Hyaluronosis, Shar-Pei Autoinflammatory Disease (SPAID),

Familial Shar-Pei Fever and Amyloidosis

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Hereditary Cutaneous Hyaluronosis (HCH): Shar-Pei over-express Hyaluronic Acid Synthase 2 (HAS2). Excess hyaluronan (HA) leads to their unique skin thickening and wrinkles because of a regulatory mutation. The mutation is a duplication that occurs in multiple copies. Individual Shar-Pei dogs will have two copies of the gene, one from each parent. The mutation may occur as a single or 5-copy gene. The mutation is a copy number variant or "CNV". Thus Shar-Pei dogs may be either CNV = 2, CNV = 6, or CNV = 10. A droplet digital PCR (ddPCR) test for their CNV will be available sometime in 2016 to aid breeders in selecting dogs lower in CNV and avoid breeding 10s to 10s. An announcement with details of where to send samples will be made when agreements with the laboratories in the U.S. and at SLU in Sweden have been finalized.

Excess hyaluronan (the main component of "mucin") may form vesicles or bubbles in the fragile skin. Hyaluronan health is integral to Shar-Pei health. Damaged or degraded low molecular weight hyaluronan is a "damage associated molecular pattern" (DAMP), a danger signal that can activate the innate immune system. Native high molecular weight HA is health promoting and healing. You may improve Shar-Pei health by preventing or offsetting damage to their abundant HA.

Familial Shar-Pei Fever (FSF) is a periodic fever syndrome that is characterized by random inflammatory events with high fever, sometimes with swelling about joint/s or muzzle, that usually last 12-36 hrs. FSF is an **autoinflammatory** syndrome (not autoimmune).

Their underlying genetic defect is an unstable duplication in a regulatory gene upstream of Hyaluronan Synthase 2 (HAS2) that is described as the "meatmouth" mutation in our March 2011 article published in PLoS Genetics. Original, traditional-type Shar-Pei with less padded muzzles, less skin thickening and wrinkling have a slightly different mutation ("traditional") in this same location. The "meathmouth" mutation with a CNV of 5 predisposes affected Shar-Pei (and some Shar-Pei mixed breeds) to inappropriate inflammatory responses. All Shar-Pei carry at least two copies of the mutated regulatory element. **Shar-Pei may have abnormal initiation and also amplification of inflammation as a result of this genetic** copy number variant (CNV) **mutation. This may result in chronic elevations of inflammatory chemical messengers in the bloodstream.** They may over-react to infection and damage. The greater the number of copies of the mutation present in the dog, the more reactive inflammation may result when HAS2 is up-regulated. Increased number of mutated copies (higher CNV of 6 or 10) has been shown to be associated with increased risk for FSF and amyloidosis. Hyaluronan is endogenously degraded and turned over rapidly: in hours, days, or weeks depending on its location in the body. The breakdown of their excessive HA into fragments for routine elimination may also contribute to autoinflammation.

A copy number variation (CNV) occurs when the number of copies of a particular gene varies from one individual to the next. A gene is the functional unit of inheritance on a DNA sequence.

Low molecular weight fragments of hyaluronan both activate and prime the inflammasome leading to the release of IL-1beta and then IL-6, two major drivers of fever and inflammation. Mutations leading to aberrant inflammasome function have been associated with the human autoinflammatory syndromes Familial Mediterranean Fever (FMF), TRAPS, CAPS and gout.

Shar-Pei with Familial Shar-Pei Fever (FSF) may :

- Have one or more bouts of unexplained fever, usually 103-107 degrees F (39.4-41.7 degrees C) but rare cases may go higher. Fever greater than 106 degrees is a medical emergency and owners should seek veterinary treatment for the hyperthermia.

- Without fever, it is NOT “classic” FSF. (Assuming not on colchicine & supplements).
- Fevers usually start before they are 18 months old but adult-onset attacks are not uncommon. Fever episodes usually become less frequent with age. Fevers may occur before 6 weeks of age.
- Fever episodes last 24-36 hours in most cases without treatment. It is possible for the fever events to be brief, lasting only a few hours.

One or more of the following signs may accompany fever episodes:

- Swelling around a joint with or without inflammation of the joint itself. One or more joints may be affected but most cases involve the tibiotarsal or hock joint (**swollen hock** syndrome). Of the dogs that had experienced periodic fever episodes, approximately 53% had experienced swollen hock/s at some time along with the fever when owners at the CSPCA National Specialty were surveyed in 1994. Be careful not to mistake the normal “socks” (excess wrinkling around the hocks) on some individual Shar-Pei for the acute swelling that occurs surrounding the hock during or around the time of a fever episode.
- Sometimes a swollen painful muzzle.
- Abdominal pain, reluctance to move, “roached” back, mild vomiting or diarrhea, shallow rapid breathing. The pro-inflammatory cascade may give these dogs flu-like symptoms and similar discomfort (without respiratory signs unless pneumonia is a component).
- CBC blood test will usually show neutrophilia (although neutropenia may occur early in the course), and often monocytosis due to activation of neutrophil and monocyte chemotaxis. Shar-Pei with FSF may have elevated alkaline phosphatase, hypercholesterolemia, hypomagnesemia, hyperglobulinemia and slight elevations in total bilirubin on blood chemistry panel. Thrombocytosis is common on routine blood work and platelet activation may be significantly involved in the inflammatory cascade.

Amyloidosis is a disease caused by abnormal deposition of the breakdown products of chronic inflammation in the extracellular matrix (between cells). The severity of disease and risk for amyloidosis will vary with the amount of inflammation initiated and the autoinflammatory over-reaction. The chronic background inflammation puts affected dogs at risk for developing reactive systemic amyloidosis which can lead to early death from kidney failure.

Not every dog with FSF will develop amyloidosis but the fevers are a warning sign that they have Shar-Pei Autoinflammatory Disease (SPAID) and are at higher risk for kidney disease. Shar-Pei Fever and Amyloidosis are two faces of the over-arching disorder SPAID. They are not one and the same. **Shar-Pei with FSF can live to over 10 yrs of age**. Two of my mother’s Shar-Pei lived to 12 ½ and 15 ½ years respectively with lifelong FSF and this is not uncommon in my patients. By doing everything you can to reduce their chronic inflammation and monitor their disease, you can help them live their best possible lives - however long that may be. Unfortunately, a combination of genetic predisposition (increased CNV) and environmental influences may lead to early death from kidney or, more rarely, liver failure due to amyloidosis in some individuals.

T**he diagnosis of Shar-Pei Fever is made after ruling out other causes of fever** with diagnostic tests indicated by the dog’s condition but a minimum baseline of first morning urinalysis, CBC, chemistry profile, T4, +/- panel for tick-borne diseases is common. Other tests, including those for autoimmune disorders, may be needed. It is a diagnosis by exclusion at this time. A genetic test for the CNV will be available later in 2016 but only explains 25% of disease risk. This is because this is a disorder due to an abnormal sentinel barrier of innate immunity. Environmental insults and triggers that impact this abnormal barrier determine if, how and where the signs may occur.

Because fever events are a marker for the presence of autoinflammatory disease, **therapy should be started early to prevent complications.** Some dogs have only one observed fever

event yet die prematurely from amyloidosis – the number and frequency of fever events does not correlate with the severity of underlying chronic inflammation. In rare instances, dogs may die of amyloidosis without any observed fever events or may have their first fever after going into kidney failure.

My current treatment recommendations for Shar-Pei Fever include 0.025-0.03 mg/kg of **colchicine** twice daily or less to bowel tolerance. I recommend that the dog be started on a low dose once daily and then gradually increased to the maximum recommended amount (up to the calculated dose above) as tolerated without diarrhea once or twice daily. For most average weight Shar-Pei, this is one 0.6 mg tablet given twice daily. Colchicine is a potent drug but it accumulates in white blood cells (the desired target for treatment) and GI signs occur long before other serious side-effects.

I have never seen evidence of any damage from colchicine except for a transient, treatable diarrhea that goes away when the drug is withdrawn in sensitive patients. Colchicine treats the underlying pathology by blocking the movement of neutrophils (one of the white blood cells), decreasing levels of cytokines (the messengers of inflammation), interfering with mast cell degranulation and blocking the formation of amyloid protein (a waste by-product of inflammation). In humans, it has proven to be safe in infants, pregnant women and when given lifelong. Treatment is for life. I have been using the drug since 1993 and have had individual patients on the drug safely for over 10 yrs. Some dogs cannot tolerate colchicine without chronic diarrhea and they are given smaller amounts or none if it is severe. Colchicine and cyclosporine (Atopica®) should not be given together because of increased risk of bone marrow suppression.

Currently, **sale of colchicine has been restricted in the U.S.A. by the FDA to one manufacturer,** Takeda purchased URL Pharma, and manufactures colchicine under the brand name "Colcrys®". Takeda has continued a **Canine Assistance Program for Shar-Pei**. There is an application for the program (income adjusted fee structure) in PDF format that may be downloaded here. Applicants must provide a valid Colcrys prescription from a licensed veterinarian, and must attest that Colcrys will be used solely for their Shar-Pei dog. Applicants who qualify for the program will be able to select a 30-day supply (60 tablets), 60-day supply (120 tablets) or 90-day supply (180 tablets) of Colcrys. Those receiving financial assistance must re-apply for the program annually. The prescribing veterinarian must complete and sign several portions of the application. Colchicine may also be prescribed and purchased legally through compounding pharmacists in tablets or flavored suspension and is available as a generic prescription drug in Canada and other countries.

I treat the fever events with 50% **dipyrone** (500mg/ml) injectable (usually 0.5-1.0 ml/dog under the skin), or meloxicam (**Metacam**®), a non-steroidal anti-inflammatory drug or NSAID (by weight per package insert instructions). Injectable dipyrone is an IL-1 beta inhibitor that is available from compounding pharmacists or may be purchased over-the-counter in many non-U.S. countries. **Aspirin** has also been reported to be effective. Some fevers are very serious and **can require emergency veterinary treatment if they approach or exceed 106 degrees F (41° C).** Shar-Pei owners should discuss treatment of acute fever events with their veterinarian because treating the fever as early as possible in the inflammatory cascade can often stop it from becoming life-threatening and it is best to have medication available on-hand at home. Avoid giving NSAIDs with corticosteroids like prednisone and your veterinarian should be alerted your dog is vomiting because gastric ulcers can be a common complication.

Use caution with ice packs or baths: external cooling efforts should be reserved only for those dogs with fevers approaching 106 degrees while en route to a veterinarian. Unless the dog's internal thermostat is reset with medication, the dog's body will simply work harder to keep the fever up and may prolong the fever event. An ice pack wrapped in a damp towel that is placed in the groin area will help cool the patient en route to emergency care.

Some fever events may be initiated by **infection**. If the fever is severe, persistent and/or poorly responsive to anti-fever drugs like dipyrone, aspirin or NSAIDs, there may be an underlying infection that needs treatment. Veterinary care should be sought whenever the fever is severe, worse than usual for that dog, lasts longer than 48 hrs or is not responding to anti-inflammatory

medication. In rare instances, a neutrophilic vasculitis and/or septic shock-like syndrome (STSS) with extensive pustules and necrotic skin sloughing can occur. The latter is often associated with bacterial hyaluronidases that break down the abundant mucin in Shar-Pei skin. This can be life-threatening and even fatal. The appearance of these signs necessitates rapid, aggressive veterinary intervention.

Your Shar-Pei should get **regular and routine monitoring of first morning urine with urinalysis (UA) as well as a CBC, blood chemistry profile and TT4**. Urine Specific Gravity at or below 1.020 is often the first sign of Shar-Pei kidney trouble and, if present, the UA should be repeated to see if the dog has a consistently low specific gravity. Medullary amyloidosis is the most common kidney disorder in Shar-Pei and proteinuria is usually a late-stage event. Idexx Laboratories now offers an early renal disease detection test, SDMA (symmetrical dimethylarginine), that is very useful in Shar-Pei at-risk for amyloidosis and is offered as part of their general blood chemistry profile. Urine protein levels should also be monitored and a urine protein to creatinine ratio performed if proteinuria is found on routine UA. SPAID patients should be examined and tests performed whenever they are not eating normally, if they are vomiting, having diarrhea for more than a few days, acting sick in any way or if they are just "not right". The bare minimum is annually in the healthy active young dog and many dogs should be checked more often.

In addition, Shar-Pei are prone to **mast cell disease** including mast cell tumors. The binding of HA to its receptor CD44 has been shown to play a critical role in regulation of murine cutaneous and connective tissue mast cell proliferation. It appears that CD44-HA regulates resident cutaneous mast cell populations. As the CD44-HA interaction may modulate local immune responses through regulation of mast cell functions, excessive HA and its subsequent damage and degradation may also play a role in the breed's predilection for allergic skin disease and other mast cell driven inflammation.

Corticosteroids (for example medications like prednisone or dexamethasone) or cortisol produced by the dog's body during stress (this may happen during a high fever or when ill) can shut down the production of hyaluronan by HAS2. These **steroids may shrink a Shar-Pei's muzzle** and they may lose wrinkles. Very low dose prednisone is sometimes used for this reason to treat severe vesicular cutaneous hyaluronosis (bubbles of mucin in skin) or lymphedema of the hocks (chronic swelling due to fluid buildup). A Shar-Pei that has a suddenly shrunken muzzle for no apparent reason should get a full physical examination by a veterinarian and laboratory testing.

Addressing Hyaluronosis (the downside to Shar-Pei Wrinkles).

Shar-Pei have a mutation that causes them over-produce hyaluronan and they may have as much as 10 times the amount of hyaluronan as a non-Shar-Pei. It is important to keep this vital normal substance as healthy as possible in this breed. Hyaluronan is the sculpting material that supports and cushions cells, shouts "Danger" when it is injured, and assists in wound healing. Hyaluronan health is central to a healthy body. Damaged, fragmented hyaluronan promotes inflammation.

Here are Twelve Points to consider when trying to optimize the health of your Shar-Pei.

Not all of these points need to be implemented but they should be considered to see if they are appropriate for your dog's best health. Discuss your plan with your veterinarian so that you can work as a team to keep your Shar-Pei in top condition.

1. Feed a High Quality diet. There is no one single diet that is best for all Shar-Pei. They may develop individual food intolerances because of their inflamed bowel and this varies greatly from dog to dog as to what is the offending food and may change over their lifetime. Some Shar-Pei do great on commercial soy-based diets, others on nutritionally balanced raw, others on premium brand venison and sweet potato. My own dogs are on a prescription

veterinary formula kibble for dogs with intestinal problems because they flourish on that nourishment and their bowel health is more consistently normal. This wide variation in what is ideal for each individual makes it difficult for owners to know what is best for their dog. I know that over-feeding cheap, grain based, over-processed junk food is a formula for making dogs (and people) unhealthy. Dogs benefit from the breakdown products of cartilage, bone and organ meat (sources of minerals, glucosamine, chondroitin sulfate, hyaluronan and vitamins). The "select cuts" of chicken breast and other muscle meats fail to provide necessary nutrients. Preparing well-balanced, nutritionally complete home-cooked meals requires advanced knowledge of dietary requirements and is highly time-consuming. If you do purchase dry kibble dog food, try to avoid purchasing more than a 2-6 week supply (depending on quality of your storage environment) to avoid the over-growth of mold, grain mites and rancidity of unsaturated fatty acids, all of which can contribute to inflammatory issues.

Some Shar-Pei with severe inflammation may need a diet low in simple carbohydrates: grain-free or containing small amounts of whole healthy fresh grains if possible. A pasture-fed meat source is preferable if money is no object (grain-fed, factory-farmed meat has a high ratio of omega-6 to omega-3 fats and is lower in antioxidants and conjugated linoleic acid). An important goal is to shift the arachidonic acid pathway away from pro-inflammatory end-products. A high dietary omega-3 to omega-6 fatty acid ratio may help reduce inflammation and result in improved overall health.

Hyperglycemia also contributes to up-regulation of hyaluronan so avoid over-feeding at any one meal to avoid blood sugar surges.

2. **High dose omega-3 fatty acids from fish oil daily.** Again, the goal is to shift to anti-inflammatory end-products but also for fish oil's resolvins and other inflammation-resolving mechanisms at high doses. A high dietary omega-3 to omega-6 polyunsaturated fatty acid ratio may help reduce inflammation and result in improved overall health including decreased anxiety. The omega-3 fatty acids, EPA & DHA, appear to decrease the production of pro-inflammatory eicosanoids, derived from arachidonic acid, as well as the cytokines IL-1β, IL-2, IL-6, interferon gamma and TNF-α. By reducing the production of these pro-inflammatory chemical messengers, omega-3 fatty acids also alter the stress response by the hypothalamic-pituitary-adrenal axis. Purchase a high quality product that is batch-tested for rancidity, heavy metals and toxins like PCBs. Rancid fish oil is much worse than no fish oil at all!

Suggested amount for approximate 20 kg (44 lb) Shar-Pei is 800mg EPA & 400mg DHA per day with food. Store in freezer or refrigerator.

3. **Lecithin:** 1-2 Tbl of granules (7.5 – 15 gms) per day in food to alter the phosphatidylcholine composition of the "hyaluronasome" in plasma membrane lipid rafts; this may impact how HA fragments are internalized for further degradation.

4. **HyVitality® or equivalent:** HyVitality is a formulation of my recommended vitamins, minerals, antioxidants and phytochemicals that were chosen for their hyaluronan (HA) health promoting effects. Reactive oxidative species (ROS) fragment native high molecular weight hyaluronan and the effects of ROS may be counter-acted by antioxidant therapy. Magnesium is integral to stabilizing HA in its high molecular form and magnesium deficiency is a common finding in the breed. Severe cobalamin (Vitamin B12) deficiency is also seen in Shar-Pei. I selected combinations of antioxidants, minerals, vitamins and plant-based supplements in HyVitality products to help maintain native undamaged high molecular weight, healthy hyaluronan. HyVitality supplies these key factors in amounts appropriate for dogs rather than giving over-the-counter products designed for humans. Working with a trusted manufacturer has allowed me to be assured of purity and quality: Made in U.S.A. in a certified GMP facility. *(Average Shar-Pei dose contains 50-80mg alpha lipoic acid, 60mg Coenzyme Q10, 80-160mg magnesium from dimagnesium malate), 1000 mcg methylcobalamin, 25mcg Vitamin K2 and a proprietary blend of Boswellia Serrata, Curcumin, Diosvein™ micronized diosmin & Trans-Resveratrol).* HyVitality is dosed by weight. More information at www.HyVitality.com.

Other additional health supplements that may help dogs with recurrent, refractory inflammatory episodes include 250 mg rutin/day, 500 mg bromelain/day, 250-500 mg MSM/day for most average-size adult Shar-Pei. I suggest that you try these separately for several weeks to see if they help.

Health supplements will often take 4-12 weeks of administration before improvement may be noted.

5. Vitamin C, 250mg. Shar-Pei with excess HA may need more antioxidants like Vitamin C. Also, I suspect that Shar-Pei may not synthesize adequate Vitamin C because Vitamin C and HA compete for similar biochemical synthetic pathways (both are formed by glucuronidation).

6. Ensure Adequate Vitamin D3. Active Vitamin D modulates the over-active toll like receptors (TLRs) in inflammatory disease, returning them to a more normal functionality. Hyaluronan fragments bind to TLRs to activate the pro-inflammatory cascade. Activation of the Vitamin D receptor inhibits maturation and causes death of mast cell precursors and can help inhibit allergic inflammatory responses.

A study out of Tufts' University showed that as many as 75% of dogs were insufficient or deficient in Vitamin D. Dogs on home-cooked diets had the lowest value and had the widest variation in their individual levels but dogs on commercial dog food were also very likely to have insufficient Vitamin D levels.

Supplementation may be needed if a dog is on a home-cooked diet without added dietary sources of Vitamin D, or who has severe allergies, arthritis or chronic inflammation.

Dog do not convert cholesterol into Vitamin D in the skin with sun exposure the way people do and require dietary sources. These include liver, other organ meats, fat from pastured ruminants, salmon oil, and cod liver oil.

Discuss baseline testing with your veterinarian if you are concerned that your dog may need supplementation. Maintenance need for Vitamin D3 in dogs has been estimated to be 50-475 IU per 10 lbs of body weight per day but more will be required to restore dogs insufficient or deficient to sufficient levels.

Vitamin D supplementation is best given in the morning with a fatty meal (along with some fatty meat or fish, cheese, butter or coconut oil, not a piece of bread or some plain kibble).

HyVitality contains Vitamin K2 and magnesium, necessary co-factors for proper Vitamin D3 absorption.

Excessive Vitamin D can lead to toxicity but is very uncommon unless due to rodenticide poisoning and massive overdose. Nevertheless, caution is advised when supplementing with Vitamin D.

7. Glucosamine and Chondroitin Sulfate: Hyaluronan is formed by glucuronidation of repeating units of N-acetyl-glucosamine so glucosamine is a vital ingredient in forming HA. Two recent studies have suggested that increasing the amount of intracellular UDP-N-acetylglucosamine by adding glucosamine: 1) increases the molecular weight of the hyaluronan produced (this is a very good thing) and 2) down-regulated HAS2 (hyaluronan synthase 2, the enzyme over-expressed in Shar-Pei), so less hyaluronan was made. Glucosamine also suppresses the activation of mast cells (important in many Shar-Pei disease processes). Chondroitin sulfate may interfere with the binding of low molecular weight HA to its major receptor CD44.

8. Thyroid Function: Treat any signs of tertiary hypothyroidism with thyroid supplementation.

Low molecular weight fragments of hyaluronan, produced in the normal dynamic process of recycling hyaluronan, may give the brain a false signal that there is damage within the dog's body

and that thyroid hormone production should be decreased to save the body's metabolic resources for healing and recuperation. Unfortunately in Shar-Pei, this can be situation normal due to their excess hyaluronan and yet it results in signs of clinical hypothyroidism Common signs include very sparse or missing coat, particularly along the back and inside of the thighs and hindquarters, with a generally brittle, lighter coat on the torso.
HA fragments may down-regulate TSH releasing hormone via TLR2 binding, leading to tertiary hypothyroidism characterized by low or low normal TSH and very low to low normal T3/T4 and I am looking at this in Shar-Pei now.
Response to therapy will be softer, thicker, and richer colored fur with hair re-growth, especially on hindquarters, and improved overall health and activity if the dog is functionally hypothyroid. Your veterinarian will monitor therapy as adjustments up/down are often needed to individualize therapy.
Primary hypothyroidism is often associated with myxedema, a form of hyaluronosis, and the conditions are entwined in ways that have yet to be fully described.

9. **Probiotics and attention to bowel health.** Skin and bowel are the immune system's biggest barriers and they are both HA rich areas. Inflammatory bowel diseases (IBD) including colitis are very common in the breed. Some flare-ups of Shar-Pei Fever and increased frequency of fever events have improved with treatment directed to eliminating over-growth of pathogenic GI bacteria in patients with IBD or stress-induced colitis. Endotoxin produced by gram negative gastrointestinal tract bacteria may trigger recurrent fever episodes and may lead to simultaneous occurrence ("outbreak") of fever episodes in multiple dogs within the same household in dogs that may share similar fecal microbiome. *(If diarrhea is frequent or persistent, discuss diagnosis and possible treatment with prescription drugs, e.g. tylosin, with your veterinarian.)*

10. **Fanatical attention to skin and ear issues.** Bathing by shampoo or washcloth wipe-downs as needed (microfiber dust cloths work well) - up to daily when skin is inflamed and at least every 2 weeks in a "healthy" Shar-Pei. Remove superficial yeast, bacteria (potential sources of hyaluronidases, enzymes that damage HA) and allergens like pollens, molds, and dust that may activate mast cells. At least weekly ear cleaning/flush unless the Shar-Pei has a large, open, healthy ear canal. It is important to keep the very commonly narrow vertical ear canal open and clean of wax and debris. The Zymox® product line has been very helpful in maintaining skin and ear health in many Shar-Pei as a first line of defense against opportunistic invaders. Ensure the top of the ear canal is open so that cleansing products can get down where they need to work (Zymox' instructions state that cleaning is not needed but most Shar-Pei need gentle scooping removal of some external debris at the very top of the vertical ear canal and outer folds. Always be very careful not to drive debris deeper into the ear canal as this may lead to impaction and serious problems.)

11. **Very low dose aspirin: only ¼ - ½ of an 81 tablet per day** in dogs with no signs of gastric upset. Platelet derived growth factor might be an important mediator in their disease and aspirin also decreases risk of thromboembolic events. Be cautious as the breed has an increased risk for GI ulceration.

12. **Detect problems early:** Your veterinarian should see your Shar-Pei regularly for a complete physical examination and regular, routine monitoring of first morning urine with urinalysis (UA) as well as a CBC, blood chemistry profile and TT4. Idexx Laboratories now offers an early renal disease detection test, SDMA (symmetrical dimethylarginine), that may be useful in Shar-Pei at-risk for amyloidosis and is offered as part of their general blood chemistry profile. Discuss frequency of visits and testing with your veterinarian but at least annually in healthy Shar-Pei and more frequently in dogs with known problems or at-risk factors is recommended.

Eliminating inflammatory triggers, supporting healthy hyaluronan, reducing silent chronic inflammation wherever possible, providing good nourishment and playful daily exercise are key to Shar-Pei health.

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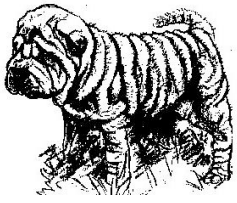

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