PAPERS AND ORIGINALS

Gonadotrophin-releasing Hormone Therapy in Hypogonadal Males with Hypothalamic or Pituitary Dysfunction

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Summary

Subcutaneous self-administration of synthetic gonadotrophin-releasing hormone 500 µg eight-hourly for up to one year by 12 male patients (five prepubertal) with clinical hypogonadism due to hypothalamic or pituitary disease resulted in the synthesis and continued release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). There was a rise in circulating androgen levels in all patients. Improvements in pubertal ratings were seen in some prepubertal patients. Potency returned in the adults and spermatogenesis was induced and maintained in the four patients who had received treatment for more than four months, total counts reaching between 7.8 and 432×10^6 spermatozoa. A fall in the FSH response to the releasing hormone occurred during spermatogenesis though LH was little affected. During the initial weeks of therapy FSH secretion usually occurred before that of LH though LH secretion was greater as treatment continued. FSH secretion also persisted for longer when treatment was stopped.

Introduction

We have recently reviewed the results of a standard 100-µg test dose of luteinizing hormone/follicle stimulating hormone-releasing hormone (LH/FSH-RH) in 155 patients with hypothalamic-pituitary-gonadal dysfunction (Mortimer *et al.*, 1973

a). Though 88% of these patients were clinically hypogonadal at the time of testing and had low endogenous gonadotrophin secretion an LH response or FSH response or both occurred in 90%. It was therefore hoped that repeated administration of the synthetic decapeptide would result in the induction of gonadotrophin synthesis, its release, and gonadal stimulation. We here report the results of such treatment.

Dose Regimen

Studies of the time course of action of the releasing hormone given by intramuscular, intravenous, and subcutaneous routes showed it to be equally effective in promoting increased circulating levels of LH and FSH by each route with a duration of action of between five and seven and three and five hours respectively (Mortimer *et al.*, 1973 b). It was therefore decided that when sufficient supplies of the material became available long-term therapy in patients with hypogonadotrophic hypogonadism would be initiated by repeated subcutaneous injections. A dose of 500 µg was used since experience showed that patients with hypothalamic or pituitary disease would require a higher dose than normal subjects to produce an adequate response. Therapy was continued with this dose administered by the patients themselves subcutaneously into the anterior abdominal wall or thigh. Injections were repeated at eight-hour intervals in view of the known time course of gonadotrophin secretion. One patient, treated when the supply of the drug was unavoidably curtailed, received a more varied regimen and is considered separately. All patients were tested before treatment and at intervals during treatment with 100 and 500 µg LH/FSH-RH, measurement of serum LH and FSH levels being carried out over a four-hour period. The duration of treatment varied from four weeks in the prepubertal patients to between 26 weeks and one year in the adults.

Patients

Twelve male patients with clinical hypogonadism and pituitary or hypothalamic disease were studied.

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PREPUBERTAL PATIENTS

Craniopharyngioma.—Four patients aged 14 to 22 years had craniopharyngiomas. Three had had excision of the tumour followed by irradiation, while one had had irradiation only. These procedures had been performed between six months and 10 years, previously. All were receiving intramuscular growth hormone therapy. Three were also receiving thyroxine and three hydrocortisone replacement.

Isolated Growth Hormone Deficiency.—One patient, aged 20 years, had isolated growth hormone deficiency. He was also receiving intramuscular growth hormone.

None of these patients except one (craniopharyngioma) showed an LH or FSH response to clomiphene given in a dose of 3 mg/kg/daily for 10 days.

ADULT PATIENTS

Isolated Gonadotrophin Deficiency.—Four patients aged 22 to 24 years had so-called isolated gonadotrophin deficiency. Previously we suggested that this syndrome probably represents a deficiency of LH/FSH-RH rather than a primary gonadotrophin deficiency (Marshall *et al.*, 1972). All had low or undetectable basal serum gonadotrophin levels which failed to respond to clomiphene. There was no evidence of a deficiency of other pituitary hormones. These patients had been treated previously with either intramuscular testosterone propionate or human chorionic gonadotrophin (HCG) or both. One patient, previously impotent and azoospermic, had received intramuscular Pergonal (human menopausal urinary gonadotrophins; HMG) and had successfully fathered a child.

Craniopharyngioma.—One 33-year-old man had had a craniopharyngioma decompressed and irradiated 19 years previously and had also fathered a child after HMG therapy. He was unresponsive to clomiphene.

Acromegaly.—A 32-year-old man had received external pituitary irradiation for acromegaly one year before treatment and he was hypogonadal. Basal growth hormone levels were reduced from 17 to 4 ng/ml and the paradoxical rise during a glucose tolerance test was reduced from 55 to 19 ng/ml. His acromegaly clinically improved. He had low 17β -hydroxy-androgen (17 -OHA) levels and greatly impaired potency.

Hypothalamic Tumour.—One patient, aged 37 years, had a diffuse hypothalamic tumour of unknown origin which went into remission after high-dose dexamethasone therapy and hypothalamic irradiation. At the time of the study he was maintained on hydrocortisone, thyroxine, and DDAVP (Edwards *et al.*, 1973) as replacement therapy. He was unresponsive to clomiphene.

All these patients had been off any form of gonadal steroids or gonadotrophin therapy for at least four months before the study began and were clinically hypogonadal, with loss of potency and body hair and small genitalia. All the patients had azoospermia in the first ejaculate produced during treatment except for the man with the craniopharyngioma, who had a total count of 600,000 dead spermatozoa, presumably lying in situ from HCG therapy terminated four months earlier.

Assays

Serum LH and FSH levels were measured by specific radioimmunoassays as described previously (Mortimer *et al.*, 1973 c) and the results expressed in mU/ml of M.R.C. standard 68/40 for LH and 68/39 for FSH, the contents of each ampoule being taken as 39.8 and 32 units respectively. Normal adult male basal levels of LH and FSH range from less than 0.4 to 6 mU/ml and from less than 0.2 to 5.9 mU/ml respectively.

Plasma 17 -OHA levels were estimated by the method of Anderson (1970). This measures predominantly testosterone and dihydrotestosterone. (Normal male range at 9 a.m. for plasma 17 -OHA 5.0–22.5 ng/ml.)

Plasma sex-hormone-binding globulin (SHBG) was measured by the method of Rosner (1972) and the results were expressed in 10^{-8} mol of dihydrotestosterone bound per litre. The normal adult male range is 2.10 to 5.1×10^{-8} mol/l. Higher levels are characteristically seen in prepubertal subjects (August *et al.*, 1969; Forest and Bertrand, 1972).

Non-protein-bound ("free") androgen levels were estimated by calculating the ratio of total 17 -OHA to SHBG. When expressed as a percentage the normal adult male range is 1.42% to 2.0%.

Plasma oestradiol was measured by radioimmunoassay (Hotchkiss *et al.*, 1971). The normal adult male range is from less than 10 to 50 pg/ml. All blood samples were separated immediately and stored at -20°C until assayed.

Gonadotrophin Responses

PREPUBERTAL PATIENTS

Craniopharyngioma.—Of the four patients with craniopharyngiomas two had undetectable serum LH levels and two had levels of 0.7 mU/ml before treatment; however, all had detectable circulating FSH (between 0.3 and 1.0 mU/ml). The responses during the initiation of therapy in one of these patients is shown in fig. 1. Three patients failed to show a response in LH to an intravenous test dose of 100 μg of the releasing hormone before treatment though a small but significant rise in FSH was seen in each case. When the first subcutaneous dose of 500 μg was given all three patients showed a rise in both LH and FSH. In the fourth patient, with detectable LH and FSH basally, there was no further response to 100 μg of the releasing hormone but a simultaneous increase in both gonadotrophins occurred when 500 μg was injected. This patient was the only one who had shown a response to clomiphene. As treatment with 500 μg was started and continued there were progressive increases in both gonadotrophins in all four patients, with LH secretion becoming equal to or exceeding that of the FSH response. Thus though initially there was a larger FSH than LH response before treatment was started, by the end of four weeks the response of LH was greater than that of FSH. Therapy was discontinued after four weeks in three patients as it was felt unwise to induce puberty while they were still receiving growth hormone therapy.

FIG. 1—Serum LH and FSH responses during four weeks of LH/FSH-RH therapy in prepubertal male patient with craniopharyngioma. N.D. = Not detectable.

Isolated Growth Hormone Deficiency.—The patient with isolated growth hormone deficiency had detectable LH and FSH levels. He had an impaired LH response but a normal FSH-response to the initial 100 μg of releasing hormone but normal LH and FSH secretion was induced by LH/FSH-RH therapy maintained for 20 weeks.

ADULT PATIENTS

All four patients with the so-called *isolated gonadotrophin*

deficiency had undetectable LH levels and in only one was FSH detectable; LH and FSH secretion was induced by long-term LH/FSH-RH therapy in each case. Two of these patients showed initial responses similar to that seen in the prepubertal patients with craniopharyngiomas, in that detectable secretion of FSH returned before that of LH. The responses in one such adult patient are shown in fig. 2. The other two patients showed a small LH response but an absent FSH response to an intravenous dose of 100 µg of the releasing hormone before treatment. LH secretion was greater initially than FSH secretion on treatment. The man with the *craniopharyngioma* had undetectable LH but measurable FSH levels basally and impaired LH but normal FSH responses to an intravenous dose of 100 µg of the releasing hormone. After the first week of therapy the levels of FSH were higher than those of LH though these relative responses were reversed by the second week. The patient with the *hypothalamic tumour* of unknown origin had detectable gonadotrophins basally and these showed normal responses to the 100 µg test. FSH secretion was greater during the first five weeks of therapy but thereafter LH was the predominant hormone secreted. The man with *acromegaly* had a basal LH level in the range seen in adult males with normal testosterone levels and he showed a normal response to 100 µg of the releasing hormone. His basal FSH values in contrast were raised and showed an excessive response to the same dose of the decapeptide.

FIG. 2—Initial serum LH and FSH responses to intravenous bolus of 100 µg and 500 µg LH/FSH-RH followed by infusion of 1,000 µg over four hours in man with isolated gonadotrophin deficiency.

EFFECTS OF THERAPY ON LH/FSH-RH TEST

In five patients (two prepubertal boys with craniopharyngiomas, the man with the craniopharyngioma, the man with the diffuse hypothalamic tumour, and one of the men with isolated gonadotrophin deficiency) the standard 100-µg LH/FSH-RH test was repeated after four to six weeks of therapy after being off treatment for one to seven days. Before treatment in these patients the response of FSH was much greater than that of LH, whereas after treatment the secretion of LH was greater than that of FSH. The levels of both LH and FSH were higher after treatment than before (fig. 3).

FIG. 3—Serum LH and FSH responses to standard test dose of 100 µg intravenous LH/FSH-RH in five patients before and after four to six weeks of therapy with releasing hormone.

Induction of Androgen Secretion and Puberty in Prepubertal Patients

Of the five prepubertal patients three were still growing on intramuscular growth hormone therapy. Gonadotrophin-releasing hormone therapy was discontinued after four weeks in these subjects since it was considered undesirable to induce puberty while they still had growth potential. All had shown a rise in gonadotrophin and 17-OHA levels during that time. The remaining two patients, aged 19 and 22 years, were also on growth hormone therapy but since their growth was slowing down it was decided to attempt to induce puberty in the hope that there would be potentiation of growth as in normal puberty. Before treatment one patient had pre-adolescent genitalia with vellus over the pubes indistinguishable from that of the abdominal wall—that is, stage 1 (Tanner, 1958). After eight weeks of treatment this patient showed an increase in spontaneous erections and stage 2 pubic hair development. The other patient before treatment had slight pubertal enlargement of the testes and scrotum with sparse growth of pigmented downy hair at the base of the penis (stage 3). After nine weeks of treatment there was an increase in testicular volume of from 6 to 12 ml on the right and from 4 to 8 ml on the left. Spontaneous erections became frequent and there was an increase in coarse pubic hair.

Gonadotrophin secretion continued within the normal basal adult male range in these subjects while treatment was maintained though the 17-OHA levels increased only slightly, from pretreatment levels of 0.4 to 1.7 ng/ml to between 1.4 and 2.4 ng/ml—that is, below the normal adult range. Plasma oestradiol levels did not change and were within the normal adult male range. Plasma SHBG was above the adult range before treatment in four patients (between 7.7 and 22.6×10^{-8} mol/l.), as is usually seen before puberty (August *et al.*, 1969; Forest and Bertrand, 1972); in the other patient it was normal (4.6×10^{-8} mol/l.). In the three patients treated for four weeks only there was no consistent change in SHBG. In the two treated for longer the SHBG levels fell. In these patients changes in circulating levels of free androgens inferred from the ratio of total 17-OHA to SHBG and expressed as a percentage rose from between 0.02% and 0.18% basally to between 0.03% and 0.32% after treatment but were still below the normal adult male range.

Induction of Androgen Secretion and Potency in Adult Patients

All seven adult patients studied had an increase in potency within seven to 14 days of beginning treatment. Before treatment 17-OHA levels reached between 1.0 and 3.1 ng/ml. In every case there was an increase in 17-OHA levels though only two patients showed a rise to within the normal range on more than two occasions. These two subjects achieved maximum levels of 15.5 and 7.5 ng/ml after two and four weeks of treatment respectively but values then fell and were maintained between 3.1 and 4.8 ng/ml. In the remaining five patients, though levels were subnormal (between 0.4 and 4.8 ng/ml) improved potency was well maintained. Three patients had normal potency. Plasma 17β-oestradiol levels remained within the normal range throughout treatment except in three patients on three isolated occasions, when raised levels of 55, 98, and 171 pg/ml were recorded.

SHBG levels were above normal before treatment in one patient (5.8×10^{-8} mol/l.), low in two patients (1.4 and 1.5×10^{-8} mol/l.), and normal in the other four (2.7 to 5.0×10^{-8} mol/l.). During treatment SHBG levels in all seven patients rose to a maximum of between 2.6 and 9.6×10^{-8} mol/l. Peak values occurred at three weeks in one patient, between six and 10 weeks in four, and at 22 and 23 weeks in the other two. Levels then fell but remained above the normal range in four of these patients (between 5.4 and 8.0×10^{-8} mol/l. at 21 to 30 weeks of therapy), and though the free androgen levels rose (17-OHA:

SHBG ratio 0.04% to 0.13% basally, rising to a maximum of between 0.19% and 0.57% during therapy) they were still well below the adult male range. Of the other three patients one had low SHBG levels throughout, with free androgen levels rising above the normal range at nine to 18 weeks, being between 4.5% and 7.4%. They were still raised at 33 weeks. One patient had normal SHBG levels throughout 10 weeks of therapy, and his free androgen levels rose from 0.3% to a maximum of 0.49%. The other patient had a normal SHBG level of 4.4×10^{-8} mol/l. before treatment, rising to 6.0×10^{-8} mol/l. at three weeks and then falling to 4.4×10^{-8} mol/l. at 28 weeks. Free androgens rose from 0.13% to a maximum of 0.30% on therapy.

SPERMATOGENESIS

Four of the adults were on treatment for between 26 weeks and one year and spermatogenesis occurred in each of them. Initially one patient with *isolated gonadotrophin deficiency* was impotent but after nine days of treatment he was able to produce a specimen which showed azoospermia. By 17 weeks, however, he produced 1.6×10^6 spermatozoa, and his count subsequently rose to 2.7×10^6 and then to 7.8×10^6 with a motility of 30% at 41 weeks (fig. 4). Another patient with *isolated gonadotrophin deficiency* had azoospermia initially but after six months produced three spermatozoa, two of which were motile. Four weeks later his count has risen to 660,000, with a motility of 60%, and after a further four weeks to 1.6×10^6 , with a motility of 20%; at 50 weeks his sperm count had reached 36.7×10^6 with a motility of 50%. In both these patients the maximum FSH levels achieved after a 500- μ g dose of the releasing hormone fell progressively as the sperm count rose but the LH levels were not consistently affected.

FIG. 4—Maximum serum LH and FSH responses to therapeutic 500- μ g dose of LH/FSH-RH in man with isolated gonadotrophin deficiency. Increasing total sperm counts are shown at top.

The results in the patient with the *craniopharyngioma* who had previously fathered a child after HMG therapy are shown in fig. 5. Initially he was completely impotent but this had improved by the end of the second week of treatment. At four weeks an ejaculate contained 600,000 dead spermatozoa, presumably

FIG. 5—Plasma 17-OHA levels during therapy with releasing hormone in man with craniopharyngioma. Clomiphene started at week 9, therapy reintroduced with 100 μ g 8-hourly from week 12 to week 15, then increased to 500 μ g 8-hourly. Increasing total sperm counts are shown at top.

lying there since gonadotrophin therapy some four months previously. By six weeks a total count of 12×10^6 spermatozoa had been recorded, and this subsequently rose to 26×10^6 at 19 weeks, 112.8×10^6 at 33 weeks, with a motility of 40%, and 432×10^6 , with 70% motility, after one year of treatment. The pattern of the FSH response in the previous two patients was repeated, LH again showing no clear changes.

The fourth patient in whom spermatogenesis was induced was the man with *acromegaly* (fig. 6). Initial investigations showed that he had a basal 17-OHA level of only 1.7 ng/ml. On treatment this rose to a maximum of 5.2 ng/ml at six weeks and was then maintained at between 3.8 and 4.5 ng/ml. When seen initially he had a much reduced potency but was able to produce a specimen for seminal analysis, which contained no spermatozoa. During treatment, however, he showed a progressive rise in total sperm counts from 50,000 to 13.6×10^6 at 25 weeks and 60.8×10^6 at 48 weeks with a motility of 40%. Before treatment he had a basal LH level of 3.8 mU/ml but raised FSH level of 17.3 mU/ml. Initially the FSH values after a 500- μ g dose of LH/FSH-RH were greater than 50 mU/ml, but these gradually fell to 1.6 mU/ml during therapy as the sperm count rose. The LH values in contrast fluctuated between 6 and 15 mU/ml without showing a well-defined pattern of response.

FIG. 6—Man with treated acromegaly. Top: Levels of 17-OHA throughout LH/FSH-RH therapy. Increasing sperm counts are shown at top. Bottom: Maximum serum LH and FSH responses to therapeutic 500- μ g dose of LH/FSH-RH.

TESTICULAR VOLUME

In all seven adult patients there was a clear increase in testicular volume—from between 1 and 3 ml before treatment to between 6 and 12 ml after 12 to 35 weeks—together with an increase in the size of the penis. Beard growth and body hair improved in three patients.

Effect of Clomiphene and LH/FSH-RH Dose Variation

The adult patients with the craniopharyngioma and the diffuse hypothalamic tumour were both unresponsive to clomiphene before LH/FSH-RH therapy. At nine and six weeks respectively LH/FSH-RH was stopped and clomiphene was given in a dose of 3 mg/kg/day. In both cases LH and FSH levels became undetectable, 17-OHA levels fell, and the patients became impotent again. Resumption of treatment with LH/FSH-RH at a dose of 100 μ g 8-hourly produced only a small increase in 17-OHA and a negligible effect on potency. When full dosage was given again gonadotrophin and androgen secretion and normal potency returned within 10 to 21 days in both patients (fig. 5).

One patient had a more variable dosage regimen. This patient, with isolated gonadotrophin deficiency, whose initial results are shown in fig. 2, had basal 17-OHA levels of 1.4 ng/ml.

He was treated initially with 500 µg of the releasing hormone subcutaneously 12-hourly. There was an increase in potency in the next two weeks though the levels of 17-OHA never rose above 2.1 ng/ml. During the first three weeks of treatment circulating levels of basal gonadotrophins increased with more LH being secreted than FSH. At that time, however, the dose of LH/FSH-RH was reduced to 200 µg 12-hourly because of short supplies and there was a marked decrease in gonadotrophin levels. By 19 weeks FSH secretion continued in response to 500 µg of the releasing hormone though LH had become undetectable—that is, the initial response pattern had again been restored. An increase in dose to 500 µg eight-hourly, however, produced a rise in both LH and FSH.

Discussion

All the patients in this study had evidence of hypothalamic or pituitary disease resulting in clinical hypogonadism with low circulating levels of 17-OHA. Two patients failed to show any gonadotrophin responses to the standard intravenous 100-µg test dose of LH/FSH-RH before treatment was started, whereas in all but two of the other 10 there was impairment of either LH secretion or FSH secretion or both. In every case, however, repeated administration of the synthetic decapeptide resulted in the initiation and maintenance of secretion of both gonadotrophins. It appears from our studies, therefore, that long-term LH/FSH-RH administration not only causes the release of the gonadotrophins but also promotes synthesis of new hormone, and these effects may persist for up to a year of continuous therapy.

In four of the five clinically prepubertal subjects FSH secretion either occurred first or rose to the normal male range of response before LH. The exception was the patient with a craniopharyngioma who was clomiphene responsive before treatment. A rise in FSH before LH was also seen in two adults with so-called isolated gonadotrophin deficiency and in the man with the craniopharyngioma. It appears that in patients with hypogonadotrophic hypogonadism secretion of FSH most commonly occurs before that of LH during continued treatment with the releasing hormone. Interestingly a similar pattern of differential gonadotrophin responses during LH/FSH-RH testing was reported to occur at the time of normal puberty by Franchimont *et al.* (1974). Prepubertal patients showed an adult type of FSH responses to LH/FSH-RH though reduced LH responses; after puberty the adult pattern with more LH than FSH secretion was reported, but these effects were better seen in female than male patients.

From our studies it is evident that prepubertal boys may achieve puberty if treatment with the releasing hormone is continued. There is an increase in testicular size with a rise in circulating androgens, greater hair growth, and enhanced potency. Also within four to six weeks the prepubertal type of gonadotrophin responses to the releasing hormone reverses to the normal adult pattern.

It is also evident that if therapy is maintained potency will return in the adult patients. Surprisingly, however, in six of the seven adult patients there was an early increase in potency, seven to 14 days after starting therapy, which was maintained despite circulating 17-OHA levels well below the lower limit of the normal male range. At these levels most other patients seen are impotent. The unusual degree of potency recorded by these subjects is not explained on the basis of normal free androgen levels in the presence of low total androgens, since levels of the binding protein SHBG were either normal or high in five of them and their free testosterone levels were well below the normal adult male range. In only one patient did low basal free androgen levels rise to the normal range during therapy and remain there. He also had low SHBG levels. Plasma oestradiol levels were also within the normal male range except on rare

occasions. The rapid return of potency in these patients may therefore have been due to factors other than those which are simply androgen-mediated. Of relevance to these observations may be the findings of Moss and McCann (1973) and Pfaff (1973), who noted a marked increase in the number of lordotic responses in ovariectomized and hypophysectomized rats after subcutaneous treatment with the synthetic decapeptide. These workers suggested that LH/FSH-RH may have a direct promoting action on sexual behaviour in rats independent of its hormone effects, and this may also be the case in man.

Apart from the return of potency, spermatogenesis was induced in four patients. Total sperm counts increased from zero (or 600,000 dead spermatozoa in one patient) to maximum values of 7.8, 36.7, 60.8, and 432×10^6 in these patients. The patient with acromegaly was particularly interesting. Before treatment he had low 17-OHA levels with LH levels in the normal range together with azoospermia despite raised FSH levels. The LH response to a standard 100-µg test dose of LH/FSH-RH was normal but the FSH response was excessive. A similar pattern of response in patients with oligospermia or azoospermia has been noted previously (Mortimer *et al.*, 1973 a). As treatment continued, however, spermatogenesis was induced, presumably as a result of the production of intratesticular androgens in the presence of FSH, and the maximum FSH values after administration of the releasing hormone began to fall as the sperm count began to rise. This pattern of response though less marked also occurred in the other patients in whom spermatogenesis was induced. This suggests that the factor produced during spermatogenesis, often called "inhibin," was being released into the circulation and was exerting a negative feedback effect on FSH secretion. It seems, therefore, that the site of action of inhibin was primarily at the pituitary level since circulating LH/FSH-RH levels were being maintained by repeated subcutaneous injections. It is also evident that pituitary responsiveness in male subjects may be modified by circulating substances other than testosterone or oestrogen.

In conclusion, therefore, we suggest that long-term treatment with LH/FSH-RH 500 µg eight-hourly self-administered by subcutaneous injection may provide an efficient means of treating patients with hypogonadotrophic hypogonadism due to diseases of the hypothalamus or pituitary and may result in the return of potency and fertility. This treatment may replace the more expensive conventional therapy with natural human gonadotrophins. The promotion of potency out of proportion to the increase in circulating androgens suggests that its place in the treatment of psychogenic impotence should be explored, and these studies are under way. Lower doses have been found to be ineffective in these patients.

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