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HEREDITARY HYPERPLASTIC GINGIVITIS OF SILVER FOXES

By

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Tumours of various types occur among captive fur animals to about the same extent as among other species of domestic animals. In the case of fur animals, however, tumours generally can be considered simply as incidental observations at autopsy. As a cause of death, tumours have only secondary significance and this may at least partially depend upon these animals seldom attaining old age in captivity (*Momberg-Jørgensen,* 1952).

The present article deals with a hereditary form of hyperplastic gingivitis in captive silver foxes.

The first appearance of the defect in Sweden.

The first pair of silver foxes imported to Sweden arrived in the autumn of 1919 from Norway. It was not until 1926, however, that the breeding of silver foxes was taken up seriously. The number of animals and the number of establishments keeping them rapidly increased up to 1939 when the second world war made it difficult to maintain the animals and dispose of the furs.

A young male fox with very good quality fur was imported from Norway by an establishment in Östergötland at the beginning of the 1940's. After a few months, the owner noticed that the teeth of the fox steadily became hidden behind an ever-increasing mass of tissue originating from the gums. As far as can be ascertained, this is the first known instance of hyperplastic gingivitis in Sweden. A similar lesion of the gums had

been previously observed on some Norwegian silver-fox establishments. The first official report of this defect was made by *Olsson* (1943). "During the past several years I have seen occasional cases of a particular fox disease. Recently this disease has occurred under circumstances and to a degree which warrant closer attention. The disease is manifested as what appears to be granulation tissue growing slowly from the gums. This overgrowth gradually extends over the teeth to bury them and make chewing impossible. Up to the present time only foxes of exceptionally good quality have been affected. In many instances it has been necessary to pelt affected animals unnecessarily early and for this reason, the disease has economic significance. Personal observations of the disease cover more than 25 foxes in various parts of the country."

The disease was rapidly disseminated and *Olsson* (1944) reported that "this disease of silver foxes is steadily spreading and several enquiries have been received from owners who bought such animals when they were apparently healthy but which developed the typical changes during the course of the summer. By the third year the lesions have usually developed to such an extent that pelting must be considered. Since affected animals practically without exception are of very good quality, it is difficult to decide whether or not they should be exhibited." At the beginning of 1945, *Olsson* added that "overgrowth of the gums continues to spread among silver foxes. Many new breeders will undoubtedly see this disease among their foxes during the course of the year". *Olsson* also mentioned at this time that various treatments were being tested but that the results were inconclusive.

PRESENT INVESTIGATIONS

During 1945, Olsson requested one of us (Dyrendahl) to attempt to determine whether or not a hereditary characteristic was involved in the occurrence of this overgrowth of the gums in silver foxes. By this time, several owners of large silver-fox breeding establishments had expressed the suspicion that heredity was a significant factor in the appearance of the disease. In order to establish an as extensive and reliable primary material as possible for genetic analysis, several large fox establishments were investigated. The most suitable for a genetic analysis was Svaneholms Silverrävgård, in Värmland, which at the

beginning of the 1940's, was one of the largest establishments in this country and in addition a very well managed one. Careful and complete records were kept for each animal, a circumstance which was of decisive value for the carrying out of this investigation. The genetic analysis described in succeeding sections covers the Svaneholm material for the 6 years 1945 to 1950. The study includes 1,080 parent animals and 7,238 pups.[1])

Clinical studies.

After a gestation period lasting 52 days on the average, most silver-fox pups are born during April. In the early autumn when the milk teeth are shed, careful inspection of a suitable restrained animal will reveal swelling of the gingiva about the posterior cheek teeth in both the upper and the lower jaws. The surface of the swelling is firm and somewhat lighter in colour than normal gingiva. The gingival swelling gradually increases in volume and at an early stage also involves the anterior portions

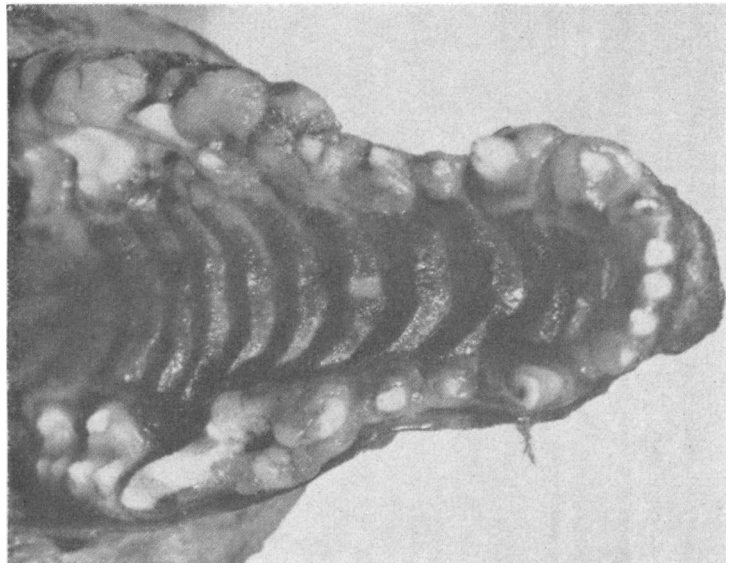

Fig. 1. The upper teeth of a silver fox embedded in proliferated gingiva.

[1]) Acknowledgement. The writers would like to thank disponent *Sverre Braanaas* most warmly for the assistance which he has given during many years and without which this study could not have been carried out. For valuable help in preparing this paper we wish to thank veterinarian *Bertil Olsson.*

of the mouth. (Fig. 1.) When once begun, the process progresses gradually but relentlessly. A confluent tumour mass develops on both the lingual and buccal aspects of the jaws as well as between the teeth. The surface is uneven with fairly pronounced lobulation in various portions. When fully developed, the hyperplastic tissue forms a confluent, cauliflower-like mass involving both the upper and lower jaws. (Fig. 2.) Growth is rather slow and it is usually

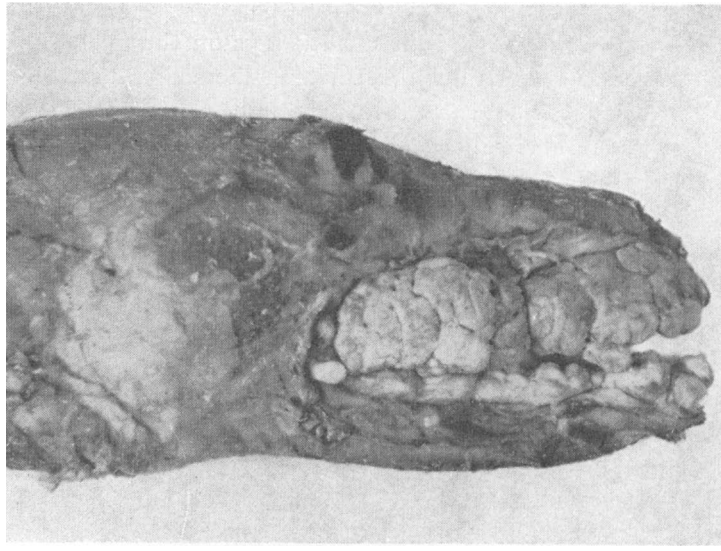

Fig. 2. The lesion progresses to resemble a cauliflower head. In older foxes, the gingival proliferation can reach such a large size that the animal is incapable of closing its mouth.

2 or 3 years before the mass reaches a size which permit it to be detected upon casual inspection of the mouth. At this stage it is readily apparent since the lips cannot cover the gingival mass. Only the highest crowns of the teeth are generally visible above the gingival mass and many teeth can be completely covered. The first premolar is missing in many such animals. Displacement and malalignment of the teeth are common. (Fig. 3.) In older foxes, the hyperplasia may reach enormous proportions and the animals become unable to close their mouths. This luxuriousness of growth led to the defect early acquiring the Swedish name "svallkött", i. e. "proud flesh".

Most fox pups are pelted in December of their first year. At this time, the gingival proliferation in most instances has not

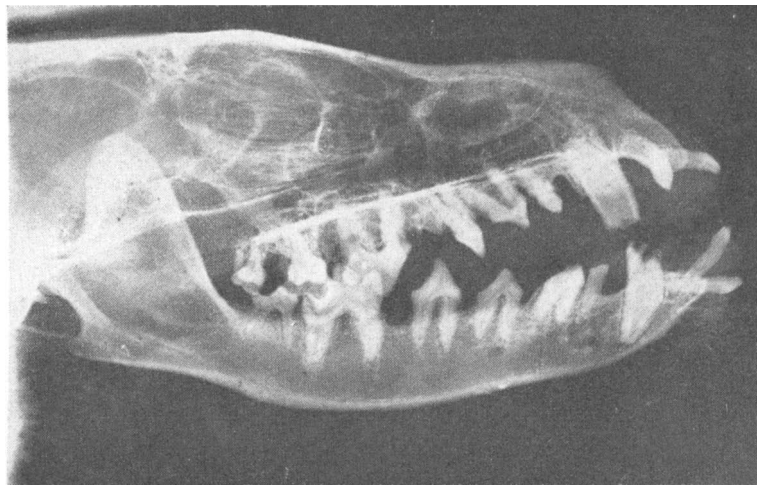

Fig. 3. Röntgenogram of the skull of a fox with gingival hyperplasia. Displacement and faulty alignment of the teeth are often seen.

reached such proportions that mastication is impaired and consequently, the animals are in a good state of nutrition and well developed. Older foxes with advanced and extensive lesions often maintain a surprisingly good condition if fed on finely-ground feed in the form of a soft porridge. Solid feed cannot be chewn when the teeth have been buried in gingiva. One unfortunate result of this condition is that the pelt over the abdomen, hind legs, and tail is damaged by saliva flowing uncontrollably out of the mouth when the foxes are curled up to rest. Females with hyperplastic gingivitis appear to be poorer dams than usual, an aspect which is illustrated by the litters of such females being significantly smaller than those of normal females (cf. page 14). The proliferations bleed easily if the fox bites hard on an object or damages the oral mucous membrane in any way. It appears, however, that the foxes do not experience any appreciable sensation of pain when biting or exposing the gums to other forms of trauma. It was early noticed that the defect occurred mainly among foxes of the best quality and this observation has since been confirmed. The correlation between hyperplastic gingivitis and good quality fur is discussed in the section dealing with genetics.

Attempts to treat or at least limit extension of the process were made in many of the earlier cases. However, no permanent effects could be obtained. Surgical excision followed by chemical

or thermal cauterization has been tried on numerous occasions. Several chemotherapeutic agents have been tried, including autogenous vaccines, all without any effect.

Pathological description.

Histological examination of proliferations from the foxes has been carried out by *Cederberg* (1952). According to *Cederberg,* these lesions can be classified as *hyperplastic gingivitis,* and he summarized his findings as follows. "Major changes are evident in the epithelium. Wide pegs and bands of epithelium extend deeply into the collagenous connective tissue. The central portions of these pegs are often necrotic and necrosis may extend up to the surface to give lobulation.

"The connective tissue is very collagenous with few cells and is heavily infiltrated by round cells. Degenerative changes, karyolysis and karyorrhexis, are seen in the deeper portions. Macrophages and occasional leukocytes are present. Mitotic figures have been observed.

"The gingival papillae show large collections of round cells. The epithelium adjacent to the enamel surface is often damaged but proliferation of epithelium to form pockets or marginal ostitis seldom occurs."

GENETIC ANALYSIS

As has been outlined above, the Svaneholm foxes upon which the genetic analysis is based included 1,080 parent animals and 7,238 pups. The parent animals ranged in age from one to nine years. The gums of the breeding animals were examined several times yearly and notes kept of the findings. In the case of the pups, the gums were regularly examined in December of the year of birth at the time of pelting or selection as breeding animals. Full details are thus available for all animals on the establishment for the years 1945 to 1950. The entire material is listed in Table 1 with details of the various matings and their results. From this table it is apparent that a genetic factor is involved since there is a significant heterogenicity in the incidence of the defect after the various matings ($\chi^2 = 116$, $f = 3$, $P < 0.001$). There can be no doubt that the occurrence of the lesion is governed by genetic factors.

Pathologically, the hyperplastic gingivitis is a specific and characteristic lesion. Variations between various affected indi-

viduals involve the degree but not the nature of the lesion. This observation suggests that monogenic heredity is involved. Several circumstances, however, indicate that inheritance is not regularly monogenic. If the lesion were regularly dominant, the mating of normal individuals would not result in affected offspring. Regularly recessive inheritance would mean that mating defective individuals could not result in normal pups. Neither of these conditions are fulfilled by the material shown in Table 1. (In this context, "normal" means free from hyperplastic gingivitis).

Table 1.
The total material covering the period 1945 to 1950.

Offspring / Parents Matings	□			○			□ + ○			Ratio $\frac{D}{D+N}$
	Normal	Defective	Total	Normal	Defective	Total	Normal	Defective	Total	
N □ x N ○[1]	2104	225	2329	1845	122	1967	3949	347	4296	0.081
D □ x N ○	605	140	745	614	97	711	1219	237	1456	0.163
N □ x D ○	432	99	531	415	75	490	847	174	1021	0.170
D □ x D ○	186	80	266	136	63	199	322	143	465	0.307
Total	3327	544	3871	3010	357	3367	6337	901	7238	0.124

[1]) D = hyperplasia - N = normal
□ = male - ○ = female

The incidence or penetrance is apparently incomplete, in any event at the ages at which the animals in this material were examined. Incidence increases directly as age which, among other things, means a different incidence for parents and their pups. The incidence of the defect among the pups was established at seven to eight months of age at the time of pelting. For the parent animals, however, the lesion has been recorded as it appeared and as a result, the incidence has steadily increased with increasing age. One consequence of this is that penetrance must be assumed to have different degrees for parents and offspring.

A population is in genetic equilibrium when the incidence of the various genes is unchanged from generation to generation and if a state of panmixia has been reached (*Li*, 1955). The question of panmixia will be discussed below. In genetic equilibrium, the frequency of various genotypes can change on condition that panmixia has been reached. The essential point is

that no systematic alteration in the incidence of the various genes occurs from generation to generation.

The present material could have included a maximum of six generations, i. e. one generation per year. Some females and to an even greater extent some of the males were used for breeding during more than one year. The mean number of litters borne by the females is 2.4 which means that the material extends over a mean of $\frac{6}{2.4} = 2.5$ generations. A systematic alteration in the incidence of the gene for the defect could scarcely come into question during this time. A priori, a selection *against* the gene can be assumed since the defect depresses the general condition of the animals, their suitability as dams, etc. On the other hand, it can be shown (page 15) that the gene is positively correlated to good fur quality and this would naturally enhance the chances of selection for this defect. Both these factors were probably mutually competetive and reduced or cancelled out their individual effects.

The following example will demonstrate the degree of panmixia within the population. The total material includes 153 defective and 633 normal female foxes (○), and 74 defective and 220 normal males (□). For panmixia, the various mating possibilities can be estimated as

normal □ × normal ○ : $0.748 \times 0.805 = 0.602$
defective □ × normal ○ : $0.252 \times 0.805 = 0.203$
normal □ × defective ○ : $0.748 \times 0.195 = 0.146$
defective □ × defective ○ : $0.252 \times 0.195 = 0.049$

The indices for the actual offspring were $\frac{4296}{7238} = 0.594$, $\frac{1456}{7238} = 0.201$, $\frac{1021}{7238} = 0.141$, and $\frac{465}{7238} = 0.064$ respectively. χ^2-analysis for each mating gives the values 0.86, 0.12, 1.21, and 34.34 respectively ($P < 0.001$). Thus, there is significant deviation only for the last mating.

A theoretically acceptable state of panmixia is very unusual within limited populations. In the present instance, however, a satisfactory result was obtained.

The following genetic analysis is based upon all parent-offspring pairs in the total material.

Analysis for the incidence of genes has been carried out mainly according to *Eriksson* (1954) and *Henricson* (1957). The following symbols have been used.

P = probability for

A = defect gene with incidence q

a = normal gene with incidence p in which $p + q = 1$ and according to Hardy-Weinberg's law, q^2 (AA) + 2 pq (Aa) + p^2 (aa) = 1

y_1 and y_2 = penetrance for q^2 (AA) among the parents and offspring respectively

x_1 and x_2 = penetrance for 2 pq (Aa) among the parents and offspring respectively in which $x_1 = x_2 = 0$ in recessive inheritance

the suffix g indicates genotype

the suffix f indicates phenotype

For recessive inheritance, insertion of the empirical incidences from Table 1 gives

For the parents: $P(AA_f) = q^2y_1 = 0.210$.

For the offspring: $P(AA_f) = q^2y_2 = 0.124$.

For phenotypical defective parents: $P(A) = 1$.

For matings between defective □ and defective ○ and individuals of the opposite sex (all genotypes):

$P(AA_g) = q$; $P(AA_f) = qy_2 = 0.205$.

Equations

$$\begin{cases} q^2y_1 = 0.210 & q = 0.605 \\ q^2y_2 = 0.124 & y_2 = 0.345 \\ qy_2 = 0.205 & y_1 = 0.580 \end{cases}$$

For matings between defective parents is obtained $P(AA_f) = y_2$ which according to Table 1 has a value of 0.307.

An additional value for y_2 can be derived (*Eriksson*, 1954) if the ratio of defective individuals resulting from mating defective and normal parents is squared and divided by the ratio of defective individuals which result from mating normal parents. In this case, y_1 is 0.340. A value for y_2 of 0.307 has a standard error of 0.021 and both the calculated y_2 values, 0.345 and 0.340 lie within the limits for twice the error of the mean. If the values for q, y_2, and y_1 which were derived from the above equation (0.605, 0.345, and 0.580 respectively) are utilized for calculating the ratios which are obtained for matings between defective and normal parents and for matings between normal individuals, (*Eriksson*, 1954) there is no significant deviation from the corresponding empirical incidences given in Table 1.

Table 2.

Male foxes, each the sire of at least 15 litters. Arranged after falling frequencies for defective and normal animals respectively.

Male no.	No. of litters	Incidence of the defect among the pups	Male no.	No. of litters	Incidence of the defect among the pups
Defective:					
H 106	15	$\frac{16}{57} = 0.281$	H 139	24	$\frac{10}{79} = 0.127$
E 850	19	$\frac{19}{71} = 0.268$	E 645	16	$\frac{7}{56} = 0.125$
K 51	21	$\frac{21}{90} = 0.233$	S 951	15	$\frac{6}{50} = 0.120$
K 152	18	$\frac{15}{74} = 0.203$	K 182	21	$\frac{10}{85} = 0.118$
D 786	15	$\frac{8}{55} = 0.145$	K 877	19	$\frac{7}{61} = 0.115$
E 967	25	$\frac{15}{111} = 0.135$	H 380	20	$\frac{7}{68} = 0.103$
P 415	16	$\frac{4}{61} = 0.066$	P 1321	23	$\frac{8}{85} = 0.094$
			E 239	22	$\frac{7}{94} = 0.074$
Normal:					
D 785	16	$\frac{17}{65} = 0.262$	H 739	23	$\frac{6}{88} = 0.068$
E 791	24	$\frac{24}{102} = 0.235$	E 884	24	$\frac{5}{82} = 0.061$
K 90	17	$\frac{14}{63} = 0.222$	K 624	30	$\frac{7}{116} = 0.060$
P 773	16	$\frac{11}{59} = 0.186$	P 1799	21	$\frac{4}{73} = 0.055$
E 112	23	$\frac{15}{86} = 0.174$	E 74	17	$\frac{3}{60} = 0.050$
P 945	17	$\frac{12}{72} = 0.167$	P 1079	16	$\frac{3}{64} = 0.047$
E 453	24	$\frac{14}{89} = 0.157$	K 102	23	$\frac{4}{102} = 0.039$
H 138	17	$\frac{11}{73} = 0.151$	K 215	17	$\frac{1}{74} = 0.014$
H 952	21	$\frac{11}{77} = 0.143$	S 655	18	$\frac{1}{69} = 0.014$

If the defect is inherited as a dominant characteristic, then it appears that the equations which could be developed for the various matings in Table 1 cannot be solved unless penetrance for homozygotes and heterozygotes (y and x respectively, see above) have a definite mutual relationship.

Calculation of gene incidence and penetrance when y and x are independent of each other can be based upon groups of offspring of individual sires (*Henricson,* 1957). Table 2 gives the incidence of the defect in groups of offspring sired by 33 males. Each of these males had at least 15 litters.

Table 2 represents a sample of the total material, Table 1. Representativity of the sample can be tested by comparing the following mating possibilities from Tables 1 and 2.

	Table 1	Table 2	$\chi^2_{f=1}$
D □ × (D + N) ○	$\frac{380}{1921} = 0.198$	$\frac{98}{519} = 0.189$	0.21
N □ × (D + N) ○	$\frac{521}{5317} = 0.098$	$\frac{225}{1992} = 0.113$	3.54
(D + N) □ × (D + N) ○	$\frac{901}{7238} = 0.124$	$\frac{323}{2511} = 0.129$	0.29

No significant deviation is present for any of the matings. The sample can be considered as representative for the total material.

If the defect is caused by a dominant characteristic, the male foxes could then be classified in three groups, one for each of the genotypes AA, Aa and aa. In random matings, these genotypes ought to give rise to defective offspring in the following incidences:

$$AA: qy_2 + px_2 \qquad Aa: \frac{qy_2 + x_2}{2} \qquad aa: qx_2$$

Before classifying the male foxes into various genotypes, preliminary calculations should be made in order to obtain an estimation of the approximate value for the incidence of the defect with dominant inheritance. This can be accomplished by calculating the incidence for the defect gene with an average penetrance z_2 in which $z_2 = y_2 = x_2$. Another possibility is to calculate the incidence of the defect gene with the assumption that $y_2 = 2x_2$, i. e. intermediate inheritance.

1. $y_2 = x_2 = z_2$

From the matings in Table 2: D □ × (D + N) ○ and (D + N) □ × (D + N) ○ page 11 is obtained:

$$\begin{cases} qz_2(1+p) = 0.129 & q = 0.275 \\ \dfrac{z_2(1+pq)}{1+p} = 0.189 & z_2 = 0.272 \end{cases}$$

The various genotypes ought to give the following incidences for the defect among their offspring:

AA: $z_2 = 0.272$ Aa: $\dfrac{qz_2 + z_2}{2} = 0.174$ aa: $qz_2 = 0.075$

2. $y_2 = 2x_2$

The equations from alternative 1 can be expressed as

$$\begin{cases} qy_2 = 0.129 & q = 0.350 \\ y_2(q + \frac{p}{4}) = 0.189 & y_2 = 0.369 \\ & x_2 = 0.185 \end{cases}$$

The various genotypes give:
AA: 0.250 Aa: 0.157 aa: 0.065

The mean for the two ratios for the respective genotypes obtained by both calculations were utilized for classification of the 33 male foxes. The foxes with offspring with a defect incidence which best agrees with the value $\dfrac{0.272 + 0.250}{2} = 0.261$ were taken as having a genotype of AA. The Aa genotypes should have an incidence in the neighbourhood of 0.166 and the aa genotypes, an incidence of 0.070.

The males in Table 2 have been classified according to the assumed genotype.

AA: H 106, E 850, K 51, D 785, E 791, K 90.
Aa: K 152, D 786, E 967, P 415, P 773, E 112, P 945, E 453, H 138, H 952, H 139, E 645, S 951, K 182.
aa: K 877, H 380, P 1321, E 239, H 739, E 884, K 624, P 1799, E 74, P 1079, K 102, S 655, K 215.

In spite of the low proportion of defective offspring, the fox P 415 must be assumed to have the genotype Aa since he is himself phenotypically defective.

$$\left.\begin{array}{lll} \text{The mean defect incidence of group AA} & \frac{111}{448} = 0.248 & \\ \text{„ „ „ „ „ „ Aa} & \frac{149}{1027} = 0.145 & \\ \text{„ „ „ „ „ „ aa} & \frac{63}{1036} = 0.061 & \end{array}\right\} \frac{323}{2511} = 0.129$$

The following equations can now be established and after inserting the values for q, y_2, and x_2 they give

$$\left\{\begin{array}{lll} q^2y_2 + 2pqx_2 = 0.129 & q = 0.422 \\ qy_2 + px_2 = 0.248 & y_2 = 0.450 \\ qy_2 + x_2 = 0.290 & x_2 = 0.100 \end{array}\right.$$

$$\left\{\begin{array}{lll} q^2y_2 + 2pqx_2 = 0.129 & q = 0.364 \\ qy_2 + px_2 = 0.248 & y_2 = 0.387 \\ qx_2 = 0.061 & x_2 = 0.168 \end{array}\right.$$

$$\left\{\begin{array}{lll} q^2y_2 + 2pqx_2 = 0.129 & q = 0.399 \\ qy_2 + x_2 = 0.290 & y_2 = 0.343 \\ qx_2 = 0.061 & x_2 = 0.153 \end{array}\right.$$

If the defect is recessive, the various males would give rise to defective offspring in the following proportions.

$$\text{AA: } qy_2 \quad \text{Aa: } \frac{qy_2}{2} \quad \text{aa: } 0$$

Phenotypically defective males are of genotype AA and had an incidence of the defect among their offspring of 0.189 (cf. page 12). The heterozygotes should produce half that incidence of defective offspring. The males in Table 2, then, can be classified according to the approximate incidences of 0.2 and 0.1 as follows.

AA: H 106, E 850, K 51, K 152, D 786, E 967, P 415, D 785, E 791, K 90, P 773, E 112, P 945, E 453, H 138.

Aa: H 952, H 139, E 645, S 951, K 182, K 877, H 380, P 1321, E 239, H 739, E 884, K 624, P 1799, E 74, P 1079, K 102, S 655, K 215.

The mating D □ × (D + N) ○ from Table 2 was described on page 12 and it was calculated that this mating resulted in a defect incidence of 0.189. For this mating, the following equations give

$$\left\{\begin{array}{lll} q^2y_2 = 0.129 & q = 0.683 \\ qy_2 = 0.189 & y_2 = 0.277 \end{array}\right.$$

With q = 0.68, the 33 male foxes should include 15.2 AA, 14.3 Aa, and 3.4 aa. The classification cited above gives 15 AA and 18 Aa. $\chi^2 = 4.16$, f = 3, $P > 0.05$ and indicates no significant deviation.

Assuming dominant inheritance and a gene incidence of approximately 0.40, the distribution among the genotypes would be AA: 5.3, Aa: 15.8, and aa: 11.9. A genotype distribution of AA: 6, Aa: 14, and aa: 13 was arrived at on page 13. There is very good agreement between these values.

In instances of incomplete penetrance it is difficult to utilize calculations of gene incidence to obtain decisive arguments for recessive or dominant inheritance. The calculations described above have not given an unequivocal answer. A point which suggests recessive inheritance are the distribution figures in Table 1. In recessive inheritance, the distribution figures for the matings N × N, D × N, and D × D should form a geometrical series *(Eriksson,* 1954) which in fact they practically do.

The sex ratio (male/female) for all the offspring (Table 1) is 0.535. This ratio does not deviate significantly from that given by *Johansson* (1947) as 0.529. If, however, the sex ratio is calculated separately for normal and defective offspring, that for the normal animals is 0.525 and that for the defective is 0.604. The difference between these two ratios is significant ($\chi^2 = 19.7$, $P < 0.001$). Furthermore, there is a significant difference in the total offspring material between the incidence of the defect in males (0.141) and in females (0.106).

This difference in sex ratio between normal and defective animals may have arisen of various causes. An independent lethal characteristic is improbable since the distorted sex ratio is associated only with defective animals.

It could also be postulated that females with a defective genotype were subject to a lethal effect and that the paucity of females was the result. Litter-size for defective females was 3.62 ± 0.07 and for normal females, 3.92 ± 0.04, t = 3.8 ($P < 0.001$). These figures taken by themselves can be adduced as support for this hypothesis. Conflicting evidence, however, lies in the fact that matings between defective animals do not give the greatest reduction in females which ought to be seen. The reduction in litter-size for defective females probably affects both sexes and is most likely a reflection of poorer environment (maternal abilities, etc., see page 5).

The genetic analysis in the preceding section was carried out without mentioning the likelihood of the responsible gene being autosomal or sex-linked. Results of the reciprocal matings D □ × N ○ and N □ × D ○ in Table 1 would seem to eliminate the sex-linked possibility. Both X-chromosome linkage and Y-chromosome linkage can be ignored. In the first instance, cross-inheritance should have appeared with one or the other of the reciprocal matings but did not. In the second instance, only the males would have been affected. The possibility of X- and Y-linkage (partial sex linkage) has not been seriously considered.

The most probable explanation for the distorted sex ratio would seem to be different degrees of penetrance for males and females.

Relationship between hyperplastic gingivitis and good quality fur.

As has been mentioned previously, practical observations had suggested some form of relationship between god quality fur and the gingival lesion. Breeders recognized at an early stage that it was mainly first-class animals which became affected but seldom animals with fur of a lower or poor quality.

This observation could be readily checked against the records which contained careful notes on the fur quality for the individual animals. Evaluation of fur quality was carried out in December of the first year for the pups at the time of pelting or selection for breeding. The animals were then divided into five classes representing various grades of fur quality. χ^2-analysis was carried out on the distribution of defective and normal animals within the various classes. For every year there were highly significant χ^2-values for heterogenecity. The empirical assertion that there was a relationship between good quality fur and hyperplastic gingivitis could thus be confirmed.

The relationship demonstrated between these two characteristics could take the form of coupling between the defect gene and the gene which governed good quality fur. The possibility of such a coupling existing in this case was studied by the method given by *Penrose* (1938). His method is based upon comparison of sibling pairs for likeness and unlikeness in the characteristics under study. Application of this method requires that chance mating has occurred and that the individuals are unselected for

the characteristics in question. Both these criteria could be met for the present material. The value for the calculated coupling factor shall significantly deviate from 0 if coupling is present. Analysis of the fox material gave a coupling factor of — 0.05 ± 0.16, a value which can be interrupted as evidence that coupling did not occur between the gene for hyperplastic gingivitis and good quality fur. The relationship apparently depends upon internal physiological or external environmental factors. It is also possible that the relationship is an example of the influence exerted by a pleiotropic gene with one gene being mainly responsible for both the gingival lesion and fur quality.

DISCUSSION

Judging by the few published reports, hereditary hyperplastic gingivitis seems to be an unusual lesion in animals. *Burstone, Bond & Litt* (1952) have described a familial gingival hypertrophy in four Boxer dogs. The lesions in this instance were unlike those seen by us in foxes. Microscopically, the canine lesions were characterized by a central area of bone and by nests and cords of cells suggestive of odontogenic epithelium. Gingival hyperplasia in dogs of unknown aetiology has also been reported by *Mulligan* (1949) and *Riser* (1949). In these cases, however, there was no indication of a possible familial relationship of the affected dogs.

Hereditary gingival fibromatosis occurs in human beings. These lesions consist of connective tissue covered by epithelium without the presence of bone or cords of epithelial cells in the stroma (*Aimes,* 1937). *Wassmund* (1935) distinguishes between inflammatory, symptomatic, and neoplastic forms of hypertrophic gingivitis. The neoplastic lesion is not the result of inflammation and has also been classified as fibromatosis. This lesion of human beings in several respects resembles that described by us in captive silver foxes. *Wassmund* points out that the lesions are completely insensitive in spite of being exposed to trauma during mastication. And as mentioned above, foxes with hyperplastic gingivitis do not experience any detectable pain during mastication or when biting solid objects. Gingival fibromatosis of human beings, according to *Wassmund,* is hereditary and he has been able to follow an affected family for four generations. From this he has concluded that inheritance is dominant. Overgrowth of the gums began in one of these

people at the age of 2 years and subsequently progressed very slowly. The lesion was excised when the affected person was 23. *Wassmund* states that the lesions often recur after surgical removal and adds that the aetiology is unknown but a hormonal disturbance is probably involved.

Weski (1920) had the opportunity of following a hereditary gingival hyperplasia, "elephantiasis gingivae", through five generations within one family comprising 39 individuals, 20 men and 19 women. Seven of the men and 10 women were affected. In every affected person, the lesion was not congenital but appeared at the time the milk teeth erupted. Later in life, extraction of one or several teeth was followed by regression of the gums to their normal dimensions, an indication of the intimate relationship between the presence of teeth and the occurrence of the lesion. The gingival lesion was also associated with a dwarfish body build and, in both men and women, with hirsutism. From our investigations, it is apparent that the gene for the gingival lesion was associated with good quality fur, i. e. fur with a dense undercoat. The hypothesis can be advanced that a hormonal disturbance is responsible for both the gingival lesion and the hirsutism and that a similar endocrine dysfunction is involved in human beings and silver foxes.

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SUMMARY

At the beginning of the 1940's a gingival lesion appeared among Swedish silver foxes and rapidly reached a high incidence on certain fox-breeding establishments. The lesion has been described as *hyperplastic gingivitis* (*Cederberg,* 1952). A similar lesion has been reported in human beings by *Wassmund* (1935) among others who considers it bo be a hereditary and dominant characteristic.

The genetic background of the lesion was studied on a large establishment where a total of 1,080 breeding animals and 7,238 pups had been maintained during the years 1945 to 1950. A positive correlation was observed between the gingival lesion and good quality fur; this correlation is not of genetic nature. An analysis for gene incidence has been carried out for the whole material. The lesion is inherited as a simple, probably recessive characteristic with incomplete penetrance. The sex ratio for affected animals shows a preponderance of males. The possibility of a greater degree of penetrance for males than females is advanced as the most likely explanation for this phenomenon.

ZUSAMMENFASSUNG

Erbliche hyperplastische Gingivitis beim Silberfuchs.

Anfang der 1940-er Jahre wurde in Schweden beim Silberfuchs ein Zahnfleischdefekt beobachtet, der in gewissen Fuchsfarmen eine schnelle und umfassende Verbreitung erreichte. Der Defekt kennzeichnete sich als eine *hyperplastische Gingivitis* (*Cederberg,* 1952). Ein ähnlicher Defekt wurde beim Menschen unter anderen von *Wassmund* (1935) beschrieben, der die Krankheit als erblich nach einem dominanten Prinzip betrachtet.

An einem Material, das aus sämtlichen Zucht- und Gebrauchstieren (1.080 Elternindividuen und 7.238 Welpen) in einer grösseren Fuchsfarm während der Jahre 1945—50 bestand, wird die genetische Natur des Leidens beleuchtet. Die Gingivitis wies eine positive Korrelation mit hoher Pelzqualität auf, eine Wechselbeziehung, die nicht genetischer Natur zu sein scheint. Am Totalmaterial wurde eine Genenfrequenzanalyse ausgeführt. Der Defekt wird wahrscheinlich von einer einfachen, vermutlich rezessiven Erbanlage mit unvollständiger Penetranz bedingt. Die Geschlechtsquote unter defekten Individuen weicht signifikant zugunsten der männlichen Tiere ab. Dies lässt sich dadurch erklären, dass die Penetranz unter Männchen höher als unter Weibchen ist.

SAMMANFATTNING

Ärftlig hyperplastisk gingivit hos silverräv.

I början av 1940-talet iakttogs i Sverige en tandköttsdefekt hos silverräv, som i vissa rävgårdar nådde en snabb och omfattande utbredning. Defekten karakteriserades som en *hyperplastisk gingivit* (*Cederberg,* 1952). En liknande defekt finns beskriven för homo bl. a. av *Wassmund* (1935), som anser att sjukdomen är ärftlig efter en dominant princip.

På ett material, bestående av samtliga avels- och bruksdjur (1.080 föräldraindivider och 7.238 valpar) inom en större rävfarm under åren 1945—50, belyses sjukdomens genetiska natur. Gingiviten har visats vara positivt korrelerad till hög pälskvalitet, en korrelation, som ej synes vara av genetisk natur. Genfrekvensanalys har utförts på totalmaterialet. Defekten betingas sannolikt av ett enkelt, troligen recessivt arvsanlag med ofullständig penetrans. Könskvoten bland defekta individer avviker signifikant till förmån för handjuren. Detta kan förklaras av att penetransen är högre bland hanar än bland honor.

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