J. Anat. (1976), **122**, 1, pp. 121–131
With 5 figures
Printed in Great Britain

Compensatory muscular hypertrophy in the extensor digitorum longus muscle of the mouse

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(*Accepted* 13 *August* 1975)

INTRODUCTION

It has been reported on numerous occasions that strenuous exercise rapidly induces skeletal muscle hypertrophy by increasing the cross sectional areas of the muscle fibres without increasing their number (Morpurgo, 1897, 1898; Hoffman, 1947; Bigland & Jehring, 1951; Crawford, 1961; Goldspink, 1964; Walker, 1966; Hamosch, Lesch, Baron & Kaufman, 1967; Goldberg, 1967; Gordon, 1967; Rowe & Goldspink, 1968; Goldberg & Goodman, 1969; Binkhorst, 1969; Schiaffino & Hanzlikova, 1970; Gutmann, Schiaffino & Hanzlikova, 1971).

Severe overloading of skeletal muscles seems to induce fibre splitting (Van Linge, 1962; Reitsma, 1969, 1970; Edgerton, 1970; Hall-Craggs, 1970, 1972; Hall-Craggs & Lawrence, 1970) and even necrosis and loss of muscle fibres (Highman & Atland, 1963). Although such apparent fibre splitting could also be interpreted as a fusion process (James, 1973), its relationship to any possible increase in the number of fibres during hypertrophy has not previously been studied. Evidence which suggests that the number of fibres is increased in exercised muscles, i.e. hyperplasia, has been obtained by several investigators (Rowe & Goldspink, 1968; Etamadi & Hosseini, 1968; Faulkner, Maxwell, Brook & Lieberman, 1971; Sola, Christensen & Martin, 1973; Yellin, 1974).

The complex morphology of many skeletal muscles makes difficult any attempt at an accurate comparison of the number of fibres in hypertrophic and control muscles. Previous studies designed to establish whether hyperplasia occurs during muscular hypertrophy have usually involved calculating the total number of fibres indirectly from *small* samples of control and hypertrophic muscles. Most muscles are too large for all the fibres to be counted directly – in a teased preparation, for example. Transverse sections of a muscle as a rule cannot be used to make direct counts since such sections rarely include all the fibres (Karpati & Engel, 1968; Maxwell, Faulkner & Hyatt, 1974). Indeed recent theoretical and experimental studies on the geometry of skeletal muscles have shown that alterations in the number of fibres per cross section of a muscle do not necessarily indicate alterations in the total number of fibres in that muscle (Maxwell, Faulkner & Hyatt, 1974). Fibres can vary in their diameters or in their lengths in different regions of a muscle, and consequently estimates of the total number present can be markedly inaccurate. Moreover, since few muscles are homogeneous with respect to their fibre type samples may be obtained which are not representative of the whole muscle.

The present study was undertaken to establish whether hyperplasia had occurred in extensor digitorum longus (EDL) muscles which had been induced to undergo compensatory hypertrophy by the surgical removal of their companion tibialis anterior muscles. Estimates of the total number of fibres in EDL muscles requiring assumptions to be made about fibre numbers in unsampled areas were specifically avoided. Using an alternative technique, comparisons were made between the increase in muscle weight and the size of their fibres as measured in supposedly representative samples. Major discrepancies between these two parameters (which should be linearly related if length and fibre number remain constant) would necessarily have to be attributed to a change in the number of fibres, for there is no reason to think that the fibre would change in length in the circumstances of the experiment.

MATERIALS AND METHODS

Operative technique

Adult male mice weighing 20–25 g were selected for study and kept individually in cages for 1 week prior to operation. The cages measured 15 cm × 30 cm. Food and water was available *ad libitum*.

Under sterile conditions and under ether anaesthesia, a mid-line longitudinal incision was made anterior to the ankle joint and extended proximally over the tibialis anterior muscle. The tendons of the tibialis anterior and extensor digitorum longus (EDL) muscles were identified as they passed deep to the extensor retinaculum. The tendon of the tibialis anterior muscle was transected at the upper margin of the retinaculum, the proximal cut end of the tendon was reflected and the nervous and arterior supply to the muscle was interrupted. The deep proximal attachments of the muscle were severed and the muscle removed. Particular care was taken to ensure that, as far as possible, the remaining leg structures were undisturbed and undamaged. The skin flaps were sutured with fine silk and the wound covered with Nobecutane®.

Mice were sacrificed at 35 and 80 days after operation. The EDL muscles from each animal were weighed and then fixed at their resting lengths in neutral buffered formalin. Particular care was taken to ensure that in each animal the EDL muscle from the operated side was fixed at the same length as that from the contralateral side. They were subsequently embedded in paraffin and sections were cut at about 6 μm. The sections were stained either with haematoxylin and eosin, or by the picro-Sirius Supra Blue GL method for the demonstration of endomysium (Sweat, Puchtler & Woo, 1964).

Quantitative technique

An image of each section was superimposed at a known magnification on a randomly orientated grid network formed by a series of horizontal and vertical straight lines. The regular lattice of points formed by the intersecting lines were used to determine the total cross sectional area (A) of each fibre using the formula

$$A = n.d^2,$$

where n is the number of intersections falling on each fibre. Values for the grid constant (d) were obtained by dividing the distance between the grid lines by the

magnification of the image. The magnification was determined by using a stage micrometer. Particular care was taken to ensure that at least 30 points fell on the smallest fibres examined. Sections used for quantitative analysis were cut from the mid belly of each EDL muscle. The individual cross sectional areas of at least 100 contiguous fibres lying in the central regions of each muscle were measured. It has previously been shown that 100 fibres are a sufficiently large sample to characterize the fibre size distribution of a skeletal muscle (Joubert, 1956). The statistical parameters listed in Table 1 were calculated for muscle fibre populations in muscles 80 days subsequent to the operation.

No correction for the shrinkage of muscle fibres was carried out. It was assumed that all muscle fibres underwent similar degrees of shrinkage in both the control and the hypertrophic muscles during fixation and processing.

RESULTS

From previous work the following histological stages of hypertrophy may be defined:

Early stage. During this stage there is a rapid gain in weight of the muscle and some increase in muscle fibre size. There are no characteristic histological changes.

Intermediate stage. During this stage there are prominent and characteristic histological changes. Most fibres possess central nuclei. In serial sections many fibres are associated with apparently newly formed structures variously termed sub-fibres (Edgerton, 1970), satellite structures (James, 1973) and satellite fibres (Yellin, 1974). Some vesicular nuclei are also visible.

Late stage. During this stage the hypertrophic skeletal muscles achieve their largest maintained weight increase when compared with control muscles. The histological features of the intermediate stage have disappeared and the seemingly normal muscle fibres achieve their largest maintained increase in diameter.

Six hypertrophic EDL muscles in each of the intermediate and late stages of hypertrophy as well as their control muscles were examined in this study.

All the hypertrophic muscles seemed larger and redder than their controls. No post-operative adhesions were seen in any animal and in each the tendon of the hypertrophic EDL muscles was completely free to move deep to the extensor retinaculum.

Hypertrophic muscles examined 35 days after removal of the ipsilateral tibialis anterior muscle were found to be in the intermediate stage of hypertrophy. Many of the muscle fibres were seen to contain central nuclei (Fig. 2). A proportion of the muscle fibres (about 7 %) seemed to be associated with newly formed 'satellite' structures identical with those previously described in hypertrophic EDL muscle of the rat (James, 1973). Occasionally they contained vesicular nuclei. In sections stained by the picro-Sirius Supra Blue GL method, contrary to expectation, the majority of the satellite structures were found to be enclosed in distinct endomysia separate from those of normal muscle fibres.

Hypertrophic muscles examined 80 days after the removal of the ipsilateral tibialis anterior muscle were found to be in the late stage of hypertrophy: none of them showed histological features characteristic of the intermediate stage (Fig. 4), nor did any of the contralateral EDL muscles (Figs. 3, 5).

Table 1. *Analysis of muscle fibre sizes and whole muscle weights*

Statistics calculated	Control animal no.						Hypertrophic animal no.					
	1	2	3	4	5	6	1	2	3	4	5	6
Mean cross sectional area (μm^2)	1020	639	1087	837	926	1047	2285	2100	2314	1740	1814	2230
Standard error (S.E.) of mean cross sectional area	52·3	32·7	55·3	47·9	55·9	54·3	115·5	77·8	91·0	101·7	108.4	88·6
Mean fibre diameter (nominal) (μm)	36·0	28·5	37·2	32·6	34·3	36·5	53·9	51·7	54·3	47·1	48·0	53·3
Skewness	−0·098	0·380	0·253	0·227	−0·101	0·291	0·504	0·164	0·114	0·137	0·493	0·316
Kurtosis	−1·444	−0·665	−0·895	−0·914	−1·117	−0·763	0·004	−0·740	−1·262	−1·109	0·038	−0·549
Weight of EDL muscle (mg)	9	9	6	7	7	9	17	15	11	13	13	15

$n \geqslant 100$ for each sample, S.E. of skewness = 0·241, S.E. kurtosis = 0·478. The statistics were calculated according to standard formulae (Sokal & Rohlf, 1969) using an IME 865 programmable desk top calculator.

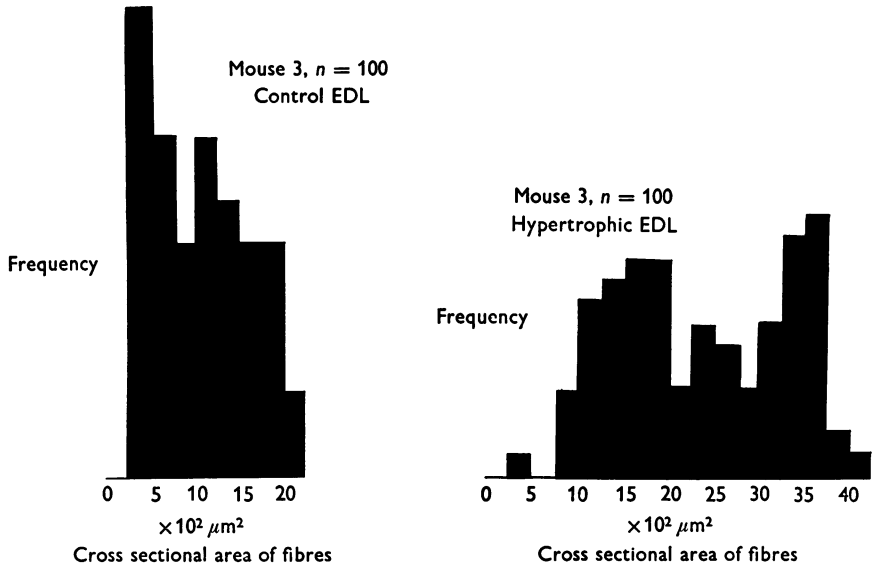


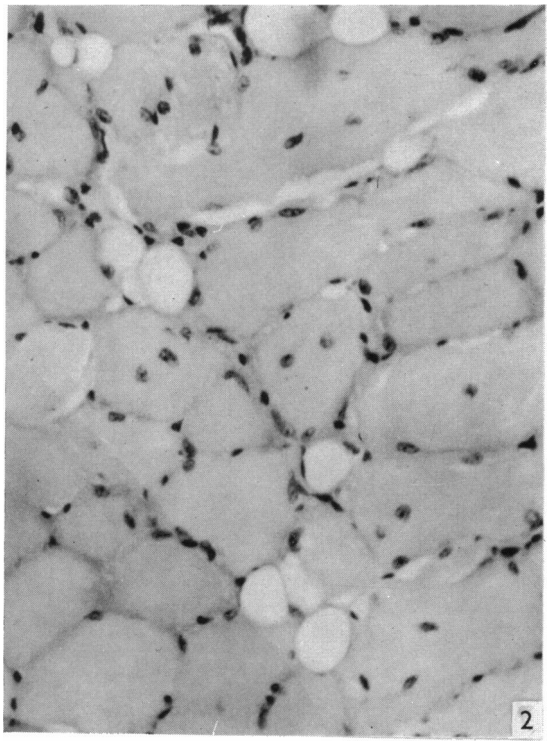
Fig. 1. Histogram illustrating fibre size–frequency distribution of control and hypertrophic muscles for a single mouse.

A detailed analysis of the muscle fibre sizes and whole muscle weights for the hypertrophic and contralateral EDL muscles is presented in Table 1. In most of the control EDL muscles there was a marked tendency for the cross sectional areas of the fibres to form a bimodal population. The increase in fibre size during the late stage of hypertrophy seemed variable. In some muscles the fibres showed an increased tendency to form a bimodal population whilst in two other EDL muscles the fibres formed a unimodal, though markedly skewed, distribution. The results indicate that the proportional increase in fibre cross sectional area exceeded the corresponding increase in muscle weight in all six animals.

DISCUSSION

The induction of hypertrophy in a muscle by means of the surgical removal of a synergist is both convenient and readily reproducible. In contrast with exercise-induced hypertrophy, there is usually a 'control' muscle available from the same animal. The contralateral EDL muscles, rather than those of unoperated animals, were preferred as controls because systematic effects, for example, general metabolic upsets following surgery or alterations in exercise patterns following operation are automatically counterbalanced thereby. In the present study slight hypertrophy may have occurred in the contralateral control: any such hypertrophy would of course reduce observable differences between the EDL muscles on the two sides.

The terms 'early', 'intermediate' and 'late' in relation to muscle hypertrophy are proposed for the following reasons. The terms relate to stages which can be identified histologically. They can be used whatever the time scale; and this is important because the rate at which a muscle hypertrophies could well vary with the particular



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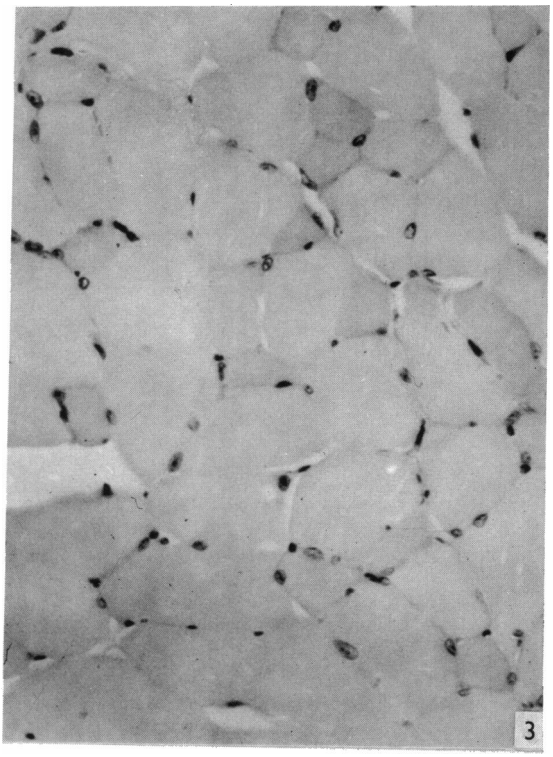

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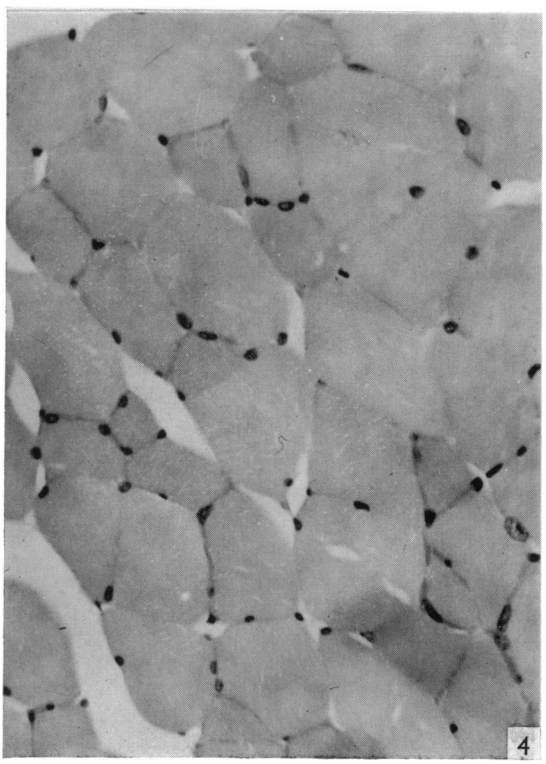

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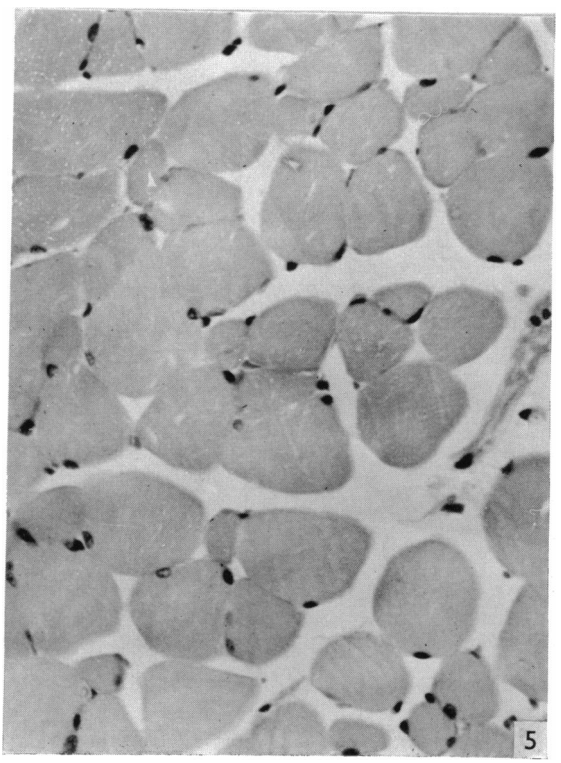

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muscle, the species body weight, metabolic rate and type of hypertrophy. It should be stressed that the intermediate stage in some cases is quite transient, and easily missed.

In the present study it can only be *assumed* that 'satellite structures' had been present at the intermediate stage of hypertrophy in those specimens which were examined at the late 80 day stage. Direct confirmation by sampling at the intermediate stage is not feasible because regenerative changes following trauma are similar to those occurring during hypertrophy and because the use of the leg may be inhibited. It has previously been suggested that, in the rat, these satellite structures either regress or fuse with mature fibres (James, 1973), though in birds they seem to be capable of forming new fibres (Sola *et al.* 1973). The absence of any final increase in the number of fibres seems to preclude any extensive transformation of satellite structures into new fibres. The presence of a distinct endomysium enclosing each satellite structure would seem to preclude their fusion with adjacent muscle fibres. Their complete regression, as with satellite cells after minor trauma (Teravainen, 1970), is therefore probable. The appearance of satellite structures, along with the other described histological changes, perhaps indicates attempts at regeneration consequent upon damage to muscle fibres caused by excessive work or excessive stretching. Alternatively, satellite structures could represent damaged or severely atrophic fibres undergoing degeneration.

In the present study no attempt was made to estimate the total number of fibres in the EDL muscle. Theoretically, it should be possible to draw some conclusion as to the occurrence of either hypoplasia or hyperplasia in a hypertrophic muscle by comparing the increase in weight of the muscle with the mean size increase of its contained fibres. For example, if the weight of a muscle increased relatively more than the mean size of its muscle fibres then hyperplasia can be suspected. In the present study, however, the mean muscle fibre size increased relatively more than the corresponding muscle weight suggesting that *hypoplasia* was occurring. Morehouse & Miller (1967) reported that the increase of connective tissue, capillaries and interstitial fluid during hypertrophy contributed only a small fraction to the total increase in weight and consequently those components were neglected in the present study. As in all previous studies on muscular hypertrophy, several possibly unwarranted assumptions were made. First, it was assumed that the small oxidative type I fibres and the larger glycolytic type II fibres (Dubowitz & Pearse, 1960) underwent the same percentage increase in size in 80 days. Gutmann *et al.* (1971) have demonstrated the validity of such an assumption after 5 days of hypertrophy. Secondly, it was assumed that all regions of the muscle underwent the same degree

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Fig. 2. Transverse section of hypertrophic EDL muscle 35 days after operation. Central nuclei typical of the intermediate stage of hypertrophy are clearly visible. H. & E. ×240.

Fig. 3. Transverse section of contralateral EDL muscle 35 days after operation. Normal histology. H. & E. ×240.

Fig. 4. Transverse section of hypertrophic EDL muscle 80 days after operation. Normal histology, but fibres larger than in control muscle. H. & E. ×210.

Fig. 5. Transverse section of control EDL muscle 80 days after operation. Normal histology. H. & E. ×210.

of hypertrophy. Thirdly, it was assumed there was no increase in the number of sarcomeres in each fibre. Though care was taken to ensure that both hypertrophic and contralateral muscles were fixed under identical conditions, any additional formation of sarcomeres within hypertrophic fibres could have resulted in shorter sarcomere lengths with spuriously broader fibres. Some workers have suggested (Mackova & Hnik, 1973) that the hypertrophy induced by surgical methods is not a true hypertrophy, partly because of the minimal weight increases shown by the hypertrophic muscles. However, the large increases in muscle weight and fibre diameter present at 80 days in the present study suggests that a true hypertrophy had taken place. In physiological and biochemical studies muscles are frequently allowed to hypertrophy for only 5 days prior to analysis, since it is often asserted that the maximum weight increase supposedly achieved at this stage indicates the completion of the hypertrophic process (Goldberg, 1967, 1972; Jablecki & Kaufman, 1972; Stewart, 1972). That marked changes continue to occur in some hypertrophic muscles after 5 days suggests that physiological and biochemical studies in the late stage of hypertrophy might yield results significantly different from those carried out earlier.

It is not clear whether any kind of exercise-induced hypertrophy is comparable with the hypertrophy induced by the surgical removal of synergistic muscles. Surgically-induced hypertrophy could be a consequence of increased work load or it could be a response to passive stretching. The latter is considered to be a powerful stimulus to hypertrophy, even in denervated muscles (Sola & Martin, 1953; Feng & Lu, 1965; Stewart, Sola & Martin, 1972; Jirmanova & Zelena, 1970; Sola *et al.* 1973). There may be different types of hypertrophy, since the effects of 'isometric' training differ significantly from those of 'isotonic' training (Rasch & Morehouse, 1957; Darcus & Salter, 1955). The surgically-induced hypertrophy in the mouse could well be more 'isometric' than that induced by exercise. That all muscle fibre types showed a similar increase in size suggests that mechanical (e.g. stretching) rather than neurological (e.g. increased voluntary movement) factors are important in the generation of surgically-induced hypertrophy. In exercise-induced hypertrophy, there is disparity in the size changes undergone by the different types of muscle fibre, possibly because of selective recruitment of motor units composed of the smaller type I fibres (Maxwell, Faulkner & Lieberman, 1973).

The observation that size–frequency distributions of the EDL muscle fibres often form a bimodal population seems to contradict previous reports of a unimodal distribution (Goldspink & Rowe, 1968). A bimodal distribution most likely reflects the presence of type I and type II fibres which are both present in the EDL muscle (James, 1971). Several factors could account for this apparent discrepancy. In the present study the contralateral 'control' muscle might have been subjected to some additional load or stretching which could have induced hypertrophy affecting only some of the fibres: pooling of data from different muscles could convert several bimodal populations to a single unimodal population: the fibre sampling technique could have distorted the fibre size distributions. In the present study care was taken to ensure that all sizes of muscle fibres and consequently all fibre types, were proportionally represented in each sample. Random selection of *single* fibres was specifically avoided to avoid population bias toward the larger fibres (Joubert, 1956). Random selection of fibres using any point scattering technique would be expected

to generate a size frequency distribution which reflects the relative cross sectional area of the different types of muscle fibre. A contiguous sampling technique, as used in the present study, which includes all the fibres in a randomly selected area, generates a size frequency distribution which more accurately reflects the relative frequency of occurrence of the different fibre types.

SUMMARY

Hypertrophy of the extensor digitorum longus muscle after surgical removal of its companion tibialis anterior muscle has been studied in mice.

Early, intermediate and late stages in the process of hypertrophy have been defined.

The proportional increase in the mean cross sectional area of fibres in a hypertrophic muscle consistently exceeded the proportional increase in the weight of the same muscle in all animals. This suggests that hypoplasia (loss of fibres) was occurring.

This work was carried out with the aid of grants from the Medical Research Council and Science Research Council of Great Britain.

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