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ABNORMALITIES OF THE FEMALE GENITAL ORGANS IN MINK HETEROZYGOUS FOR THE HEGGEDAL FACTOR (SHADOW FACTOR)[1)]

By

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As has been stated earlier, the Heggedal factor is a dominant, autosomal, hereditary factor with homozygous lethal effect, and it seems to be allelomorphic to Black Cross and Royal Silver (*Nes & Slagsvold,* 1955; *Nes,* 1963 a & b).

In the further account of these and certain other colour types their genotypes will be stated, use being made of the following gene symbols:

S^H = Heggedal (Shadow factor), S = Black Cross, S^R = Royal Silver, F = Bluefrost, a = Aleutian, b = Royal Pastel, p = Silverblue, and s, f, A, B and P are the respective nonmutant allels in Standard Dark.[2)]

It has already been pointed out that the Heggedal factor, which in single dose has an extremely depigmentating effect on the fur, also seems to lead to a certain lowering of the viability of the kits. This has been noticeably strong when the Heggedal factor has

[1)] These investigations have been carried out with the aid of the Agricultural Research Council of Norway and of The Norwegian Fur Breeder's Association.

[2)] As this publication forms part of a more comprehensive work, which has in part already been published, I have for the sake of consensus not used the new names for the colour types of mink which have been introduced in Scandinavia by Nordiske Jordbruksforskeres Forening — Subseksjonen for Pelsdyravl (1963).

occurred together with the Black Cross factor in the combination type called Heggedal White, AA pp $S^{H}S$ and aa pp $S^{H}S$ (*Nes*, 1963 b). In combination with its recessive allel, as in Sapphire Shadow (aa pp $S^{H}s$) and Blue Shadow (AA pp $S^{H}s$) the lowering of the viability of the kits has been considerably less (*Nes*, 1963 a). Further, it has been found that fertility has been much lower in females with the Heggedal factor than in those without this factor.

In order to find the cause of these reproductive failures a preliminary investigation was made of a small number of females from The Research Station for Furbearing Animals in Heggedal. In a Blue Shadow female which had been mated two years in succession without giving progeny there was found by autopsy a marked abnormality of the uterus. As such abnormalities might be a plausible explanation of the fact that there were so many empty females among the heterozygotes, this finding gave a stimulus to further investigations in this field. If abnormalities were found, however, to be the sole explanation of sterility in these females, the frequency would have to be considerably higher than what *Dabczewski* (1960) found in his material of 245 empty females of other colour types, among which there were 3, i. e. 1.2 %, with developmental disturbances of the genital organs. As will be seen below, this proved also to be the case.

The abnormalities, which were mostly restricted to the uterus and vagina, resembled those found in cattle with the socalled white heifer disease, which occurs with high frequency in Dairy Shorthorn, but which has also occurred in Holstein Frisian, Aberdeen-Angus, Jersey, Guernsey and Ayrshire (*Fincher & Williams*, 1926; *Hart*, 1939; *Day*, 1944; *Spriggs*, 1946; *Rendel*, 1952; *Laing*, 1955; *Rollinson*, 1955; *Hanset*, 1959, 1960 a & b & 1961). Vaginal occlusion or imperforate vagina in mice has a similar manifestation (cf. *Marx*, 1936; *Fekete*, 1938; *Gowen & Heidenthal*, 1942; *Chase*, 1944; *Strong & Hollander*, 1949; *Grüneberg*, 1952). Further, great agreement was found between the abnormalities in this mink and the abnormalities of the genital tract in piebald hamster (*Orsini*, 1952; *Foote*, 1955). They called to mind also abnormalities found in human beings, such as atresia vaginae (*Weissenberg*, 1928), Hymen imperforatus (*McIlroy & Ward*, 1930) and hereditary absence of the uterus (*Delbet*, 1940; cf. *Gates*, 1952).

MATERIAL AND METHODS

The material for continued investigation of the female genital organs in mink has come from 5 farms in Norway and 2 in Sweden. It consists in part of empty females and in part of young females which have not yet been tried in breeding, and comprise for the most part Sapphire Shadow, but includes also a certain number of Blue Shadow besides a few Blue Shadow Carrier for Aleutian (Aa pp $S^{H}s$), which in the following account are grouped with Blue Shadow (Aa pp $S^{H}s$). Of these colour types, all of which were heterozygous for the Heggedal factor, we examined altogether 341 females. 136 of these were mated without getting any kits, and 205 were young females pelted before the first breeding season.

For purposes of control autopsies were made of 169 empty females without the Heggedal factor, of which 133 were Sapphire, 31 Royal Pastel, 3 Silverblue and 2 Standard Dark females.

The autopsies were performed mainly in connection with the pelting in November-December. The female carcases were in some cases sent to The Veterinary College of Norway for examination and in others the examination was performed in the course of visits to the mink farms in the pelting season. In the latter case the abnormal, and likewise the suspected material was taken to the abovenamed institution for closer investigation.

The colour types Blue Shadow and Sapphire Shadow are rather similar, and it is difficult or even impossible to distinguish Blue Shadow and Blue Shadow Carrier for Aleutian from each other. In pelting and in the forwarding of the animals the breeders have sometimes found it necessary to group them together. The same has therefore had to be done in the elaboration of the material (cf. table 1, the last, but one row). In some cases, however, it has been found possible to distinguish between Sapphire Shadow and Blue Shadow.

The investigation was carried out in the following way: After laparotomy the genital organs were first examined in situ. With a syringe, a 0.5 % solution of eosin was first injected into the uterus in order to ascertain whether there was open passage rearwards in the sheath and forwards through the uterine tubes. After removal, the vestibulum, vagina and the caudal part of the uterus were opened for inspection. If as a result of this examination, which also comprised the ovaries, no occlusion or any other anatomical deviation was discovered, the genital organs were regarded as normal. In the contrary case a more detailed investigation was performed, in order to localize possible occlusion in the uterine tubes or in the cervix or vagina. Suspected tissue, especially of the uterine tubes, was serially sectioned for microscopic examination, and in order to compare the structure of the malformed organs with the normal, micropreparations from other areas were also made — fixation in 4 % neutral formalin, staining with haematoxylin and eosin, Van Gieson's stain and Perl's Prussian blue reaction.

RESULTS

Frequency of the abnormalities.

By autopsy of the above material it was found that malformations of the genital organs occurred with great frequency in females which were heterozygous for the Heggedal factor.

Table 1.

The results of the autopsy of mated, but empty Sapphire Shadow and Blue Shadow females from the farms A, B, C, D and E. With regard to the age distribution, see text.

Colour type	Number of females autopsied	Age in years	Females with malformation of the genital organs	
			Number	Percentage
Sapphire Shadow	84	1.5	35	41.7
Blue Shadow	9	1.5	4	(44.4)
Sapphire Shadow + Blue Shadow	43	1.5 and 2.5	15	34.8
Total	136	—	54	39.7

As table 1 shows, we found by examination of 84 about 1.5 year-old empty Sapphire Shadow females that about 42 % of them had malformed genital organs. Among 9 empty Blue Shadow females of same age we found 4, i. e. a good 44 % with the same kind of malformations. This latter material was scanty, but it indicates that there is no essential difference between Sapphire Shadow and Blue Shadow when it relates to the frequency of such anomalies. In the mixed group of 43 empty Sapphire Shadow and Blue Shadow females there were approximately 35 % which had malformations of the genital organs. There were about equal numbers of each colour type in this group, but the colour indication was uncertain and the marking in part incomplete, for which reason the result is not specified. 36 of them are said to be about 1.5 years old and 7 are said to be about 2.5 years old. Among the latter were found two with malformations. It is nevertheless probable that the older females have contributed to reduce the frequency of malformations in this group relatively to the firstmentioned. As an average for the whole material of 136 empty Sapphire Shadow and Blue Shadow females, the frequency of malformed genital organs was nearly 40 %.

Table 2.

The results of the autopsy of about 1.5 year-old mated, but empty females of various colour types without the Heggedal factor (control group). They are derived from the farms A, C, F and G.

Colour type	Number of females autopsied	Malformation of the genital organs
Sapphire	133	0
Silverblue	3	0
Royal Pastel	31	0
Standard Dark	2	0
Total	169	0

As control, 169 about 1.5 year-old empty females, all of which had normally developed genital organs (Table 2), were autopsied. Of these 136 were Sapphire and Silverblue females. The difference between these and the 136 empty Sapphire Shadow and Blue Shadow females, with respect to frequency of malformations, is highly significant ($\chi^2 = 64.903$, 1 d.f., $P < 0.0005$).[1])

It should be noted that nearly one-half the empty Sapphire females were derived from Sapphire × Sapphire Shadow matings.

As an example of the distribution at the individual farms it may be mentioned that at farm A there were autopsied in 1961 33 about 1.5 year-old empty Sapphire Shadow females, of which 12 were malformed, i. e. 34 %. At the same time there were autopsied 19 empty Sapphire females of same age, all with normal genital organs. 18 of these were derived from the same litters as the Sapphire Shadows or were from litters from the same combination of parents. From the latter we should have expected 6 with malformations, if these had occurred in the females irrespective of colour type. Thus there was a clear difference between females with and without the Heggedal factor, and this was significant at the 1 % level ($\chi^2 = 6.658$, 1 d.f., $0.005 < P < 0.01$).

Autopsies were performed on 205 young *virginal* Sapphire Shadow and Blue Shadow females (see table 3). Among these, 38 were found with malformed genital tract, i. e. 18.5 %. Of the autopsied young females, 105 were derived from farm B and 100 from farm F, i. e. from a Swedish and a Norwegian farm

[1]) All chi-squares are adjusted for continuity (Yates' correction).

Table 3.
Results of the autopsy of young virginal Sapphire Shadow and Blue Shadow females.

Farm	Number of females autopsied	Females with malformation of the genital organs	
		Number	Percentage
B	105	19	18.1
F	100	19	19.0
Total	205	38	18.5

respectively. Thus the frequency of uterus abnormalities was approximately the same at the two farms.

The material from both these farms consisted for the most part of Sapphire Shadow, but also of some Blue Shadow females, without these being separated from each other. In the material from farm F there was, however, reliable determination of colour as regards 15 Blue Shadow females, and of these, 4 had malformed genital organs. These figures too give no indication of essential difference between the two colour types with respect to the frequency of such abnormalities (cf. the frequency of malformations in empty Blue Shadow and Sapphire Shadow females).

Pathological anatomy.

In the present investigations no malformation of the vestibulum or vulva has been found, and except in one case, the ovaries have not deviated from the normal. On the other hand, certain defects in the uterus and cervix and in the cranial part of the vagina were found. Exceptionally they have also comprised one of the uterine tubes. The abnormalities have consisted of a local aplasia or a hypoplasia of the said region of the genital tract, and have usually revealed themselves as constrictions, which have isolated certain areas of the genital tract. These have usually been more or less distended by retained secretion.

The malformations could vary greatly from animal to animal. They were nevertheless formed according to three different patterns, and on this basis they have been divided into three main groups:

I. Bounding of the rostral part of the vagina and secondary cystic distension of this, and usually with more or less cystic distension of the uterus.

II. Absence of the rostral part of the vagina and of the cervix uteri, and often of corpus uteri, accompanied by distension of the rest of the uterus.

III. Bounding of one cornu uteri with cystic distension of this, the other cornu being normal.

In the present material the abnormalities were distributed in approximately 50, 39 and 11 % of the cases in the respective groups.

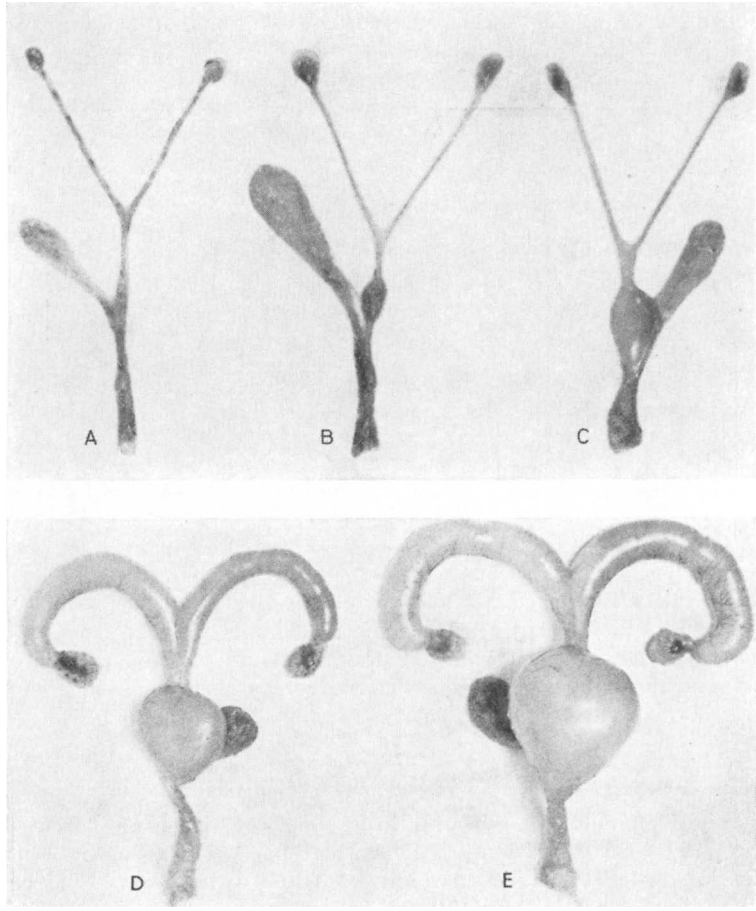


Fig. 1. A: Normal genital organs from a Sapphire Shadow female, about 1.5 years old, B and C: Malformed genital organs from two Sapphire Shadow females, about 7 months old, autopsied on November 15, D and E: From two Blue Shadow females about 10 months old, autopsied on February 25. Note difference in size of the vaginal cysts and the different distension of the uterine horns. (Ca. 0.5 ×).

GROUP I.

Owing to the amount of retained uterine secretion, great difference are found with respect to the dilatation of the malformed uterus and vaginal areas in this group (cf. Figs. 1 and 2). The anatomical shape was more constant. However, the variations found tell quite a lot about the development of the abnormalities. Four cases have been selected for more detailed description, in order to show the main variations within this group. The descriptions in all three groups relate to empty females approximately 1.5 years and 2.5 years old. The former were mated in one breeding season, the others in two breeding seasons. Parts of the genital organs, which are not mentioned, were normal.

Fig. 2. Shows the carcases of two Sapphire Shadow females with malformations of the genital organs, A: About 1.5 years old, with a large vaginal cyst and slightly distended uterine horns, (cf. Case 1), B: About 2.5 years old (Case 2) with a very large vaginal cyst and greatly distended uterine horns. (Ca. 0.3 ×).

Case 1. Sapphire Shadow female, about 1.5 years old.

In this female the abnormalities consisted, inter alia, in a delimination and a dilatation of the rostral part of the vagina (in the following called vaginal cyst). This cyst had a diameter of 5.5 cm in craniocaudal direction and 4.0 cm transversely to the animal (fig. 3).

The uterine horns were 8 cm long and had an external diameter of 3—4 mm. (In 22 normal females pelted at the same time the length was 4.30 cm (s = 0.41) and the external diameter varied from 2 to 3 mm). The uterine horns had a normal connection with the uterine tubes, which appeared to be normally developed. A short corpus

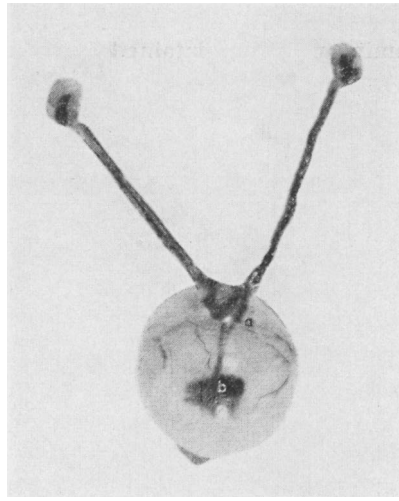


Fig. 3. Malformed genital tract of an approximately 1.5 years old Sapphire Shadow female (Case 1). The duct a-b, leading from the uterine corpus to the vaginal cyst, is made conspicuous by injecting a solution of methylene blue in the uterus and by replacing the secretion of the cyst with milk. (Ca. 0.5 ×).

uteri was attached to the vaginal cyst. Secretion from the cyst could not be pressed out in the corpus. It looked therefore as if there was complete closure between these sections. However, by injecting a methylene blue solution into the uterine horns it was possible to see a narrow duct leading backwards in the dorsal wall of the cyst and debouching down into this (a-b fig. 3). The length of the duct was about 2.5 cm and the diameter, which was 3 mm at the outlet from the uterus, decreased backwards to 1 mm at the mouth.

The cyst was completely closed backwards, and its caudal boundary was situated on the vagina about 1 cm rostrally to the entrance of the urethra, i. e. about 0.7 cm rostrally to the hymen folds. The distance from rima vulvae to the caudal limit of the cyst (later termed the vaginal depth = the actual length of the female copulation organ) was 2.5 cm. The wall of the cyst had an even, smooth and greyish inner surface, with a number of small desquamated areas. The microscopic structure resembled that of the vagina, but the wall was considerably thinner. On the inside it was lined with a stratified squamous epithelium (see fig. 4 B). In the lamina propria no glands could be found. The tunica muscularis was composed of an inner circular and an outer longitudinal layer. The lamina propria and in particular the muscularis were considerably thinner than in a normal vagina.

The narrow duct in the cyst wall connecting the distended corpus with the cyst was throughout almost its entire length lined with a

stratified squamous epithelium. Only in a short area close to the corpus uteri a simple cuboidal or low columnar epithelium was found. In this part the lamina propria contained a few glands. The border between the two types of epithelium was distinct (see fig. 4 A).

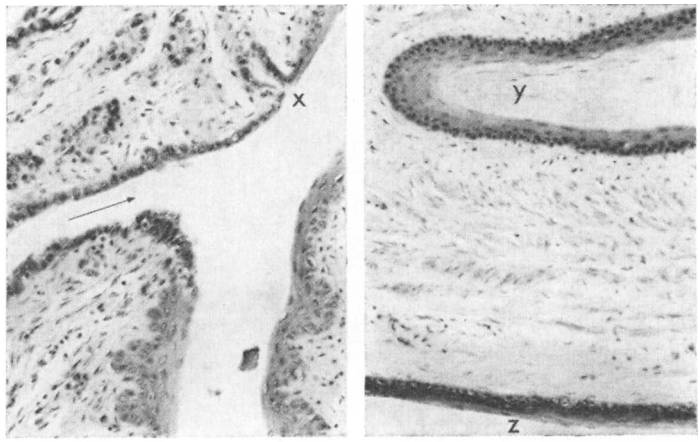


Fig. 4. Photomicrographs of sections of the duct a-b, Fig. 3 (Case 1). A: Section at a. The arrow in the duct at the outlet of the corpus uteri indicates the caudal direction. X a uterine gland on the border between the simple cuboidal of culumnar epithelium and the stratified sqaumous epithelium lining the duct. At the top right corner a loop of this is outside the photomicrograph, but the last-mentioned epithelium is clearly seen below. B shows a section at the caudal end of the duct (at b, Fig. 3). Y the duct still lined with stratified squamous epithelium. Z the stratified squamous epithelium lining the vaginal cyst (H-E staining). (Ca. 80 ×).

The endometrium had an almost normal appearance. In the somewhat distended corpus, however, the epithelium was lower than is normal, and characterized as cuboidal. In the cornua the epithelium was columnar, possibly a little lower than in normal animals at the same age, put to death at the same time of the year (cf. A and B, fig. 5). As in normal animals the myometrium was composed of an inner circular layer and an outer longitudinal layer of smooth muscles. Between the two layers the vascular layer was found.

Case 2. Sapphire Shadow female, about 2.5 years old.

This female was mated in two breeding seasons. A marked distension of the abdomen was observed after the first season, but the abdomen became still more distended after the second season. The animal then became somewhat sluggish, but the appetite was fairly good.

The malformations of the genital organs had resulted in considerably greater retention of uterine secretion in this female than in the foregoing one (cf. fig. 2 B). The weight of the genital organs was 155 g and the volume of retained secretion was 130 ml.

The right uterine horn was about 15 cm long and its diameter ranged from 1.3 to 2.3 cm. The corresponding uterine tube and ovary

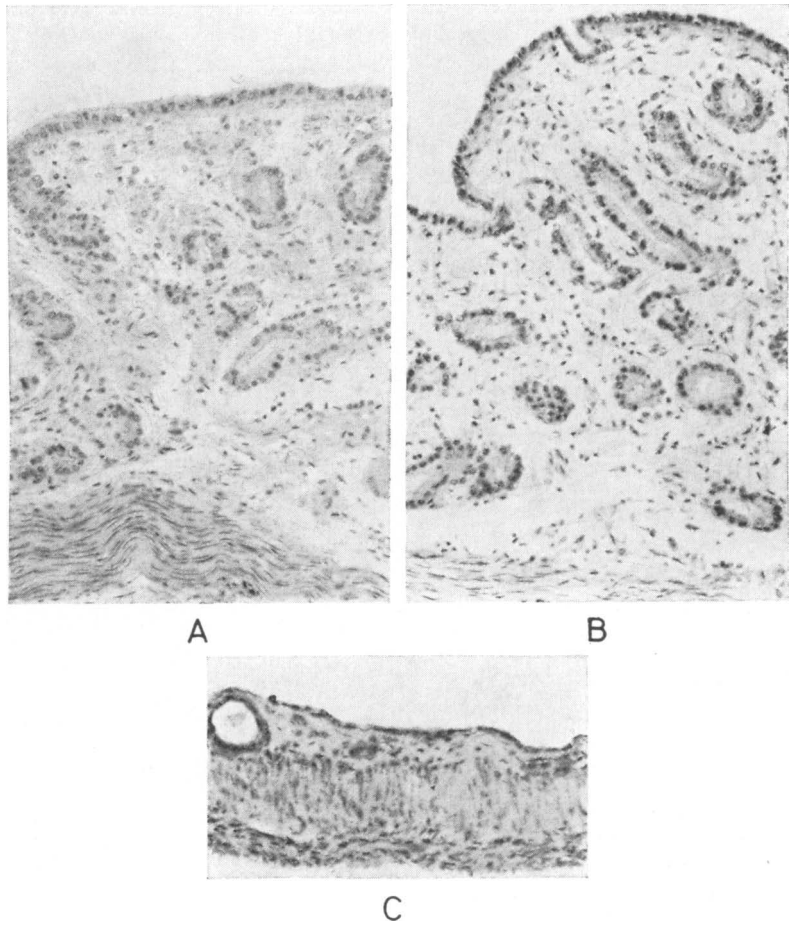


Fig. 5. A: The endometrium and a part of tunica muscularis of a uterine horn in a normal, approximately 1.5 years old, Sapphire Shadow female autopsied on December 10. B: The same from a Sapphire Shadow female with malformation of the genital tract (Case 1), of same age and autopsied at same time. No distension of the uterine horn (see text). C: Section of wall of a distended uterine horn of an approximately 2.5 years old Sapphire Shadow female (Case 2). In the top left corner a distended uterine gland. Cf. text (H-E staining). (Ca. 100 ×).

were normal. On the left side the horn had a caudal distended part and a cranial cordlike one. The former was 3 cm long and had the same diameter as the right horn. The latter, which was 5 cm long and 2—3 mm thick, was solid and composed of connective tissue and smooth muscles. Rostrally the cordlike part of the uterine horn was joined to a mass of tissue, not unlike the ovary and its surrounding bursa. By microscopical examination the tissue was found to be connective and adipose tissue containing coils of the uterine tube. The expected ovary could not be found. Serial sections showed that the uterine tube was partly extended, whilst other part were solid, without any lumen.

The uterine corpus was extended and approximately 1 cm long. This was closely attached to the vaginal cyst, and the two cavities communicated by means of two holes in their walls. They had a diameter of about 3 mm and the distance between them was about 1.5 mm.

The vaginal cyst, which was somewhat elongated in craniocaudal direction, was slightly flattened and measured about $8.5 \times 6.5 \times 5.0$ cm. Its caudal boundary was situated on the vagina about 0.9 cm cranially to the hymen folds. The vaginal depth was about 2.7 cm. The lining of the cyst had a greyish colour and had for the most part a smooth surface, but in some areas marked desquamation could be seen. The microscopic structure of the cyst wall is similar to that found in Case 1.

The thickness of the wall in the distended cornua and corpus of the uterus was only about one-fifth of that of a normal uterus. The epithelium was lower (cf. fig. 5, B and C), the lamina propria and the tunica muscularis were considerably reduced. The endometrium contained only a few glands.

Case 3. Sapphire Shadow female, about 1.5 years old.

The malformation of the genital organs was of the same type as in the foregoing cases.

The cyst on the vagina was somewhat egg-shaped, its longest diameter about 3 cm and the shortest about 2 cm. The caudal boundary was situated about 0.7 cm rostrally to the hymen folds, and the vaginal depth was about 2.4 cm. Rostrally the vaginal cyst communicated by means of an approximately 2 mm long fissure in the cyst wall with the left uterine horn. There was complete closure toward the right uterine horn. The uterine horns were connected with each other for a distance of 2 mm, but there was no communication between them and thus no corpus existed. The right horn was about 12 cm long and had a diameter of 1.5—2 cm, whilst the corresponding measurements for the left uterine horn were about 8 and 1 cm respectively. The difference in size is apparently due to the fact that the left uterine horn, unlike the right one, had pressed some of its secretion over into the distended part of the vagina. Thereby it had contributed to the cyst formation.

The uterine tubes were open and the ovaries seemed to be normally developed. No microscopical examination was performed.

Case 4. Sapphire Shadow female, about 1.5 years old.

The malformations of the genital organs were of the same type as the foregoing ones, but the dilation of the vaginal area involved was small, and the content of secretion was scanty. It was spindle-shaped, about 1.5 cm long and about 0.8 cm in diameter at the thickest part. It was completely closed at both ends and its caudal boundary was situated 0.6 cm rostrally to the hymen folds. The vaginal depth was approximately 2.2 cm. Rostrally the vaginal cyst bordered the uterine corpus. The uterine horns, which were cystically distended, had a length of about 12 cm and a diameter of 1.5—2 cm. The uterine tubes were open and the ovaries seemed to be normally developed. No microscopical examination was performed.

In general it may be said of the malformations in this group that they are characterized by delimination and a cystic dilation of the cranial part of the vagina and as a rule a more or less pronounced distension of corpus and cornua uteri. Mostly the uterine corpus is well developed, but may be lacking. Usually the uterine horn is uniform throughout its entire length, but may also be broken by a constriction, in rare cases by several constrictions. It is also observed that a uterine horn may consist of a dilated part and a hypoplastic and compact part (Case 2).

As a rule the tubo-uterine connection is open, but may be broken by a constriction at the tip of the horn. The uterine tubes and the ovaries are usually normal. Only one exception to this rule has been recorded (Case 2).

The caudal boundary of the vaginal cyst has in all cases more or less reduced the vaginal depth. In the group under discussion the rostral end of the copulatory organ was found to be 0.6—1.2 cm rostral to the external orifice of the urethra, i. e. about 0.3—0.9 cm rostral to the hymen folds. The vaginal depth has in this material of young and older females varied from 1.8 to 2.7 cm. In 19 malformed young females it was on an average 2.15 cm ($s = 0.28$), whilst in 22 normal young females it was 3.85 cm ($s = 0.28$). The difference, i. e. the length of the vaginal area involved in the malformation, was on an average 1.7 cm. The length of the vagina (measured from the hymen folds to the external orifice of the uterus) was in the normal females on an average 2.30 cm ($s = 0.18$). Thus about three-fourths of the vagina was involved in the malformation.

Rostrally the boundary of the cyst was usually situated close to the uterus, and it seemed as if the cervix, and sometimes the corpus or at least part of it, were included in the cyst. By a

systematic examination of the epithelial lining of four cysts in this group, however, only stratified squamous epithelium was found. Simple epithelium was found only a very short distance along the most rostral end of the duct connecting the uterus to the cyst. This indicates that the cyst itself and the major part of the narrow duct are developed from the vaginal area of the Müllerian ducts. It seems likely that the rostral boundary of the cyst is formed by a constriction in the area where the cervix is normally developed. Whereas the vaginal cyst is completely closed caudally, it has in the great majority of cases proved to have communication with the corpus or with the uterine horn, if the corpus has been lacking. As a rule the corpus was found to be connected to the cyst by a fine duct passing backwards in the dorsal cyst wall and then debouching into the cyst. The length of the duct has varied, and the entrance to the cyst has therefore been situated at a certain distance from its cranial pole, but usually not behind the centre of the cyst (cf. development). By such connection there will be a valvular effect, so that the secretion in the cyst cannot, or can only with difficulty, be pressed forwards into the uterus, whilst the passage in the opposite direction is easier. This may afford an explanation of the fact that the corpus and cornua are in such cases often less distended by retained secretion than in cases where these sections have open connection (communication) with the cyst through one aperture or two apertures in the cyst wall (cf. Cases 1 and 2).

This arrangement with communication through one aperture or two apertures in the cyst wall has been rare in the present material. The frequency of the cases with only one aperture in the cyst wall may, nevertheless, be questioned, as they are difficult to distinguish from those with an extremely short duct. In one case (Case 3) there was one aperture which led forwards to one uterine horn. The other horn was completely closed toward the vaginal cyst. When, as in this case, no corpus is found, we would also expect that the uterine horns might have connection with the cyst each through its aperture. But this has not been observed in the present material. On the other hand one case exists where there are two apertures in the cyst wall, which lead cranially to a dilated corpus (cf. Case 2).

Complete cranial closure of the vaginal cyst has only been found in one case (Case 4). The delimited vaginal area contained in this case little retained secretion, and the cystic distension

was therefore small. On the other hand the uterine horns were greatly dilated by retained uterine secretion. This diversity from the aforementioned types of abnormality in this group shows that the cystic distension of the delimited vaginal area is in all essential respects due to the retained uterine secretion, which has been pressed backwards, a circumstance which might have been expected in view of the secretory conditions in uterus and vagina.

GROUP II.

Besides the variation in the cystic dilatation there were also in this group found some variations in the anatomical structure. In order to show the chief of these, the three following cases have been selected for detailed description (Cases 5—7).

Case 5. Blue Shadow female, nearly 2.5 years old.

This female was mated two years in succession without getting kits. Already after the first breeding season its abdomen distended, but this became still more marked after the second breeding season. Thus in the course of the spring and summer the animal showed symptoms of ascites and was treated by tapping of fluid (cf. Symptoms). As will appear from fig. 6 A, the genital organs were greatly malformed. The rostral part of the vagina, besides cervix and corpus uteri, was totally lacking. The vagina ended blindly about 0.7 cm cranially to the hymen folds. Residues of the area in front could only be discerned as a streak of connective tissue, which was lost in the broad ligament. The vaginal depth was 2.3 cm. The right uterine horn was much enlarged, but with only moderate quantities of retained secretion (cf. Tapping). It was approximately 15 cm long and 3—4.5 cm wide in half-filled state and had no open connection with the tube or with the rest of the uterus. The left uterine horn consisted of one large and three small individual retention cysts, besides a 2.5 cm long and 2—3 mm thick solid strand next to the ovary. This consisted of connective tissue, and smooth muscles. The tube was normally developed.

The uterine secretion was practically odourless, a triffle viscous, and had a dark greenish-brown colour. Bacteriological examination was negative. The microscopical structure of the distended uterus corresponds to that described in Case 2.

Case 6. Sapphire Shadow female, about 1.5 years old.

In this female the uterine horns were extremely dilated and had a length of about 17 cm and a diameter of up to 2.3 cm (fig. 6 B). The tubo-uterine communication was broken on the right side by a constriction at the tip of the uterine horn, but was open on the left side. The uterine tubes seemed to be normally developed. The uterine horns

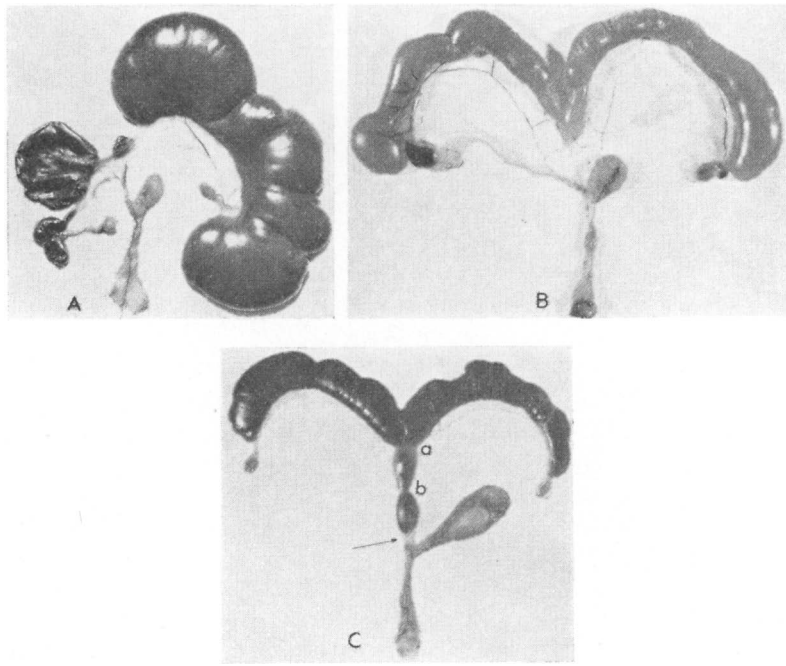


Fig. 6. Malformed genital tracts of three females. A: Blue Shadow, approximately 2.5 years old (Case 5). B: Sapphire Shadow, approximately 1.5 years old (Case 6), and C: Sapphire Shadow of same age (Case 7). The constrictions at a and b indicate partition walls which prevent communication between the corresponding parts of dilatated uterus. The arrow indicates a part of the broad ligament of the uterus connecting the malformed uterus to the vagina, which is shorter than normal. (Ca. 0.25 ×).

coalesced and formed a short corpus uteri. This ended blindly, the cervix and rostral part of the vagina being lacking. The vagina ended about 1.7 cm in front of the hymen folds. Thus it was only a short piece of the vagina which was malformed, and the vaginal depth, which was about 3.5 cm, was not substantially less than in normal females of same size. Histologically the uterus was indistinguishable from the malformed uterine horns in case 2.

Case 7. Sapphire Shadow female, about 1.5 years old.

The rostral area of the vagina was lacking in this female, and the vaginal depth was about 2.5 cm. The uterine horns, which were extremely dilated, were about 11 cm long and up to 2 cm in diameter (fig. 6 C). The communication with the left uterine tube was broken by a constriction at the tip of the uterine horn, whereas the connection with the right uterine tube was open. However, the tubes appeared to be normal on both sides.

The uterine horns had no communication with each other, but — as will appear from the picture — they joined together to form a structure of hourglass shape, approximately 5 cm of length and with a maximum diameter of about 1.5 cm. At the constrictions a and b, fig. 6 C, there were partition walls which divided the said area into two cysts. These had no communication with each other, nor with the uterine horns. The histological picture was the same for these cysts as for the uterine horns, and corresponded to what is described for dilated uterine horns in Case 2.

In general it may be said of this group of malformations that the rostral part of the vagina, the cervix, and in part also the corpus uteri, have not developed. The aplasia of the vagina, however, varied considerably from animal to animal. In some animals it only comprised an insignificant portion of the vagina's cranial end, whilst in others it included most of the vagina, so that the cranial boundary of this was situated only a few millimetres (4—5) in front of the hymen folds. Thus the vaginal depth varied considerably more in this group than in group I. In this material, consisting chiefly of young females it varied from 1.8 to 3.5 cm. In the case of 17 malformed young females it was on an average 2.45 cm ($s = 0.45$).

Complete absence of corpus is rather common in this group, but as a rule the uterine horns are united in a corpus-like section, which may vary in shape. The most usual in this material is that described in Case 6 (fig. 6 B).

With respect to the uterus, it should be noted that in this group cases have been found with more constrictions of the uterine horns than in the other groups. The tubo-uterine communication has in certain cases been broken by a constriction at the tip of the uterine horn, but the tubes have been normal. The same is true of the ovaries.

GROUP III.

Besides variation in the cystic dilation, there were differences in the anatomic form. To show the most important of these differences we have selected 2 cases for more detailed description.

Case 8. Sapphire Shadow female, about 1.5 years old.

This female had one malformed and one normal uterine horn. As fig. 7 A shows, the right horn was entirely separated from the rest of the uterus and was greatly distended by retained secretion. The length was 8 cm and the diameter 1.8 cm at the thickest part. It was

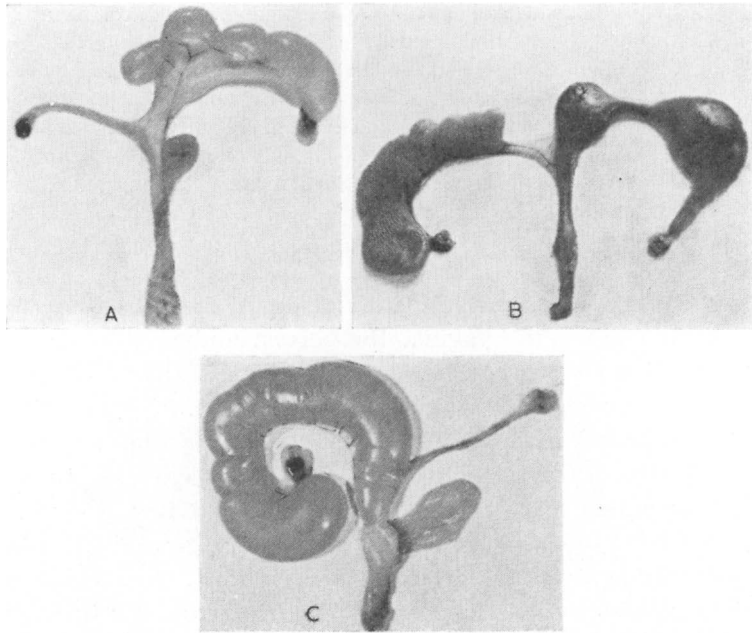


Fig. 7. Shows malformation of the genital tracts in three females. A: Sapphire Shadow about 1.5 years old (Case 8). B: Blue Shadow, 1 year old, pregnant in right uterine horn (left foetus dead at time of autopsy, right one alive). C: Sapphire Shadow, about 1.5 years old (Case 9), has been pregnant in right uterine horn. Two dark spots, clearly seen in the original photo, indicate implantation sites of two foetuses. (Ca. 0.35 ×).

connected with the rest of the uterus solely by the broad ligament, but had open connection with the tube, which seemed to be normal.

The left uterine horn was normally developed. It was 5.5 cm long, had an external diameter of 2—3 mm and had an open connection with cervix and vagina, which appeared to be normal. The vaginal depth was 3.4 cm.

The microscopical structure of the wall in the normal uterine horn corresponds in general to what is described in Case 1, whereas the distended horn is similar to Case 2 in this respect.

The female with the said malformations was empty, but, as will appear from fig. 7 B, such females can be pregnant in the normal uterine horn.

Case 9. Sapphire Shadow female, about 1.5 years old.

The malformations in this female deviated in some respects from those observed in the previous cases. Thus the abnormal left uterine horn was not separated from the rest of the uterus (cf. fig. 7 C). It was extremely dilated and had a length of 14 cm and a diameter of 2—2.5

cm. Caudally it was bounded by a somewhat distended vagina, but was separated from this by a partition wall in the cervical area. The right uterine horn was of normal size, approximately 5 cm long and had a diameter of 3 mm. About 2.5 cm cranially to the said wall it joined the left horn and continued in the form of a narrow duct backwards in the dorsal wall of the vagina, passing into the latter about 8 mm caudally to the rostral end. The vaginal depth was 3 cm. The female had been pregnant in the right uterine horn, where there were distinct marks after the implantation sites of two foetuses.

The histological changes in the section from the dilated uterus correspond to those found in Case 2.

In general it may be said of the abnormalities in this group that they are characterized by delimitation and cystic distension of one uterine horn, whilst the other is normal.

In some the malformed uterine horn is completely separated from the rest of the uterine (Case 8). In others it is connected to the vagina, but is separated from this by a constriction (partition wall).

The vagina may vary somewhat with respect to length and diameter. In some cases it is normal, in others it is somewhat distended (Case 9), and it has also been found that it may be extremely constricted cranially. In the former case the vaginal dept will be fairly normal or a little diminished, whilst in the latter case, according to measurements performed on live mink, it may appear to have less depth than it has in reality. Thus in live mink a vaginal depth of 2.2 cm was measured in one case, whereas it was actually about 3.0 cm. In the other 9 cases in this material it has on an average been 3.1 cm (variation 2.8—3.4 cm) measured in dead females.

The malformations in this group are less marked than in the other groups. Thus no extra constrictions have been found in the present material on the malformed uterine horn. Tubes and ovaries have been normal and the tubo-uterine junction has been open in all. On the whole the defects have not been greater than that the females have in some cases been pregnant in the normal uterine horn (cf. fig. 7 B & C).

The cystic dilatation.

The cystic dilatation, which is due to retention of the uterine secretion, increases with the age of the females. But the uterine secretion seems rather to increase cyclically than linearly. In the female kits no significant retention will be found before pelting

time, November-December, i. e. when they are approaching sexual mature age (cf. fig. 1 B & C). The quantity of retained uterine secretion increases rapidly before and during the first breeding season. Thus in February we find a considerably larger dilatation of the malformed areas of the genital tract (cf. fig. 1 D & E). In the mating season and up to the time of normal parturition, the retention seems to be at its maximum. The size of the abdomen increases and the females usually look as if they are pregnant. The cystic dilatation is usually considerable already after the first breeding season (cf. fig. 2 A).

In females which have been allowed to live, we have observed still further increase of the cystic dilatation in connection with the second breeding season (cf. Case 2, fig. 2 B & Case 5, fig. 6 A). In one case it was observed that the size of the abdomen increased even during the spring and early summer. It looked like a case of increasing ascites.

The largest retention of secretion is found in connection with malformations of types I and II. In malformations of type III there is free outlet for the secretion from one uterine horn.

With regard to the *nature of the secretion,* we have found that it is practically odourless and a trifle viscous. The colour may vary from light yellow to a more or less greenish-brown colour. Cases have also been observed where the secretion has had a light yellowish tint in one uterine horn, whilst it has been dark greenish-brown in the other. The dark colour, which is most usual in adult females, is apparently due to hemorrhages and decomposition of the blood. This assumption is supported by the fact that by histological examination (Perls' Prussian blue reaction) it was found hemosiderin accumulations in the lamina mucosa of the cavities containing the dark secretion, whereas by corresponding examination of cavities with light secretion, only a negligible quantity of hemosiderin could be found. (The hemosiderin test is only performed in a few cases).

Development of the malformation.

On the background of the normal development of the genital organs the said variations in the abnormalities provide a good basis for an estimation of the way in which they have developed.

In development of the female genital organs the whole genital tract, with the exception of the vestibulum (sinus urogenitalis) is formed from the Müllerian ducts. These are developed from

the coelomepithelium and are situated symmetrically along the primordial kidney in the form of two strands, which subsequently develop into ducts.

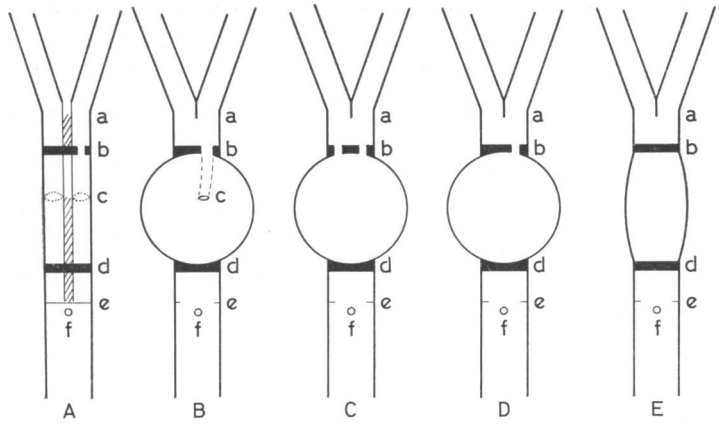
The caudal ends of the Müllerian ducts enters the sinus urogenitalis. In the caudal part the two ducts fuse together to form the vagina and the caudal part of the uterus. The length of this fusion determines the various uterine forms. In mink there is a bicorn uterus (uterus bicornis) with a short corpus and a somewhat longer cervix.

The caudal boundary of the Müllerian ducts is the hymen, which in mink females is faintly marked by fine transversal folds of the mucous membrane. The vestibular section of the genital tract, which lies caudally to the hymen, is formed by the cloaca being divided into the sinus urogenitalis (vestibulum) ventrally and the rectum dorsally. The gonads develop as ridge-like thickenings on the ventro-medial surface of the primordial kidney. The anlage consists of a mesenchymal core covered by the germinal epithelium (*Zietzschmann & Krölling*, 1955).

The abnormalities in mink seem to be restricted to the Müllerian ducts and are of the category designated as hypoplasia or aplasia segmentalis ductus Mülleri.

The abnormalities recorded in group I indicates that the development has in general proceeded in the way shown diagrammatically in fig. 8.

Retardation or arrest of the canalization and of the fusion of certain areas of the Müllerian ducts causes constrictions, obliterations or other malformations of the corresponding parts of the genital tract. Thus there is invariably a complete closure of the vagina in front of the hymen folds (cf. fig. 8). Similarly it usually causes various forms of malformation of the cervix, sometimes with complete closure (cf. fig. 8 E). In the same manner often constrictions or obliterations of the corpus and cornua uteri are formed. With respect to Case 1, fig. 3, the development of the duct which passed from the corpus caudally in the wall of the cyst may be explained in the way that the medial walls of the Müllerian ducts are persisting in an area corresponding to the rostral part of the vagina (b-c, fig. 8 A). A corresponding area of the Müllerian duct has then developed into a narrow duct (b-c, fig. 8 B), opening caudally into the bounded vaginal area and cranially into the corpus. The cervix has been open on the same side. (Cf. Case 1, fig. 3, where it can



F i g. 8. Diagrammatic illustration of development of the malformation in Group I, such as the anatomical finds indicate that it has proceeded. The caudal parts of the Müllerian ducts, as well as sinus urogenitalis, are drawn in. By resorption of the medial walls, a-b become corpus and cervix, b-e vagina. On the stretch b-c they may be persisting — and the duct b-c is then formed (B). b = the constricted part of cervix uteri which may be completely closed (E) or may have one opening (B and D) or two openings (C). d = constriction (closing) of the vagina. e = hymen (hymen folds). f = the external urethral orifice (see text).

be seen that the duct emerges a little to the right of corpus). The corresponding part of the other Müllerian duct has formed a blind sac, the cervix being closed on that side. Thus when retained uterine secretion has been pressed backwards from the cornua and corpus, the blind sac, together with the caudal part of the closed vaginal area, has developed into a cyst, which has enclosed the said duct in its wall.

C, D, E, fig. 8 illustrate the development of vaginal cysts without the said duct. In these cases there are no persisting medial walls of the Müllerian ducts in the distended part of the vagina. In the case shown in fig. 8 C, the cervix has been canalized on both sides, i. e. there is communication between the corpus and the cyst through two apertures in the cyst wall. This was found in Case 2.

If the cervix is only canalized on the one side, a corresponding communication will be obtained through a single hole in the wall of the cyst, fig. 8 D. In this material no case just like this has been found, but in Case 3 such a connection was found

between the cyst and the one uterine horn, as no corpus was formed.

When canalization in the cervical area has failed to occur in both the Müllerian ducts, the isolated area of the vagina has been completely closed in front, fig. 8 E. This has been observed in one case in the present material (Case 4).

The malformations in group II may be explained as being due to the fact that the development of the same sections of the Müllerian ducts have been still more severely retarded. This has caused a complete aplasia of the rostral part of the vagina. The same applies to the cervix and in part to the corpus also. As already mentioned, more constrictions of the uterine horns have been observed in this group than in the other two groups — a fact which suggests that we are faced here by a stronger retardation of the normal development.

In group III it has apparently had a smaller influence. The one uterine horn is completely separated from the rest of the uterus, or delimited from this by a constriction in the cervical area. On the other hand we do not find here any complete constriction of the other uterine horn, and the vagina is normal or only slightly deformed.

Hereditary conditions.

The described malformations of the genital organs in mink have hitherto only been demonstrated in females of Sapphire Shadow (aa pp $S^{H}s$), Blue Shadow (AA pp $S^{H}s$) and Blue Shadow Carrier for Aleutian (Aa pp $S^{H}s$). In the control group, which included Sapphire (aa pp ss) and Silverblue (AA pp ss), no female has been found with malformation. In other words, the malformation has only manifested itself in mink with the Heggedal factor. As stated above, this difference between mink with and without the Heggedal factor is significant. It seems clear therefore that the Heggedal factor directly or indirectly gives rise to this anomaly. Thus the abnormalities of the genital organs may be explained as a result of a pleiotropic effect of this hereditary factor.

With regard to this effect on the female genital organs, it acts as a dominant hereditary factor, with incomplete penetrance and varying expressivity. As will appear from table 3, the penetrance in the females has been about 18.5 % (18.54 ± 2.71). Hitherto no malformation of the male genital organ has been

found. This suggests that the said pleiotropic effect of the Heggedal factor is sex-limited.

Symptoms and diagnosis.

The abnormal females seem to have normal estrus and are usually willing to mate. The males have, however, often difficulty in performing the mating act with such females. After many unsuccessful attempts the females become more or less exhausted and hostile. This is probably the reason why certain breeders have come to the conclusion that such females do not have normal heat, whereas the majority maintain the opposite view. The animals have often difficulty in clinging together during mating, a circumstance which is probably due to the reduced vaginal depth in the malformed females. Mating difficulties which express themselves in a similar way may also occur in mink which do not have malformations in the genital organs, and they cannot therefore be said to be pathognomonic for this state.

Other symptoms of the anomaly are an enlargement of the abdomen, which is a direct consequence of retention of secretion and the cystic dilatation of uterus and vagina. According to our observations, this is especially associated with the breeding season and the gestation period. The condition is therefore easily confused with pregnancy. In some cases we have also seen growth of the nipples, and the condition has taken the form of a pseudopregnancy.

Although the amount of secretion may be very large, especially after two breeding seasons, it seems seldom to inconvenience the animals in any significant degree. But we have an instance where the general condition was affected. This revealed itself in reduced appetite and lassitude (Case 5). The condition, which resembled ascites, improved after tapping off the secretion.

It should be noted that in differential diagnostic respects the anomaly may be confused with ascites. The frequency of this latter ailment is, however, very small in comparison with the frequency of uterine malformations in the genotype in question. The chance of these ailments being confused is therefore very small.

It should be noted, further, that in the material under discussion we have not found any case where the abnormal uterus has been affected by any inflammation. The possibility of confusion with an exudative inflammation does, however, exist. Metritis is

not altogether unusual in mink. As a rule it is connected with a purulent infection at birth, it may be in association with retained placenta, and the process is then often prolonged. A typical pyometra may then occur, with considerable increase in the size of the abdomen and a chronic stinking flow from the vagina (*Momberg-Jørgensen*, 1952). In the abnormal females, on the other hand, we have not found any flow from the vagina. This difference, in addition to the other symptoms, should furnish a reliable basis for distinguishing these ailments.

As we have seen, the vaginal depth is more or less reduced in most of the females with these malformations. It is therefore to a large extent possible to distinguish abnormal and normal females from one another by measurement of the vaginal depth. This can be done already in the pelting season November-December.

The depth will vary somewhat, according to the size of the females, and it is advisable therefore to compare the measurements from fairly equal-sized animals. It varies also with the thickness of the instrument and the pressure exerted on the instrument. The same person ought therefore to perform all the measurements and the same instrument be used. A knob-probe, diameter 2—2.5 mm, with graduated scale seems to be suitable. With a drop of liquid paraffin on the probe it will slide more easily into position. To avoid passing it into the urethra the probe should be allowed to slide in along the dorsal wall of the vestibulum.

On the basis of the mean vaginal depth and the standard deviation in normal and abnormal animals the possibility of forming a correct diagnosis seems to be quite good (cf. Pathologic anatomy). If we had put the lower limit for normal vaginal depth at 3.0 cm and pelted all females below this, we should have expected to get culled nearly all those with abnormality of type I and nearly 90 % of those with abnormality of type II: At the same time we should have risked pelting only about 1 ‰ of the normal females. In group III there were in the present material only 2 out of 10 females which had a vaginal depth below 3 cm, whilst 4 lay accurately at 3 cm and would have been the subject of doubt if they should have been culled solely on this ground.

On the whole it must be reckoned that we shall always find borderline cases where there may be doubt about the diagnosis and that the result is not so favourable as the calculation above

indicates. But with a certain amount of practice the frequency of such erroneous diagnoses will be relatively small. By repeating the examination before the mating, viz. at the end of February, the retention of secretion usually gives some support to the diagnoses, especially in those with vaginal cyst. They can then often be felt through the abdominal wall. As the pelt is still relatively good, an examination and pelting of abnormal females at this time will usually answer the purpose.

In order to test the usefulness of the methods in practice a breeder (S. Heglum) examined his 15 young females of Blue Shadow on February 25. He measured the vaginal depth with a knob-probe 2.0 mm thick. In 11 animals the measurements varied from 3.0 to 4.0 cm, in 4 they varied from 2.0 to 2.5 cm. The latter were regarded as abnormal. The diagnoses were verified by palpation, and autopsy showed that all four had malformed genital tracts, 3 of type I (cf. fig. 1 D and E) and 1 of type III. The latter had a constricted vagina in front, and the measured depth was therefore less than normal. The 11 other females were later found to have normal genital organs. (This test of the method was arranged and the results controlled by the writer).

DISCUSSION

With regard to localization of the abnormalities, it should be noted that in the present material only one defective uterine tube has been found (Case 2). This tube, as a matter of fact, also forms an exception in that the connection with the ovary was completely broken. Otherwise malformations of the uterine tubes have a tendency to escape observation. The present investigations indicate, nevertheless, that the tubes are as a rule normally developed. This is in accordance with what has been found in cattle with white heifer disease or similar malformations (*Spriggs,* 1946; *Teige,* 1956).

The ovaries were normally developed in all the females except in the case mentioned above, where one of the uterine tubes had no connection with the corresponding ovary. It is probable that the ovary was developed, but that it had escaped notice. When this abnormality was noted, the mink carcase was no longer available for closer examination. *Dabczewski* (1960) found in one Standard Dark female that the right ovary lay loose in the fat of the abdomen, whilst the corresponding uterine horn and uterine tube were atrophic. A similar condition may have

asserted itself in this case also. The rule seems to be that the abnormality is restricted to the area of the genital organs which are developed from the Müllerian ducts and effects the vagina, cervix, corpus and cornua uteri, and exceptionally the uterine tubes, whilst the ovaries, vestibulum and vulva, which have a different origin, remain normal. That the abnormalities are restricted to definite organs or regions is usual, and we have also examples of the said localization in other animals. Thus the malformations characterized as white heifer disease are also restricted to the areas formed by the Müllerian ducts (*Spriggs*, 1946). In the so-called sexual gland hypoplasia, which may affect both sexes and has been found in Swedish highland cattle, it is, on the other hand, at any rate primarily, only the gonads which are affected (*Eriksson*, 1938 a & b, & 1943; *Lagerlöf*, 1939; *Lagerlöf & Settergren*, 1952; *Lagerlöf & Boyd*, 1952; *Settergren*, 1954).

With respect to localization of the abnormalities in the Müllerian ducts, it should be noted that in the present material no case was discovered with imperforate hymen, such as has been found in white heifer disease (*Spriggs*, 1946). The caudal constriction of the vagina has often been situated near the hymen folds, but always in front of these.

As we have seen, females with abnormalities of type III may be pregnant in the normal uterine horn. How often this occurs does not appear from the present material. The animals which have given birth to kits were not included in the empty females. This would in such case have led to a relatively lower frequency of malformations of type III in empty females than in the female kits in this material. A tendency in this direction is also recorded, but it is not significant. (9 % of the defective empty females and 13 % of the defective virginal females were afflicted with this type of malformation). Otherwise there is ground for thinking that some of these abnormalities will create a disposition to birth difficulties in such females.

Among young virginal Sapphire Shadow and Blue Shadow females it was found that the frequency of abnormalities was 18.5 %, whilst among young empty females of the same colour types it was about 42 %.

On the basis of these frequencies we should expect that approximately 44 % of the total number of mated young females were empty and 31 % of the females which had normal genital tract. By way of comparison it may be mentioned that in a

material derived from three farms and consisting of 71 young Sapphire Shadow females, mated with Sapphire males, the frequency of empty females was 47 % and the corresponding frequency among females with normal genital tracts was calculated to be about 35 %. Thus there is relatively good agreement between the calculated and the found percentage of emptiness in all females mated. As regards the Sapphire Shadow females with normal genital tract, the corresponding frequencies are reckoned to be of about the same order as the frequency found by *Johansson* (1955) in 164 Sapphire females mated with Sapphire males. 31.7 % of these females were empty.

In view of the poor breeding results which the Shadow females gave, the males were preferably used in the breeding. For this reason it has been difficult to obtain sufficient material for elucidating the fertility of Shadow females with normally developed genital organs. Expressed in percentage of fertile matings, however, it seems to be fairly good. With regard to the litter size, it may be mentioned that in a material which was collected in 7 mink farms and consisted of 106 litters obtained by mating Sapphire Shadow females with Sapphire males, the average litter size was found to be 3.7 kits at weaning. In 433 litters resulting from reciprocal crosses carried out at the same farms at the same time there was obtained an average litter size of 4.1 kits at weaning (*Nes*, 1963 a). The difference is not significant and the average litter size obtained by mating Sapphire Shadow females with Sapphire males is acceptable. In other words, it should be possible to obtain respectable results by using normal escapers in the breeding. And with a view to reducing the frequency of the hereditary factor or factors which may exert an influence on the penetrance of the Heggedal factor with respect to these abnormalities it should be an advantage to use the normal Shadow females in the breeding in preference to the males of same colour type. Unlike the normal females, the males form an unselected breeding material as far as the modifying hereditary factors are concerned. No corresponding abnormalities have hitherto been found among the males.

With regard to the apparently sex-limited character of the abnormalities it may be mentioned that there has not been any remarkable high frequency of sterility among the males which would indicate that the anomaly necessarily manifests itself among them. On the other hand it is conceivable that the expres-

sivity of the abnormalities is less in their case, the result being, for example, that only one ductus deferens is closed. In such case the males would not be sterile and the abnormality would easily be overlooked. In a material consisting of poultry, *Finne & Vike* (1949) found Atresia ductus deferentis dextra in a cock which had sired many daughters with Atresia isthmi. On the other hand, similar abnormalities in piebald hamster (*Orsini,* 1952) and in cattle with white heifer disease affected only the female sex (*Spriggs,* 1946).

With regard to the hereditary conditions, the abnormalities can, as stated, be explained as a pleiotropic effect of the Heggedal factor, which in this respect has an incomplete penetrance and a varying expressivity. What factors influence the penetrance and the expressivity have not been elucidated. We have above indicated the possibility that it may relate to modifying hereditary factors, but environmental factors (external and/or internal) may also wholly or in part be responsible for the variations found in this respect (*Hadorn,* 1961). For purposes of comparison it may be mentioned that, when it is a question of variations in the occurrence of white heifer disease in roan and white Shorthorns, *Rendel* (1952) thinks that a combination of environmental factors is the most probable explanation, but he does not rule out the possibility that modifying factors exert an influence. *Hanset* 1960 a & b) reckons that this anomaly may be due to a physiological action of the gene for white (N), generally in double dose, supplemented by one or several recessive genes at loci independent of locus N. Other investigators have come to the conclusion that these abnormalities are due to a gene which is linked to the factor for white in Shorthorn cattle (*Boyd,* 1944; *Gilmore,* 1949). In conformity with this hypothesis it is conceivable that the abnormalities in mink are due to a gene which was so closely linked to the Heggedal factor that no crossing over had yet occurred which had resulted in malformed recombination types without the Heggedal factor or Shadow-coloured mink without the gene in question.

On the basis of information from the owner of the first Heggedal mutant, Mr. Rolf Wiig, Heggedal, the average fertility in females with the Heggedal factor seems always to have been less than in corresponding mink without this factor. It can be assumed therefore that it is the same mutation which has caused these abnormalities and the light colour. Whether or not it is

related to a gene mutation or a chromosome mutation is not as yet clear. No numerical or morphological change of the chromosomes has been demonstrated (*Nes,* 1962). Morphological changes can, however, by the technique used, easily escape attention, and a chromosome mutation cannot therefore be ruled out. Thus it is conceivable that the mutation comprised a chromosome segment with several loci. But as long as this is inherited as a unit, it will in its effect not diverge from a point-mutated gene with corresponding pleiotropic effect.

Apart from this it seems to be usual for the genes to have multiple effects, and the colour factors form no exception in this respect. Thus we have several dominant factors with homozygous lethal effect. Of such may be mentioned the two allelomorphic genes for colour in platinum fox and white face fox respectively (*Tuff,* 1938; *Mohr & Tuff,* 1939; *Cole & Shackelford,* 1943; *Johansson,* 1947 & 1948; *Shackelford,* 1948). In addition, the Bluefrost factor in mink may also be mentioned. The Stewart factor, which like the former has a strong depigmentating effect on the fur, is not lethal in double dose, but the males are sterile and the females have reduced fertility (*King,* 1951; *Shackelford & Moore,* 1954; *Zimmermann,* 1963). Also in other respects it is noticed that there is often a certain connection between white or light colour and pathological states. Thus the white colour in the mutant mink Hedlund White, which is due to homozygosity for a recessive gene, often seems to be accompanied by deafness and frigidity, especially on the part of the females (*Shackelford & Moore,* 1954; *Hanset,* 1960 c; *Zimmermann,* 1963). White heifer disease frequently occurs in white cows of the Dairy Shorthorn breed (*Hutt,* 1946; *Spriggs,* 1946; *Finlay,* 1949; *Rendel,* 1952; *Laing,* 1955; *Kock et al.,* 1957). Also in other breeds the animals which have less pigment seem to be most affected by these abnormalities (*Young,* 1953). We also find to be true with respect to hypoplasia of the sexual glands in Swedish highland cattle (*Settergren,* 1954). And the degree of the aplasia of the urogenital organs in piebald hamster varies according to the degree of piebaldness (*Orsini,* 1952).

The present material is not suitable for throwing light on these conditions in the Shadow mink, but it does not seem improbable that here too there may be a connection between degree of lightness and expressivity, possibly penetrance, when it relates to the malformations of the female genital organs. In such case

it would be in accordance with the hypothesis that modifying factors assert themselves in these respects.

CONCLUSION

1. The described abnormalities of the genital organs in female mink with the Heggedal factor (S^H) in single dose seem to be restricted to the areas which are formed by the Müllerian ducts, and chiefly affect the vagina and cervix, corpus and cornua uteri, whereas the uterine tubes are as a rule normal.
2. The abnormalities are due to a pleiotropic effect of the Heggedal factor. In this respect it seems to be sex-limited and acts as a dominant hereditary factor with incomplete penetrance and varying expressivity.

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SUMMARY

In Sapphire Shadow (aa pp S^Hs), Blue Shadow (AA pp S^Hs) and Blue Shadow Carrier for Aleutian (Aa pp S^Hs) a malformation of the female genital organs has been demonstrated and described. The malformations seem to be restricted to the areas which are formed by the Müllerian ducts and chiefly affect the vagina and cervix, corpus and cornua uteri, whilst the uterine tubes are as a rule normal.

Among females which are empty after their first breeding season the frequency of these malformations was almost 42 % and among virginal young females 18.5 %.

The abnormalities seem to be due to a pleiotropic, possibly sex-limited effect of the Heggedal factor (Shadow factor S^H). With respect to these malformations, the Heggedal factor acts as a dominant hereditary factor with incomplete penetrance and varying expressivity. The penetrance in the females was approximately 18.5 % (18.54 ± 2.71).

A method for demonstrating the malformations in live mink is described.

ZUSAMMENFASSUNG

Missbildungen der Geschlechtsorgane bei Nerz-Weibchen, die bezüglich des Heggedal-Faktors (Shadow-Faktors S^H) heterozygot sind.

Bei Saphir Shadow (aa pp S^Hs), Blue Shadow (AA pp S^Hs) und Blue Shadow Carrier für Aleutian (Aa pp S^Hs) wird eine Missbildung der weiblichen Geschlechtsorgane nachgewiesen und beschrieben. Die Missbildungen scheinen auf die von den Müllerschen Gängen gebildeten Bereiche begrenzt zu sein und berühren vorzugsweise Vagina und

Cervix, Corpus und Cornua Uteri, während die Tubae Uterinae im allgemeinen unberührt bleiben.

Unter gepaarten unfruchtbaren Weibchen nach der ersten Sexualsaison betrug die Häufigkeit dieser Missbildungen fast 42 %, und unter virginalen jungen Weibchen 18,5 %.

Die Missbildungen scheinen auf eine pleiothrope, möglicherweise geschlechtsbegrenzte Wirkung des Heggedal-Faktors (Shadow-Faktors) zurückzuführen zu sein. Bezüglich dieser Missbildungen entsteht der Eindruck eines dominanten Erbfaktors mit unvollständiger Penetranz und variabler Expressivität. Die Penetranz bei den Weibchen betrug etwa 18,5 % (18,54 ± 2,71).

Ein Verfahren zum Nachweis der Missbildungen bei Lebenden Nerzen wird beschrieben.

SAMMENDRAG

Misdannelser av kjönnsorganene hos minktisper heterozygote for Heggedalfaktoren (Shadowfaktoren S^H).

Hos Safir Shadow (aa pp S^Hs), Blue Shadow (AA pp S^Hs) og Blue Shadow Carrier for Aleutian (Aa pp S^Hs) er det påvist og beskrevet en misdannelse av de hunlige kjönnsorganer. Misdannelsene synes å være begrenset til de områder som dannes av de Müllerske ganger og rammer fortrinsvis vagina og cervix, corpus og cornua uteri, mens tubae uterinae som regel er normale.

Blant parete, ikke drektige tisper etter förste avlssesong var hyppigheten av disse misdannelser nesten 42 % og blant virginelle ungtisper 18,5 %.

Misdannelsene synes å bero på en pleiotrop, muligens kjönnsbegrenset virkning av Heggedalfaktoren (Shadowfaktoren). Med hensyn til disse misdannelser, virker den som en dominant arvefaktor med ufullstendig penetrans og varierende ekspressivitet. Penetransen hos tispene var omlag 18,5 % (18,54 ± 2,71).

En metode til påvisning av misdannelsene hos levende mink er beskrevet.

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