Effect of Corynebacterium parvum on the Proliferative Rate of Granulocyte-Macrophage Progenitor Cells and the Toxicity of Chemotherapy

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ABSTRACT

We have studied the interaction of Corynebacterium parvum and a variety of cell cycle-specific and cell cycle-nonspecific chemotherapeutic agents on granulocyte-macrophage progenitor cells [colony-forming units culture (CFU-c)] in C57BL/6 mice. In vitro thymidine suicide studies showed an increased rate of proliferation of bone marrow CFU-c 24 hr after C. parvum injection. In vivo toxicity of cell cycle-specific agents but not of cell cycle-nonspecific agents for bone marrow CFU-c was increased 24 hr after C. parvum injections. The increased numbers of CFU-c in the spleen, induced by C. parvum, were also sensitive to a cell cycle-specific agent for up to 7 days after C. parvum injection. The findings suggest differences in the kinetics of proliferation of splenic compared to bone marrow CFU-c. The relative time of administration of chemotherapy and immunostimulants such as C. parvum will have to be carefully considered in the design of clinical trials.

INTRODUCTION

Injections of Corynebacterium parvum have been shown to be synergistic with the antitumor effect of chemotherapy in some experimental tumor models (5, 8, 10-12). Because C. parvum can stimulate reticuloendothelial proliferation and granulocyte and macrophage proliferation, it has been suggested that C. parvum might be of value in decreasing the hematopoietic toxicity of chemotherapy (6, 19). However, we have hypothesized that a more rapid rate of proliferation of the granulocyte-macrophage progenitor cells (CFU-c) after C. parvum might increase rather than decrease the hematopoietic toxic effect of cell cycle-specific chemotherapeutic agents (14). Previously, we have reported that, when C. parvum is injected into mice shortly before 5-FUra injections, there is increased CFU-c toxicity and increased lethality (12, 13). The present studies were undertaken further to explore the dose and time response course of increased CFU-c toxicity of 5-FUra when 5-FUra was injected after C. parvum. We have also examined the effect of C. parvum pretreatment on the CFU-c toxicity of a variety of cell cycle-specific and cell cycle-nonspecific chemotherapeutic agents. Finally, we have used a [3H]-thymidine suicide technique to study more directly the proliferative rate of the bone marrow CFU-c after C. parvum injection.

MATERIALS AND METHODS

Culture of Mouse Granulocyte-Macrophage Progenitor Cells (CFU-c). The mice used in these studies were 2- to 4-month-old C57BL/6 males obtained from The Jackson Laboratory, Bar Harbor, Maine. In each experiment, only animals of similar ages were used. Mice were killed by cervical dislocation, and the spleens and femurs were removed aseptically. Bone marrow cells were flushed from the femurs with McCoy's medium, and a single-cell suspension was obtained by repeated pipetting. Single-cell suspensions of spleens were obtained by teasing with sterile needles and repeated pipetting. A modification of the soft agar culture technique for CFU-c, developed by Bradley and Metcalf (3), was utilized and has been previously described more extensively (14). Briefly, the culture medium was a modified McCoy's medium (Grand Island Biological Co., Grand Island, N. Y.) to which 15% fetal calf serum (Grand Island Biological) a penicillin-streptomycin mixture (Microbiological Associates, Inc., Bethesda, Md.), and 0.3% Difco Bacto-agar (Difco Laboratories, Detroit, Mich.) were added. For assay of bone marrows, 50,000 bone marrow cells in 1 ml of medium were added to each 35-mm plate to which had previously been added 0.025 ml of postendotoxin mouse serum as a source of CSF. After plates were allowed to gel at room temperature for 20 min, they were incubated for 7 days at 37° in a humidified 10% CO2-90% air atmosphere. Colonies were scored with a dissecting microscope, and aggregates containing 50 or more cells were scored as colonies. Spleens were cultured routinely at 100,000 cells/plate in a similar fashion.

In Vitro [3H]Thymidine Suicide of CFU-c. The proliferative state of the bone marrow CFU-c was assayed in a modification of the in vitro [3H]Thymidine suicide technique as described by Iscove et al. (17). Femoral bone marrow suspensions were divided into 3 portions. To a 1-ml volume of 1 of these cell suspensions were added 20 μg [3H]Thymidine (1 mCi/ml)-24 μg dThd per ml (New England Nuclear, Boston, Mass.). After incubation at 37° for 20 min with intermittent agitation, the uptake of [3H]Thymidine was then stopped by the addition of 10 ml of ice cold McCoy's medium containing 100 μg of dThd per ml. The tube was centrifuged at 200 × g for 10 min following which the supernatant was pipetted off and the
cells were resuspended in McCoy’s medium. After 2 washes the final cell concentration was determined by a hemocytometer count, and the cells were cultured as described previously. Control cultures were performed in similar fashion with dThd added. In addition cells were plated in the routine fashion without the incubation or washing steps.

Drugs. C. parvum (Coparvax), Lot CA 380 (Burroughs Wellcome Co., Research Triangle Park, N. C.), at 7 mg (dry weight) per ml suspension of washed formalin-killed organisms in 0.9% NaCl solution containing 0.01% thiomersalate was used in these experiments. Azathioprine (Imuran) and L-phenylalanine mustard (Alkeran) were obtained from Burroughs Wellcome. Doxorubicin hydrochloride (Adriamycin) was obtained from Adria Laboratories Inc., Wilmington, Del. Cyclophosphamide (Cytoxan) was obtained from Mead Johnson Laboratories, Evansville, Ind. 5-(3,3-dimethyl-1-triazenyl)-1H-imidazole-4-carboxamide was obtained from Dome Laboratories, West Haven, Conn. Daclinomycin (Cosmegen) was obtained from Merck Sharp & Dohme, West Point, Pa. Methotrexate sodium was obtained from Lederle Laboratories, Pearl River, N. Y. Vinblasine sulfate (Velban) was obtained from Eli Lilly & Co., Indianapolis, Ind. 5-FUra was obtained from Roche Laboratories, Nutley, N. J.

RESULTS

Effect of Varying Doses of C. parvum on CFU-c and the Sensitivity of CFU-c to 5-FUra Toxicity. Dose-dependent decreases in the total number of bone marrow cells per femur were observed 48 hr after i.p. injection of C. parvum (Chart 1), which were accompanied by dose-dependent increases in the apparent incidence of CFU-c, i.e., an increase in the number of colonies developing per plate of 50,000 bone marrow cells. Injection of the higher doses of C. parvum led to increased total numbers of assayable CFU-c per femur.

We, as well as others, have shown that there is a dose-dependent decrease in the number of bone marrow cells developing into colonies after injection of 5-FUra (7, 13), and we interpret the decreased colony formation as an index of the toxicity of 5-FUra for CFU-c (Chart 2). Also, we have previously shown that, over a wide range of 5-FUra doses, injection of 5-FUra 24 hr after i.p. injection of 1400 μg C. parvum increases the degree of depletion of CFU-c from the bone marrow (13). In the present studies we chose to use a dose of 20 mg 5-FUra per kg, which would have a minimal toxicity for CFU-c in normal mice, reducing CFU-c about 10% when assayed 24 hr after injection. When the standard dose of 20 mg 5-FUra per kg was injected 24 hr after varying doses of C. parvum and 24 hr prior to assay, there was a greater depletion of bone marrow CFU-c when the 5-FUra was injected 24 hr after injection of the higher doses of C. parvum (Chart 3). This finding was in contrast to the experiment shown in Chart 1, which showed increased numbers of CFU-c per femur following injection of the higher doses of C. parvum alone.

Effect of Time on C. parvum-Induced Changes in CFU-c Numbers and the Sensitivity of CFU-c to 5-FUra Toxicity. We wished to determine how long after injection of C. parvum the increased sensitivity of the bone marrow CFU-c to 5-FUra persisted. Also, since we have previously found that C. parvum injection causes both a splenomegaly and a marked increase in the numbers of CFU-c in the spleen at 7 days, we wished to examine the 5-FUra sensitivity of the splenic CFU-c at varying times. We chose the 350-μg i.p. dose of C. parvum as this dose has been shown to have an antitumor effect in animals (30, 36) and was in midrange of the dose response in the previous experiments. Injection of 350 μg C. parvum alone caused no changes in bone marrow CFU-c numbers per femur at anytime from 2 to 22 days after injection (Chart 4). In the groups of mice in which 20 mg 5-FUra per kg were injected i.p. on Days 1, 3, 7, 15, and 21...
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Chart 3. Effect of an i.p. injection of 20 mg 5-FU per kg 24 hr after varying doses of C. parvum i.p. on bone marrow cell count, the number of CFU-c per 5 x 10⁶ bone marrow cells, and the number of CFU-c per femur. The varying doses of C. parvum or the 0.1-mI dose of 0.9% NaCl solution for the control group were injected i.p. 48 hr before assay and the 5-FU 24 hr before assay. Each point represents the mean ± S.E. (bars) of 6 mice. Asterisks, significant differences from the 0.9% NaCl solution control group: *, p < 0.05; **, p < 0.01; ***, p < 0.001.

Chart 4. Effect of 20 mg 5-FU per kg (A) or 0.1 ml 0.9% NaCl solution (•) on bone marrow CFU-c numbers when injected i.p. at 1, 3, 7, 14, and 21 days after 350 µg C. parvum were injected i.p. on Day 0. Assays were performed 24 hr after 5-FU or 0.9% NaCl solution injection. Each point represents the mean ± S.E. (bars) of 10 mice for C. parvum groups and of 4 mice for untreated groups (O). Asterisks, significant differences between C. parvum groups injected with 5-FU 24 hr before assay versus C. parvum groups injected with 0.9% NaCl solution 24 hr before assay: *, p < 0.05, ***, p < 0.001.

Chart 5. Effect of an injection of 350 µg C. parvum i.p. on spleen weight at varying times after injection with 0.9% NaCl solution (•) or 20 mg 5-FU per kg (A) injected i.p. 24 hr before assay. Each point is the mean ± S.E. (bars) of 10 mice for C. parvum-injected groups and of 4 mice for untreated control groups (O) (the same mice described in Chart 4). Asterisks, significant differences between C. parvum-injected mice injected with 5-FU 24 hr before assay versus groups injected with 0.9% NaCl solution 24 hr before assay: *, p < 0.05.

after the C. parvum injections and 24 hr prior to assay, the 5-FU injected on Days 1 and 3 caused significant toxicity for the bone marrow CFU-c, but there was no measurable toxicity for the bone marrow CFU-c of the same dose of 5-FU.
Table 1

Effect of various chemotherapeutic drugs on bone marrow CFU-c with and without pretreatment with C. parvum

C. parvum (350 µg; 14 mg/kg; 45 mg/sq m) was injected i.p. 48 hr before the CFU-c assay. All assays were performed 24 hr after the test drug was administered. All test drugs and 0.9% NaCl solution were injected i.p., except for L-phenylalanine mustard and its 0.9% NaCl solution control group, which were administered by gavage.

<table>
<thead>
<tr>
<th>Drug</th>
<th>0.9% NaCl solution 24 hr before 0.9% NaCl solution</th>
<th>C. parvum 24 hr before test drug</th>
<th>0.9% NaCl solution 24 hr before test drug</th>
<th>C. parvum 24 hr before test drug</th>
<th>p&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Predominantly cell cycle-specific</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine</td>
<td>22,700 ± 2,160&lt;sup&gt;c&lt;/sup&gt;</td>
<td>9,570 ± 1,050</td>
<td>2,460 ± 406</td>
<td>0.0005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dactinomycin</td>
<td>18,200 ± 4,840</td>
<td>20,500 ± 1,610</td>
<td>15,800 ± 1,760</td>
<td>NS&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>18,400 ± 744</td>
<td>20,100 ± 1,550</td>
<td>12,500 ± 1,010</td>
<td>6,640 ± 1,330</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>13,400 ± 1,640</td>
<td>11,500 ± 2,680</td>
<td>13,800 ± 2,320</td>
<td>NS&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vinblastine</td>
<td>21,800 ± 823</td>
<td>21,100 ± 1,120</td>
<td>20,700 ± 1,360</td>
<td>NS&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>29,500 ± 1,500</td>
<td>12,100 ± 1,170</td>
<td>12,300 ± 1,180</td>
<td>NS&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decarbazine</td>
<td>26,800 ± 1,330</td>
<td>7,550 ± 786</td>
<td>7,930 ± 1,370</td>
<td>NS&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L-Phenylalanine mustard</td>
<td>24,400 ± 3,150</td>
<td>21,800 ± 2,680</td>
<td>11,400 ± 1,060</td>
<td>9,350 ± 1,300</td>
<td>NS&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Calculated by Student's 2-tailed t test.
<sup>b</sup> Calculated according to the formula of Freireich et al. (15).
<sup>c</sup> Mean ± S.E. for 10 mice, except for dactinomycin for which each value represents 5 mice.
<sup>d</sup> NS, not significant.
FUrA injected on Days 7, 15, and 21 after the C. parvum injections (Chart 3).

Consistent with many previous observations, injection of 350 μg C. parvum caused a marked splenomegaly with a peak at Day 8 and with a partial regression in spleen size by Day 22 (Chart 5). The injection of 20 mg 5-FUrA per kg 24 hr prior to assay of the C. parvum-treated animals consistently led to lower spleen weight on Days 2, 4, 8, and 15 but not on Day 22. After injection of C. parvum alone, there were marked increases in the numbers of CFU-c in the spleen, which peaked at Day 8 and had returned to near normal by Day 22. A dose of 20 mg 5-FUrA per kg injected 24 hr prior to assay on Days 2, 4, and 8 after C. parvum injection caused a depletion of the CFU-c from the spleen, but this same dose of 5-FUrA injected on Day 14 after C. parvum was no longer significantly toxic to the remaining splenic CFU-c (Chart 6).

**Effect of C. parvum on the Bone Marrow CFU-c Toxicity of Various Antineoplastic Drugs.** We have previously postulated that the increased sensitivity of CFU-c to 5-FUrA toxicity when 5-FUrA is injected after C. parvum is at least in part due to an increased proliferative rate of the CFU-c induced by the C. parvum. Therefore a series of experiments was carried out to test the toxicity of a variety of predominantly cell cycle-specific and cell cycle-nonspecific chemotherapeutic drugs. The data are presented in Table 1. The variation in numbers of CFU-c in the 0.9% NaCl solution injected control groups in the different experiments is a reflection of variations in culture conditions. Doses of cell cycle-specific drugs, which were high enough to cause a depletion of CFU-c in 0.9% NaCl solution pretreated animals consistently caused a greater depletion of CFU-c in animals injected with 350 μg C. parvum 24 hr prior to the test drug. The doses of cell cycle-nonspecific drugs chosen for testing were in a range that caused significant CFU-c toxicity and also approximated doses used clinically. The cell cycle-nonspecific drugs tested did not have greater CFU-c toxicity when injected after C. parvum.

**In Vitro [3H]dThd Suicide Assay of the Proliferative Rate of Bone Marrow CFU-c.** The proliferative state of the bone marrow CFU-c of C. parvum-injected mice was studied by determining the degree to which a brief exposure to high-specific-activity [3H]dThd would inhibit colony formation. The process of incubation with dThd and repeated washing led to a 15% increase in CFU-c per 50,000 cells. This enrichment was presumably due to a differential loss of non-colony-forming cells during the manipulation. Twenty-four hr after C. parvum, 59% of the proliferative capacity of CFU-c was destroyed by [3H]dThd, compared to 29% of 0.9% NaCl solution treated controls ($p < 0.001$) (Table 2).

**DISCUSSION**

Previous studies from our laboratory have demonstrated that relatively large single doses of C. parvum (1400 μg/mouse; 180 mg/sq m) injected i.p. caused a sustained increase of serum CSF with the development of increased numbers of CFU-c in the spleen and increased peripheral blood granulocytes and monocytes (14). These doses of C. parvum also increased the hematopoietic toxicity and lethal toxicity of 5-FUrA (13). We postulated that this increased 5-FUrA toxicity might be related at least in part to an increase in the proliferative rate of the CFU-c caused by the ability of C. parvum to elevate CSF. CSF(s) is the operational term for a family of leukopoietins that are necessary for the _in vitro_ clonal proliferation of CFU-c and is elaborated by cells of the monocyte-macrophage series (16, 21). Although a wide variety of stimuli can cause a transient elevation of CSF _in vivo_, CSF elevation in the serum after C. parvum injection is unusual in the degree of elevation, which is sustained over a long period of time (14). We have suggested that elevated CSF levels and possibly other mechanisms, by increasing the percentage of CFU-c in DNA synthesis, increased the toxic effect of the cell cycle-specific pyrimidine analog 5-FUrA on this compartment of the hematopoietic system. However, we, as well as others (24, 29), have also observed alterations in the levels of hepatic and lung drug-metabolizing enzymes; thus it was also recognized that increased toxicity of 5-FUrA might be related to changes in 5-FUrA metabolism after C. parvum injection. Fisher _et al._ (9) have shown that C. parvum does alter the rate of metabolism of cyclophosphamide. We interpret the _in vitro_ [3H]dThd suicide study reported here as providing direct proof that an increased percentage of the CFU-c are in DNA synthesis following injection of the 350-μg dose of C. parvum. This finding is consistent with our findings that it was only the predominantly cell cycle-specific drugs that had their CFU-c toxicity enhanced by C.

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**Table 2**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Without incubation</th>
<th>dThd incubation</th>
<th>[3H]dThd incubation</th>
<th>% of survival of CFU-c after [3H]dThd incubation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9% NaCl solution</td>
<td>73.4 ± 4.2</td>
<td>85.7 ± 5.8</td>
<td>59.0 ± 4.4</td>
<td>70.9 ± 5.8</td>
</tr>
<tr>
<td>C. parvum</td>
<td>108 ± 6.9</td>
<td>126.8 ± 6.6</td>
<td>52.0 ± 4.6</td>
<td>41.2 ± 3.6</td>
</tr>
</tbody>
</table>

**a** Dose, 20 μCi/mL.

**b** Calculated as Colony formation after [3H]dThd incubation / Colony formation after dThd incubation × 100.

**c** Mean ± S.E.

**d** Dose, 350 μg/mouse i.p.
parvum pretreatment. The [³H]dThd study indicated that, 24 hr after the 350-μg dose of C. parvum, the number of CFU-c in DNA synthesis had approximately doubled. We conclude that the change in proliferative rate of the CFU-c is the major factor responsible for the increased toxicity of cell cycle-specific agents following C. parvum injection.

In a previous study (14) we found that high doses of C. parvum caused either no change in bone marrow CFU-c numbers 1 to 7 days after 1400 μg C. parvum or a reduction in bone marrow CFU-c numbers 24 hr after C. parvum in 1 experiment. In the present studies we have found a significant increase in assayable bone marrow CFU-c 48 hr after injection of 700- or 1400-μg doses of C. parvum but not after injection of lower doses. The reason for the differences between these 2 series of experiments is unclear. The batch of C. parvum in the 2 studies was different, but possibly more important are variations in the mice. Another example of variation is the response to C. parvum, which we have found, is that, for occasional batches of C57BL/6 mice, 350-μg doses of C. parvum i.p. were lethal when given weekly × 3 whereas in many other studies we have not seen lethal toxicity from 10 repeated injections of either 350 or 1400 μg C. parvum. We speculate that the reason for these differences between batches of mice may be related to an undetected infection in an occasional batch of mice.

Both specific immune responses and nonspecific mechanisms have been implicated in the antitumor action of C. parvum. When C. parvum is injected directly into the tumor or mixed with irradiated tumor cells, the antitumor response is sensitive to T-cell depletion and therefore is presumably due to a potentiation of host responses to tumor specific antigens (1, 25–27, 34). However, after systemic administration of C. parvum, the antitumor response can be independent of specific immune responses (2, 4, 26, 31, 33, 35). Studies from several laboratories have implicated the CFU-c as important in the development of the immunologically nonspecific antitumor activity after systemic injection of C. parvum. Increases in relative and absolute numbers of bone marrow CFU-c after C. parvum injection have been documented (6, 14, 32), as well as increases in the spleen CFU-c numbers (14). Fisher and Wolmark (8) have also demonstrated that the CFU-c from C. parvum-injected mice can proliferate in vitro into clones of macrophages that have nonspecific tumor-inhibitory effects. The present experiments provide additional data that it is not only the numbers of CFU-c that increase after C. parvum but also the proliferative rate of CFU-c and presumably the numbers of macrophages and/or granulocytes that are produced. If CFU-c proliferation and production of macrophages is an important part of the antitumor activity of C. parvum, it would be important not to administer cell cycle-active chemotherapeutic agents during the time, after C. parvum injection, when CFU-c are proliferating more rapidly and are more sensitive to toxicity.

The present studies provide some preliminary information on the kinetics of CFU-c proliferation after C. parvum. The experiments shown in Charts 3 and 5 on 5-FUra toxicity for the CFU-c in bone marrow and the spleen show that 5-FUra was quite toxic for both bone marrow and splenic CFU-c 24 hr after C. parvum injection. However, by Day 8 there was no longer any detectable 5-FUra toxicity for bone marrow CFU-c, whereas 77% of the spleen CFU-c were depleted by the same 5-FUra injection. By Day 18, splenic CFU-c while still elevated were no longer sensitive to the 20-mg/kg 5-FUra dose. These findings suggest that there can be different proliferative rates for the spleen and bone marrow CFU-c at any particular time. Although we have consistently found serum CSF elevated after 350 μg C. parvum for 14 days, it is certainly much too simplistic to propose that serum CSF alone controls in vivo CFU-c proliferation. Since there are CFU-producing cells in the spleen and bone marrow (16, 21), it might be anticipated that CSF concentration in the local microenvironment of the CFU-c in the spleen and bone marrow may be quite different from the levels of CSF in the serum. In addition negative feedback mechanisms capable of decreasing CFU-c-proliferative rates in vitro have been recognized (20), and presumably are operative in vivo also.

The single doses of 350 μg (approximately 45 mg/sq m) C. parvum injected i.p. into the mice in these experiments, although commonly used in animal experimentation, are higher than the human doses of 1 to 10 mg C. parvum per sq m, which are currently injected i.v. into humans (18, 23). It is not entirely clear how the high single doses of C. parvum used in animal experimentation are to be compared to the repeated smaller i.v. doses used in humans. However, Scott and Warner (28) have found that weekly i.v. doses of 5.25 mg/sq m in mice both caused a 7-fold increase in spleen weight and were capable of activating macrophages to inhibit tumor growth nonspecifically in vitro. We have found that doses of C. parvum as low as 1 mg/sq m, when injected i.v. into mice, can cause elevation of serum CSF (R. S. Foster, Jr., unpublished data). Further studies are required to determine whether the lower i.v. doses of C. parvum are capable of increasing the proliferative rate of CFU-c in a fashion similar to the 45-mg/sq m i.p. doses used in the present experiment.

Although the present studies have emphasized the increased toxicity of cell cycle-specific chemotherapeutic agents administered shortly after C. parvum, it is quite possible that C. parvum injected after a course of chemotherapy might decrease hematotoxicity. We have previously published some limited data that support this possibility (13). Certainly, the issue of relative time of administration of chemotherapy and immunostimulants such as C. parvum will have to be carefully considered in the design of clinical trials.

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REFERENCES


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