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Survey of recent situation of chromosome pathology in different breeds of german cattle [1]

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Summary

1. With the aim to elucidate the etiological role of chromosome anomalies in pathology of domestic animals karyotype analyses had been performed routinically in 847 newborn calves with congenital malformations, furthermore in adult cattle with hereditary diseases, andin individuals with malformations of genital organs. The investigations have been realized during the past 10 years within the three large breeds of the cattle population of Hessen. Chromosome anomalies of different types have been found in 141 probands.

2. Considering the impossibility in karyotyping all calves with congenital anomalies extensively, most of them being stillborn, and in regard of the impractibility of a cytogenetic exploration of whole the population, it seems to be impossible to derive more than rough estimations of the real frequencies of chromosome anomalies within the observed population.

3. The first rank of different types of chromosome anomalies is occupied by the 1/29 translocation, followed by the trisomy 18. (In this connection the XX/XY chimerism in freemartins is not taken in consideration because its frequency is depending exclusively from the frequencies of heterozygous twins within the different breeds). Considering their real frequencies both types of chromosome anomalies dont possess a noteworthy economical importance within the observed population in the present situation. All other chromosomal anomalies, especially autosomal structural defects, too, are found only sporadically, though accumulated in certain families. This is the case in bovine hereditary parakeratosis, and in hereditary nanism.

4. The occurrence of several probands with the trisomy 18 syndrome (lethal brachygnathia trisomy syndrome) in a family together with gonosomal numerical anomalies is estimated to be the expression of a familiar disposition to disturbances of meiosis, resp. mitosis.

5. On the basis of autopsy findings in 18 cases of trisomy 18 syndrome, and those of 9 cases of bovine hereditary parakeratosis the symptomatology of those, by chromosome anomalies caused, resp. with chromosome anomalies combined, syndromes was determined. Significantly increased frequencies of autosomal breaks in parents of parakeratosis calves may be used as markers in order to identify heterozygotes in families suspected of this hereditary disturbance of zinc metabolism.

(1) This article has been presented to the 3rd Colloquium of Cytogenetics of Domestic animals, May 31-June 2 1977, Jouy-en-Josas, France.

Introduction

The following report presents the results of systematic cytogenetic studies in newborn calves with congenital malformations, in adult individuals with disturbances of sex differentiation, and those which have been fallen sick with maladies caused by (or combined with) chromosomal aberrations. Those results have been obtained in the regional population of cattle in Hessen (Fed. Republ. of Germany), composed of the four breeds Black Pied Lowland (partially *Holstein-Friesian*), *Red Pied Lowlands*, *German Simmental* (*Fleckvieh*), and *German Red Cattle*, during 1968 till May 1977.

The report offers a review of prior papers of the authors emphazising recent advances in etiological and nosological research in Bovine Hereditary Parakeratosis, and the Trisomy 18 Syndrome.

The results of cytogenetic observations reported in this paper are not derived from systematic investigation of whole the population, but the sample of karyotyped animals collected from the population is preselected regarding pathological traits of the animals only. Therefore, it seems to be inconvenient to derive out of those figures presented in Table 1 statistically established informations about the frequencies of chromosomal defects within the population, and differences of chromosomal defects within the population, and differences of frequencies between the breeds. But, if we compare the percentages of chromosomal anomalies with the numbers of examined animals belonging to the different breeds, extending from 3.8 p. cent in *Black Pied Lowlands* (partially *Holstein-Friesian*), 2.7 p. cent in *Red Pied Lowlands*, to 14.1 p. cent in the German Simmental Cattle (Table 2) we may establish the number of chromosomal aberrations being biased in disfavour of the Simmental breed. The real relations of percentages of chromosomal anomalies to the percentages of breeds composing the population you may evaluate by a short glance at the left column of Table 2.

Table 1 exhibit that regularly only *three types of structural and numerical autosomal aberrations* are found in the observed population associated with different pathological traits of newborn calves or of adult patients during the last five years. Incidentally or seldom gonosomal numerical aberrations are observed, except the XX/XY chimerism, which is not from interest in this connection, mainly four types of them. The roughly estimated frequencies of the different types of autosomal anomalies are differing in wide range; none of them gained a remarkable expansion with corresponding economical importance.

1. — Structural autosomal anomalies

a) From this group the *1/29 translocation* take with 13 cases the first rank in the order of precedence in the breed of German Simmentals, followed by the *trisomy 18* in all breeds. The translocations, identified by different methods of banding technique, were represented only by the 1/29 type. Other types, f.i. the 1/25 translocation, STRANZINGER and FÜRSTER (1976) found within a family of *German Simmental* of Bavaria, or those of HARVEY and LOGUE (1975) who identified a new 13/21 translocation in the Swiss Simmental breed, did'nt occur till this very moment in our breeds. In contrast to the observations of GUSTAVSSON *et al.*, who saw distinct repression of fertility in translocation heterozygotes, in our breeds all female translocation bearers revealed an undisturbed fertility. The discre-

TABLE I

Incidence of karyotypic abnormalities in German breeds of Bos taurus (Preliminary closed 31-5-1977)
Incidence des anomalies caryotypiques dans les races bovines allemandes (liste arrêtée provisoirement le 31-5-1977)

Breed	Total animals karyotyped	How ascertained	Abnormal karyotypes		Remarks
			Nature	Number	
Black Pied Lowland	368	Newborn and adult cattle with different pathological phenes	60, XX/60, XY	33	Twins of freemartin type
			60, XX/60, XY	1	Bovine autonomous XX/XY-syndrome
			60, XX/61, XX (18 +)	1	Trisomy 18 syndrome
			60, XY/61, XY (18 +)	3	Trisomy 18 syndrome
			Different autosomal and gonosomal breakages and other structural aberrations	9	Hereditary Parakeratosis (A 46)
Red Pied Lowland	218	Newborn and adult cattle with different pathological phenes	60, XX/60, XY	25	Twins of freemartin type
			61, XX (18 +)	1	Trisomy 18 syndrome
			60, XY/61, XY (18 +)	1	Trisomy 18 syndrome
			59, XX; t (1, 29)	4	Heterozygous Robertsonian translocation
Black Pied Lowland × *Red Pied Lowland*	19	Newborn and adult cattle with different pathological phenes	60, XX/60, XY	1	Twins of freemartin type
			61, XY (18 +)	1	Trisomy 18 syndrome
			61, XX (18 +)	1	Trisomy 18 syndrome

TABLE I (*suite*)

Breed	Total animals karyotyped	How ascertained	Abnormal karyotypes		Remarks
			Nature	Number	
German Simmental	212	Newborn and adult cattle with different pathological phenes	60, XX/60, XY	27	Twins of freemartin type
			60, XX/60, XY	1	Bovine autonomous XX/XY-syndrome
			61, XXX	1	X-Trisomy
			60, XX/90, XXY	1	Diploidy-Triploidy mosaicism
			61, XXY	2	Bovine hypogonadism
			61, XY (18 +)	2	Trisomy 18 syndrome
			61, XX (18 +)	3	Trisomy 18 syndrome
			60, XY/61, XY (18 +)	3	Trisomy 18 syndrome
			60, XX/61, XX (18 +)	1	Trisomy 18 syndrome
			Autosomal breakages	3	Hereditary nanism
			59, XX; t (1, 29)	7	Heterozygous Robertsonian translocation
			59, XY; t (1, 29)	3	Heterozygous Robertsonian translocation
			59, XX; t (1, 29)/60, XY	2	Heterozygous Robertsonian translocation
			60, XX/59, XY; t (1, 29)	1	Heterozygous Robertsonian translocation
Red Pied Lowland × *German Simmental*	20	Newborn and adult cattle with different pathological phenes	61, XY (18 +)	1	Trisomy 18 syndrome
German Red	10	Newborn and adult cattle with different pathological phenes	60, XX/60, XY	1	Twins of freemartin type
			61, XX (18 +)	1	Trisomy 18 syndrome (Red Danish cattle)
Total	847			141	

TABLE 2

Structure of cattle population, i. e. percentages of breeds, in the observed region and number of karyotyped animals (1968-V/1977)

Structure de la population bovine, pourcentages d'animaux dans chaque race présentée dans la région observée et nombre d'animaux étudiés (1968 à 1977)

Percentage of breeds in population	Karyotyped animals			
	Normal	Pathologic(*)	Total	%
Black pied Lowlands 52.3 . . . . . (partial *Holstein-Friesian*)	5	368	373	3.8
Red pied Lowlands 33.7 . . . . . (partial *Netherland's Maas-Yjssel-Rhine* Cattle)	5	218	223	2.7
German Fleckvieh 12.3 . . . . . (*German Simmental*)	91	212	303	14.1
German Red and Yellow Cattle 1.0 . . . . . (partial *Red Danish Milk Cattle*)	3	10	13	

(*) *Different pathologic traits, especially congenital malformations of different types.*

(*) Différents traits pathologiques, surtout les malformations congénitales des différents types.

pancies between the phenotypical effects of translocations in Swedish and Norwegian breeds (REFSDAL, 1976) probably are attributed to the comparatively very small sample of karyotyped animals corresponding to the low distribution of translocations in our breeds.

b) — *Autosomal aberrations in Bovine hereditary parakeratosis* (BHP)

Since 1960 it has been observed in several regions of the world a metabolic disturbance in *Holstein-Friesian* breed, which very soon had been recognized to be caused by a nutrient zinc deficiency (MILLER and MILLER, 1960), which is connected with more or less severe lesions of the skin in the sense of parakeratotic dermatosis and other pathological traits. The hereditary etiology of this syndrome, originally named " parakeratosis " (LEGG and SEARS, 1960), had been first stated in Denmark by ANDRESEN *et al.* (1970), who described a new lethal trait, A 46, found in the descent of a *Friesian* bull belonging to the wide spread group of *Friesian* bulls named ADEMA (" ADEMA disease ") (WEISMANN and FLAGSTAD, 1976). Later on STÖBER (1971) and TRAUTWEIN (1971) confirmed such observations by own investigations in *Holstein-Friesian* calves in North-West-Germany. The chromosomal situation of those animals have been explored by HERZOG and HÖHN (1971) who, for the first time found typical autosomal defects in all parakeratotic patients, which consist in chromatid and isochromatid breaks and different types of autosomal associations (quadri- and triradial figures), gaps, dicentric and acentric chromosomes (fig. 1).

The Hereditary Parakeratosis is caused by an autosomal recessive Mendelian factor, and is manifesting in an age of 4-8 weeks with the symptoms of stomatitis,

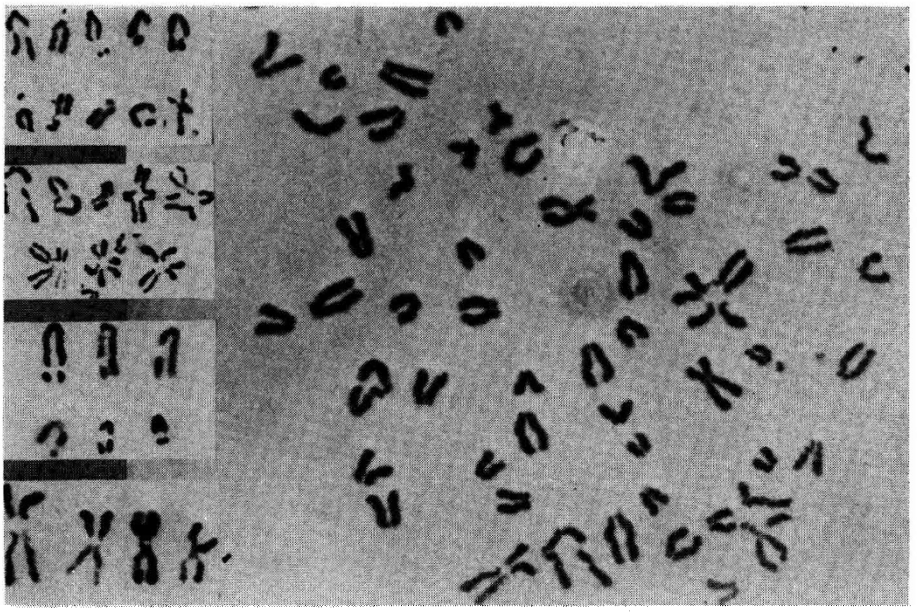

FIG. 1. — *One of the metaphases being typical for Hereditary parakeratosis in bovine showing several types of association figures.* Left edge: *A collection of different types of breaks, gaps and association figures originating from several patients suffering from BHP. — All autosomal aberrations found in BHP are resembling largely those of human* BLOOM'S *syndrome, and* FANCONI'S *syndrome.*

Métaphase typique d'un animal atteint de parakératose bovine montrant plusieurs types d'association. Côté gauche : *Différents types de cassures, coupures et associations trouvés chez plusieurs animaux souffrant de BHP. Toutes les aberrations autosomales trouvées chez BHP ressemblent à celles des syndromes de* BLOOM *et de* FANCONI *chez les humains.*

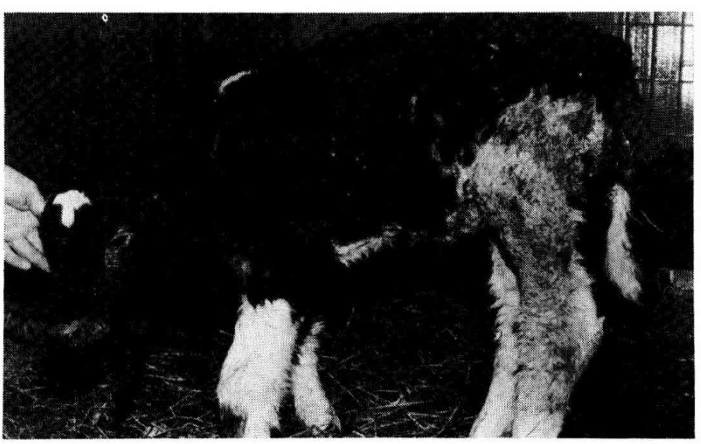

FIG. 2. — *Widespread parakeratotic dermatoses in the regions of thighs, abdomen, environments of eyes and of muzzle. The patient died with pneumonia (increased disposition to infectious diseases!). Black Pied Lowland calf, Reg. No. 4263/77.*

Dermatoses parakératosiques étendues dans les régions des cuisses, de l'abdomen, autour des yeux et du museau. Plus tard l'animal est mort d'une pneumonie (prédisposition accrue pour les maladies infectieuses). Veau Pie noir des Plaines, cas n° 4263/77.

conjunctivitis, widespread dermatoses (fig. 2), retardation of development with lethal effect within 4-6 months except the patients are treated with zinc substitution.

Autosomal breakages markers in heterozygotes for Bovine Hereditary Parakeratosis?

Originally, there aroused some doubts wether the chromosome anomalies observed in patients with BHP are acting a role in the etiology of this lethal trait, but, rather only being one symptom of this syndrome together with several others. But, the demonstration of the chromosome anomalies described above in all patients with BHP (Table 3), and, moreover the observation of breakages in metaphases of white blood cells in the parents of BHP calves with few exceptions seem to elucidate a more important role of those autosomal structural defects in pathogenesis of this metabolic disturbance. Table 4 is demonstrating a frequency of breaks in autosomes of fathers of HP calves of 11.1 p. cent, and in those of mothers of 9.5 p. cent on the average of all karyotyped parents. In comparison with the frequencies of breaks in the normal Black Pied Lowlands population of Germany from 0-0.028 p. cent (EL-NAHASS *et al.*, 1976) to 4.1 p. cent in an own control sample (Table 5) the difference between the values of 11.1 p. cent resp. 9.5 p. cent and of 1.5 p. cent are significant.

TABLE 3

Autosomal breakages and other structural anomalies in metaphases of white blood cells from calves suffering with BHP
Cassures autosomales et autres anomalies structurales dans les métaphases de globules blancs de veaux atteints de BHP

No.	Chiffre (1) of calves	Examined metaphases	% Defective cells	Breaks		Other (2) anomalies %
				chromatid %	isochromat. %	
1. . . .	13	315	37.8	30.05	52.46	17.49
2. . . .	14	200	23.5	31.60	28.90	39.5
3. . . .	15	204	23.6	32.5	35.6	31.9
4. . . .	16	142	27.4	21.4	35.7	42.9
5. . . .	17	109	32.1	27.5	39.7	32.8
6. . . .	22	185	29.0	40.7	40.0	19.3
7. . . .	23	108	14.9	36.8	47.4	15.8
8. . . .	206	224	23.7	28.4	53.7	17.9
9. . . .	305	296	22.6	36.8	38,6	24.6

COMMENT: *The calves No. 1, 4 and 5 suffered in the time of blood sampling with an acute BHP without therapy, whereas the other calves already had been substituted with $ZnCO_3$. The therapy with Zn exhibit a decreasing effect on the frequencies of chromosomal anomalies.*

REMARQUE : Les veaux N° 1, 4 et 5, souffraient, à l'époque de la prise de sang, d'un BHP aigu, il n'était pas soigné tandis que les autres veaux recevaient déjà $ZnCO_3$. Le traitement au zinc a entraîné une diminution de la fréquence des anomalies chromosomiques.

(1) The chiffres of calves correspond with those in the paper of STÖBER, PITTERMANN and KLUG (1974).

(2) Anomalies other than chromatid and isochromatid breaks, such as gaps, centromeric breaks, acentric fragments, association figures, polyploid cells.

TABLE 4

Autosomal breaks in metaphases of white blood cells of parents of parakeratosis calves
(*Breed:* Black Pied Lowlands)

Cassures autosomales dans les métaphases de globules blancs chez des parents de veaux atteints de parakératose
(*race:* Pie noir des Plaines)

No.	Chiffres of Father resp. Mother	Parents of calf No.	Number of examined metaphases	Number of cells with breaks	%
1	II	15 + 17	49	5	10.2
2	V	16	33	3	9.0
3	VI	13	32	7	21.8
4	Scirocco	20	30	1	3.3
			Bulls ø		11.1
5	Erle	16	8	0	0
6	Atlantis	13	119	10	8.4
7	Espe	14	11	1	9.1
8	Sabine	17	48	11	22.8
9	Elfi	?(1)	54	4	7.4
			Cows ø		9.5

(1) *Mother of a calf which died from acute BHP without karyotype analysis.*

(1) Mère d'un veau qui mourut d'un BHP aigu sans analyse caryotypique.

TABLE 5

Autosomal breaks in a group of unsuspicious Black Pied Lowland bulls used in A.I.
(*Control group*)

Cassures autosomales dans un groupe de taureaux d'insémination non suspects de parakératose
(*groupe témoin*)

1	Croft	668	—	287	8	2.8 (1)
2	Elms	700	—	84	3	3.5
3	Esch	702	—	30	0	0
4	Stad	703	—	30	0	0
5	Danz	761	—	30	0	0
6	Sulz	739	—	30	0	0
7	Pass	819	—	100	1	1.0
8	Isny	824	—	70	3	4.1
9	Trol	825	—	90	1	1.1
					Control group ∅	1.4

Annotation: *The significance of the difference between the means of relative frequencies of cells with autosomal breaks within parents of parakeratosis calves (Table 4) and within the control group (Table 5) have been proved by the U-test corresponding to* MANN-WHITNEY-WILCOXON *at a level of* $\alpha = 0.01$.

Remarque: L'étude de la signification de la différence entre les moyennes des fréquences relatives des cellules porteuses de carences autosomales chez les parents des veaux atteints de parakératose (tabl. 4) et entre le groupe de contrôle (tabl. 5) a été fait à l'aide du test U qui correspond à MANN-WHITNEY, WILCOXON au seuil de $\alpha = 0{,}01$.

(1) Karyotyped on behalf of lack of libido; all other routinically.

Therefore, it seems to be justified to declare relatively high frequencies of autosomal breaks to be characteristic for the heterozygous condition of the gene " Hereditary Parakeratosis ". In bovine adults suspicious to be heterozygous for BHP, autosomal breaks exceeding a limit of about 5 p. cent may assigned to detect heterozygosity. Self-evident, this assertion must not neglect the fact, that some other causes may produce structural defects in chromosomes than BHP.

c. — *Autosomal breaks in cases of Hereditary Nanism*

Autosomal breaks too had been observed in 1976 in three calves belonging to the sibship of a Simmental bull bred in Baden-Württemberg. This bull brought about 25 p. cent dwarf calves within his offspring, obviously being heterozygous for an autosomal quasi dominant Mendel factor " Hereditary Nanism ", a viable non chondrodysplastic, proportionate dwarfism. The breaks occurring in the first blood sample in frequencies of about 30-43 p. cent of metaphases of white blood cells diminished in the course of one month about 50 p. cent (Table 6). The father of the dwarf calves didn't exhibit any chromosome anomaly.

TABLE 6

Frequencies of autosomal breaks in calves with hereditary nanism
(Breed: *German Simmental*)

Fréquences des cassures autosomales chez des veaux atteints de nanisme héréditaire
(race: *Simmental allemande*)

Chiffre of calf	Date of blood sampling	Number of examined cells	% Breaks
A 191	6- 9-76	100	30
Female	4-10-76	100	16
A 192	6- 9-76	100	34
Male	4-10-76	100	11
A 193	6- 9-76	100	43
Female	4-10-76	100	22

This spontaneous elimination of cells with chromosomal defects seems to affirm the doubts about the etiologic resp. pathogenetic role of autosomal breaks, because the possibility the breaks are caused for instance by an intervention in mitotic processes by virus particles in contaminated culture medium or by latent infections of the probands by IBR-IPV virus or others is not to be ruled out.

2. — Autosomal aneuploïdies

In contrast to the tremendous role of numerous trisomies causing in human beings nearly 10 typical malformation syndromes, and a high percentage of spontaneous abortions, in cattle this group is represented only by one single trisomy, the trisomy 18.

The " trisomy 23 " found in several cases of nanism of calves in Rumania by GLUHOVSCHI *et al.* (1972) had not been established in other populations till now. Moreover the supernumerary autosom in those cases had not been identified by banding techniques.

The " Lethal Brachygnathia Trisomy Syndrome " (LBTS) (Trisomy 18 syndrome)

and its cytogenetic background first had been published by HERZOG and HÖHN in 1968. Afterwards this syndrome combined with a trisomy of an autosome belonging to the group C had been established by MORI *et al.* (1969) in Japan, and, furthermore by DUNN *et al.* (1972) in U.S.A. In the meantime, we collected 18 cases of LBTS in all breeds of our region, i. e. in

Black Pied Lowlands	4 cases, in
Red Pied Lowlands	2 cases, in
German Simmentals.	9 cases, and in
Crossbred Red Pied Lowl. ×	
Red Danish Milk Cattle	1 case (Table 1)

In present, we are not able to present a statistically proved assertion of the real frequencies of this syndrome, and the differences of frequencies between breeds, because in most cases the probands with the pathologic traits of LBTS are stillborn. Therefore, it is not possible to gain viable tissue cultures from them beyond the limit of 48 to 72 hours post mortem. Indeed, we get the impression, that this autosomal aneuploidy gained a broader distribution, preferably in the *German Simmental*, than primarily supposed.

In this connection, we are allowed to discuss the identification of those autosome of the C group involved in the trisomic process, and, which had been identified by the *Standardization Conference of Reading* 1976 to be the autosome No. 17. In regard to the statistical impossibility to separate the autosome No. 17 from No. 18 by biometrical methods (arm length) it seems to be without any significance to destine the position of both autosomes in the karyogram more or less arbitrary (fig. 3). Therefore, we prefer to insist in the original designation of " trisomy 18 " preliminary ascertained in our first publication of 1968 (HERZOG and HÖHN) before usage of banding techniques.

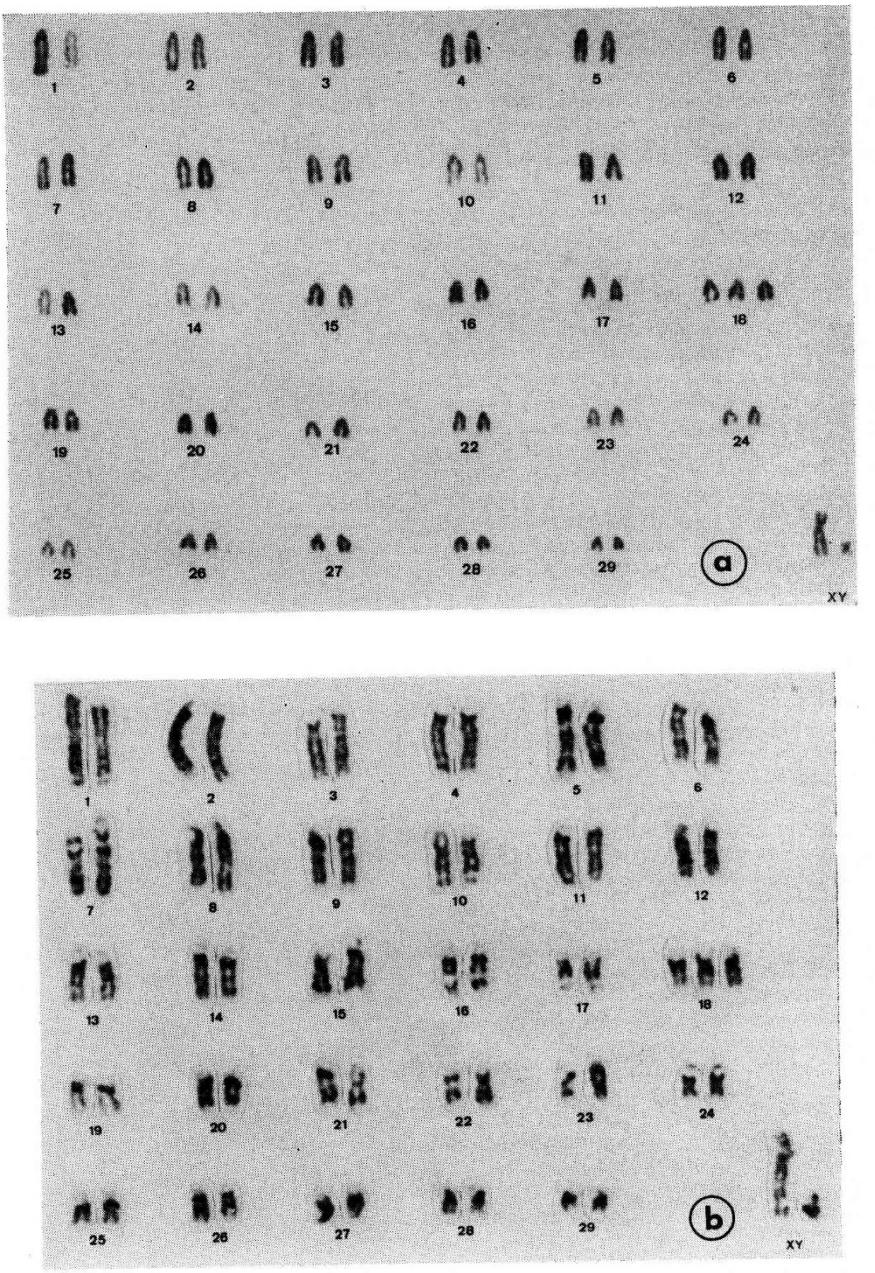

FIG. 3. — *Identification of the trisomic autosom with autosom No. 18.*

a) Empirical arrangement without banding (orcein painting).
b) Identification by means of G banding technique.

Identification de la trisomie autosomale n° 18

a) Arrangement empirique sans marquage (coloration à l'orcéine).
b) Identification au moyen de la technique de marquage G.

Pathology of the Lethal Brachygnathia Trisomy Syndrome

The association of several different types of congenital malformations composing the LBT syndrome had been analyzed by means of autopsies of the 18 probands; the results are summarized in the following Table 7:

TABLE 7

Phenotypical traits of the Lethal Brachygnathia Trisomy Syndrome (N = 18)
Phénotype des animaux atteints de trisomie 18 (N = 18)

Range of precedence	Defects			
	Obligatory	%	Optional	%
1	Brachygnathia inf.	78		
2	Cryptorchidism	70		
3	Hydrocephalus int.	50		
4			Vitiae cordis	28
5			Nanism (fetal hypoplasia)	22
6			Arthrogryposis of carpus	22
7			Curvatures of spine	17
8			Hypoplasia of kidneys	17

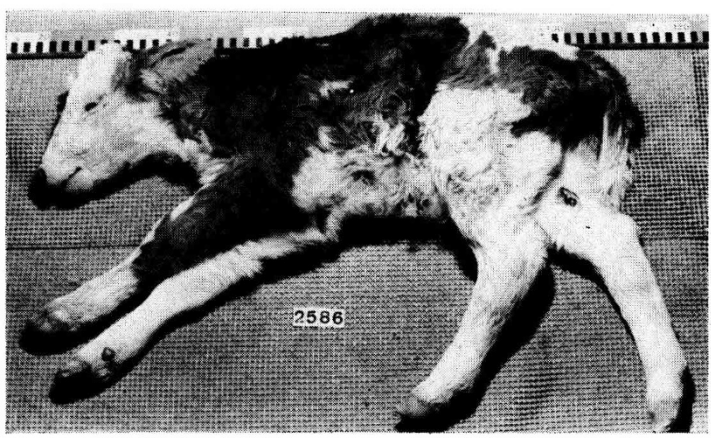

FIG. 4. — " Regular " phenotype of bovine LBT syndrome: *Stillborn male calf with trisomy 18, brachygnathia inf., kyphoscoliosis, anomaly of gyration of cerebrum, hypoplasia of cerebellum, cryptorchidism and aplasia of scrotum. Normal birth weight* (Red Pied Lowland, Reg. No. 2586/70).

Phénotype classique d'un veau atteint du syndrome LBT : *Veau mâle mort-né avec la trisomie 18, brachygnathie inférieure, kyphoscoliose, anomalie des circonvolutions cérébrales, hypoplasie du cervelet, cryptorchidie et aplasie du scrotum. Poids à la naissance normal* (Pie rouge des Plaines, cas n° 2586/70).

Other incidentally defects observed in LBTS probands are:

— Maxillo-facial dysplasia, mostly connected with
— Palatoschisis (cleft palate),
— Aplasia of cerebellum,
— Ascites and Hydrothorax,

all with a high variability of manifestation and combination of traits. Apparently the structure of this syndrome on no account is homogeneous: several probands with trisomy 18, partially with trisomy 18 mosaics, deviate from the scheme presented in Table 7. We like to quote as illustrations of those irregular types, the

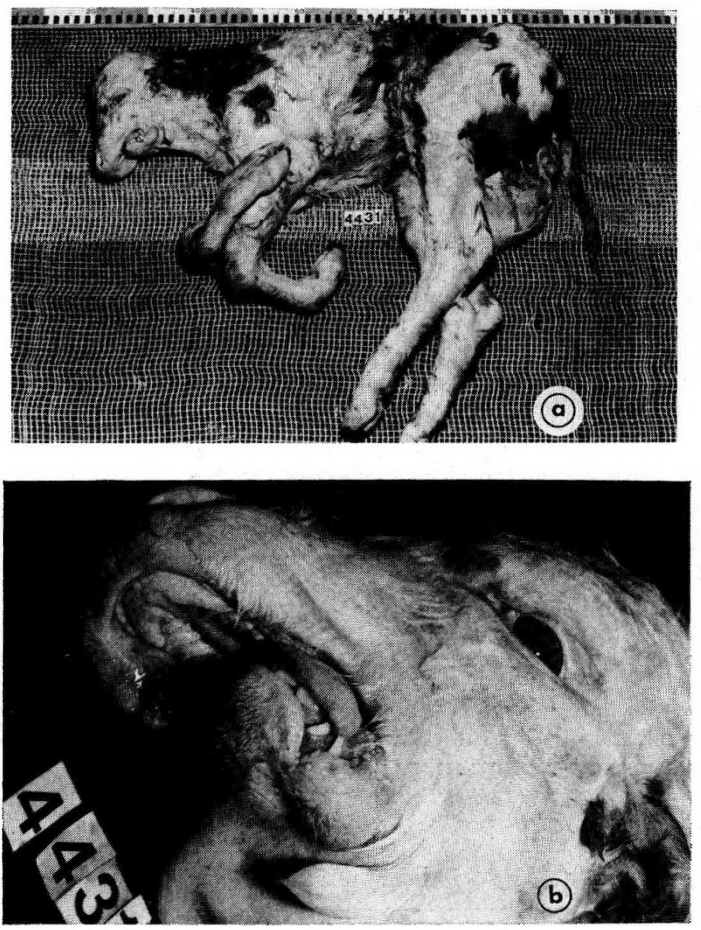

FIG. 5. — Exceptional phenotype of LBT syndrome: *Stillborn male calf with trisomy 18, extreme dysplasia of mandible and cleft palate* (*b*), *hydrocephalus int., Cryptorchidism, extremely high birth weight* (*43,6 kg*), *carpal arthrogryposis* (*a*) (German Simmental, *Reg. No. 4431/76*).

Phénotype inhabituel du syndrome LBT : *Le veau mâle mort-né atteint de trisomie 18 présentait une dysplasie extrême de la mandibule avec une fissure palatine* (*b*) *une hydrocéphalie interne, une cryptorchidie, un poids à la naissance assez élevé* (*43,6 kg*), *une arthrogrypose du carpe* (*a*) (Simmental allemand, *cas n° 4431/76*).

case with a trisomy mosaic (60, XX/61, XX, 18 +) exhibiting extremely severe dysplasias of the face, hydrocephalus, cleft palate, and multiple arthrogrypotic anomalies of all limbs, HERZOG and HÖHN published in 1974. During 1976 a similar case with dysplasia of mandible, cleft palate, arthrogryposis of front limbs, and gigantic development had been registered (fig. 5). The karyotype of this stillborn calf (Reg. No. 4431/76) revealed 100 p. cent of trisomy 18 metaphase in cultured kidney cells.

Etiology of LBT syndrome

The empiric impression, the LBT-syndrome being genetically influenced, is derived from several observations of its familiar incidence in the breed *German Red Pied Lowlands* as well as in *German Simmentals*. Especially in the descent of two bulls belonging to the last mentioned breed used in A.I. we found three different types of meiotic disturbances, which are establishing the initial supposition of " an inherent genetical disposition to meiotic disturbances " in these families, we uttered in 1970. In this paper we demonstrated the occurrance of one case of XXY-syndrome, and another with X-trisomy in one half sib group. 1975 and 1976 these observations had been supplemented by three cases of trisomy 18 (fig. 6). Moreover, one of the involved bulls, the DIVO 1744 brought during the past 10 years on the whole 7 descendents with the Lethal Brachygnathia Fetal Hypoplasia Syndrome (Table 8), all stillborn. Out of this reason we succeeded only in two cases (4162 and 4348) in gaining viable tissue cultures post mortem, mostly from kidneys, and to demonstrate the trisomy 18.

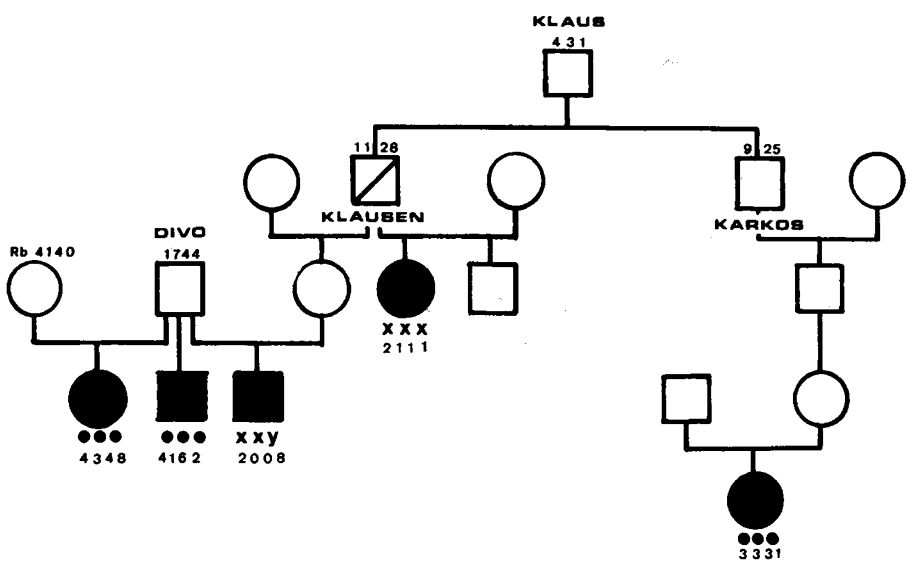

FIG. 6. — *Familial accumulation of numeric gonosomal aberrations with trisomy 18* (●●●) *in two families of* Simmental *bulls. (Compare with* RIECK et al., *1970.)*

Accumulation d'anomalies gonosomales numériques accompagnant la trisomie 18 (●●●) *dans deux descendances de taureaux* Simmental (*comparer avec* RIECK et al., *1970*).

TABLE 8

Teratogram of the Simmental bull DIVO 1744
Used in A.I. from 8-9-1966 till presence
First inseminations: 17 000. Descendents: ~ 12 400

Tératogramme du taureau Simmental DIVO 1744 utilisé en I.A. depuis le 8-9-1966:
17 000 pour inséminations premières, 12 000 descendants

*	1	1318	♂	2-7-67	*Brachygnathia inf.*, Palatoschisis, Skoliose LWS, Zystennieren, Kryptorchismus, *allg. fetale Hypoplasie.*
*	2	1400	♂	31-10-67	*Brachygnathia inf.*, Hydrocephalus int., Kryptorchismus, Kugelherz, *allg. fetale Hypoplasie* (Nanismus).
	3	2008	♂	24-10-67	XXY-Syndrom: Kastratentyp, bilaterale Hodenhypoplasie.
	4	3351	♀	1- 1-73	Atresia ani, Rectovaginal-Fistel, Stenose der Urethra, Cor triloculare biatrium.
*	5	3356	♂	12- 1-73	*Brachygnathia inf.*, Palatoschisis, Ascites congenita, Scrotumaplasie, Kryptorchismus, Ventrikelseptum-Defekt.
	6	3453	♂	2- 5-73	Anophtalmie-Anurie-Syndrom.
	7	3478	♀♂	25- 4-73	♂: Aplasia bulbi sin., Ankyloblepharon.
*	8	3783	♀	26-12-73	*Brachygnathia inf., allg. fetale Hypoplasie* (Nanismus).
	9	3791	♂	17- 4-74	Palatoschisis, Karpalarthrogrypose bdsts.
□	10	4162	♂	10-10-75	*Brachygnathie-Trisomie-Syndrom:* Allg. fetale Hypoplasie, Hydrocephalus int., Cryptorchism. inguin. bilat.
	11	4185	♀	24- 9-75	Brachyurie.
□	12	4348	♀	11- 5-76	*Brachygnathie-Trisomie-Syndrom:* Allg. fetale Hypoplasie, Hydrocephalus int., Hydrothorax + Ascites congen.
	13	4390	♂	10- 7-76	Palatoschisis, Hydrothorax.
*	14	4617	♀	8- 3-77	*Brachygnathia inf., allg. fetale Hypoplasie* (Nanismus), Palatoschisis, Hydrocephalus int.

Frequency of malformations: 1: 885 (0.11 %)

(*) Stillborn calves, karyotyping not possible.
□ Stillborn calves, viable post mortem tissue cultures and successful karyotyping.

Those relative seldom observations, self-evident, are not suitable for calculating a mode of heredity involved with the manifestation of the LBT syndrome, because in both systems of heredity, in the monogenic and in the polygenic, it depends on the frequencies of the corresponding genes in the population, which are absolutely unknown. But, the unique accumulation of meiotic resp. mitotic disturbances in two families among some hundreds of unsuspicious sibships steadily controlled in the breeds of our region rules out an accidental coincidence of such rare events.

In human cytogenetics it have been reported about " familial chromosomal aberrations " (ZELLWEGER, 1966) or about " recurrent aneuploidies " in certain families (IINUMA *et al.*, 1973) relatively often during the last 17 years. Not only the appearance of different types of autosomal trisomies in consecutive pregnancies are kept in mind here, but those of autosomal together with gonosomal aneuploidies in various combinations in sibships and in consecutive generations of certain families. Such as trisomy E together with trisomy 21, trisomy 21 with trisomy X (SINGER *et al.*, 1972), trisomy 21 and KLINEFELTER'S syndrome (IINUMA *et al.*, 1973). Concluding from those observations " the presence of a familial tendency to non disjunction cannot be disregarded " IINUMA *et al.* stated 1973. Considering the detection of a trisomy 18 and a trisomy 21 in half-siblings, both from different fathers, DAVID and JONES conclude 1975 that it may be possible that in some

woman is a predisposition to nondisjunction. Their opinion, certain families apparently being " more prone to the occurrence of chromosomal aneuploidy ", we estimate —together with all observations mentioned above— as confirmation of our hypothesis of a " familial disposition to meiotic disturbances " in cattle, we postulated in 1970 (RIECK *et al.*). Furthermore, we appreciate the appearance of two cases of LBTS (with proved trisomy 18), and several more cases of a from pathological point of view identical malformation syndrome (without evidence of a trisomy because the probands have been stillborn) in the half-siblings group of the bull DIVO (Teratogram (Table 8) as a further proof for the same genetic background of the autosomal and gonosomal aneuploidies and their pathological effects.

3. — Polyploïdies

Polyploidies in general are incompatible with vitality of mammals. Nevertheless, some cases in human infants with triploidies (69, XXX) have been published in the past five years. Some of them survived to birth, others even nine days post partum (DE GROUCHY *et al.*, 1974). In cattle, too, tetra- to dekaploidies have been found in individuals of Charolais cattle with double muscled condition (culard) in percentages from 17 to 24 p. cent of examined cells (POPESCU, 1968).

One of us (RIECK) demonstrated 1973 a case of diploidy/triploidy mosaicism in a *German Simmental* individual, quite a similar case DUNN *et al.* published in 1970. The XXY gonosomal complement of this mosaic obviously was the cause of masculinization of the gonads, and of disturbances of differentiation of the sinus urogenitalis. This type of polyploidy seems to remain a unique case.

Some doubts about the etiological role, resp. pathogenetic significance of certain chromosome anomalies have been mentioned above. Apparently this turns out to be true in a high degree concerning the polyploidies observed in white blood cell cultures.

> This problem grew acute in human genetics considering the observations, that up to 100 p. cent polyploidy has been found in cultures of amniotic-fluid cells gained by amniocentesis from pregnant women with normal diploid embryos. It has been suggested that prolonged cultivation of cells increases the frequencies of polyploid cells. This tendency to disturbances of mitosis in cells in culture could be avoided by introduction of a special technique (NAKAKOME *et al.*, 1972).

In regard to our experience with a " control group " of nearly one thousand routine charges of tissue cultures we believe to possess sufficient estimations of frequencies of polyploid cells cultured from normal animals. The observations on chorionic cells of human beings, therefore, may not be verified in bovine cells of streaming blood, and of other organs. In comparison with our results obtained in the " control group " the significance of polyploidy findings statistically may be proved, self-evident on the assumption of constant conditions of culture techniques. Out of this reason we are convinced the polyploidies not to be artificial products of culture techniques, but representing a *symptom of lability of cells in performing the mitotic processes in culture.* This seem to be the case especially in endomitotic polyploidies, in most cases tetraploidies, observed in nearly 25 probands with congenital defects of central nervous system and eyes of newborn calves (HERZOG and HÖHN, 1971). These findings recently have been confirmed by further observations in the same category of defects by STIX (1978). The

same functional lability of mitosis in culture WEINHOLD demonstrated conclusively 1970 in aneuploid and polyploid white blood cells and tumor cells of cows with lymphatic leukaemia, estimating this phenomenon to be a fundamental characteristic of mitotic disturbances of tumor cells.

> Cells which reveal the tendency to polyploidization in culture are estimated in human oncology to be a " characteristic feature of malignant change " of a blastoma (KNOERR-GÄRTNER, H. and M., 1977).

This interesting phenomenon of abnormal cellular functional behaviour in realization of mitosis in culture is till now very poorly understood. It requires further investigation, because its explanation with disturbing influences by culture medium, mentioned above, apparently not at all is its only cause. In teratological aspects it is to evaluate whether cell types exhibiting polyploidization in culture may have similar or homologous effects on developmental processes of certain blastema (neuroblastema f. i.) in embryos as in malignant blastomas.

Hence, we may infer, that the problem of polyploidy in mammals include two items:

(1) Polyploid cells in culture are they a symptom of cellular functional lability, resp. insufficiency, to realize mitotic processes in artificial medium, or,

(2) are they originally present in blood cells or cells of other organs, and, assertive, how many percent of polyploid cells in mosaics are sufficient to disturb the embryological development or to individual mortality?

4. — Gonosomal numeric anomalies including gonosomal chimaeras

The most comprehensive contingent of chromosomal aberrations presented in Table 1 is represented by the *gonosomal numeric anomalies*, first of all the XX/XY chimerism of freemartins, and other gonosomal mosaics. Notwithstanding the high share of this type of blood chimerism, the XX/XY chimerism possess little significance in connection with the present discussion, because the frequency of freemartins only depends from the frequencies of dizygotic twins in the different breeds. High interest, indeed, is to be claimed to the problem of the XX/XY mosaicism in singleborn animals and in isosexual twins. Although the reports on this extraordinary type of gonosomal mosaicisms seem to increase recently, the frequency of the so called " Autonomous XX/XY syndrome " in the breeds of Germany is very low. The last case we observed in Black Pied Lowlands in 1974 in the environment of Hanover (RIECK, 1975). The pathogenic activity of those second X-chromosome in genetic male individuals, obviously originating from a " whole body mosaicism " (BENIRSCHKE, 1970) seem to be rather obscure in the present. Partially those XX/XY individuals are absolutely normal, another part of them exhibit more or less severe disturbances of differentiation of sexual organs within wide limits of variation.

Likewise very low population frequencies in German breeds exhibit the *gonosomal trisomies*, i. e. the bovine XXY syndrome, a homologue to the human KLINEFELTER's syndrome, and the trisomy X. Since 1967 (RIECK, 1970), and 1970 no further gonosomal trisomy had been observed. A symptom of their scarcity in other European cattle breeds, too, is the finding of only one more case of

an X trisomy in a heifer of the Norwegian Red cattle in 1976 (NORBERG *et al.*, 1976), not at all in all other breeds in the world.

Most of the cases of intersexuality or of malformations of sexual organs without intersexuality in cattle are not combined with (or caused by (?)) gonosomal aberrations.

Conclusions

In spite of a large amount of karyograms which had been collected in the course of etiological research of developmental disturbances in cattle during the last ten years it is impossible in the present moment to gain an impression of true frequencies of chromosomal anomalies, considering the lack of comprehensive investigations of whole of the population. Moreover, the fact, relatively seldom to obtain surviving cells from stillborn calves being fit to divide in tissue culture make it impossible to get real figures of frequencies of chromosomal defects. Nevertheless the findings of chromosomal anomalies associated with congenital malformations in newborn calves, or with clinical symptoms in adolescent animals allow some rough estimations of their frequencies and their economic importance. So, it is evident that the incidence of trisomy 18 in all breeds just follow that of 1/29 translocation; the frequencies of all other chromosome aberrations are ranging widely below those just mentioned.

Considering the chromosome aberrations specialized in groups of anomaly types it had been found within the group *of structural autosomal defects* cases of hereditary nanism combined with breakages in the sibship of a bull of *German Simmental* breed; breakages and reunion figures in calves suffering from Hereditary parakeratosis (" Zinc deficiency syndrome ") in *Black Pied Lowlands*, furthermore breakages too in a solitary case of hydrocephalus, rachimyeloschisis etc. The group of *numerical autosomal aberrations* (aneuploidy) is represented by the trisomy 18 alone, causing the " Lethal Brachygnathia Trisomy Syndrome "; whereas the group of *polyploidies* mainly consisted in tetraploidies observed in primary cultures of blood cells originating from several cases of different defects of the central nervous system.

The etiological role of structural anomalies of autosomes in disturbances of embryological development is not quite clear yet. It is not known whether the chromosome defect is merely a symptom in the range of others within a syndrome, or, whether it reveals pathological effects autonomously in sense of an effective etiological factor. But, there is strong evidence autosomal breaks being markers for heterozygosity of healthy parents of calves with Hereditary parakeratosis.

The group of *gonosomal numerical anomalies* is represented particularly by the XXY syndrome, the " Bovine hypogonadism ", and the X trisomy, both being very seldom in the observed populations. The different mosaicisms, i. e. the diploidy/triploidy mosaic, include of course a multiplication of gonosomes in triploid cells resulting in disturbances of genital development such as the different types of intersexuality. This group comprises also the " Autonomous XX/XY syndrome " in singletons and isosexual twins.

Certain observations exhibit a hereditary disposition of families to disturbances of meiotic and/or mitotic processes, based on the presence of autosomal together with gonosomal aneuploidies in two families of the *German Simmental* breed.

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Résumé

Situation actuelle de la pathologie chromosomique dans différentes races bovines allemandes

1. Dans le but de préciser le rôle étiologique des anomalies chromosomiques en pathologie des animaux domestiques, des analyses caryotypiques ont été entreprises chez 847 veaux nouveaunés présentant des malformations congénitales, chez des bovins adultes atteints de maladies héréditaires et chez les individus ayant des malformations des organes génitaux. Ces travaux ont été réalisés parmi trois grandes races d'une population de Hesse pendant ces dix dernières années. On a trouvé 141 individus porteurs de diverses anomalies.

2. On n'a pu fournir qu'une estimation grossière des fréquences des anomalies chromosomiques dans la population observée en raison de l'impossibilité, d'une part de faire le caryotype de tous les veaux atteints d'anomalies congénitales (la plupart d'entre eux étant morts-nés) et d'autre part, d'étudier toute la population.

3. Les types d'anomalies chromosomiques les plus fréquemment rencontrés sont la translocation 1/29 tout d'abord, suivie de la trisomie 18. Le chimérisme XX/XY chez les freemartins n'a pas été considéré parce que sa fréquence ne dépend que de celle des faux jumeaux dans les différentes races. A l'heure actuelle, les fréquences réelles de ces deux types d'anomalies chromosomiques n'ont pas une importance économique digne d'attention dans la population observée. Toutes les autres anomalies, surtout les remaniements structuraux autosomaux existent seulement de façon sporadique, sauf accumulations chez certaines familles. C'est le cas pour la parakératose héréditaire bovine et pour le nanisme héréditaire.

4. L'existence de plusieurs animaux porteurs à la fois de la trisomie 18 et d'anomalie numérique des gonosomes, s'explique par une prédisposition familiale aux erreurs méiotiques.

5. Les syndromes ont été déterminés à partir des résultats d'autopsie des 18 cas de trisomie 18 et de ceux des 9 cas de parakératose héréditaire. Chez les parents des veaux atteints de parakératose on a mis en évidence une augmentation du nombre de cassures autosomales. Ceci pourrait servir de marqueur pour identifier les hétérozygotes dans les familles suspectées d'être vectrices de cette maladie.

Zusammenfassung

Übersicht über die neueste Situation der Chromosomen pathologie in verschiedenen deutschen Rinderrassen

1. Mit dem Ziel der Aufklärung der ätiologischen Rolle von Chromosomenanomalien wurden bei den drei grossen Rassen der hessischen Rinderpopulation in den letzten 10 Jahren bei 847 Tieren Karyotypbestimmungen durchgeführt. Es handelt sich dabei um Neugeborene mit kongenitalen Anomalien, um erwachsene Probanden mit genetisch beeinflussten Erkrankungen und um Individuen mit Missbildungen der Geschlechtsorgane. Bei 141 Probanden wurden Chromosomenaberrationen verschiedener Typen gefunden.

2. Da weitaus die meisten der mit morphologischen Anomalien behafteten Kälber tot geboren werden, eine Karyotypanalyse bei diesen daher nicht möglich und eine systematische cytogenetische Exploration der Gesamtpopulation technisch nicht durchführbar ist, können aus diesen Ergebnissen nur rohe Anhaltspunkte für die realen Frequenzen von Chromosomenanomalien in der untersuchten Population gewonnen werden.

3. In der Häufigkeit der einzelnen chromosomalen Anomalie-Typen steht — vom XX/XY-Chimärismus der Freemartins abgesehen — die 1/29-Translokation an erster Stelle, gefolgt von der Trisomie 18. Beide besitzen wegen ihrer geringen tatsächlichen Frequenz in der beobachteten Population in der gegenwärtigen Situation nur eine geringe züchterische und ökonomische Bedeutung. Auch alle anderen morphologischen autosomalen Anomalien, vorwiegend in Gestalt von Brüchen, finden sich nur vereinzelt, jedoch familiär gehäuft bei der Bovinen Hereditären Parakeratose und beim erblichen Zwergwuchs. Die gonosomalen numerischen Anomalien werden ebenfalls selten angetroffen.

4. Das Auftreten mehrerer Probanden mit dem Trisomie 18-Syndrom (letales Brachygnathie-Trisomie-Syndrom) gemeinsam in einer Familie, in der früher bereits Fälle von gonosomalen numerischen Anomalien festgestellt wurden, lässt auf eine familiäre Disposition für Mitose- bzw. Meiosestörungen schliessen.

5. An Hand der Autopsiebefunde von 18 Fällen des Trisomie 18-Syndroms und der von 9 Fällen von Boviner Hereditärer Parakeratose wird die Symptomatik dieser von Chromosomenanomalien erzeugten, bzw. mit ihnen verbundenen Syndrome festgelegt. Dabei werden bei den Elterntieren von Parakeratose-Kälbern erhöhte Frequenzen von autosomalen Brüchen nachgewiesen. Diese können daher als Marker zur Erkennung von Heterozygoten in parakeratoseverdächtigen Familien herangezogen werden.

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