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Grafts of Fetal Dopamine Neurons Survive and Improve Motor Function in Parkinson's Disease

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Neural transplantation can restore striatal dopaminergic neurotransmission in animal models of Parkinson's disease. It has now been shown that mesencephalic dopamine neurons, obtained from human fetuses of 8 to 9 weeks gestational age, can survive in the human brain and produce marked and sustained symptomatic relief in a patient severely affected with idiopathic Parkinson's disease. The grafts, which were implanted unilaterally into the putamen by stereotactic surgery, restored dopamine synthesis and storage in the grafted area, as assessed by positron emission tomography with 6-L-[¹⁸F]fluorodopa. This neurochemical change was accompanied by a therapeutically significant reduction in the patient's severe rigidity and bradykinesia and a marked diminution of the fluctuations in the patient's condition during optimum medication (the "on-off" phenomenon). The clinical improvement was most marked on the side contralateral to the transplant.

WHEN GRAFTS OF FETAL DOPAMINE (DA)-rich mesencephalic tissue are implanted into the DA-depleted caudate-putamen of rodents and nonhuman primates with neurotoxin-induced parkinsonism, they can improve many of the motor impairments (1). In rats, such graft-induced amelioration of motor deficits is critically dependent on the ability of the grafted neurons to restore dopaminergic neurotransmission in the deafferented area

surrounding the transplant, and sustained graft effects require survival and continuous function of the implanted dopaminergic neurons (2, 3).

Clinical trials with transplanted fetal mesencephalic tissue have been initiated in patients with Parkinson's disease in the last 2 years. In the few cases reported (4, 5), some symptomatic improvement has been observed, but it remains unclear if any of these changes can be attributed to graft-induced restoration of dopaminergic transmission in the striatum, or if they have been caused by nonspecific aspects of the surgical intervention (6). For the further development of this therapeutic approach, it is critical to establish (i) whether fetal nigral allografts can survive in the environment of the diseased parkinsonian brain; (ii) whether such grafts are able to restore DA functions in the affected striatum; and (iii) whether the survival of DA-synthesizing neurons can be correlated to a therapeutically valuable recovery of affected motor function. This study was designed to address these questions.

A severely affected patient with dramatic diurnal fluctuations in disability, despite optimum medical therapy, was selected after having given his consent. The patient is a

49-year-old man with Parkinson's disease, which began with unilateral tremor and rigidity in the right arm in 1977. Initial treatment with L-dopa was successful, but in 1984 he developed progressively worsening "on-off" phenomena, with rapid, often unpredictable, fluctuations in motor performance from a mobile, or on, state to an off, or rigid state, with manifest symptoms of Parkinson's disease. At the beginning of the study (April 1988) he was rated stage III on the scale of Hoehn and Yahr (7). During off periods he had severe rigidity, hypokinetic movements, and a moderate tremor in the right arm; less marked symptoms were evident in the left arm and legs. During on periods he displayed only very minor symptoms. The patient was taking daily doses of 700 mg of L-dopa (combined with benserazide), 10 mg of bromocriptine, and 6 mg of benzhexol chloride; these doses remained unchanged during the period of the study both before transplantation and in the 5 months thereafter. For 11 months before the operation the patient was assessed clinically and kept a daily log of his disability, scoring motor symptoms every 30 min (Fig. 1A). The duration and frequency of off periods were relatively stable preoperatively. On the average he had four to five daily off periods and spent 40 to 50% of the time in a severe off state. A preoperative 6-L-[¹⁸F]fluorodopa positron emission tomographic (PET) scan showed the left putamen to be markedly deficient in DA-synthesizing capacity (Table 1); the right putamen was also affected, but to a lesser extent.

Immunosuppression was begun 2 days before transplantation (8). Dissociated ventral mesencephalic tissue from four fetuses (aged 8 to 9 weeks) was implanted stereotactically in the anterior, middle, and posterior part of the left putamen (9), the side contralateral to the most affected limbs. There were no complications. The implantation procedure was similar to one we have used previously (5) with three potentially important changes: the implantation cannula was considerably thinner (1.0-mm versus 2.5-mm outer diameter); the medium used for storage and dissociation of the tissue was a balanced, pH-stable salt solution rather than saline; and the technique of loading the cannula was improved so that virtually all the tissue could be used. In addition, the time of storage before transplantation was shorter for this patient.

During the second month after transplantation there was a marked reduction of both the time spent in off periods and the number of daily off periods (Fig. 1A). The patient noted a progressive reduction of rigidity, particularly in his right arm, and improvement of mobility during the night and in the

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morning before the first L-dopa dose. He was now able to sleep through the night, without additional intake of L-dopa, which had been impossible during the preoperative assessment period. After the first L-dopa dose, he spent the rest of the day on with or only a single brief off period, during which he had mild parkinsonian symptoms. No further changes were noted between 3 and 5 months postoperatively.

Clinical assessment of the symptoms of Parkinson's disease was performed randomly during off periods (at 1- to 2-week intervals, two to eight times each test day) with the patient receiving full medication. Rigidity was scored in the neck and extremities according to a 0 to 3 rating scale. Beginning during the second postoperative month, there was a gradual reduction of muscle tone in all joints examined (Fig. 1B). Although the change was bilateral, it was most pronounced in the right arm, which had been severely rigid preoperatively. The rigidity almost completely disappeared between 2 and 3 months postoperatively.

We performed a battery of neurological tests. A test of successive movements (time to perform 20 pronations and supinations) (Fig. 1C) showed the most marked differences between on and off phases in the preoperative period (9 s for both arms in on and 14 and 24 s for the left and right arm, respectively, during off phases). From 2 to 3 months after surgery, the patient exhibited a marked improvement of movement speed during off in the right arm and a similar change (although of lesser magnitude) in the left arm. The big difference in performance time (10 s) between the arms before surgery disappeared entirely.

The speed of a series of self-paced arm and hand movements was measured before the first morning dose of L-dopa, at 12 months before surgery and at 5 months after surgery (Fig. 1D) (10). The reaction time (RT) decreased slightly on the right side after grafting, whereas that on the left was unaffected. There was also a significant bilateral improvement of the speed of all flexion movements. In addition, the interval between the onset of the squeeze and the flexion movements in the sequential task decreased after surgery on the right but not on the left side (Fig. 1D).

The effects on motor performance of a single dose of L-dopa were tested after a drug-free period of 14 hours (5). In the tests before transplantation, the patient was severely rigid and hypokinetic before L-dopa administration, and when the effect of L-dopa disappeared (after 90 to 120 min) he rapidly returned to the same condition (Fig. 2A). This pattern showed a gradual change after transplantation (Fig. 2B). After the

fifth postoperative week, his motor performance before L-dopa intake progressively improved, and the duration of the drug-induced on phase was longer in all postoperative tests (range, 150 to 165 min). Indeed, after the ninth week the movement speed in the pronation-supination test during the morning off period was close to that recorded during the subsequent L-dopa-induced on period. Furthermore, there was no immediate major worsening of motor symptoms at the end of the on periods in the tests performed at 14 to 22 weeks; few parkinsonian symptoms were evident, even 4 hours after the L-dopa intake.

Using PET with 6-L-[¹⁸F]fluorodopa as tracer, we assessed striatal presynaptic dopaminergic function by measuring ¹⁸F-labeled DA formation and storage (11). The 6-L-[¹⁸F]fluorodopa is converted into ¹⁸F-labeled DA, concentrated, and retained within

DA terminals. The calculation of an influx constant (K_i) gives a measure of the degree of irreversible tracer storage and retention, which is proportional to the number of functioning dopaminergic terminals (11). The postoperative PET measurement performed 5 months after surgery, when compared to that recorded 12 months before surgery, showed an increase in tracer uptake of 130% within the transplanted (left) putamen (Table 1 and Fig. 3). Whereas the uptake of 6-L-[¹⁸F]fluorodopa had been considerably lower in the left putamen than the right putamen before transplantation (left to right ratio, 0.5), the uptake was similar on the two sides in the measurement after transplantation (ratio, 0.98).

Two conclusions can be drawn from this study. First, implantation of fetal DA-rich mesencephalic tissue into the striatum can lead to a therapeutically valuable, sustained

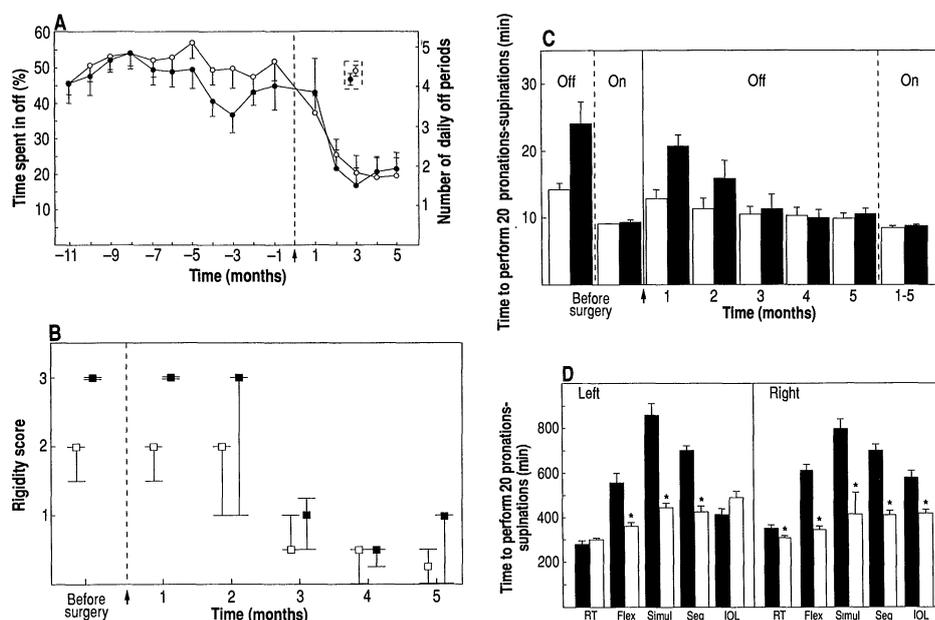


Fig. 1. Clinical assessment of the symptoms of Parkinson's disease. (A) The patient performed daily autoscoring of on and off periods from 11 months before surgery to 5 months after implantation. ●, The mean monthly percentage of awake time spent in off phase. ○, The mean number of off periods per day for each month. Bars, 99% confidence limits. The single circles with bars in the dashed box show the respective mean values and 99% confidence intervals for the entire 11-month preoperative period. (B) Limb rigidity in the off state. Rigidity was rated in the left (□) and right (■) wrist on a scale from 0 (no rigidity) to 3 (severe rigidity), with increments of one half. The median value for the different time points is shown, with the lines representing quartiles. The preoperative score is based on 104 observations made over 1 to 11 months before implantation, and each of the postoperative scores is based on 8 to 18 measurements. (C) Time taken to perform 20 pronations-supinations with the left (open bars) and right (solid bars) arm in the on and off state. Mean of measurements (with 99% confidence limits) taken over 1 to 11 months preoperatively (99 measurements in on and 153 in off) and 1 to 5 months postoperatively (85 measurements in on and 12 to 37 measurements during each month in off). (D) Performance of simple and complex arm and hand movements in the off state were measured before (solid bars) and after (open bars) surgery according to Benecke *et al.* (10) by a computer-based system with electromyographic registration to record the onset of muscle contraction. The histograms plot the time taken to initiate a wrist movement in response to a visual signal (simple reaction time, RT); time taken to flex the elbow through 15° (Flex); time taken to flex the elbow at the same time as an isometric squeeze of the hand (Simul); time taken to flex the elbow after a preceding squeeze (Seq); interval between onset of squeeze and flexion movement in a sequential task [interonset latency (IOL)]. Data are means of at least ten measurements ± SEM. Asterisks indicate significant preoperative versus postoperative differences ($P < 0.05$, unpaired *t* test). Average data from a group of eight age-matched normal subjects were 190 ± 4 ms (RT), 229 ± 13 ms (Flex), 216 ± 12 ms (Simul), 244 ± 12 ms (Seq), and 244 ± 11 ms (IOL).

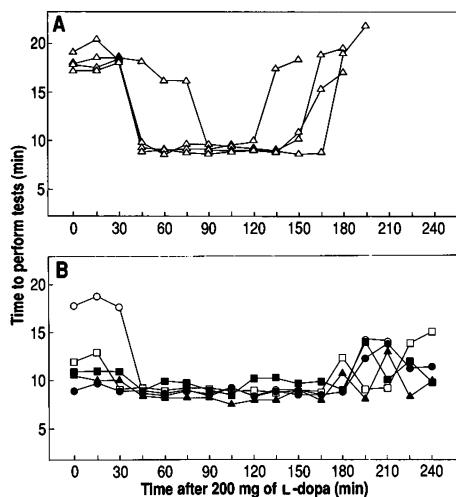


Fig. 2. Effect on motor performance of a single dose of L-dopa given after a 14-hour drug-free period. The time taken to perform 20 pronations-supinations with the right arm was recorded every 15 min up to 4 hours after the administration of 200 mg of L-dopa with 57 mg of benserazide. Each line represents an individual trial performed at 9:00 a.m. (the patient fasted overnight). (A) The performance in four trials conducted 2 to 4 months before grafting. (B) The performance in five trials, performed at approximately monthly intervals, 5 to 22 weeks after transplantation. O, 5 weeks; □, 9 weeks; ●, 14 weeks; ■, 18 weeks; and ▲, 22 weeks.

improvement of motor function in a patient with idiopathic Parkinson's disease. Second, the clinical improvement is correlated with an increased synthesis and storage of DA selectively in the left putamen, that is, at the site of implantation. The interpretation that the reduction of parkinsonian symptoms in this patient is due to graft-derived dopaminergic reinnervation of the striatum, and hence to a surviving functional graft, is supported by several observations. (i) Spontaneous fluctuations and placebo effects, which are common in Parkinson's disease, seem unlikely because the symptomatology was very stable over the 11-month preoperative assessment period. During the second and third postoperative month, the patient showed a gradual and marked improvement of motor function, most pronounced on the side contralateral to the transplant. This time course is consistent with the slow development of a growing graft (12). (ii) The patient continued to receive the same doses of medication throughout the study to minimize the risk that clinical improvement could be due to transient changes in medication. (iii) The possibility of a deficient blood-brain barrier at the transplantation site, which could hypothetically lead to a more efficient, focal entry of systemically administered L-dopa or bromocriptine to the brain parenchyma adjacent to the graft is not supported by grafting experiments in

Table 1. The 6-L-[¹⁸F]fluorodopa uptake 12 months before and 5 months after implantation of ventral mesencephalic tissue into the left putamen. Influx constants (K_i , min^{-1}) are given with the occipital lobe as reference (11). Data are from the plane centered approximately 4 mm above the intercommisural line, which is the middle of the three planes on which caudate and putamen are both seen, and therefore is least likely to suffer from partial volume effects. Although only one preoperative scan was possible because of radiation considerations, some measure of the interassay variability of the measured values may be derived from the nonoperated regions. Thus, over a 17-month period, the nonoperated caudate and putamen values changed by 0 to 30% and the medial frontal cortical activity (not shown) by 20%. This suggests an interassay variability of up to 30%, which is exceeded by the observed changes in the transplanted left putamen.

Area	Region	Preoperatively	Postoperatively	Postoperatively/Preoperatively	Normal subjects*
Caudate nucleus	Left	0.0081	0.0082	1.0	0.0111 (\pm 0.0030)
	Right	0.0076	0.0101	1.3	0.0106 (\pm 0.0028)
Putamen	Left	0.0024	0.0056	2.3	0.0095 (\pm 0.0021)
	Right	0.0048	0.0057	1.2	0.0096 (\pm 0.0015)

*Values (\pm SD) obtained from a group of normal subjects [n = 17, mean age 50 (\pm 15) years]

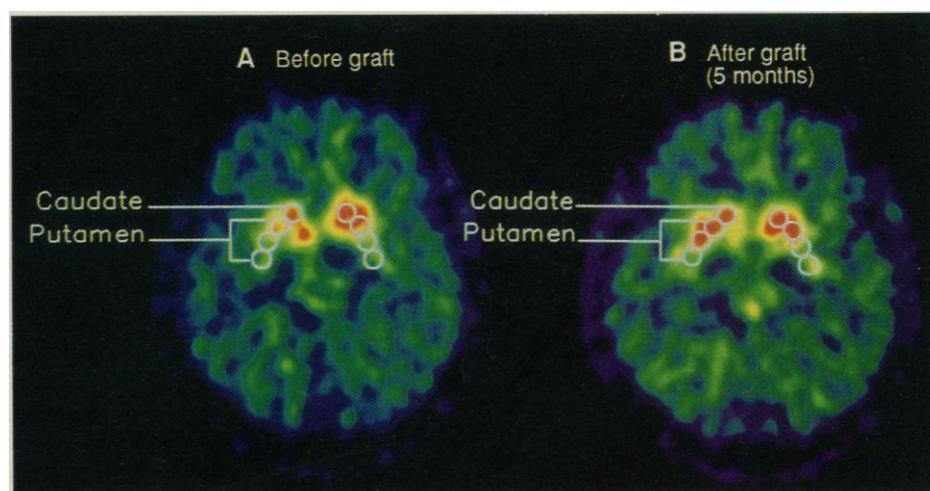


Fig. 3. PET scans obtained with 6-L-[¹⁸F]fluorodopa at the level of the caudate and putamen. The planes have an axial resolution of 7 mm at full width half maximum and are contiguous. The plane illustrated is at approximately 4 mm above the intercommisural line. The scan shows activity in caudate and putamen (A) before and (B) after the grafting. The figure shows cumulative radioactivity recorded in the scans collected between 30 and 120 min. It reflects the spatial distribution of uptake, which is quantified as described in the text and presented in Table 1. A clear focal increase of the tracer is seen in the anterior aspect of the left putamen. The color code is arbitrary, with red representing the highest uptake and blue the lowest.

animals. Intracerebral grafts of neuronal tissue establish a well-developed blood-brain barrier within 1 to 2 weeks of implantation (3, 13). During this early post-transplantation period, no symptomatic improvement was observed in our patient. (iv) Other nonspecific effects of the stereotactic surgery can probably be ruled out since two patients subjected to adrenal medulla autotransplantation in the putamen (14) and two patients who were subjected to neural grafting in both the caudate nucleus and the putamen (5) showed much less improvement. In fact, animal experiments have indicated that the changes in the implantation procedure introduced in this patient (for example, the smaller size of the implantation instrument and the improved handling of the tissue) lead to less tissue damage at the implanta-

tion site and a substantial (at least 20-fold) increase in the survival of implanted fetal DA neurons (15).

Our data demonstrate that human fetal DA neurons can survive, grow, and restore striatal DA synthesis and storage in a patient with idiopathic Parkinson's disease subjected to continuous antiparkinsonian medication. This survival leads to significant therapeutic effects, despite the graft being confined to only part of the striatal complex on one side. Five months after transplantation, the implanted dopaminergic neurons must still be regarded as fairly immature, and they may therefore continue to grow, possibly leading to further clinical improvement. The future assessment of this patient will also show whether these neurons can survive permanently, or if they will be destroyed

either by the underlying disease process or by immunological rejection (16). Although our findings support the idea that neural grafting can be developed into an effective therapy in Parkinson's disease, further work is necessary to optimize the transplantation procedure with respect to the yield of surviving DA neurons and the location and number of implantation sites necessary to achieve the largest symptomatic improvement.

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8. A combination of low-dose cyclosporin, azathioprine, and low-dose prednisolone was used [H. Brynger *et al.*, *Transplant. Proc.* **20** (suppl. 3), 261 (1988)].
9. Tissue was procured from four fetuses obtained at routine suction abortions, with informed consent from the women and with approval by the Research Ethical Committee at the University of Lund. The women were negative for HIV and hepatitis B. The fetuses were 8 to 9 weeks postmenstrual age (crown-to-rump lengths measured with ultrasound were 20 to 25 mm). The fetal tissue fragments were rinsed (5) and stored in buffered Hanks balanced salt solution (HBSS; pH 7.4) for 1 to 3 hours at room temperature. The ventral mesencephalon was dissected from each fetus and cut into six to ten pieces, which were incubated in trypsin for 20 min (5) and then rinsed repeatedly with HBSS. The pieces were partially dissociated (5) in HBSS just before the first implantation in a final volume of approximately 80 μ l. The time between abortion and initiation of implantation surgery was 2.5 to 4 hours. Implantation was performed at three sites in the left putamen with a stereotactic technique (5). For each site, 20 μ l of the dissociated tissue was drawn into the instrument (outer diameter, 1.0 mm). The graft tissue was injected along a 10-, 12-, and 14-mm linear tract, respectively, in eight 2.5- μ l portions for 15 to 20 s each. Between each injection there was a 2-min delay, and the cannula was then retracted 1.5 to 1.7 mm. After the final injection, the cannula was left in situ for 8 min before being slowly withdrawn from the brain. At the end of the surgery, the remaining cell suspension was relatively free of tissue pieces, and the viability was assessed to be 70% [P. Brundin, O. Isacson, A. Björklund, *Brain Res.* **331**, 251 (1985)]. The remaining cell suspension was taken for bacteriological analyses and found to be sterile.
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11. The L-dopa and other medications were withdrawn 18 hours before each PET scan and 100 mg of carbidopa was given 75 min before and a further 50 mg was given 30 min before injection of tracer, in order to increase 6-L-[¹⁸F]fluorodopa uptake. As a result, regions rich in dopaminergic neurons show increased unidirectional transport of the tracer. The ratios of uptake in dopamine-rich regions (striatum) to uptake in regions poor in dopaminergic nerve terminals (for example, occipital cortex) are not altered (K. L. Leenders *et al.*, *J. Cereb. Blood Flow Metabol.* **9** (suppl. 1), S419 (1989)). The 6-L-[¹⁸F]fluorodopa (270 MBq) was injected intravenously with a Harvard pump over 2 min for the first scan and 134 MBq were given for the second [K. L. Leenders *et al.*, *J. Neurol. Neurosurg. Psychiatry* **49**, 853 (1986)]. Sequential PET scans were performed from the moment of the tracer injection, initially over 1-min periods gradually lengthening to 10-min scans, such that a total of 28 scans were collected over 2 hours. Scanning was performed with a CTI931/12/08 (Knoxville, TN) machine, and transmission data were collected with a 68Ga/68Ge ring source to correct for tissue attenuation. The orbito-metal line was aligned with the lowest slice, and head movement was prevented by a custom-made polyurethane mold. The field of view of the scanner was 10.7 cm, thus encompassing virtually the whole brain from cerebellum to vertex. The slice thickness was 7 mm in the reconstructed image with no interslice dead spaces. The resolution within the scan was 8.5 \times 8.5 mm. Anatomical localization was confirmed with the atlas of J. Talairach *et al.* [*Atlas d'Anatomie Stéréotaxique du Tégumentaire* (Masson, Paris, 1967)]. The pattern of tracer uptake greatly helps anatomical localization, as both the caudate nucleus and putamen are very clearly delineated, especially when all the scans taken over 120 min are added together for the purpose of illustration. Tissue and arterial plasma radioactivity was monitored for 120 min after tracer injection. Regions of interest of the size of the resolution element were placed in standard fashion such that one was placed in each caudate nucleus, and then three were placed along the axis of each putamen. The size was determined by the area of maximal striatal uptake seen in scans of normal people. The activity was corrected to the time of injection, and measurements were made as a function of time from the 28 available scans. Striatal tracer uptake was related to that in a large area of occipital cortex in which there are few, if any, dopaminergic terminals. The regional data were analyzed graphically to calculate K_i for each region [C. S. Patlak and R. G. Blasberg, *J. Cereb. Blood Flow Metab.* **5**, 584 (1985)].
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16. Eight months after transplantation, the marked improvement of motor function persists and PET scan continues to show an area of increased 6-L-[¹⁸F]fluorodopa uptake in the left putamen.
17. We thank the patient for his cooperation throughout the study; L. Mangalanayagam for her expert patient care and assistance in collecting study data; I. Ahlsten, H. Edvall, and J. Legrádi for valuable technical assistance; and B. Mattsson for illustrations. Supported by grants from the Swedish Medical Research Council (04X-8666), the Thorsten and Elsa Segerfalk Foundation, and the Bank of Sweden Tricentenary Fund.

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