

'1999 ACVIM PROCEEDINGS: WHEATEN TERRIER PLE-PLN

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SUMMARY:

Soft Coated **Wheaten** Terrier (SCWT) dogs are predisposed to several diseases which may be confused with each other because of similar clinical signs: PLE (protein-losing enteropathy), PLN (protein-losing nephropathy), RD (juvenile renal dysplasia), and less commonly, Addison's disease. These may be distinguished by diagnostic tests. Although the precise modes of inheritance of these diseases are not known, analysis of pedigrees of almost 200 **PLE/PLN** dogs showed that these dogs are related to a common male ancestor. Dogs with RD are also closely related. Members of the SCWTCA (SCWT Club of America) have begun an Open Registry to help identify affected dogs and their close relatives, in an effort to avoid breeding dogs at risk for these diseases.

HISTORY:

In 1984 two separate studies from **Europe**^{1,2} reported juvenile renal dysplasia in SCWT dogs. These reports described closely related young dogs presenting ill with chronic renal failure at 4.5 weeks to 30 months (all died before 3 years of age). The mode of inheritance is unknown but surmised to be autosomal and recessive. There is no sex predilection. Common clinical features were **polyuria/polydipsia**, isosthenuria, azotemia, and small kidneys. Some dogs had diarrhea and/or anemia; only 2 of 12 dogs described had proteinuria. None had hypoalbuminemia nor **ascites**. Histopathology showed renal dysplasia changes including many immature (fetal) glomeruli, persistent fetal mesenchyme, and tubular dilatation.

Breeders of SCWT dogs in North America also recognized that renal failure was a problem in SCWT dogs here, but the renal failure was not always well characterized. In America, in addition to young dogs dying with renal failure, a middle-aged population of dogs (mean ~ 6 years old) was also dying with renal failure. Some of these middle-aged dogs showed **ascites**, and some died suddenly. More confusion occurred among breeders since some dogs related to these dogs had similar signs of illness (weight loss, gastrointestinal signs, and sometimes ascites), but they did not always have renal failure.

Addison's disease, another predisposition in the SCWT breed,³ could mimic other gastrointestinal or renal diseases with signs of weight loss, vomiting, diarrhea, **polyuria/polydipsia**, azotemia, and/or sudden death. Food allergies seen in this breed⁴ (not necessarily leading to full-blown PLE) could also cause gastrointestinal signs and weight loss. There were rumors and confusion among breeders since many dogs were not tested adequately enough to characterize the cause of their illness. With the help of conscientious breeders of the SCWT Club of America (SCWTCA), data began to be centralized, accumulated, and studied retrospectively at the University of Pennsylvania. Diagnostic criteria for each disease were defined, and more diagnostic tests were advised to help characterize the cause of the clinical signs. We were then better able to help the breeders understand the nature of the diseases they were dealing with, and to help owners in the management of the affected dogs.

DISEASES DEFINED:

At VHUP in the **1980's**, it became clear that there were several diseases to which this breed was predisposed, and which were previously confused because the clinical presentations were so similar (see Table 1). These diseases were protein-losing enteropathy (PLE), protein-losing nephropathy (PLN), juvenile renal dysplasia (RD), and rarely, Addison's disease. Since only a handful of dogs (originally from European stock) were used extensively as the prime breeding stock in North America in the **1960's-1970's**, it is not surprising that some inherited predispositions have become evident.

In 1990, Littman and Giger described 33 related SCWT dogs with PLE and/or PLN.⁵ By 1997, 222 affected dogs were retrospectively studied in detail." A common male ancestor was identified among 188 pedigrees available. Most of the dogs were diagnosed at 4-7 years of age (range 6 mos. to 12 yrs.), and female dogs predominated. Common clinical signs were vomiting, diarrhea, weight loss, and **effusions**. Thromboembolic complications sometimes caused sudden death. The middle-aged dogs with azotemia also often had proteinuria, hypoalbuminemia, and hypercholesterolemia. These dogs were diagnosed with protein-losing nephropathy (**PLN**).^{5,6} Kidney biopsies of these dogs did not show renal dysplasia changes but showed glomerulonephritis and/or glomerulosclerosis. Another population of middle-aged dogs might show similar signs of illness (weight loss, gastrointestinal signs,

and possible **ascites**) but they did not have proteinuria nor azotemia; these dogs often had panhypoproteinemia and hypocholesterolemia, without evidence of **melena** or anemia. These dogs were diagnosed as having protein-losing enteropathy (**PLE**).^{5,6} Histopathologic lesions of the intestine included inflammatory bowel disease (IBD, usually lymphocytic-plasmacytic enteritis), lymphangiectasia, and/or granulomatous lymphangitis. PLE occurred earlier in life (-4.5 yrs) than PLN (-6 yrs) or combined **PLE/PLN**; some dogs with PLE later developed PLN or presented with combined **PLE/PLN**. It appears that PLE precedes PLN and either continues or subsides while PLN develops and progresses.

THEORIES:

Concurrent PLE and PLN is rarely found in dogs. Only in **Basenjis**⁷ with PLE (due to immunoproliferative small intestinal disease) is there a predisposition for concurrent PLN. But these Basenjis have hyperglobulinemia, whereas the SCWT-PLE dogs have hypoglobulinemia, and the Basenjis do not show the female predisposition that is seen in the affected SCWT dogs.

Many SCWT dog owners have noticed food hypersensitivities in their **dogs**.⁴ Food allergies may play a role in SCWT-PLE; perhaps food antigens could be involved in immune-complex deposition in SCWT-PLN glomerulonephritis. Studies concerning food hypersensitivity and **PLE/PLN** are being conducted by Dr. Shelly Vaden, et al at **NCSU**.⁸⁻¹² However, since dogs of other breeds with food allergies do not often have associated GN, there may be a more widespread immuno-regulatory or vascular/collagen disorder which affects both the intestine and kidney in these SCWT dogs. Dr. Vaden is studying possible mast cell function abnormalities in these dogs. With funding from SCWT organizations and the AKC, Dr. Vaden is studying a colony of affected SCWT dogs as well as **SCWT-Beagle** crosses. These studies will help define the mode of inheritance, possible immunopathogenesis of the protein-losing diseases, and suggest early screening tests.

The genetic defects involved in SCWT PLE/PLN may be complex. The expression of the illness may involve exposure to environmental triggers, such as food or infectious agents. This could explain the higher incidence of affected middle-aged or older animals. Since IBD is probably a multifactorial disorder, defects may be inter-related. For example, disruption of the barrier function in the gut (e.g., caused by infection or dietary factors) may lead to exposure of the mucosal immune system to enteric antigens to which they are not tolerant. This may result in chronic local T cell activation, inflammation, and tissue damage. This scenario may be exacerbated by any underlying immunological abnormality. For example, enteric bacteria appear to trigger colitis in the IL-2 deficient mouse model because gnotobiotic (germ-free) IL-2 deficient mice do not manifest **colitis**.¹³ Similarly, a SCWT dog may hold the full component of genes necessary for the genetic predisposition for developing **PLE/PLN**, but if the dog is not exposed to the environmental trigger(s), the phenotype may not be expressed.

DIAGNOSTIC TESTS:

To help identify dogs affected with PLE, PLN, and/or RD, diagnostic tests including serum biochemistry, urinalysis, urine protein/creatinine ratio, fecal API testing, radiographs (for kidney size), and biopsies of kidney and/or small intestine may be helpful. Electrolyte determinations (**Na/K**) and an ACTH stimulation test help rule out Addison's disease. Early **predictors**^{8,14} of PLE/PLN may be eosinophilia, increased fecal API (alpha-I -protease inhibitor), and increased urine protein/creatinine ratio (with a non-inflammatory urinary sediment). There are no DNA markers available, nor specific immunologic tests as yet to help in identifying dogs which are at risk for future disease manifestations, or which may appear normal but pass on "at risk" genetic material. Thus, screening tests of SCWT dogs are recommended annually (or twice yearly in dogs 4-7 yrs that are closely related to affected dogs).

MANAGEMENT:

Since the immunopathogenesis of these diseases is not yet worked out, the same general management used for other dogs with PLE or PLN is used. Fecal examinations for parasites/microbes and serology for dirofilariasis and tick-borne diseases may help identify more specific treatment for PLE or PLN, respectively. Dogs with PLE are often given hypoallergenic and/or low fat diets, MCT oil, and antibiotics to change enteric flora, immunosuppressants, and immunomodulators. Dogs with PLN may be treated for chronic renal failure. The proteinuria, hypertension, and thromboembolic complications may be treated with enalapril and low-dose aspirin. The prognosis is only fair to poor for PLE (median survival -5 mos.), and poor for PLN (median survival -3 mos.)."

INCIDENCE and EFFORTS TO HELP THE BREED → THE OPEN REGISTRY:

A large number of SCWT dogs appear to be affected with PLE and/or PLN. Dr. Slater at Texas A&M estimates that 10-15% of the SCWT breed is affected with these diseases. This is devastating for such a small breed. Perhaps many more dogs are “at risk” or are able to pass on “at risk” genetic components to progeny. There are as yet no definitive tests to predict which dogs are at risk for future development of PLE/PLN or RD. There are no genetic tests, which help identify dogs, which appear normal but may pass on components of these predispositions. But we do know that affected dogs are related to other affected dogs, in other words, the predisposition is inherited.

To help stop rumors and in an effort to help breeders choose dogs less closely related to known affected dogs, conscientious breeders decided to start an Open Registry a few years ago. Since so much (confidential) information was already gathered at the University of Pennsylvania, we were asked to help in this endeavor by contacting owners and co-owners of documented cases of PLE, PLN, and RD, and asking them for permission to publish and share that information. Only very small minorities of active SCWT breeders have not joined in this effort. Currently there are 292 members in the SCWT Club of America and there are 369 Open Registry members. The Open Registry (as of Feb 99) includes 207 dogs affected with PLE and/or PLN, or RD. Information given includes the dog’s AKC or CKC registration # and name, the “call” name, names of sire/dam, date of birth, age at diagnosis, sex/neuter status, diagnosis, the criteria by which the diagnosis was based (e.g., blood, urine, biopsy tests), and the date of death.

MORE INFORMATION:

Dr. Shelly Vaden has a very informative **website** concerning the SCWT diseases and the ongoing research at NCSU. The **website** address is www.cvm.ncsu.edu/research/SCWT. Dr. Brian Wilcock at the University of Guelph, Ontario Veterinary College, and Dr. Meryl Littman at the University of Pennsylvania have funding from the SCWT Clubs to receive and interpret histopathology samples (usually of kidney and small intestine) at no charge to the owner. Dr. Littman offers advice to owners, breeders, and their veterinarians concerning the diagnosis and management of these diseases. All information is confidential. If the case meets the criteria for an affected dog, Dr. Littman will ask for permission from the owners for the dog to be listed in the Open Registry, which she helps coordinate for the SCWTCA.

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TABLE 1: COMPARISONS OF DISEASES TO WHICH SCWT DOGS ARE PREDISPOSED

	RD^{1,2}	PLN^{5,6}	PLE^{5,6}	ADDISON'S³
Age of Onset	<1-3 yrs	Mean ~ 6 yrs	Mean ~ 4.5 yrs	Young (in general)
Sex Predilection	None noted	Female: male=1.6	Female: male=1.7	Female (in general)
PU/PD	Yes	Only 25% had PU/PD	No, unless on steroids	Yes
Vomiting/Diarrhea	Yes	Yes	Yes	Yes
Ascites/edema	No	Possibly	Possibly	No
Azotemia	Yes	Eventually	No	Possibly (pre-renal)
Kidney Size	Small	May be normal	Normal	Normal
Hypoalbuminemia	No	Yes	Yes	Possibly (melena)
Hypoglobulinemia	No	No	Yes	Possibly (melena)
Hypercholesterolemia	No	Yes	Hypocholesterolemia	No
Low Na/K ratio	Not noted	Rarely (-7 0%)	Rarely (-7 0%)	Yes
Urine Specific Gravity	Isostenuria	Mean 7.023	Mean 7.033	Low (medullary washout)
Proteinuria	None or mild	Yes	No	No
Histopathology (K=kidney; I=intestine)	Fetal glomeruli, fetal mesenchyme (K)	Glomerulonephritis, glomerulosclerosis (K)	IBD, lymphangiectasia, lymphangitis (I)	

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