Environmental and Genetic Factors as Sources of Variation in Skeletal Muscle Fibre Number

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Abstract

The understanding of skeletal muscle growth is an important goal in animal science and in human medicine. The purpose of this review is to demonstrate the importance of muscle fibre number for muscle growth and the influence of selected genetic and environmental factors on muscle fibre number. The total number of muscle fibres is mainly determined prenatally when multinucleated myofibres form from myoblasts. In general, muscle fibre number remains almost unchanged during postnatal growth, and it is inversely correlated to the size of the individual muscle fibre. Species-specific differences in muscle mass are primarily due to differences in the number of muscle fibres. With respect to gender, in some cases male muscles were reported to exhibit more muscle fibres than female muscles. Differences in muscle mass obtained by breeding and selection are due to changes in both muscle fibre number and muscle fibre size. Genetic variability and heritability are sufficiently high to use fibre number and fibre size in farm animal selection. Moderate postnatal feed restriction does not influence muscle fibre number, whereas strong feed restriction is able to induce fibre loss. The prenatal period of muscle development is more sensitive to nutritional deficiencies in reducing fibre number. Physical activity has been shown to influence postnatal muscle fibre number. Activity stimuli are able to induce increases, whereas disuse of muscles may be followed by decreases in muscle fibre number. The postnatal application of growth promoters induces no changes in muscle fibre number, whereas the prenatal period seems to be more sensitive to hormonal factors.

Key words: exercise, growth, muscle, muscle fibre, nutrition, review, selection.

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The understanding of growth and development of skeletal muscle is one of the most important goals in animal and meat science and is also related to particular aspects of human medicine. The major component of a given muscle is the constituent muscle fibres. Muscle mass is therefore largely determined by the number of muscle fibres and the size of those fibres. Although being essential functional components within the muscle as a physiological unit, fat cells, connective tissue, capillary network and nerve fibres are of lesser importance in the determination of muscle size.

Postnatal growth of skeletal muscle is mainly realized by increases in length and girth of the muscle fibres, but not, with some exceptions, by increases in muscle fibre number. Muscle fibre hyperplasia in mammals is largely completed during gestation and fixed by about the time of birth, while many factors postnatally will affect the size of fibres. Therefore, at first sight, increases in muscle fibre size seem to exhibit priority over fibre number in contributing to postnatal increases in muscle mass. However, the number of muscle fibres within a muscle has been found to be of high importance for the growth potential of skeletal muscle, for endurance fitness and the adaptability to environmental stress, and in farm animals also for meat content and meat quality developing after slaughter.

The purpose of this review is to highlight the importance of muscle fibre number for muscle growth, and to explain the antagonistic correlation between muscle fibre number and size. We wish also to demonstrate the influence of selected genetic and environmental factors on muscle fibre number such as intrinsic genetic differ-

ences, genetic selection, nutrition, exercise and the application of selected growth promoters.

Prenatal Development and Postnatal Growth of Muscle Fibres

During embryonic development myoblasts develop from myogenic precursor cells which are of mesodermal origin. These cells are determined to enter the myogenic lineage. The determined myoblasts are able to proliferate and to divide to establish a pool of myoblasts. Special signals cause the myoblasts to exit the cell cycle, to stop dividing and to differentiate. They begin to express muscle cell-specific proteins and finally fuse to form multinucleated myotubes. During myogenesis muscle fibres develop from two distinct populations. Fibres which form during the initial stages of myoblast fusion are primary myofibres which provide a framework for the larger population of smaller secondary fibres (e.g. [9]) formed during a second wave of differentiation from fetal myoblasts. Another population of myoblasts does not form fibres but stays close to the myofibres - these are termed satellite cells. These cells are able to divide and serve as the source of new myonuclei during postnatal growth [111, 163]. They contribute to growth of the fibres and also participate in regeneration processes. Myonuclei themselves remain mitotically quiescent. The importance and relations of these different myogenic lineages are not yet clarified. It seems however, that the lineages are not related to fibre type composition [70]. Fibre formation is largely completed around the time of birth in mammals and around the time of hatching in birds.

During postnatal growth, the increase in skeletal muscle mass is mainly due to an increase in muscle fibre size (hypertrophy). As mentioned above this process is accompanied by the proliferative activity of satellite cells which are the source of new nuclei incorporated into the muscle fibres. After birth total muscle fibre number has been reported to remain unchanged in mammals and birds by most authors. No significant changes in postnatal fibre number have been found in mice [50, 113, 152, 188, 190], rat [14, 32, 47, 149, 155], pig [35, 176], cattle [138, 195] chicken [23, 51, 165] and quail [20, 46].

Some reports have indicated increases in skeletal muscle fibre number shortly after birth in mice [137], rat [130, 179], and pig [43, 181]. In these studies fibre counts were done on histological transverse sections. It is possible that the increase in fibre number during the first days of postnatal life in rodents is a result of maturation of the existing myotubes rather than a production of new fibres. This is supported by the work of Ontell and coworkers [119, 120] that suggests that the apparent increase in fibre number during the first days of the postnatal period is due to elongation of existing myotubes and the breaking up of clusters of small fibres which are present at birth and which cannot be identified in the light microscope. This may be true also for pig muscle, since fibre formation is known to be completed at about day 70 of gestation [180]. It is easy to imagine that myoblast alignment to form fibres does not lead to fibres of full length from the beginning, at least in bigger muscles from big animal species. Figure 1 demonstrates the postnatal development of muscle fibre thickness and muscle fibre number in different muscles of mice, pig and cattle. Muscle fibres grow in size towards a plateau, whereas fibre number remains constant after initial increases shortly after birth in pigs and mice.

Furthermore it has also been suggested that muscle fibre number decreases throughout life from birth to old age. Decreases from youth to adulthood have been reported in rats [3, 17, 90, 130], guinea pigs [34], dogs [72], and cattle [12]. In some cases a change in muscle fibre architecture during growth can cause an apparent decrease in fibre number and this may explain some of

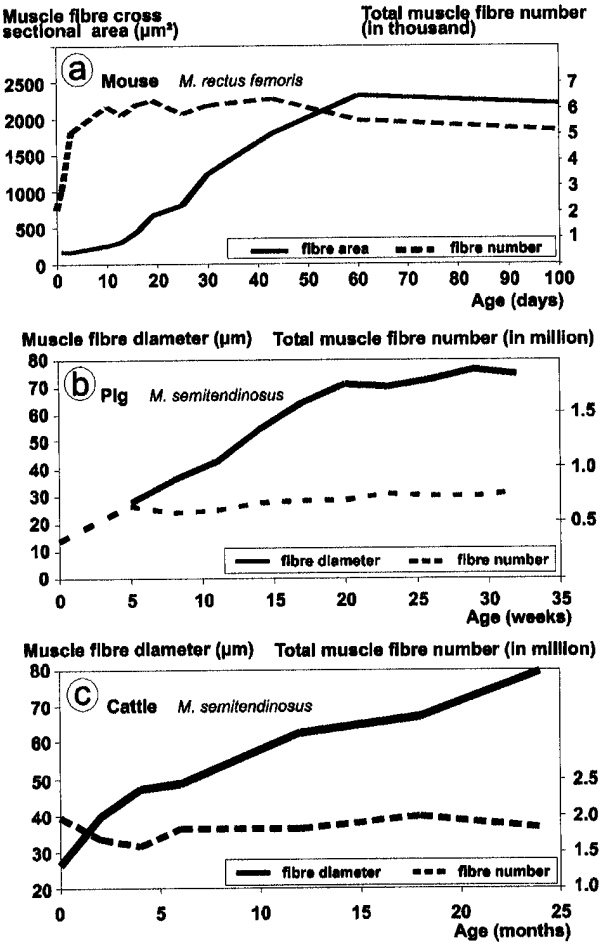

Figure 1. Postnatal development of muscle fibre thickness (cross sectional area or diameter) and total muscle fibre number per muscle cross section in a. Rectus femoris *muscle of laboratory mice [137], b.* Semitendinosus *muscle of Landrace pigs [35, 139], c.* Semitendinosus *muscle of Holstein Friesian cattle [195].*

these results [174]. In other cases the phenomenon may be due to age-related changes in the state of physical exercise which has an influence on total muscle fibre number and will be discussed in a later section.

At this point an interesting phenomenon of muscle growth should be emphasized. Postnatal muscle fibre hypertrophy strongly depends on the total number of muscle fibres within a muscle. The postnatal growth rate of the individual muscle fibre is lower at high fibre numbers and higher at low fibre numbers. Muscle fibre number is inversely correlated with muscle fibres thickness, whereas both parameters are positively correlated with muscle cross sectional area ([41, 89, 121, 137, 172]; Table 11). An explanation for this clear antagonism between fibre number and fibre size would be that more nutritional energy becomes available for the individual fibre when the fibre number is low. However, the correlation coefficient is not -1.0 which means that some animals exhibit fast growing fibres despite high fibre numbers.

Additionally, in the light of the inconsistency of the results it should be mentioned at this point that the determination of total muscle fibre number includes a series of technical problems. It can be carried out in different ways, and possibly differences in the results obtained may depend, at least in part, on the fibre counting technique used. Fibre counting from histological cross sections is still the technique most frequently used. Inaccuracies arise when muscles are of the multipennate type [52, 174] or when fibres terminate intrafascicularly [183, 186]. Gollnick and coworkers [52] calculated the number of fibres by direct counts of individual fibres dissected from nitric acid-treated muscle. The nitric acid digestion technique seems to be more accurate, if breaks in fibres can be excluded and very thin fibres are not overlooked. Finally, fibre number can be determined by measuring fibre fragments derived from transverse sections by a Coulter counter [187], but this method has not been used frequently.

In summary, the total number of muscle fibres is mainly determined pre-natally when multinucleated myofibres form from myoblasts. Increases in the apparent number of fibres shortly after birth are most probably due to the elongation of existing myotubes. In general, muscle fibre number remains almost unchanged during postnatal growth although decreases with aging cannot be excluded.

Intrinsic Genetic Differences in Fibre Number

Species

Body size and body weight of vertebrates are known to be remarkably different. Differences in muscle mass are related to muscle fibre number or size. A collection of data showing the *Longissimus* muscle fibre diameters from small and large animals (poultry and mammals) indicates that the differences in body size are not sufficiently reflected by differences in muscle fibre size (Table 1). The mean diameters range among the species from about 20 to 80 µm which is a factor of 4. However, when comparing the body weight between the shrew and the whale, there is a factor of 2.5 million [79]. Interestingly, the largest fibres are not from the whale as the largest mammal, but from the pig. Further examples comparing identical muscles between rat and mouse or between pig and cattle, are given in the Tables 2 and 3 respectively. Cattle exhibit 3 to 4 times higher fibre numbers than pigs, but same size or even smaller muscle fibres. Between mouse and rat muscles the factor is 3 to 4 for fibre number, but only 2 for fibre diameter. In conclusion, species-specific differences in muscle mass are

Table 1. Muscle fibre diameter of Longissimus *muscle in adults of different species.*

Species	Fibre diameter (µm)	References
Chicken	20	[88]
Goat	22	[88]
Shrew	19	[79]
Sheep	25	[88]
Pig (wild)	72-85	[6, 125]
Pig (domestic)	40-80	[35, 88, 129, 170]
Fallow-Deer	19	[154]
Reindeer	45	[33]
Buffalo	26	[88]
Zebu	78	Wegner unpubl.
Yak	70	Wegner unpubl.
Cattle	55-67	[79, 194, 195]
Elephant	51	[79]
Whale	55	[79]

Table 2. Muscle fibre number and diameter in two muscles of the laboratory mouse and rat.

Species	Extensor digitorum longus	Soleus
	Fibre number	
Mouse	1000-1300	450-860
Rat	2600-3500	2000-3050
	Fibre diameter (µm)	
Mouse	20-41	25-28
Rat	39-64	47-60

[7, 85 , 98, 112, 131, 133, 134, 144, 152, 155, 179, 188]

Table 3. Muscle fibre number in two muscles of cattle and pigs (in million).

Species	Semitendinosus	Longissimus
Pig	0.55-0.83	0.66-1.09
Cattle	1.70-3.36	2.51-3.77

[35, 170, 195]

primarily due to differences in the total number of muscle fibres. Possibly the evolutionary increase in muscle fibre size is limited by physiological reasons in that normal cell function is maintained only as long as a certain limit in cell size is not overexceeded.

Gender

Contradictory results have been reported concerning the determination of the number of muscle fibres by gender (Table 4). Sex-related differences in the number of muscle fibres have been reported for rats [81, 144], cattle [124], chickens [142] and humans [65, 116]. In these cases males exhibited higher muscle fibre numbers compared to females. Conversely, no differences were found between male and female rat *Soleus* muscles [32], several mouse muscles [113, 152, 188] dog *Pectineus* muscle [72], pig *Longissimus* muscle [38, 122, 143, 170] and human *Vastus lateralis* muscle [157, 158].

Studies undertaken by Tobin and Joubert [191] revealed that the sex difference in muscle fibre number of rat *Levator ani* muscle is under the control of testosterone during the perinatal period. Testosterone treatment in later postnatal periods is able to increase muscle growth in a direct or indirect manner (for reviews see [44, 168]) by stimulating satellite cell proliferation and muscle protein synthesis [80, 81, 193]. Fibre number is not increased. From this action of testosterone and the knowledge about the events of myogenesis it might be concluded that differences in muscle fiber number between males and females can arise by hormonal action if differences in androgen hormones are sufficiently high during the period of prenatal fibre formation. With regard to early postnatal increases in fibre number, which were discussed above, it is possible that testosterone may stimulate the longitudinal growth of existing myofibers and in this way increase the fibre number per muscle cross section. Additionally, differences in fibre number have been related to different physical activity between male and female muscles [65]. The influences of physical activity on muscle fibre number are described below.

In conclusion, a number of differences in the total number of muscle fibres seems to exist between female and male muscles in that male muscles exhibit higher fibre numbers than female muscles. However, to what extent these differences are due to hormonal actions, to different patterns of activity and/or to other factors remains unclear.

Effects of Genetic Selection on Muscle Fibre Number

Genetic variability/heritability

Whether and to what extent a biological trait is heritable and changeable by selection largely depends on its genetic variability, its heritability and its genetic correlation to the criteria used in selection. As shown in Table 5 about half (mouse) or two thirds (pig) of the phenotypic variation in muscle fibre number is due to genetic origin. This proportion is relatively high as compared to performance traits commonly used in selection of farm animals. The coefficients of heritability estimated for muscle fibre number (Table 6) ranged from 0.12 to 0.88, most lying between 0.2 and 0.5. These results demonstrate that muscle fibre number is not exclusively determined genetically as has been previously presumed owing to its relative constance during postnatal life. Maternal influence on fibre number has been reported to be about 17% of the phenotypic variance for mouse *Extensor digitorum longus* muscle [135].

Correlated responses to growth selection

Differences in muscle mass obtained by breeding and selection are due to changes in both muscle fibre number and muscle fibre size. This can be concluded from a series of selection experiments for large body size or rapid growth rate with several species including mouse [1, 16, 61, 96, 126, 133, 141, 179, 189], pig [198, 199], chicken [2, 107, 146, 147, 165], quail [46] and turkey [23].

The influence of growth selection on muscle fibre number is also apparent from differences between ani-

Table 4. The influence of gender on muscle fibre number examined in different species and muscles.

Species	Muscle	Effect	References
Mouse	*Soleus, Tibialis anterior, Biceps brachii Extensor digitorum longus, Sternomastoideus*	None	[113, 152, 188]
Rat	*Soleus*	None	[32]
	Extensor digitorum longus, Levator ani	male > female	[81, 144]
Chicken	*Extensor hallucis longus*	male > female	[142]
Dog	*Pectineus*	None	[72]
Pig	*Longissimus*	None	[38, 122, 143, 170]
Cattle	*Longissimus*	male > female	[124]
Human	*Tibialis anterior*	male > female	[65]
	Biceps Brachii	male > female	[116]
	Vastus lateralis	None	[157, 158]

Table 5. Phenotypic and genetic standard deviation (S_p, S_g, %) of muscle fibre number and size (cross sectional area or diameter).

Species/*Muscle*	Fibre number		Fibre size	
	Sp	Sg	Sp	Sg
Mouse/*Extensor digitorum longus*	18.9	9.3	17.8	8.2
Pig/*Longissimus*	25.9	17.1	13.6	7.6

[37, 135]

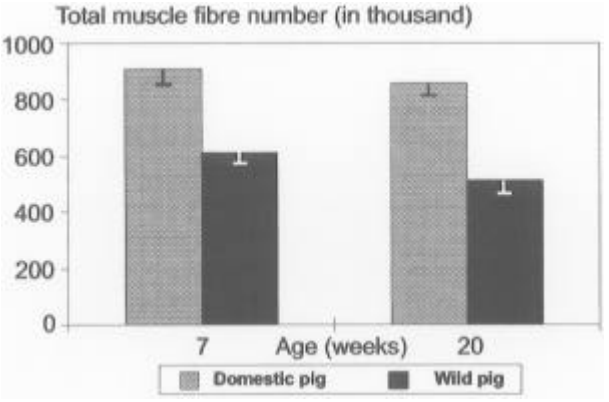

Figure 2. Muscle fibre number per Semitendinosus *muscle cross section in domestic pigs and in wild type pigs kept under almost identical conditions until 7 or 20 weeks of age (LSMeans, SE; [43]).*

mals of different genetic breeds or between wild and domestic types of the same species. No marked differences in muscle fibre number of *Longissimus* muscle were found between different modern meat type pig breeds and crosses in contrast to the 'older' fatty Saddle Back breed which has lower fibre number ([38, 87]; Table 10). Staun [170] found some differences when comparing several European pig breeds 20 years ago (Table 9). The European domestic pig, which was derived from the European wild pig exhibits larger fibres [6, 43, 196] but also higher numbers of fibres as found for *Semitendinosus* muscle ([43]; Figure 2). Moreover, clear differences in muscle fibre number between Large White and Miniature pigs were reported [177].

Some evidence exists that selection for growth rate or body size increases both muscle fibre number and size, whereas selection for protein and muscle mass as carried out in modern breeding programs mainly increases muscle fibre size. Selection for growth rate leads to increased myoblast or satellite cell proliferation rates. More muscle fibres are formed and no changes in muscle DNA/protein ratio occur [15, 16, 18, 46, 99, 126]. The results suggest that differences in muscle fibre hyperplasia in response to selection for growth were primarily due to differences in myoblast proliferation rates. In contrast, for modern meat type chicken [77, 86, 105], pigs selected for meat content [115] or for mice selected long-term for protein content [133] decreased muscle DNA/protein or nuclear/cytoplasm ratios have been reported.

There are suggestions that the extent of hypertrophic and/or proliferative response depends on how the applied selection leads to changes in the hormonal system, especially in the growth hormone/IGF-I axis. IGF-I is an important growth factor which stimulates myoblast and satellite cell proliferation [45, 197]. Plasma levels of growth hormone and/or IGF-I were significantly changed in response to growth selection in mice [104, 109, 156]. Differences in body weight of GH transgenic mice, specifically offspring of a hemizygous transgenic sire and a non-transgenic dam, could be explained mainly by differences in muscle fibre number [67]. The plasma of highly growth selected mice without increased fat deposition contained significantly elevated levels of IGF-I,

Table 6. Coefficients of heritability (h^2) for muscle structure traits.

Species *Muscle*	Fibre number	Fibre size (area or diameter)	References
Mouse			
Extensor digitorum longus	.23-.24	.16-.21	[135]
Soleus	.44-.68	.07	[113]
Chicken			
Pectoralis superficialis	.12-.49	.00-.26	[95]
Pig			
Longissimus	.66-.88	.17-.31	[171]
	.43-.48	.30-.50	[172]
	.28-.41	.22-.34	[42, 26]
	.22	.34	[89]
Cattle			
Longissimus	.35	.74	[121]

Ranges arise from the application of different methods to estimate heritability coefficients.

whereas GH levels were actually decreased [104]. Both plasma growth hormone *and* IGF-1 concentrations were not higher in broiler chickens highly selected for muscle mass compared to slow growing Bantam chickens [105].

Double muscling in cattle

The condition of double muscling (DM) in Belgian Blue and Piedmontese cattle is a particular case of excessive muscle fibre formation (hyperplasia). Skeletal muscles of DM cattle contain almost double the number of fibres than those of other cattle breeds whereas no obvious differences are apparent in muscle fibre thickness ([69, 123, 195]; Tables 7 and 8). The increase in muscle fibre number is associated with increases in muscle mass by 20% and upwards [164, 195]. Prenatal studies with DM cattle suggest that the higher number of muscle fibres is a consequence of delayed differentiation and extended myoblast proliferation [127]. The double muscled phenotype arises from mutations in the myostatin gene [56, 82, 103]. Myostatin is a growth and differentiating factor (GDF-8) that belongs to the transforming growth factor-beta (TGF-ß) superfamily and has been identified as an important negative regulator of muscle development in a mouse model of gene deletion [102]. In Belgian Blue cattle an eleven base pair deletion in the coding region of the myostatin gene prevents the expression of the myostatin protein, whereas Piedmontese cattle have a G to A transition in the same region [56, 82, 103]. An autosomal recessive inheritance has been suggested for the DM condition [56]. The detailed physiological mechanisms by which myostatin affects muscle development remain to be investigated.

Practical importance in animal breeding

From genetic correlation coefficients and results of selection experiments it has been concluded that selection for high fibre numbers at moderate fibre size are most advantageous in achieving both high meat content and good meat quality. When increases in fibre size are overemphasized in response to selection this seems to reduce the capacity of the fibres to adapt to activity-induced demands which in turn is associated with stress-susceptibility and poor meat quality in modern meat type pig breeds [21, 39, 40, 41, 48, 93, 199]. Moreover, it can also be demonstrated by simulated selection with mouse and pig data that if muscle structure traits were included in selection indices, selection responses in commonly used traits could be markedly improved [26, 134].

It should be emphasized in this regard that the phenotypic antagonism between fibre size and number mentioned above is based on genetic background (Table 11). The genetic correlation coefficients between fibre size and number estimated for mouse, chicken and pig were found to range from -0.4 to -0.8. Consequently, selection of animals with high muscle mass realized mainly by large fibres will in turn produce offspring with low fibre number. That it is possible to produce more meat by high muscle fibre numbers has been shown by a selection experiment with pigs [198]. Divergent selection on high or low muscle fibre diameter in *Longissimus* muscle, but each of them connected with low backfat/muscle ratio, increased muscle thickness in equal terms but produced meat of extremely different structure and quality (Table 12). The latter was poor in the high line and good in the low line and the proportion of stress-susceptible (MHS-positive) pigs was zero in the low line. Lengerken and coworkers [93] investigated the relationship between muscle fibre number and pH value of pig *Longissimus* muscle and meat percentage after slaughter. They were able to demonstrate that there is a range of optimum muscle fibre number which guarantees both high meat percentage and good meat quality. Those animals should be preferentially chosen for selection.

The discussed relation between fibre number, fibre size and fibre metabolism is obvious in pigs, but not in cattle. No correlations between fibre characteristics and meat quality traits were found in normal cattle breeds (e.g. [195]). However, double-muscled cattle exhibit paler meat and higher proportions of glycolytic fibres despite higher fibre numbers and same fibre size compared to other cattle breeds (e.g. [195]) suggesting that fibre size and fibre metabolism may be also independently related to ultimate meat quality.

To summarize the effects of genetic selection differences in muscle mass are due to changes in both muscle fibre number and muscle fibre size. The genetic background of the different selection responses in relation to

Table 7. Muscle fibre number (LSMean±SD, in million) in Semitendinosus *muscle of different cattle breeds kept under almost identical conditions [195].*

	Age (month)		
Cattle breed	2	6	18
Galloway	1.56 ± 0.31^{A}	1.89 ± 0.24^{A}	1.73 ± 0.40^{A}
German Angus	1.85 ± 0.42^{A}	1.66 ± 0.35^{A}	1.84 ± 0.29^{A}
Holstein Friesian	1.68 ± 0.38^{A}	1.82 ± 0.52^{A}	2.00 ± 0.41^{A}
Belgian Blue	3.55 ± 1.18^{B}	3.06 ± 0.83^{B}	3.46 ± 0.67^{B}

Significant differences between breeds indicated by different letters ($P < 0.05$), n = 5 to 12 per group.

Table 8. Fibre number and size in Longissimus *muscle in bulls of different cattle breeds [121].*

Cattle breed	Fibre number (in million)	Fibre diameter (µm)
Brown	2.0147	62.1
Light spotted		
A	2.4236	52.4
B*	1.7933	67.5
Black Pied	2.0580	62.2
Charolais	2.5314	58.2

* contains a high portion of the Pinzgauer genotype.

Table 9. Muscle fibre number and diameter (Means) in Longissimus *muscle of different pig breeds [170].*

Pig breed	Fibre number (in million)	Fibre diameter (µm)
Piétrain	1.022	70.7
Danish Landrace	1.056	64.4
Duroc	0.730	68.3
Yorkshire	0.768	76.2
Deutsches Edelschwein	0.738	77.6
Veredeltes Landschwein	0.904	77.4

Table 10. Muscle fibre number and diameter (Mean±SD) in Longissimus *muscle of different pig breeds (Fiedler 1988, unpublished, and [87]).*

Pig breed (n)	Fibre number (in million)	Fibre diameter (µm)
German Landrace (694)	1.041±0.280	68.9±9.5
German Large White (137)	1.016±0.251	70.0±8.4
Leicoma (1052)	1.061±0.275	68.6±9.4
Schwerfurter (77)	1.109±0.309	68.9±10.7
Piétrain (26)	1.107±0.178	71.3±8.8
Saddle Back (17)	0.909±0.178	67.1±7.8

gated. One-sided increases in muscle fibre size are to be expected when using selection programs which are preferentially directed to increases in muscle mass. Genetic variability and heritability are sufficiently high to use muscle fibre number and muscle fibre size as criteria in selection. From genetic correlations and correlated responses of selection it is concluded that both muscle mass and meat quality/stress adaptability could be significantly improved when considering muscle structure traits in pig breeding.

Environmental Influences on Muscle Fibre Number

Postnatal nutrition

Adequate nutrition is essential for normal skeletal muscle growth. Malnutrition during postnatal growth reduces body weight and skeletal muscle weight. Feed restriction both in quantity and in quality (protein deficient diets) has been reported to lead to decreases in muscle fibre diameters in mice [50, 131], rat [59, 62, 91, 100, 155, 185], hamster [50, 64], rabbit [64], pig [36, 101, 172, 178], sheep [78], cattle [11], rhesus monkey [25] and human [22, 108]. The decreases in muscle fibre size are accompanied by a reduction in muscle nuclear number or DNA content with increased DNA/protein or nuclear cytoplasm ratios [49, 110, 150, 155, 178, 182, 185].

With regard to changes in muscle fibre number in response to postnatal dietary restriction contradictory results have been reported. Fibre numbers were not influenced by postnatal malnutrition in post-weaning mice [50, 131, 150, 131] and rats [7, 49, 125, 155, 185], in pigs [172, 178] and human [22, 62, 108]. An example of responses of muscle fibre size and number is given in Figure 3.

Lower fibre numbers were found in different muscles of hamsters and rats, but not in rabbits and guinea pigs in response to temporary postnatal starvation [63, 64]. Lower fibre numbers were also counted in muscles from weanling rats which were fed for 9 days at 25% volun-

Table 11. Phenotypic and genetic correlation coefficients (r_P, r_G) between fibre number, fibre size (area or diameter) and muscle cross sectional area (MCA).

Trait pair	Species	r_P	r_G	References
Fibre number / MCA	Mouse	+0.4/+0.5	+1.1	[135]
	Chicken	+0.3	+0.7	[95]
	Pig	+0.3 / +0.5	+0.4/+0.7	[41, 172]
Fibre thickness / MCA	Mouse	+0.6	+0.5	[135]
	Chicken	+0.5	+0.7	[95]
	Pig	0 / +0.3	0/+0.5	[41, 172]
Fibre number / Fibre thickness	Mouse	-0.3/-0.6	-0.4	[135]
	Chicken	-0.4	-0.4	[95]
	Pig	-0.8	-0.7/-0.8	[41, 172]

Table 12. Results of a four-generations divergent selection on high and low Longissimus *muscle fibre diameter together with low backfat/muscle ratio in German Landrace pigs [198].*

Trait	High (n = 31)	Low (n = 68)	Difference Low/High (%)
Muscle thickness (mm)	49.3	49.4	0
Fibre diameter (µm)	90.0	81.6*	91
Fibre number index[§]	310	379*	122

* significant differences at $P < 0.05$; [$] calculated from ultrasound measured muscle thickness and fibre number per unit area in muscle biopsy sections

tary intake [91]. Ihemelandu [73] reported lower fibre numbers in mouse *Soleus* muscle after feeding protein deficient diet to the mothers during suckling and subsequently to the young after weaning up to 9 weeks of age. Fibre number was also decreased when rats were undernourished throughout gestation *and* lactation at about 50% of feed intake of the dams [7]. In contrast, Glore and Layman [49] did not find any decrease in *Soleus* or *EDL* muscle fibre number at the same level of restriction when the periods of gestation and lactation were studied separately. Moreover, there were no differences in muscle fibre number when mice were raised in litters of different size as 4, 8 and 12 [131, 188], although clear differences in growth rate were achieved by this method.

Prenatal nutrition

Prenatal undernutrition in pigs has been shown to be related to lower muscle fibre numbers and myonuclear numbers or DNA content as evidenced by the comparison of small with large weight piglets (e.g. [60, 200, 201]). Also experimentally induced undernutrition during pregnancy has been reported to decrease muscle fibre

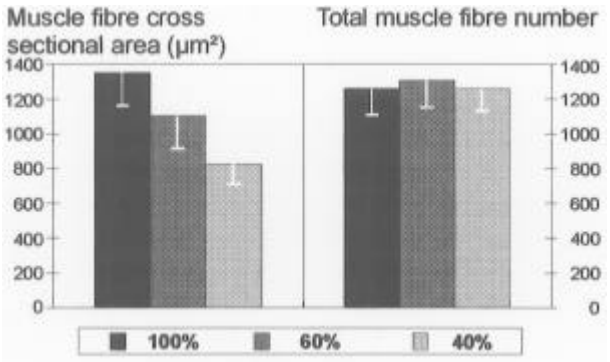

Figure 3. Extensor digitorum longus *muscle characteristics of laboratory mice in response to post-weaning quantitative feed restriction (Means, SD; [131]).*

number and/or myonuclear number in rats (e.g. [49]), in guinea pigs (e.g. [27, 29]) and in pigs [148]. The lasting negative effect of prenatal undernutrition on postnatal growth is commonly recognized (e.g. [128]). Doubling of maternal feed intake of sows during gestation tended to increase *Semitendinosus* muscle fibre number and lead to narrowing in the distribution of fibre number [31]. The offspring showed higher average daily gains and higher gain/feed ratios from days 70 to 130 of age. Mechanisms responsible for the influence of maternal nutrition on fetal myogenesis may involve alteration in IGF levels [30] or in placental morphology and efficiency [28].

In summary, whether postnatal malnutrition is able to induce muscle fibre loss seems to depend both on the intensity and on the time period (developmental stage and duration) of dietary restriction. Only severe restriction (starvation, 75% restriction) seems to cause fibre loss, whereas moderate undernutrition exclusively affects fibre hypertrophy by means of reduced nuclear and protein accumulation. However, it seems to be important in mice and rats, whether the lactational period is included into longer periods of undernutrition. Probably, the elongation of existing myotubes which leads to an increase of apparent fibre number during early postnatal growth in mice [119, 120] cannot be completed when the animals are undernourished during early postnatal life. From studies with fetal sheep Swatland and Cassens [184] concluded that lower fibre numbers will result when the longitudinal growth of intrafascicularly terminating fibres is inhibited by undernutrition during late gestation. The prenatal period of muscle development is much more sensitive to nutritional deficiencies, because this period includes muscle fibre formation. Maternal nutrition and/or nutrient availability seem to be key factors in the regulation of myogenesis.

Physical activity

It seems to be important to what extent environmental conditions allow or force physical exercise, because the individual state of physical activity has to be considered as a relevant determinant of skeletal muscle structure.

Activity-induced muscle growth is reported to be accompanied by changes in muscle fibre size and number. Daily training for endurance running on a treadmill has been shown to increase fibre number in the cross section of *Plantaris* muscle in guinea pigs after 8 weeks [34] or of *Rectus femoris* muscle in mice after only 3 weeks ([132]; Figure 4). Moreover, in these cases fibre size was significantly reduced compared to untrained controls and no increases in muscle mass were observed.

On the other hand, it has long been recognized that adult skeletal muscle can achieve tremendous increases in size and strength in response to weight-lifting exercise. The increase in weight can be produced experimentally by ablation of synergistic muscles, by chronic stretching or by weight lifting. Several studies have

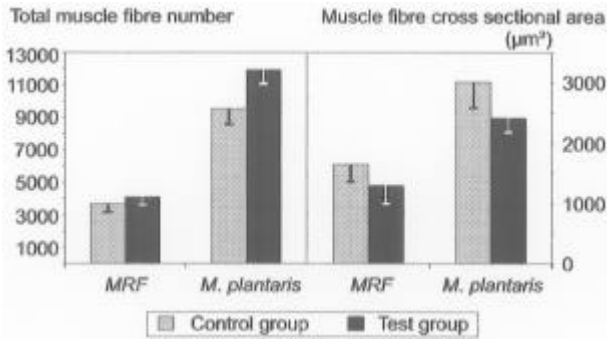

Figure 4. Muscle fibre number and cross sectional area (Means, SD) in cross sections of Plantaris *muscle in guinea pigs [34] and of* Rectus femoris *muscle (MRF) in laboratory mice [132] after 8 or 3 weeks of endurance running on a treadmill.*

suggested that compensatory hypertrophy [71, 151], tonic stretching [20, 166], and muscle growth induced by weight-lifting exercise [53, 54] may be the result of hypertrophy of existing fibres and/or an increase in fibre number. Table 13 demonstrates the differences in fibre number of ALD muscle in quail in response to stretch-overload [20]. Other studies have demonstrated that increased muscle mass is due primarily to an enlargement of muscle fibres without increases in their number (e.g. [52] in rats). Although for different models of activity-induced muscle growth there is evidence of muscle fibre hyperplasia and hypertrophy or of hypertrophy alone, clearly, skeletal muscle fibres appear to possess the appropriate mechanisms for both responses.

What are the mechanisms which could result in exercise-induced increases in muscle fibre number? Severe overloading seems to induce fibre splitting [76, 58, 145]. However, the results support the view that if muscle fibres do undergo longitudinal division this process is of minor importance. According to Gollnick and coworkers [52] and Gonyea and coworkers [54] the number of bifurcated fibres, determined by the nitric acid method of fibre counting, is very low and does not differ significantly between control and overloaded muscles.

On the other hand, muscle fibre degeneration, necrosis and loss of fibers [66, 75, 94, 132, 160, 161, 162] have been observed in response to overloading (Figure 5).

Table 13. Effect of 30-days stretch overload of the left wing on Anterior latissimus dorsi *muscle fibre number in the Japanese quail [20].*

Group	n	Right wing	Left wing	Difference, %
Unweighted control				
Aged	3	1256±112	1262±116	9.8±0.1
Left wing stretched				
Adult	16	1248±34	2013±142*	59.6±9.4
Aged	16	1247±44	1858±141*	47.2±8.1

* significantly different to right wing at $P < 0.05$

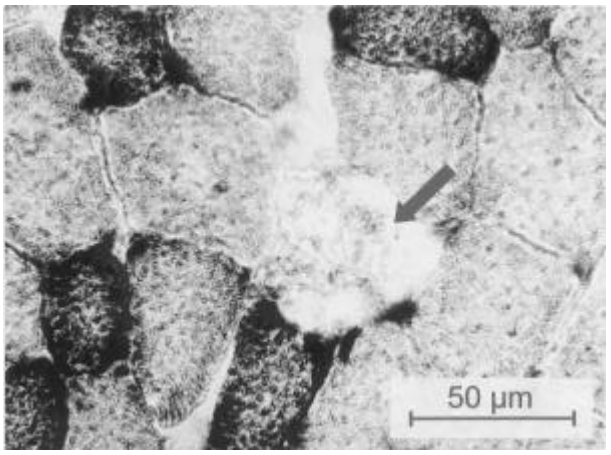

Figure 5. Signs of muscle fibre degeneration in Rectus femoris *muscle cross section obtained from untrained laboratory mice after running to exhaustion on a treadmill (NADH-tetrazolium-reductase staining).*

Eccentric running, flying or weight overloading produces focal injury of myofibres at multiple levels in the muscle. The damage is expressed by alterations of the morphological structure of the muscle and by an increase of muscle-specific proteins in the blood (e.g. [68, 106]). Satellite cells are activated to proliferate and form new myotubes that regenerate the muscle [5, 24, 74]. By the immunohistochemical detection of nascent fibres in response to overload degeneration or experimentally induced myonecrosis [94, 149] it has been shown that lost fibres can be effectively replaced. The morphology of regeneration in skeletal muscle has been described in detail by Schmalbruch [159]. New fibres may be formed by different cellular mechanisms. The latter study also indicates that fibre splitting results from regeneration and that 'fragments' represent individual fibres which are closely attached because they have developed within the same basal lamina.

It is assumed that the leakage of mitogens contributes to satellite cell stimulation. However, satellite cells are activated all over the muscle in response to exercise [75]. Inoue and coworkers [74] reported that a rapid increase in androgen receptors following electrical stimulation of rat *Gastrocnemius* muscle occurred suggesting that muscle sensitivity to androgen is enhanced and may contribute to muscle hypertrophy. Androgen hormones are known to stimulate satellite cell proliferation (e.g. [80]).

Figure 6 summarizes the events in activity-induced changes in fibre number and fibre size by a simplified hypothetical model. A more detailed model has been presented previously by Taylor and Wilkinson [186].

Spectacular results which suggest an interaction between the effects of genetic selection and physical exercise on fibre multiplication were presented by Cherel et al. ([23]; Figure 7). They compared the postnatal devel-

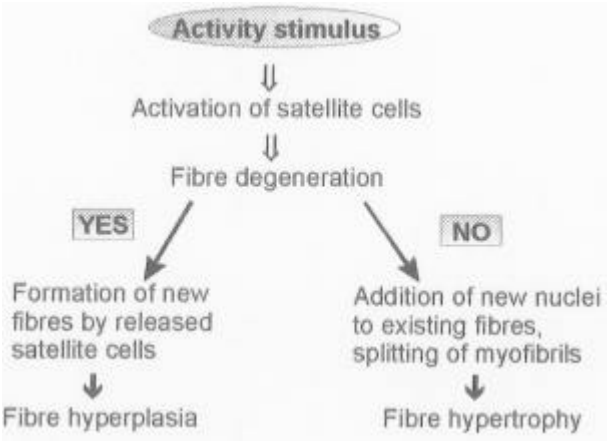

Figure 6. Hypothetical model for activity-induced increases in muscle fibre number or muscle fibre size.

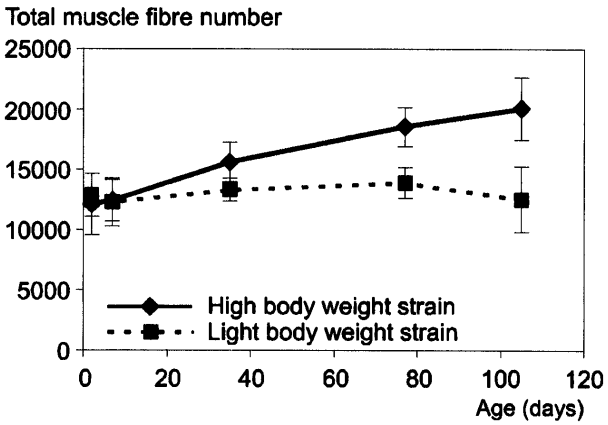

Figure 7. Muscle fibre number in Anterior latissimus dorsi *muscle cross section in two strains of turkey (Means, SE; [23]).*

opment of *Anterior latissimus dorsi* (ALD) muscle in heavy- and light weight strains of turkeys. Muscle fibre number remained unchanged after hatching in the low line, whereas it increased with age in the high line, selected for weight and muscle mass at 15 weeks of age. Usually differences in muscle fibre number between differently selected lines are apparent at hatching in poultry or by birth in mammals. By morphometric and immunocytochemical analysis it was shown that this increase in fibre number in the high line was due to nascent myofibres. Possibly the condition of the selection-induced increase in wing weight is comparable to that obtained by the application of weight overload to chicken or quail muscle, which were reported to induce new fibre formation. In this case the higher fibre number in the high line would be a secondary consequence of selection on muscle mass.

Further evidence for the importance of physical activity on fibre hyperplasia and fibre hypertrophy is demonstrated by immobilization and denervation as experimental negative models in contrast to activity-induced growth. Immobilization results in a decrease in muscle mass. Immobilization atrophy of muscle is clearly accompanied by decreases in muscle fibre cross sectional area (e.g. [83, 202]). Decreases in fibre number of rat *Soleus* muscle in response to hindlimb immobilization were reported by Booth and Kelso [13] and Oishi and coworkers [117] as shown in Table 14. In contrast, there was no evidence of fibre number decrease in rat *Triceps brachii* muscle [112] or *Soleus* muscle [19] after hindlimb immobilization. Inactivation by denervation of frog *Cutaneous pectoris* muscle clearly lead to a decrease in fibre number [4]. Decreases in fibre size and fibre number seem to be the result of focal degeneration of cell ultrastructure after immobilization and denervation of muscle as shown by Guba and coworkers [57] for the rabbit and by Anzil and Wernig [4] for the frog. In this respect it can be suggested that postnatal decreases in muscle fibre number with age (as mentioned above) at least in part may be related to decreased levels of physical exercise.

In summary, the occurrence of muscle fibre hyperplasia differs amongst some experimental models of activity-induced growth. Whether or not fibre hyperplasia occurs may be due to differences in the magnitude and duration of the stimulus on the one hand and to the capacity of the fibres to adapt on the other hand. If new fibre formation is a consequence of preceding fibre degeneration, then an increase in net fibre number by an activity stimulus depends on the extent of both these processes. Skeletal muscle fibres adapt to an activity stimulus when an alteration in the normal level of activity is of sufficient magnitude and duration to exceed an adaptive threshold which depends on the pre-existing capacity of a muscle fibre. This capacity is important for determining whether a muscle responds with fibre hypertrophy or fibre hyperplasia. In contrast to activity induced muscle growth, chronic disuse of muscle causes muscle atrophy associated with reductions in fibre size and number.

Growth promoters

Growth is known to be regulated substantially by the neuro-endocrine system as well as paracrine and autocrine actions of hormones and growth factors, and the influence of environmental stimuli on the individual are widely mediated by the induction of hormonal actions. This has lead to a series of attempts to modify animal growth by administrating hormones or hormonal factors.

Table 14. Fibre number of the Soleus *muscle from control and immobilized limbs in rats [117].*

Trait	Control	Immobilized
Body weight (g)	362.7±37.0	
Muscle weight (mg)	152.8±16.1	83.8±20.8*
Total fibre number	2903±115	2504±236*

* significantly different to control at $P < 0.01$.

However, there is only limited information on the influences on skeletal muscle structure, especially muscle fibre number. In this regard growth hormone and beta-adrenergic agonists are the two most studied growth promoting substances.

Postnatal application of growth hormone (GH) clearly stimulates muscle fibre growth as has been shown in different species [8, 10, 92, 118, 136, 140, 167, 192]. Mainly acting via IGF-I, growth hormone is able to stimulate both satellite cell proliferation and protein synthesis in muscle. Little information is available about postnatal GH action on muscle fibre number. In two experiments with pigs it was found that porcine somatotropin (pST) treatment did not significantly change the apparent muscle fibre number in *Longissimus* muscle calculated from fibre number per unit area and muscle cross sectional area ([136, 143]; Table 15). Somewhat lower fibre numbers in *Soleus* and *Biceps brachii* muscles have been found in mice with pituitary dwarfism as compared to their phenotypically normal litter mates [175], suggesting that prenatal or early postnatal fibre formation in the mouse may be under the control of growth hormone. This idea is also supported by the results obtained with GH transgenic mice reported by Hikida and coworkers [67]. Furthermore, it cannot be excluded that GH contributes to new fibre formation by stimulation of satellite cell proliferation in regenerating muscle. Ullman and Oldfors [192] showed that rat muscles recovered much faster when the animals received daily injections of recombinant human GH after experimentally induced ischaemic necrosis or degeneration.

Growth-promoting effects on muscle by stimulating fibre growth are also known to be exerted by beta-adrenergic agonists [9, 85, 98, 153, 194]. Muscle fibre hypertrophy seems to be achieved mainly by reduction of proteolytic activity after long-term application. There is also some evidence for increases in protein synthesis as a short-term response to beta-adrenergic agonists. However, beta-adrenergic agonists do not stimulate satellite cell proliferation (except ractopamine; [55]) as has been shown for growth hormone. Consistent with GH action the number of muscle fibres was not increased in response to clenbuterol in rats [98, 144] and in broiler chickens [142].

Recently, several attempts have been made to influence prenatal growth by different growth promoters. The administration of porcine somatotropin (pST) during different stages of gestation was able to affect fetal growth [84, 139, 140, 173]. Newborn piglets of low and mean birth weight exhibited higher muscle weights, increased numbers of muscle fibres in *Semitendinosus* muscle and higher muscle DNA and protein content when their mothers had been treated with pST from day 10 to 24 or from day 10 to 27 of gestation ([139, 140]; Figure 8). As shown in Table 16 the number of primary and secondary fibres in *Semitendinosus* muscle was increased by this pST treatment. Nutrient availability in terms of glucose

Table 15. Total muscle fibre number index (Means±SD, in thousand) of* Longissimus *muscle in response to 70 days porcine somatotropin (pST)-treatment in German Landrace pigs [143].*

Sex	Control	2 mg pST/d	4 mg pST/d
Gilts	471.0±112.6	523.7±181.9	486.7±117.0
Castrates	513.8±117.6	483.3±121.3	478.2±124.7
Boars	446.1±104.5	434.3±108.9	478.7±163.0

* calculated from loin muscle area at slaughter (≈ 200 d of age) and fibre number per mm² in muscle biopsy sections at the final biopsy term (about 185 d of age).

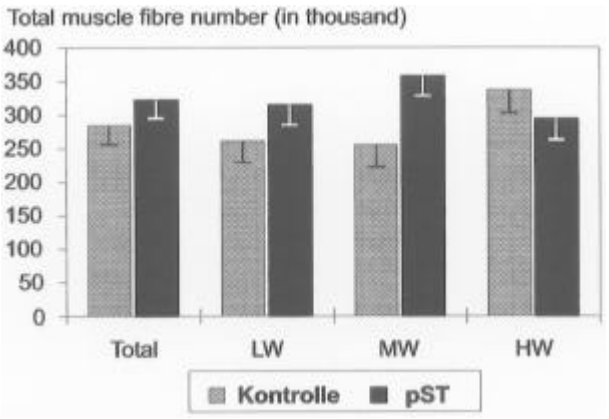

Figure 8. Semitendinosus *muscle fibre number of newborn piglets born to gilts treated with porcine somatotropin during early gestation (between days 10 and 24/27; summary of 3 experiments, n = 86; LSMeans, SE). Data are separately shown for the total number of piglets, and for the piglets of the lightest (LW, but > 800 g), mean (MW), and heaviest (HW) birth weight within the litter (139, 140 plus Rehfeldt 1999, unpublished).*

Table 16. Semitendinosus *muscle fibre number per cross section (LSMeans, in thousand) in response to porcine somatotropin (pST) - treatment during early gestation (days 10 to 27 of gestation) in newborn piglets of mean birth weight (Rehfeldt 1996, unpublished).*

Trait		Semi-tendinosus	Psoas major
Total muscle fibre number	Control	255.8	213.5
	pST	357.6*	216.2
Primary fibre number	Control	12.0	8.8
	pST	15.2*	9.1
Percentage of primary fibres	Control	4.75	4.42
	pST	4.40	4.20

* $P < 0.1$ for difference between control and pST

and free fatty acids was increased by GH action. The results suggest that elevated maternal GH concentrations increase the number of proliferating myoblasts in an indirect manner. It was concluded that maternal growth hormone is a significant determinant of skeletal muscle development and muscle fibre formation in fetuses. Opposite effects were obtained in an experiment with rats which were fed the beta-adrenergic agonist clenbuterol during gestation and lactation [97]. Muscle weights, protein, RNA, DNA content and total muscle fibre number were clearly reduced in the offspring.

In conclusion, the hypertrophic response of postnatal muscle to growth hormone or beta-agonists is commonly based on muscle fibre hypertrophy, but not on muscle fibre multiplication. This mechanism represents the common growth pattern of healthy postnatal muscle under normal requirements. However, the available results suggest that the prenatal or pre-hatching developmental stage is much more sensitive to hormonal factors as has been shown above also for nutritional factors. However, the mechanisms of action are much less understood.

Conclusions

From the discussed environmental and genetic influences on pre- and postnatal skeletal muscle growth strategies can be derived to develop practical approaches to altering muscle fibre number. In farm animal production these will be preferentially based on genetic selection or on environmental modulation of prenatal myogenesis. It would be less practical in animal production to impose extensive exercise programs during postnatal life to increase fibre number.

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