A HERITABLE CONNECTIVE TISSUE DISEASE OF DOGS AND MINK RESEMBLING EHLERS-DANLOS SYNDROME OF MAN

I. SKIN TENSILE STRENGTH PROPERTIES*

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ABSTRACT

Clinical changes observed in a heritable connective tissue disease of dogs and mink include fragility, hyperextensibility, and laxity of the skin. Skin fragility is the most severe and consistent change noted in the affected dogs and mink. Tensile strength of the skin was reduced to one-twenty-seventh that of normal in affected dogs and one-thirteenth that of normal in affected mink. The syndrome in dogs and mink is proposed as a homolog of the Ehlers-Danlos syndrome of man, a rare heritable connective tissue disease, which is clinically characterized by skin fragility, skin and joint hyperextensibility, and skin laxity.

The Ehlers-Danlos syndrome (ED-S) of man, a rare heritable connective tissue disease, is recognized primarily on the basis of characteristic clinical changes and its inheritance pattern. A triad of cardinal clinical signs associated with the human syndrome includes fragility of the skin and peripheral blood vessels, laxity of the skin, and hyperextensibility of the skin and joints (1–5). Less frequently observed changes include formation of mollusk-like skin tumors (2), movable subcutaneous spherules (5), and numerous other mesenchymal defects (3, 4). Although forme-fruste cases have been reported (3), some authors consider that fragility of the skin is the most consistent clinical criterion and must be present in authentic cases (4, 6, 7). The ED-S of man is inherited as an autosomal dominant trait (5, 8).

A condition in dogs and mink resembling the ED-S of man has been reported (9–12). Skin fragility, laxity, and hyperextensibility are the primary clinical changes noted in affected animals, especially dogs, and these heal resulting in broad, thin scars (Figure 1). The

syndrome in dogs and mink has an autosomal dominant mode of inheritance (11).

The purpose of this report is to present results of skin tensile strength studies performed on ED-S dogs and mink and to compare them with those described for the ED-S of man.

MATERIALS AND METHODS

Affected and nonaffected dogs and mink studied were from colonies of animals maintained at Washington State University. Tensile strength studies were performed on the skin of 6 dogs; 2 affected and 1 nonaffected 16-month-old littermates and 2 affected and 1 nonaffected 13-month-old littermates. The dogs were euthanatized by the intravenous administration of sodium pentobarbital. The skin was removed in one piece and the subcutaneous fat and muscle were removed from the skin as close as possible to the dermis. Twenty full-thickness skin samples were taken from predesignated sites on the skin of each dog. Seven samples each were removed from the right and left sides beginning at the level of the first cervical vertebrae and extending posterior to the level of the third sacral vertebrae; 2 samples were removed perpendicular to the midline on the right and left shoulder; 2 samples were removed perpendicular to the midline from the right and left thighs; and 2 samples were removed parallel to the midline at the level of the first cervical vertebrae and the third sacral vertebrae. Samples were stamped out in a uniform size using a tooled steel dumbbell-shaped die. The die measured 0.6 cm. in width at the midpoint and 5 cm. in length. After removal, the samples were immediately placed in petri dishes on absorbent paper moistened with phys-
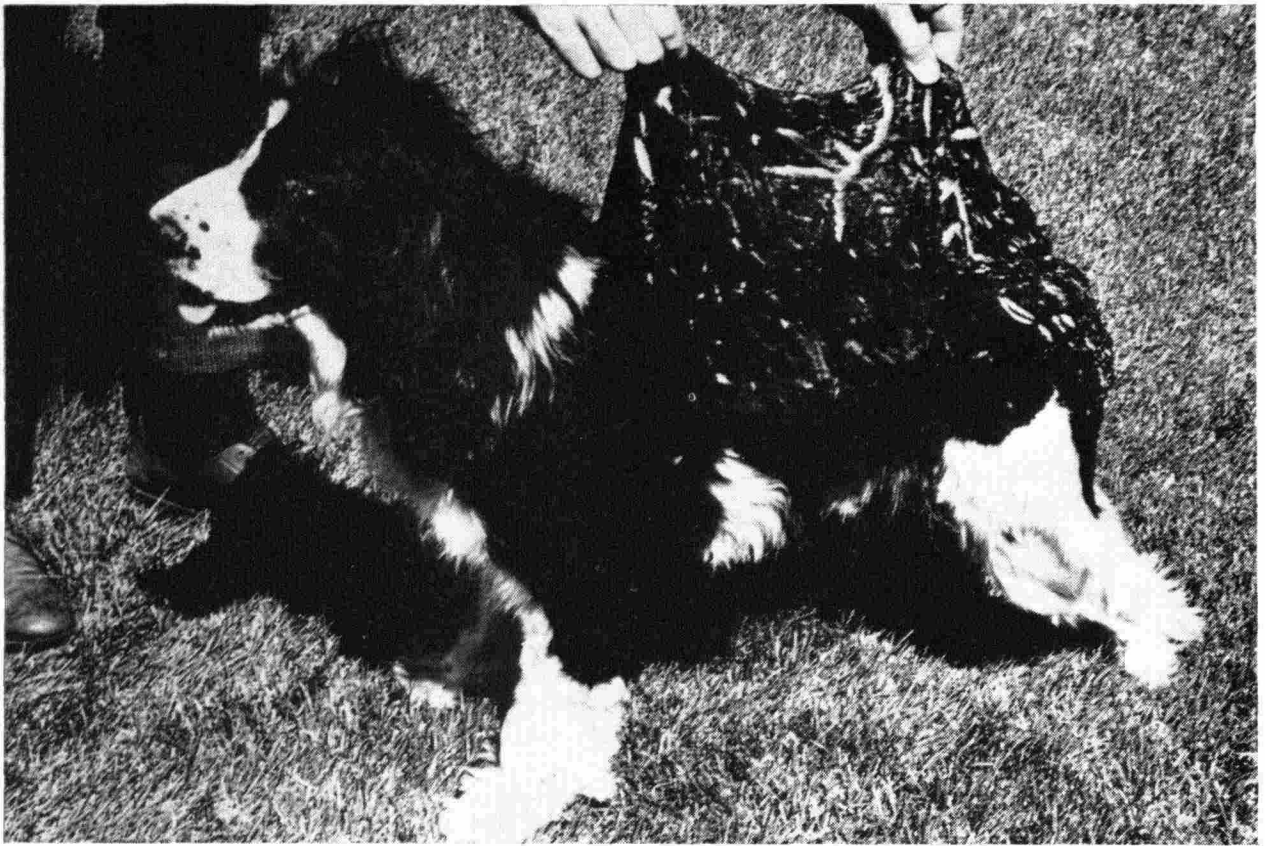
FIG. 1. Affected dog demonstrating numerous, healed, broad scars and striking hyper-extensibility of the skin.

iologic saline and testing was performed within 3 hours after removal of the skin samples.

All tensile strength determinations were performed at room temperature on a table model Instron tester. A tensile load cell of 5, 10, 20, 50, 100, and 200 pounds was used. The samples were placed in specially designed tooled aluminum grips, each grip having a removable inlaid jaw which was tightened by means of 2 screw bolts. The jaws were lined with Type 18 silicone carbide abrasive cloth to assure firm gripping of the skin samples. The upper grip was connected to a movable lower cross-head on the Instron tester. Each of the 20 samples were placed in the grips and stretched by applying a uniform speed of 2 cm. per minute until they broke. The breaking load was recorded on a potentiometer-type graphic recorder. The error of resolution of the recorded under the conditions employed was less than 1%. Data from those samples slipping out of the clamps or breaking at the point of insertion in the clamp were discarded. The breaking strength was measured in pounds, recorded, and converted to pounds per square inch (psi.) utilizing data from caliper measurements of skin thickness. The values for affected and non-affected dogs in each age group were averaged and the standard deviations determined. Tensile strength studies were performed in the same manner on 4 affected and 3 nonaffected adult mink.

RESULTS

Dogs. The tensile strength of the skin of affected dogs was reduced as compared to control dogs and this change was found in all

areas of the body examined. The average tensile strengths ±1 standard deviation for the 16-month-old affected dogs was 109 psi. ± 61 psi. as compared to 2670 psi. ± 469 psi. for their non-affected littermate. Skin tensile strength for the 13-month-old dogs was 70 psi. ± 34 psi. for affected dogs and 2550 psi. ± 585 psi. for their nonaffected littermate. Figure 2 depicts the average of the skin tensile strength and range for the combined data from the 16- and 13-month-old affected and nonaffected dogs.

Mink. The skin tensile strength of affected mink was markedly reduced in all areas of the body as compared to that of the control mink skin. The average tensile strength ± 1 standard deviation was 96 psi. ± 44 psi. for affected mink and 1241 psi. ± 125 psi. for nonaffected mink. The average of the mink skin tensile strength data and the range is shown in Figure 3.

DISCUSSION

Fragility of the skin is believed to be the most unique clinical trait of the ED-S of man (4, 6, 7). Ronchese (7) has stated that "the peculiar fragility of the skin, from a dermatologic and practical standpoint, is the main feature of the disease." Rollhauser (13)
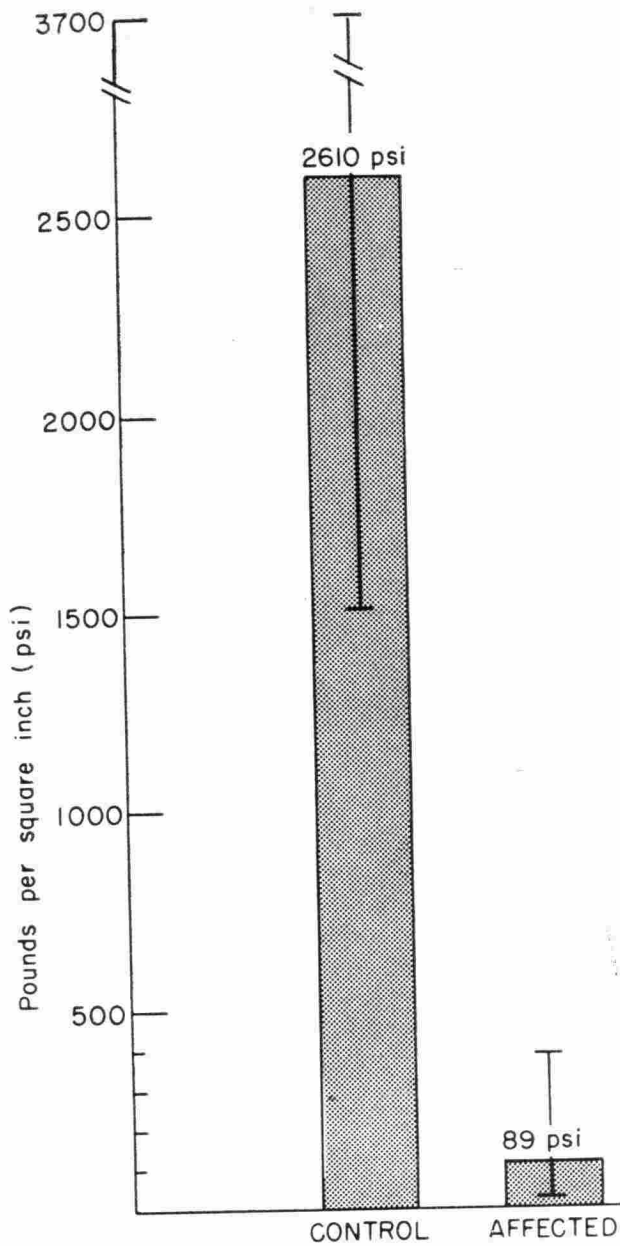
FIG. 2. Comparison of tensile strength of affected and nonaffected dogs' skin in pounds per square inch (psi). The vertical lines in each bar represent the range.

performed tensile strength studies on the skin from a 35-year-old man afflicted with the ED-S. His study showed that the tensile strength of skin from this ED-S patient was reduced to approximately one-fifth that of normal skin of human subjects in this age group (480 psi., affected; 2280 psi., nonaffected).

Fragility of the skin is the most severe clinical manifestation of the syndrome in dogs and mink as in affected human beings. We have found that the tensile strength of affected dogs' skin is reduced to approximately one-twenty-seventh that of nonaffected dogs' skin (94 psi., affected; 2610 psi., non-affected) and that affected mink skin is reduced to approximately one-thirteenth that of nonaffected

mink skin (96 psi. affected; 1241 psi., non-affected).

The dermal component or components primarily involved in the skin defect of the syndrome in man, dogs, and mink has not been definitely resolved. On the basis of the skin fragility and accompanying reduction in tensile strength, however, it seems logical that collagen fibers would be altered. The collagen fiber is the primary component of the dermis and has been shown to be the major contributor to the tensile strength of the skin (13–15). Elastic fibers, the second most abundant fibrous component of the dermis, are believed to contribute only minimally to the tensile strength of the skin as there is 20 times more collagen than elastin in the dermis and the tensile strength of collagen is about 100 times that of elastin (16).

Hyperextensibility of the skin is also believed to be a result of an alteration of the collagenous framework. Smith (17) stated that the stretch of the skin was inversely related to its collagen content and that the elastic fiber component was more closely associated with the retraction after stretching. Jansen (18) and Summer (4) have pointed out that the degree to which the collagen fibers could be extended was dependent on the
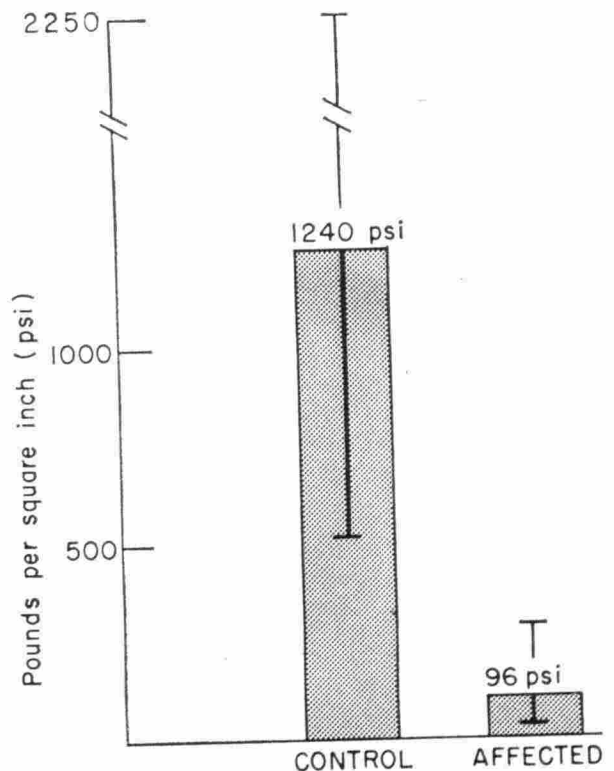

FIG. 3. Comparison of tensile strength of affected and nonaffected mink skin in pounds per square inch. Vertical lines represent the range.

extent to which these fibers could glide along each other. Therefore, the collagen "wickerwork" arrangement was believed to be the limiting factor. Further support that the collagen fiber is involved in the ability of the skin to stretch was offered by Weschler and Fisher (19) who noted that in sclerodermatous skin there was an increase in apparently normal collagen but a decrease in elastic fibers and that the stretch and retraction of the skin were either markedly limited or absent. On the other hand, Turnbridge, *et al.* (20) could demonstrate no histologic change in the collagen fibers of the dermis from ED-S cases other than a diminution in number and they concluded that the extensibility of the skin was a consequence of the predominance of elastic fibers.

We believe that the syndrome in dogs and mink displays marked clinical and genetic similarity to the ED-S of man and that further study of the syndrome in dogs and mink may delineate the basic defect involved in the human syndrome. In addition, the syndrome in dogs and mink represents one of the few delineated heritable connective tissue dysplasias of animals, and, as such, will be useful as a model for more basic studies of connective tissue metabolism and dysfunction.

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