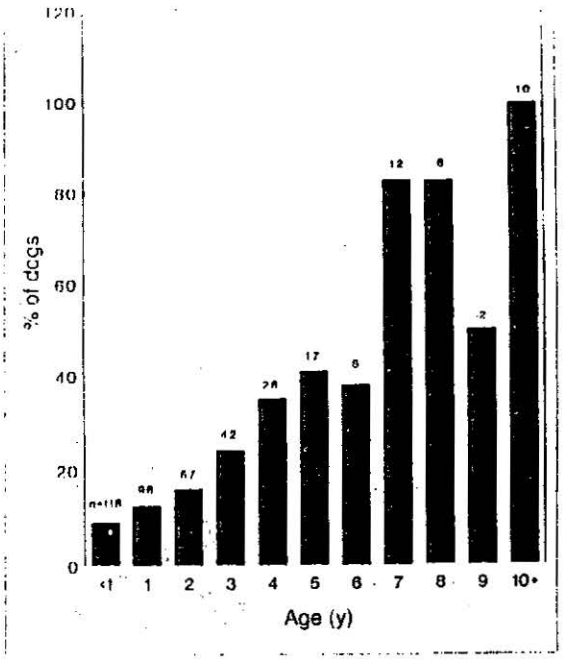

Figure 4. Beardow and Buchanan's study. Age specific prevalence of left apical systolic murmurs grades 1-6 in 394 Cavaliers. The numbers above the columns represent the numbers of dogs in each group. The percentage of murmur-positive dogs increases with age.

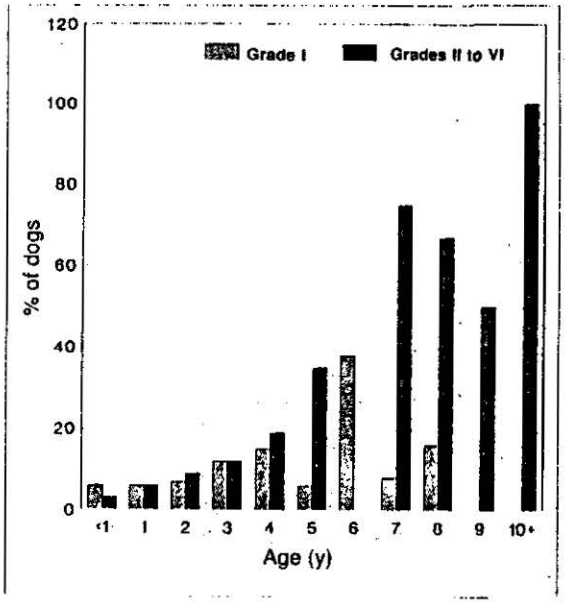

Figure 5. Beardow and Buchanan's study. Age specific prevalence for murmurs grade 1 and grades 2-6 in 394 Cavaliers. The percentage of dogs with grade 2-6 murmurs increases with age.

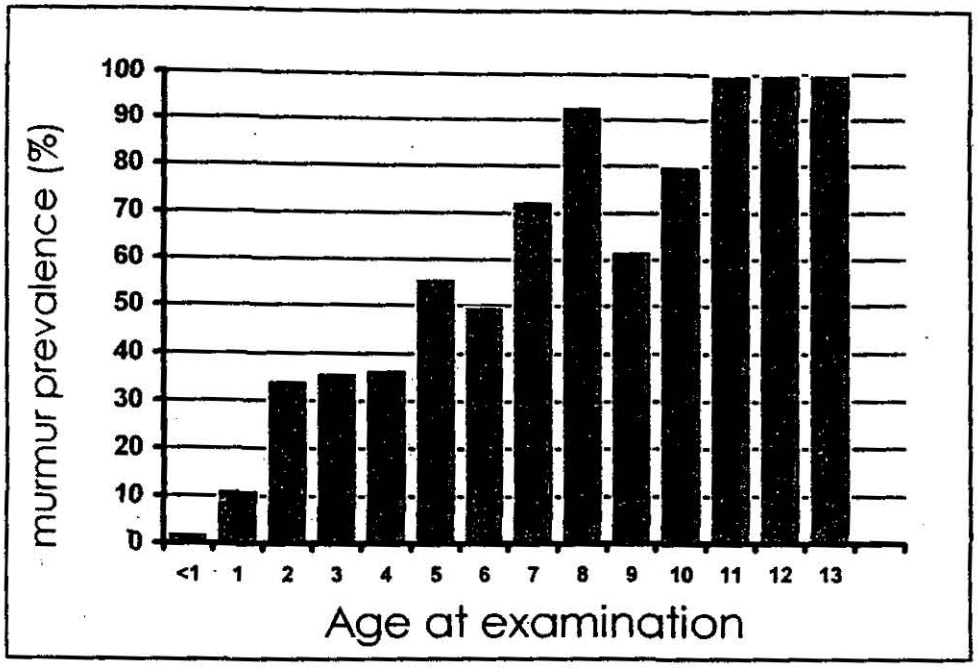

Figure 6. Dr. Darke's early survey of heart murmurs in Cavaliers. The prevalence increases with increasing age. Over 30% of dogs 2-4 years old, 50%at age 5-6, and all dogs 11 years and older had heart murmurs.

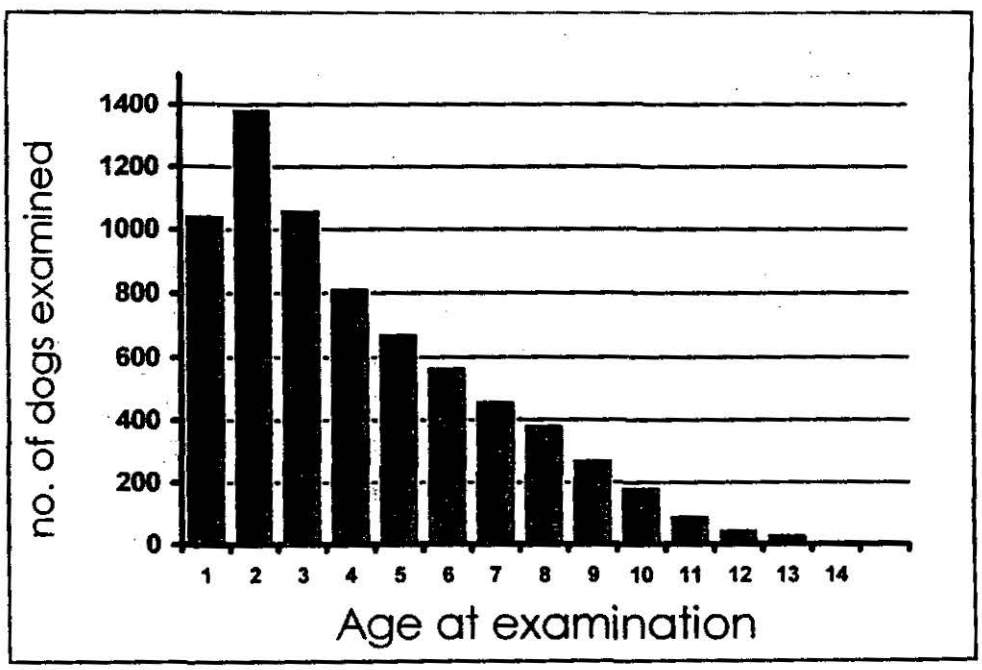

Figure 7. Recent studies in the U.K. Number and ages of dogs examined. Very few dogs in the older age groups were seen.

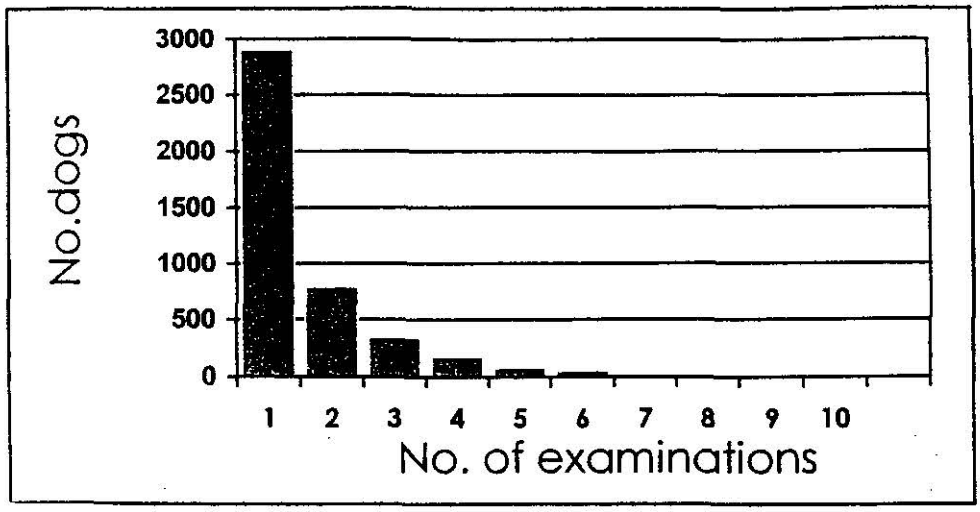

Figure 8. Recent studies in the U.K. Most of the dogs were seen only once, a few had multiple examinations.

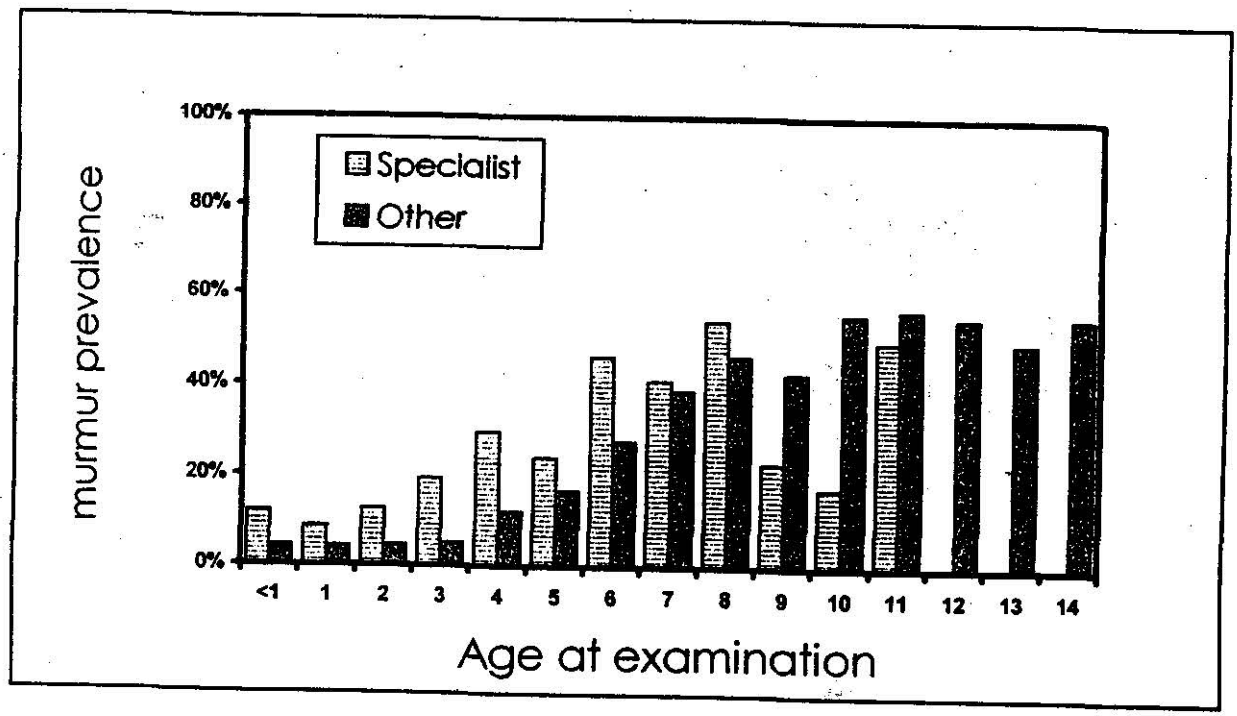

Figure 9. Recent studies in the U.K. Prevalence of murmurs at different ages shown as detected by specialists vs. generalists. Specialists detect more murmurs in younger dogs. Prevalence appears to have gone down when compared to earlier studies, probably due to the small number of older dogs.

DESIGN OF THE SWEDISH STUDY IN CAVALIERS

Suitable age (5 years) for screening was chosen.

All Cavaliers born in 1988 were listed.

Sires were listed.

Examination, classification and selection of sires.

Dams and offspring listed.

Examination of dams and offspring

Exclusions.

Analysis.

Figure 10. Stepwise design of the study of the *relationship between* parental cardiac status in Cavaliers and the prevalence and severity of chronic heart valve disease (CVD) in the offspring. Five year olds were chosen for the study because of the likelihood that many would have developed CVD at this age.

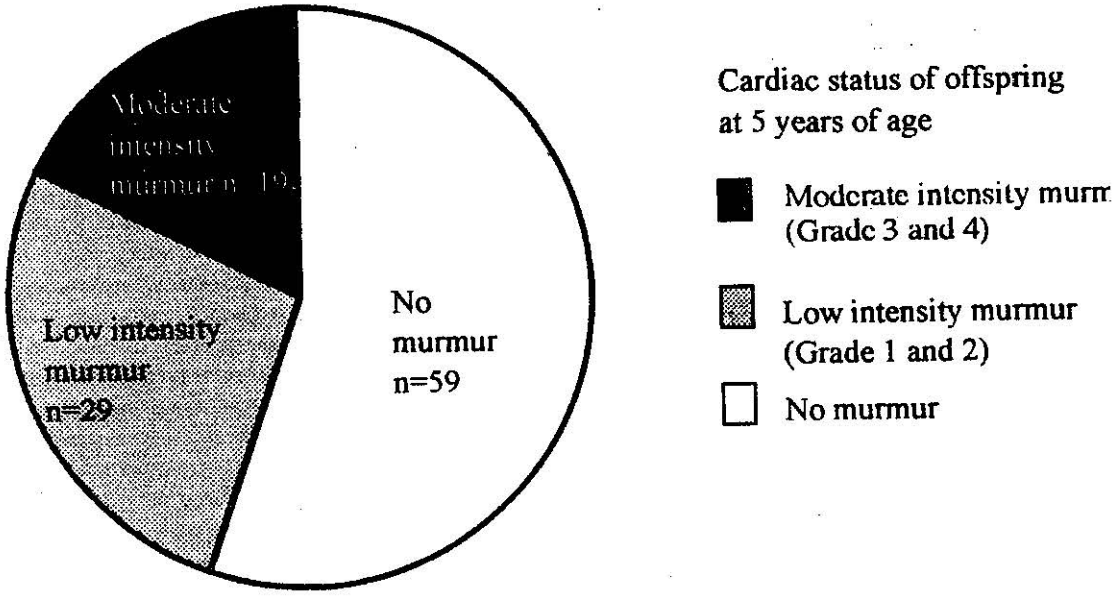

Figure 11. Results of the Swedish study. Proportion of 5 year old offspring with or without murmurs. No murmur:59, low intensity murmur: 29, Moderate intensity murmur:19, High intensity murmur: none.

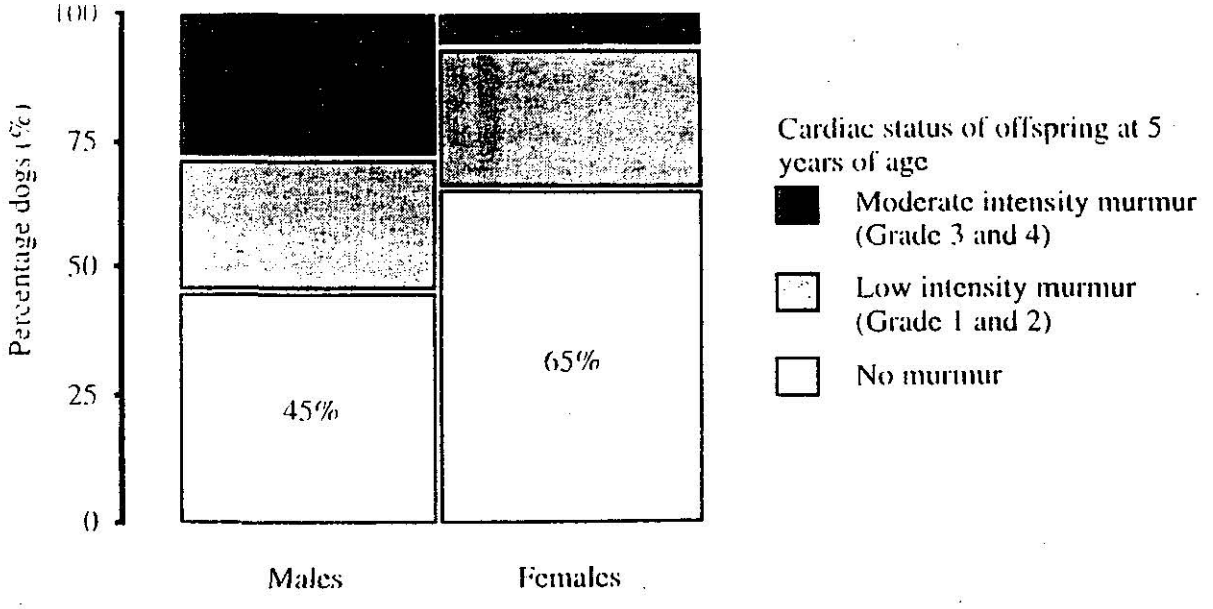

Figure 12. Results of the Swedish study. Effects of sex on the cardiac status. The male offspring had a larger percentage of murmurs than did the female.

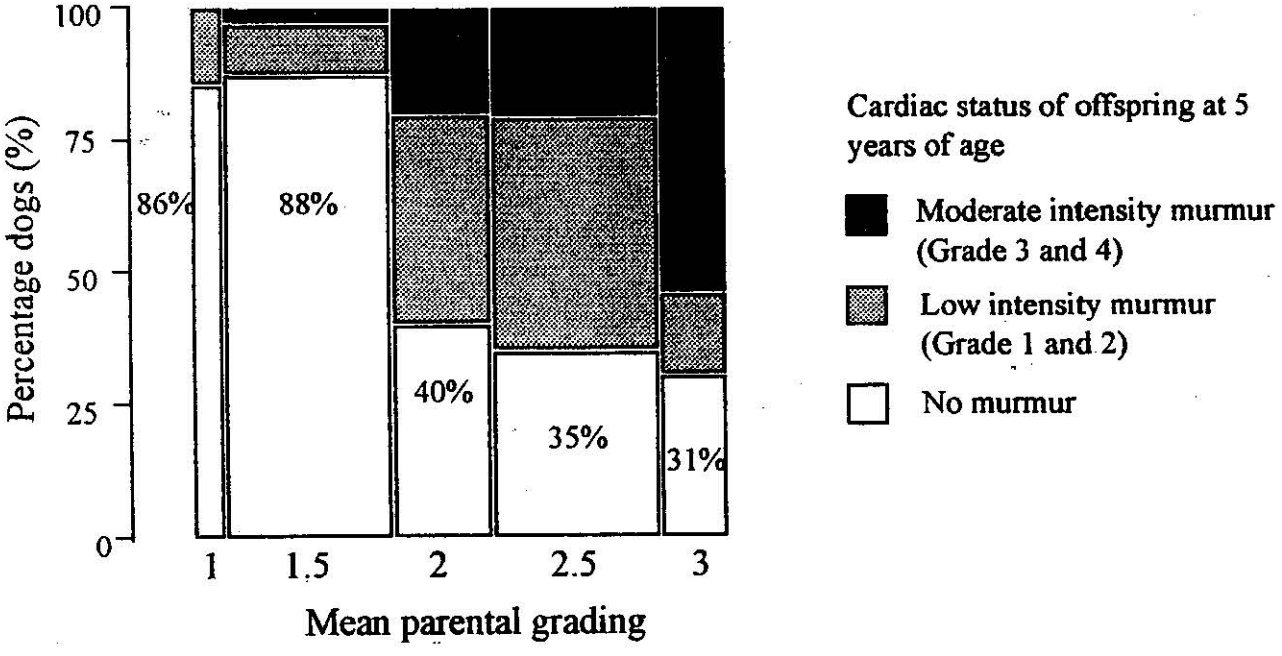

Figure 13. Results of the Swedish study. Relationship between the mean parental cardiac status and the prevalence and intensity of heart murmurs in offspring. Parents with a low mean cardiac status (1-1.5) produced few offspring with murmurs; 88-86% were murmur-free. Parents with a high mean cardiac status produced a large number of offspring with heart murmurs; only 31-40% were murmur-free.

MURMUR INTENSITY AS A SCREENING TEST FOR CVD

Definitions of test results	Mitral valve disease Present	Absent	Totals
Positive; murmur intensity greater than 2/6	39	**4**	**43**
Negative; murmur intensity 0-2/6	**1**	35	**36**
Total	40	39	79

Figure 14. Auscultation of heart murmurs as a screening test for CVD. **4/43** screening positive dogs were normal (false positive); **1/36** screening negative dogs did have disease (false negative).

SENSITIVITY OF A SCREENING TEST

	Positive for disease	Negative for disease	Total
Test positive	**39**	4	43
Test negative	1	35	36
Total	**40**	39	79

Figure 15. Evaluation of a screening test. **Sensitivity** is the proportion or fraction of dogs that do have disease (40), that are correctly identified as positive (39) by the test. **Sensitivity is 39/40=97%.**

SPECIFICITY OF A SCREENING TEST

	Positive for disease	**Negative for disease**	Total
Test positive	39	4	43
Test negative	1	**35**	36
Total	40	**39**	79

Figure 16. Evaluation of a screening test. **Specificity** is the proportion or fraction of dogs that do not have disease (39), that are correctly identified as negative (35) by the test. **Specificity is 35/39= 90%**

PREVALENCE

	Positive for disease	Negative for disease	**Total**
Test positive	39	4	43
Test negative	1	35	36
Total	**40**	39	**79**

Figure 17. Evaluating data. Prevalence is the proportion of whole population (79) that are truly affected (40). **Prevalence is 40/79=50%.**

POSITIVE PREDICTIVE VALUE

	Positive for disease	Negative for disease	**Total**
Test positive	**39**	4	**43**
Test negative	1	35	36
Total	40	39	79

Figure 18. Evaluating data. Positive Predictive Value is the proportion of dogs who test positive (39) who truly have the disease (43). **Positive predictive value is 39/43=90%.**

NEGATIVE PREDICTIVE VALUE

	Positive for disease	**Negative for disease**	**Total**
Test positive	39	4	43.
Test negative	1	**35**	**36**
Total	40	39	79

Figure 19 Evaluating data. Negative Predictive Value is the proportion of dogs that test negative (35) that truly do not have the disease (36). **Negative predictive value is 35/36=97%.**

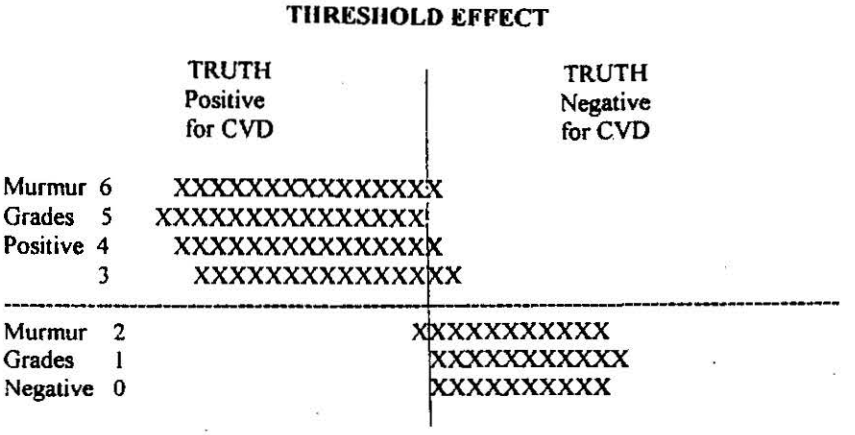

Figure 20. Threshold effect. If the test threshold (—) is lowered so that grade 2 is in the test-positive group and only grades 1 or 0 were test-negative, a few more true positives would be found, but more test-negative would be classified as "Positive for CVD".

SCREENING PROGRAM FOR CVD

Tests must be easily and widely available

Tests must be specific
and must identify dogs
likely to produce offspring with CVD

Tests must not be overly sensitive
and must not reject
an excessive portion of the breeding stock

Cost of testing should not be prohibitive

Programs established
must be widely supported
and uniformly implemented.

Figure 21. Factors of importance in establishing breeding programs for CVD.

References

Swenson L, Häggström J, Kvart C, Juneja RK. Relationship between parental cardiac status in Cavalier King Charles Spaniels and prevalence and severity of chronic valvular disease in offspring. JAVMA 1996; 208:2009-2012.

Beardow A, Buchanan J. Chronic mitral valve disease in Cavalier King Charles Spaniels: 95 cases (1987-1991). JAVMA 1993; 203:1023-1029.

Häggström J, Hansson K, Kvart C et al. Chronic valvular disease in the Cavalier King Charles Spaniel in Sweden. Vet Rec 1992; 131:549-553.

Darke PGG. Valvular incompetence in Cavalier King Charles spaniels. Vet Rec 187; 120:365-366.

Häggström J. Chronic valvular disease in Cavalier King Charles Spaniels: Epidemiology, inheritance and pathophysiology. Theses, Faculty of Veterinary medicine, University of Agricultural Sciences, Uppsala, Sweden.

Patterson D. Hereditary congenital heart defects in dogs. J Small Anim Pract 1989; 30:153-165.

Swenson L, Audell L, Hedhammar Å. Prevalence, inheritance and selection for hip dysplasia in seven breeds of dogs in Sweden, and cost/benefit analysis of a screening and control program. JAMVA 1996.

Swenson L. Chronic valvular disease (CVD) in Cavalier King Charles Spaniels; Inheritance, breeding opportunities and strategies. Proceedings of Seminar, 2 November 1996, Intervet UK Ltd. and the Cavalier King Charles Spaniel Club [UK]; January 1997: 25-32.

Buchanan JW: Patent ductus arteriosus. Seminars in Vet Med and Surg 1994; 9:168-174.

Buchanan JW, Beardow AW and Sammarco CD: Femoral artery thrombosis in Cavalier King Charles Spaniels. JAVMA 1997; 211:872-874.

Beardow AW and Buchanan JW: Chronic mitral valve disease in Cavalier King Charles Spaniels: 95 cases (1987-1991). JAVMA 1993; 203, 1023-1029.

Buchanan, JW and Bucheler J: Vertebral scale system to measure canine heart size in radiographs. JAVMA 1995; 206, 194-199.

SUMMARY

SYMPOSIUM ON CHRONIC HEART VALVE DISEASE (CVD) IN CAVALIER KING CHARLES SPANIELS.

CVD is a significant disease in Cavaliers.

CVD is more prevalent in Cavaliers than in other breeds.

CVD starts at an earlier age in Cavaliers than in other breeds.

CVD in Cavaliers is more prevalent in males than in females.

CVD status of parents has a major effect
on the probability and progression of the disease in offspring.

CVD is probably a multi factorial polygenic threshold trait.

Breeding values based on parental status,
and perhaps earlier generation status,
may allow breeding young murmur-free dogs.

RECOMMENDATIONS FOR BREEDING

- Breeding must be selective.

- Breed only dogs at least 2 ½ years old and murmur-free whose parents were murmur-free at the age of 5 years.

The result would be the same as breeding 5 year-old murmur-free dogs.

Figure 22. Summary and Recommendations.