Transitional Cell Carcinoma in Scottish Terriers

By Elizabeth Warfield, Warscot Scottish Terriers©

For the past 10 years, I have bred and shown Scottish Terriers. Being an active member of the breeder community, I have known many people who have lost Scotties to Transitional Cell Carcinoma (TCC) which is better known as bladder cancer. Over the years, TCC has become increasingly common in the breed. After researching the topic in depth, I was amazed by what I found. TCC is killing our beloved pets in record numbers. From 1975 to 1995 learning veterinary hospitals have recorded an increase of TCC by over 600 percent! In the past thirty years, something has changed and our Scotties seem to be at the front of the war against Transitional Cell Carcinoma. In fact they are 18 times more likely than other breeds to get TCC

Let’s start at the beginning, namely what is Transitional Cell Carcinoma? TCC is a specific type of cancer that involves the urinary bladder and will often grow to incorporate the ureters and kidneys; it is the most common cancer of the urinary bladder. TCC is a type of Neoplasia, that is a new and abnormal formation of tissue that serves no useful function, but grows at the expense of the healthy organism. TCC is a dangerous form of cancer because it readily metastasizes. According to Dr. Deborah Knapp approximately 37% of dogs diagnosed with TCC had metastasis at the time of diagnosis. Obviously this is a serious disease. The key for survival is early diagnosis and treatment.

Clinically TCC is difficult to treat because it is difficult to diagnose. TCC has symptoms that are often similar to a bladder infection. Dogs with TCC can have blood in their urine, urinate frequently, or struggle to urinate or seem painful during urination. It is also common for dogs with TCC to start limping in addition to the above symptoms, due to metastasis in surrounding bone. It is estimated that eventually 50% of dogs with TCC will metastasize especially to bone and lung tissue. Diagnosis of TCC can be tricky because many of the diagnostics are invasive and expensive.

To better understand this epidemic, Scottish terrier enthusiasts as a group have begun to seriously evaluate what has changed in the past thirty years. The latest research has proven a link between some commercial lawn treatment and Transitional Cell Carcinoma in Scottish Terriers. Another suggested link has been genetics. The Internet has made the world a much smaller place. As a breeder, the popular stud dogs are only an e-mail away. Even though more dogs are available today than in the past, the gene pool of the Scottish Terrier is still relatively small. Thus, attention has to be focused upon potential genetic linkages.

The simple fact that Scotties are 18 times more likely than other breeds to contract TCC highly suggests that there is a genetic link. A recent DNA study called Canine Hereditary Urothelial Malignancy Study or C.H.U.M.S. took blood samples and pedigree’s from Scottish Terriers from across the nation. After talking with Dr. Fredrick Leach, the primary researcher, he said that C.H.U.M.S. suggested that environmental factors are likely more prominent than we had previously though. This leads us back to the pesticides and their role in the TCC epidemic.
Scottish Terriers are "Earth Dogs." By virtue of their love for the earth (i.e. digging in the dirt, rolling in the dirt, eating the dirt, and any other naughty thing they can think of) our Scotties are exposed to any chemical that we treat our yards with. Last year a study was released from Perdue that indicates a strong link between herbicides and TCC. In the study people with TCC positive dogs and control dogs were given a survey about lawn treatments and the frequency of use. The study verifies that specific chemicals cause an increase in Transitional Cell Carcinoma in Scotties; More specifically 2,4 diclorphenoxyacetic acid and other "phenoxy" chemicals. Scottish Terriers who were exposed to phenoxy herbicides are 4.4 times more likely to get TCC than Scotties who were not exposed to phenoxy herbicides1. This information opens a “Pandora’s box” full of questions, such as why the bladder?

In previous studies 2,4D (2,4 diclorphenoxyacetic acid), a common ingredient in household herbicides, had been linked to canine malignant lymphoma in pet dogs1. According to the EPA, 2,4-D has not been labeled as a carcinogen due to insufficient evidence. 2,4-D is the most commonly used herbicide in nonagricultural sector.7 Annually about 40 million pounds of it is used in the US alone! It is a very good herbicide, because it selectively kills broad leaf weeds while leaving grasses unharmed, and is commonly in weed and feed type product.

An interesting piece of trivia, 2,4-D as well as it’s Geometric Isomer 2,4,5-T are the active ingredients in “Agent Orange.” The chemical 2,4,5-T is classified as a carcinogen in the United States and is not currently used, however the only difference between a carcinogenic chemical, and an EPA approved herbicide is 1 hydrogen atom. As shown in the image 2,4-D (on top) has a circled hydrogen atom, where as the carcinogen 2,4,5-T has a Chloride atom at the same place. These chemicals are shaped similarly as a hormone in plants called "Auxin." It is responsible for embryo development, leaf formation, orientation (i.e. the ability to find up), and the ability to shed dead leaves and flowers. On the cellular level 2,4-D is able to enter the cell via a protein on the outside of the cell that mistakes 2,4-D for the hormone Auxin. Once inside the plant cell the 2,4-D causes chaos. It inhibits the cells 'biological clock' which is responsible for programmed cell death as well as cellular division. 2,4-D also changes DNA as it’s translated in the cytoplasm, and changes the cells ability to regulate the passage of electrolytes into and out of the cell.

What makes 2,4-D deadly to some plants is that it is similar enough to the hormone Auxin to be actively transported into the cell, but is unable to pass out of the cell. As it accumulates in the cells, the plants dies. In animals, when 2,4-D is ingested, it is not able to be broken down into smaller compounds and exits the body with the same chemical composition as when it entered the body. 2,4-D is excreted from the kidneys in the form of urine. It is understandable how 2,4-D could enter the cells in the bladder of a dog when compared with how it enters a plant cell.

Another source of contact to pesticides is from flea and tick treatment. Most people don’t realize how nasty the "old generation" of flea treatments are. For example, pyrethrins are very toxic to fleas, which is why it is used for flea control. Pyrethrins are also highly toxic to cats, it cause neurological symptoms along with a high fever. The toxicity of this chemical is
widely known in the veterinary industry, yet it is still sold throughout the nation in the form of shampoos, dips, powers, collars, and sprays that are readily available at all pet stores. The active ingredients in question include organophosphates, pyrethrins, pyrethriods, and carbamates.

Current studies have proven a link between these chemicals and Transitional Cell Carcinoma. The study conducted at Purdue University compared the frequency of TCC to dogs exposed and not exposed to insecticides and herbicides. The table below is taken from Purdue’s presentation on TCC in Scotties.

### Table 1.

<table>
<thead>
<tr>
<th>Access to treated lawn or garden</th>
<th>TCC Cases</th>
<th>Controls</th>
<th>Odds Ratio</th>
<th>P-value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>-- Insecticides</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None or sporadic</td>
<td>47</td>
<td>56</td>
<td>2.30</td>
<td>0.03</td>
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<tr>
<td>Seasonal or year-round</td>
<td>29</td>
<td>15</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>-- Herbicides</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None or sporadic</td>
<td>37</td>
<td>57</td>
<td>1.00</td>
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</tr>
<tr>
<td>Seasonal or year-round</td>
<td>39</td>
<td>14</td>
<td>4.29</td>
<td>0.0001</td>
<td></td>
</tr>
</tbody>
</table>

As shown, Scotties who were exposed to insecticides or herbicides were more likely to contract TCC than those who were not exposed. These chemicals are different from 2,4-D in that they become fat soluble because they are typically mixed with up to 96% petroleum products, this may be a reason that overweight and obese dogs are more prone to TCC than animals in good body condition. The above-mentioned pesticides are mixed in a lipid (fat based) solution, and when applied on the dog, it will be readily stored in fat cells.

**Dr. Knapp**

The more excess fat a dog has, the greater the caring capacity for these toxins. The new generations of topical flea treatments have been showed to be safer to dogs and humans and have not been associated with an increased risk in Transitional Cell Carcinoma.

**Diagnosing TCC**

Now that we have a better understanding of what Transitional Cell Carcinoma and what some possible causes are, what do you do if you think your dog has TCC? The experts all seem to agree that in older Scottish Terriers any cystitis or urinary trouble is Transitional Cell Carcinoma until proven otherwise! The challenge is getting to the diagnosis. The most common place to start is a Urinalysis; this is when the urine is tested for its chemical composition and the cellular content, if cells are present, they are evaluated under a microscope. Some components that are commonly observed suspended in urine are cells like red blood cells, white blood cells, and the cells that line the urethra and bladder called epithelial cells. On microscopic evaluation it is possible to see abnormal transitional cells. This is a strong indicator of TCC. The problem with diagnosing TCC with urinalysis is that only about 30% of animals with TCC shed cancerous transitional cells.

A new development in TCC diagnosing is a urine dipstick that tests for tumor antigens in the urine. The problem with this test is that the dipstick gave a large number of false positive results (rumored up to 78% specificity.) Commonly occurring chemical changes in urine
such as glucose (in diabetics), protein, or blood can alter the accuracy of the results. The dipstick test is relatively new and not widely used in clinics in this area.

Another diagnostic that is frequently used in dogs that are suspected to have a urinary disorder is Double Contrast Cystograph. That is when a radiopaque liquid (substance that reflects X-Rays and appears white on the radiograph) and air are injected into the bladder via a urethra catheter. The radiopaque liquid lines the wall of the bladder and the air forms a bubble in the middle of the bladder. This technique helps to show any masses in the bladder. The downside of this technique is that once a mass is confirmed, the radiograph does not give an indication of what type of cell is causing the mass. Therefore even after a positive double contrast radiograph, a biopsy or cytological evaluation may be warranted.

The experts all seem to agree that ultrasound is called for in Scotties with urinary disorder. In a recent interview Dr. Bob Kramer said

“I don’t think it’s ‘crying wolf’ to go straight to (an abdominal) ultrasound... Even if TCC isn’t found, we can still catch some Cushing’s Disease, early renal, and early hepatic disorders... If TCC is found we are able to check the abdominal lymph nodes and check for metastasis.”

Abdominal Ultrasound can confirm a mass in the bladder and it can also give information as to whether or not the tumor is excisable and the ultrasound can also facility fine needle aspirates via ultrasound guidance. More invasive and expensive options include surgical exploration, and laparoscopic exploration. But these methods are only useful if there is no metastasis and if the cancer is in a place where it can be removed.

According to Dr. Deborah Knapp:

“A diagnosis of TCC requires a tissue biopsy”, expert and key researcher on transitional cell carcinoma in Scotties. No matter what venue an owner chooses the biopsy gives the diagnosis.”

If your dog has TCC, treatment options are limited. Surgical removal is the best treatment if the tumor is removable. According to Dr. Rischen, up to half of the bladder can be removed safely as long as the important structures are left intact (i.e. the ureters and the bladder sphincter). Surgery is not an option if the cancer affects the opening of the bladder. The other treatment options are medical. Radiation is available, but has not been proven to have an enormous amount of success.

Chemotherapy alone is an option, although not as effective as other methods. Cisplatin, a commonly used chemotherapy drug was found to have marginal results. In a 1990 study of 15 dogs, no dogs had a complete remission and only two had a “partial remission,” (tumor size decreasing by less than 50%). The drug’s efficacy was found to produce a median survival of about 114 days.

**Peroxicam Is Common Treatment**

The most common treatment involves the use of Peroxicam, an older Non-Steroidal Anti-Inflammatory Drug (or NSAID). Peroziam was accidentally found to anticancer results in some dogs. Peroxicam inhibits a specific enzyme called cyclooxygenase-2 or COX-2. COX-2 in the body is responsible for making prostaglandins and is specifically found at the site of inflammation within the body. Drugs like Peroxicam, and other NSAID’s inhibit cyclooxygenase-2 enzymes and decrease inflammation and provide pain relief. However
recently COX-2 has been identified as a substance that promotes epithelial oncogenesis (tumor grow.) Therefore, if COX-2 related drugs promotes tumor formation, then COX-2 inhibitors should be able to stabilize if not reduce tumor size. Because it is an anti-inflammatory, it reduces swelling or tumor size.

Dr. Knapp published a study on Peroxicam and found that it had better results than chemotherapy alone. In a study involving 34 dogs treated with TCC, two dogs had complete remission; 4 dogs had a partial remission; and 18 dogs were stabilized (no tumor growth). The median survival rate was 181 days with Peroxicam. The most notable aspect of Peroxicam was that it was generally well tolerated and many owners reported an increase in activity and improved alertness. Unfortunately chemotherapy and Peroxicam, when used together have been shown to have toxic effect on the kidneys. The good news, however is that the new generation of NSAID’s are much gentler on the kidneys and are currently under investigation by Purdue. According to Dr. Deborah Knapp it could be another year or two before the studies are concluded but the results are looking hopeful!

According to Vandra Huber who used the drug to treat bladder cancer in McVan’s Proud Mary of Jovial, the drug seemed to work. An ultrasound diagnosed Tina as having TCC in the horn of the bladder. Because of the location, surgery was not an option. Peroxicam was utilized to prolong Tina’s life. While Tina seemed to have more energy on the drug. She also did not seem to strain as much as before she was treated. “Owners should be prepared to deal with a lack of control in urination when the drug is administered. Because the tumor is shrinking, urine flows more freely. But because the cancer involves the bladder, dogs tend to lose control of their bladder,” she explained. “But what’s an additional clean up job if it means the dog is more comfortable and lives longer.”

**Vegetables Help Prevent TCC**

Recent research suggests that the likelihood of TCC can be reduced significantly by adding leafy vegetables to the diets of Scottish terriers. In a recent case-control study compared 92 older Scottish terriers with TCC and a comparable group of 83 nonaffected. Owners completed a lengthy questionnaire about the food and nutrition of their Scotties. Ninety-five percent of the dogs in both groups consumed dry commercial dog food. However, after adjustment for age, weight, neuter status, and coat color, consumption of vegetables at least 3 times/wk was associated with a 70% reduction in TCC. Carrots were fed most often. However, when green leafy vegetables were added, the odds of contracting TCC decreased even further. Extrapolating from research on human, the researchers believed that the presence of carotenoids and retinol in green and yellow vegetables provided a protective effect against the development of bladder cancer.

In conclusion, research suggests that no one factor is primarily responsible for Transitional Cell Carcinoma in Scotties. It is our moral obligation as breeders to be vigilant with our stock and be transparent about the prevalence of bladder or other forms on cancer that affects our lines and our Scottish Terriers. The best way to ensure that this occurs is to keep a record of all dogs that are affected and to be transparent. With a more open line of communication breeders can together identify lines that have had little instance of TCC and incorporate them into breeding programs.

A relative new service can help us do this job. The VetCancer Registry collects data about cancer in dogs and cats. It only includes cases diagnosed by histopathology. The data are basic, but are in a format that allows anyone to easily manipulate the data to discover
trends in animal cancer. According to the VetCancer website, by pooling data from multiple sources and multiple practitioners and researchers, trends can be spotted. To have a Scottie included in the database, a veterinarian must submit the case. The case is held as pending and enter it into the database as soon as VetCancer receives a necropsy, biopsy, or cytology report confirming the diagnosis. If the animal is alive when the data is submitted, VetCancer requests regular updates. Learning about the progression of cancer is as important as diagnosing and finding genetic linkages.

As pet owners individuals also need to be aware of environmental hazards that affect the long and short term health of our Scottish Terriers. We also can add vegetables to the diets of our dogs. And lastly as friends of the breed and pet owners we need to be an advocate for our animals. If you think your pet has TCC or if your Scottie has urinary problems yell and scream until someone listens. Get an ultrasound, and if needed get second opinions.

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