PYRUVIC ACID

I. COLLECTION OF BLOOD FOR THE DETERMINATION OF PYRUVIC AND LACTIC ACIDS

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The accurate determination of pyruvic and lactic acids is a matter of considerable theoretical and practical importance. These acids play a rôle in the metabolism of carbohydrates, and they are found in increased concentration in the blood in conditions of thiamine deficiency. Recently we suggested (1) the determination of the ratio of lactic to pyruvic acid in the blood as a measure of oxidative conditions in tissues, and we have applied it to various studies now in progress dealing with muscular exercise and the reaction of human subjects to high altitude.

Large and indeterminate losses, which make the results valueless, may occur during collection and subsequent handling of blood samples. Until recently, samples of blood to be used for this determination have been collected with syringes and then transferred to bottles containing oxalate. Wilkins, Weiss, and Taylor (2) were the first to show that pyruvic acid disappears from such samples. This was confirmed by Bueding and Wortis (3), who suggested the use of sodium monoiodoacetate for the "stabilization" of the pyruvate. Bueding and Goodhart (4) have recently recommended the addition of 1 per cent each of iodoacetate and fluoride to samples of oxalated blood.

Consistent results, without apparent loss or gain of pyruvic acid during collection of the sample, can be obtained by using a very simple procedure. Blood is withdrawn from the vein by means of 2 or 5 cc. syringes, and the volume is adjusted to the mark, after which the sample is expelled in a fine stream through the needle into a measured volume of precipitant. The procedure eliminates not only the use of a sample bottle containing oxalate

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1 It is not generally realized that the ordinary glass syringes are instruments of considerable precision. Their use is not mentioned in any of the standard text-books or manuals on analytical chemistry. In the past, syringes have been used either as a part of apparatus for the rapid automatic measurement of liquids, or their construction has been modified in order to increase the accuracy. They should find wider application in biochemical analysis.
and fluoride, but also a pipette. The entire operation is accomplished in 30 to 45 seconds. This method has been in use many years in our labora-
tory for other types of determinations (5), and in these and the determina-
tion of pyruvic acid the maximum error has never been greater than ±1.5
per cent. This is within the limits of error of the present methods for
pyruvic and lactic acids.

As far as we are aware, the pyruvic and lactic acid content of freshly
drawn untreated blood has never been determined. In this paper we
shall discuss the effect of various factors, such as stasis during collection
of the sample and the presence of iodoacetate, oxalate, fluoride, and other
salts, on the pyruvic acid content of such blood.

EXPERIMENTAL

The subject rested in an easy chair 1 hour before the beginning of the
experiment. The majority of experiments was not begun until at least
3 hours after a meal.

The sample was withdrawn with a minimum of stasis before collection;
the tourniquet (a soft rubber tube, $\frac{3}{4}$ inch in diameter) was removed
immediately after entry of the needle into the vein. This precaution was
observed throughout, despite the repeated finding that moderate stasis
during the collection of the sample does not apparently affect the pyruvic
and lactic acid levels. However, the subject was cautioned against
clenching and opening the hand, since muscular movements may affect
the results.

Blood was collected by means of carefully cleaned, dry, sterile (auto-
claved) 5 cc. syringes fitted with 21 gage hypodermic needles. Warm
syringes were never used.

The syringe was held vertically, it was tapped a few times to loosen
any bubbles of air adhering to the walls, and the plunger was moved up-
ward slowly until the blue line coincided with the 5 cc. mark. The sample
was then rapidly ejected in a fine stream through the needle into 5 volumes
of a cold 10 per cent solution of trichloroacetic acid contained in a cork-
stoppered 50 cc. centrifuge tube. The contents of the tube were mixed
immediately and then centrifuged. The tube was placed in the re-
frigerator and it was kept there until the time of analysis. Pyruvic acid
was determined in the clear supernatant solution by a modification of the
Lu (6) method.

It is important to keep the extract or contents of the tube cold. After several
hours in a warm room, an increase of 0.05 to 0.20 mg. per cent of “pyruvic acid”
(hydrazone-binding substances) is often noted.
In experiments involving the use of solutions of iodoacetate or of other salts, about 1 cc. of the solution was drawn into the syringe. The walls were wetted by the solution, after which the air and excess of solution were expelled. In experiments involving the use of fluoride, the sample was collected in a syringe containing a weighed quantity of the salt. The approximate final concentrations of added substances were iodoacetate 0.8, potassium oxalate 0.2, sodium fluoride 0.4 per cent. The final concentrations of sodium chloride, sodium sulfate, and sodium bicarbonate were osmotically equivalent to 0.8 per cent of sodium iodoacetate.

The time required for sampling varied somewhat with each individual, due to such factors as the size of the vein, the venous pressure, position of the needle in the vein, etc. In a series of twenty determinations, from 12 to 34 seconds were required for the withdrawal of blood past the 5 cc. mark (about 6 cc.). The average time of half filling the syringe was 9.2 seconds. From 19 to 38 seconds, or an average of about 27 seconds, elapsed from the time of half filling to the time at which the sample was expelled into the precipitant.

The accuracy of measurements by means of syringes can be seen from the following data. Ten syringes, taken at random, delivered duplicate volumes of standard acid as follows: 5.05, 5.05; 5.00, 5.00; 5.05, 5.00; 4.99, 5.00; 4.93, 4.94; 5.00, 5.00; 4.98, 4.97; 4.95, 5.00; 5.00, 5.00; 4.97, 4.98 cc. The agreement of the duplicates should be noted. The extreme deviations from the average were ±1.2 per cent. Since each syringe was numbered by the manufacturer, the results could be corrected if desired.

Blood, although quite opaque, can be measured with equal accuracy, as indicated by the following experiment. 125 mg. of dextrose were added to 100 cc. of whole blood. 5 cc. samples were precipitated by means of zinc hydroxide (7) and the sugar was determined by the Shaffer-Hartmann-Somogyi (8) method. When measured by means of a standard pipette, the sample contained 197 mg. of sugar per 100 cc. Single samples measured by ten syringes taken at random from stock contained 194, 194, 195, 194, 195, 197, 193, 195, 194, and 194 mg. per 100 cc.

If pyruvic acid only was to be determined, blood was withdrawn by means of 2 cc. "precision" (or tuberculin) syringes. The extreme deviation from the manufacturer's calibration of twelve syringes taken at random from stock, as in the case of 5 cc. syringes, was ±1.2 per cent.

Sodium iodoacetate solutions were prepared from the recrystallized acid either by neutralizing with sodium hydroxide, as recommended by Bueding and Wortis, or by adding slightly less than the required amount of sodium bicarbonate. In either case, the results were the same. Recrystallization of the acid appeared to be necessary, since the addition of solutions prepared from the uncrystallized acid (Eastman, No. 1371) resulted in a rapid increase of pyruvic acid.
Dr. Ancel Keys of the University of Minnesota, Minneapolis, has found (private communication) a somewhat smaller maximum deviation of ±1 per cent.

The volumes of solution wetting the walls of 5 cc. syringes and remaining in the needle were 0.095, 0.11, 0.095, 0.11, 0.10, 0.10, 0.11, 0.097, 0.105, 0.090 cc. Again, the close agreement of the data should be noted. Because of this, in experiments involving the use of solutions it was not considered necessary to transfer a measured volume into the syringe as recommended by Bueding and Wortis. The volume of solution remaining in the syringe was assumed to be 0.1 cc. Since about 6 cc. of blood were withdrawn, the results were multiplied by 6.0/5.9, or 1.02.

For the determination of lactic acid, 15 cc. of the clear supernatant solution of the precipitated sample were treated with the Van Slyke CuSO₄-Ca(OH)₂ reagents, the volume was adjusted to 250 cc., and the mixture was cleared by centrifugation. Lactic acid was determined in 100 cc. aliquots⁴ by a modification of the Shaffer method (9). The titrations were carried out with 0.0025 N iodine solution.

**Results**

Before discussing the results, it should be pointed out that the method used in this investigation differs considerably from that of other workers in this field. In preceding studies, blood has been collected in a syringe and then either transferred to a bottle containing oxalate or heparin, or it has been defibrinated (2-4, 10). In every instance the composition of the blood has been altered; in no instance has the fresh unchanged blood been studied. The substance whose effect is to be determined is added to measured volumes of the prepared blood. The initial determinations, which serve as controls, are then made. All of these operations require many minutes. These procedures undoubtedly effect some change in the activities of the leucocytes and red blood cells. It is not altogether unlikely that the high concentration of salt per se may account for some of the effect, since it upsets the normal ionic equilibrium between cells and plasma. Furthermore, since no effort is made to prevent loss of CO₂, the blood may become considerably more alkaline. It is obvious that the changes which occur within a few minutes cannot be evaluated accurately by such a procedure.

In our experiments, frequent samples were withdrawn, usually simultaneously, from the right and left arms. The order in which the samples

⁴ The clear solution contains much calcium trichloroacetate, which decomposes on heating, yielding base. It is therefore necessary to modify the lactic acid reagent. 1 liter of reagent should contain 50 cc. of syrupy (85 per cent) H₃PO₄ and 200 gm. of MnSO₄·4H₂O.
were collected is shown in Tables I to IV. It will be noted that a "control" sample was taken before and after each set of samples in which the effect of a variable was to be determined. For example, the effect of incubation at room temperature (Table I) was determined by comparing the results from samples which were precipitated as soon as possible (less than 30 seconds after filling the syringe one-half) with those from samples held 1, 2, and 3 minutes in the syringe before the contents were expelled into the precipitant. The alternately collected, immediately precipitated samples constituted the controls. The advantage of this method is that fresh blood, without any added salt, is used in every instance.

Effect of Sodium Iodoacetate—Samples collected in syringes containing iodoacetate, as a rule, contained slightly more pyruvic acid than those collected without preservative (Table I). Although the pyruvic acid content did not change during the 1st minute of incubation at room tem-
perature, it was definitely increased after 3 minutes of incubation. Some samples showed a slight increase of pyruvic acid after only 2 minutes of incubation. The determination of lactic acid was difficult in such samples, partly because of the high blank, and partly because of the greater variability in the results of titrations of duplicate samples.

**Table II**

*Effect of Various Salts on Blood*

<table>
<thead>
<tr>
<th>Subject</th>
<th>Substance added</th>
<th>Incubation in syringe at room temperature</th>
<th>Left arm</th>
<th>Right arm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pyruvic acid</td>
<td>Lactic acid</td>
<td>Pyruvic acid</td>
<td>Lactic acid</td>
</tr>
<tr>
<td></td>
<td>mg. per cent</td>
<td>mg. per cent</td>
<td>mg. per cent</td>
<td>mg. per cent</td>
</tr>
<tr>
<td>L. P.*</td>
<td>None</td>
<td>0.86</td>
<td>7.2</td>
<td>8.4</td>
</tr>
<tr>
<td></td>
<td>Fluoride</td>
<td>0.61</td>
<td>8.9</td>
<td>14.6</td>
</tr>
<tr>
<td></td>
<td>Oxalate</td>
<td>0.72</td>
<td>9.6</td>
<td>13.3</td>
</tr>
<tr>
<td></td>
<td>Iodoacetate</td>
<td>0.91</td>
<td>12.3</td>
<td>13.5</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>0.78</td>
<td>8.6</td>
<td>11.0</td>
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<tr>
<td>M. K. R.</td>
<td>None</td>
<td>0.80</td>
<td>8.3</td>
<td>10.4</td>
</tr>
<tr>
<td></td>
<td>Fluoride</td>
<td>0.89</td>
<td>8.3</td>
<td>9.3</td>
</tr>
<tr>
<td></td>
<td>Oxalate</td>
<td>0.54</td>
<td>8.7</td>
<td>16.1</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>0.98</td>
<td>9.8</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td>Oxalate</td>
<td>0.94</td>
<td>8.8</td>
<td>9.4</td>
</tr>
<tr>
<td>C.†</td>
<td>None</td>
<td>0.57</td>
<td>10.1</td>
<td>17.7</td>
</tr>
<tr>
<td></td>
<td>Fluoride</td>
<td>0.87</td>
<td>10.0</td>
<td>11.5</td>
</tr>
<tr>
<td></td>
<td>Oxalate</td>
<td>1.05</td>
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<td>11.0</td>
</tr>
<tr>
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<td>0.91</td>
<td>9.5</td>
<td>11.9</td>
</tr>
<tr>
<td></td>
<td>Fluoride</td>
<td>0.92</td>
<td>14.4</td>
<td>15.6</td>
</tr>
<tr>
<td></td>
<td>Oxalate</td>
<td>0.61</td>
<td>11.7</td>
<td>19.5</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>0.88</td>
<td>11.5</td>
<td>13.1</td>
</tr>
</tbody>
</table>

* Subject ate breakfast at 7.30 a.m. Samples were collected from 11.35 a.m. to 12 noon.
† Subject vomited after collection of fourth set of samples. Collection of last four samples was begun 23 minutes later.
‡ Subject pale, felt faint.

In samples without added substances, no significant difference of the pyruvic acid content was noted between those immediately precipitated and those incubated for varying periods of time up to 3 minutes. The lactic acid content also was not apparently increased. This was further indicated by the constancy (within the limits of experimental error) of the ratio of lactic to pyruvic acid. See also the results from Subject L. P. in Table II.
Effect of Oxalate, Fluoride, and Other Salts—Bueding and Goodhart have shown that the addition of 1 per cent of fluoride to oxalated blood does not prevent the disappearance of pyruvic acid, although it does prevent an increase of lactic acid. This quantity of fluoride is considerably greater than that used by previous investigators. The series of determinations shown in Table II indicate a rapid loss of pyruvic acid in blood containing about 0.4 per cent of sodium fluoride. The loss appeared to be small in samples which were immediately precipitated. In accord with common experience, the lactic acid content was not measurably increased.

<table>
<thead>
<tr>
<th>Salt</th>
<th>Subject V. H.</th>
<th>Subject M. H., Experiment 1</th>
<th>Subject M. H., Experiment 2</th>
<th>Subject L. P.</th>
<th>Subject E. S.</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td></td>
<td>0.69</td>
<td>0.78</td>
<td>0.72</td>
<td></td>
</tr>
<tr>
<td>NaCl, 11.2%*</td>
<td></td>
<td>0.66</td>
<td>0.77</td>
<td>0.92</td>
<td>0.65</td>
</tr>
<tr>
<td>NaHCO₃, 16%*</td>
<td></td>
<td>0.47</td>
<td>0.70</td>
<td>0.78</td>
<td>0.73</td>
</tr>
<tr>
<td>None</td>
<td></td>
<td>0.65</td>
<td>0.65</td>
<td>0.65</td>
<td>0.54</td>
</tr>
<tr>
<td>Na₂SO₄, 18%*</td>
<td></td>
<td>0.60</td>
<td>0.82</td>
<td>0.81</td>
<td>0.70</td>
</tr>
<tr>
<td>None</td>
<td></td>
<td>0.75</td>
<td>0.63</td>
<td>0.95</td>
<td>0.69</td>
</tr>
<tr>
<td>NaCl, 25%</td>
<td></td>
<td>0.65</td>
<td>0.99</td>
<td>0.95</td>
<td>0.67</td>
</tr>
<tr>
<td>None</td>
<td></td>
<td>0.72</td>
<td>1.00</td>
<td></td>
<td>0.67</td>
</tr>
</tbody>
</table>

*The use of these solutions in 5 cc. syringes yielded a final concentration in the blood osmotically equivalent to 0.8 per cent of sodium monoiodoacetate. The bicarbonate did not dissolve completely. The suspension was saturated with CO₂ before use. It was agitated during filling and emptying of the syringe.

The addition of 0.2 per cent of oxalate also brought about a loss of pyruvic acid, but the rate of removal was smaller than with fluoride. No apparent loss was noted in samples which were immediately precipitated. However, a considerable diminution in pyruvic acid was noted in all samples after 3 minutes of incubation. The lactic acid content was not apparently altered by keeping the samples 3 minutes at room temperature.

The effect of salts, to which reference was made above, is shown in Table III. Sodium chloride, when present in a concentration osmotically equivalent to 0.8 per cent of monoiodoacetate, definitely increased the pyruvic acid content in two experiments. In the third experiment, the concentration was slightly lower (perhaps within the limits of experimental error), 0.65, as compared with 0.72 and 0.73 in the control samples. At
the same osmotic concentration of sodium sulfate, a trend toward a lowered pyruvic acid content was noted in every experiment. The greatest losses of all were noted in the samples which contained sodium bicarbonate. The solution of bicarbonate was saturated with CO2 just before the experiments. This was done in order to minimize the possible effect of a rise of pH of the blood and to provide a means of testing the comparative effect of the bicarbonate ion. At a somewhat higher concentration of sodium chloride, with a 25 per cent solution, the pyruvic acid content appeared to be unaltered in two experiments and slightly decreased in another experiment.

**Table IV**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Stasis</th>
<th>Left arm</th>
<th>Right arm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pyruvic acid</td>
<td>Lactic acid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mg. per cent</td>
<td>mg. per cent</td>
</tr>
<tr>
<td>L. P.</td>
<td>None</td>
<td>0.95</td>
<td>10.8</td>
</tr>
<tr>
<td></td>
<td>Stasis</td>
<td>0.98</td>
<td>14.9</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>1.07</td>
<td>14.3</td>
</tr>
<tr>
<td></td>
<td>Stasis</td>
<td>0.97</td>
<td>13.7</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>0.95</td>
<td>13.2</td>
</tr>
<tr>
<td>W. P. M., Ex-</td>
<td>None</td>
<td>1.25</td>
<td>1.18</td>
</tr>
<tr>
<td>experiment 1</td>
<td>Stasis</td>
<td>1.20</td>
<td>1.36</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>1.20</td>
<td>1.09</td>
</tr>
<tr>
<td></td>
<td>Stasis</td>
<td>1.08</td>
<td>1.11</td>
</tr>
<tr>
<td>W. P. M., Ex-</td>
<td>None</td>
<td>0.87</td>
<td>0.89</td>
</tr>
<tr>
<td>experiment 2</td>
<td>Stasis</td>
<td>0.82</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>0.78</td>
<td>9.9</td>
</tr>
</tbody>
</table>

**Effect of Stasis**—It has long been held that asphyxial conditions favor the production of lactic acid by tissues. Such conditions greatly alter the ratio of lactic to pyruvic acid (1). It would seem, therefore, that pyruvic acid should be determined only in blood which has been collected without any stasis whatsoever. In practice, however, this is not feasible. In the majority of instances, the insertion of the hypodermic needle into the vein is accomplished in a minimum of time, and with a minimum of injury to the vein and surrounding tissue, only when the vessel has been engorged with blood by the momentary application of the tourniquet. It is particularly necessary in experiments requiring the collection of many samples at accurately spaced intervals.

In order to test the effect of stasis, unusually severe conditions were
employed. The tourniquet, instead of being applied temporarily, until the needle had been inserted into the vein, as is the custom in this laboratory, was applied for a period of 2 minutes before the collection of the sample was begun. The tourniquet remained on the arm until the collection was complete. Alternate samples of blood, which served as controls, were collected without any stasis whatsoever. The results in Table IV show that these unusual conditions affected the pyruvic and lactic acid content of the blood very slightly, if at all. Of special interest is the finding that the ratio of lactic to pyruvic acid was not significantly changed. Apparently the flow of blood was not greatly impaired by the application of the tourniquet.

**DISCUSSION**

The experiments of previous workers have shown that pyruvic acid disappears rapidly from defibrinated, heparinized, or oxalated blood. In all of these procedures the blood becomes more alkaline. That the changes may be due to the presence of the oxalate or to the increased alkalinity has not apparently been recognized. Since oxalate has not been shown to have an effect on any of the intermediary reactions of carbohydrate occurring in blood, it has been assumed that the oxalate is of no consequence and that the analytical results represent the changes which occur in freshly drawn blood. The study of “stabilizing” agents so far has been limited to iodoacetate. That a similar effect, although perhaps not so pronounced, may be obtained with other salts, which do not have the specific effect of iodoacetate, has not been considered.

This study indicates that some salts bring about the disappearance of pyruvic acid while others effect an increase. Thus pyruvic acid disappears rapidly on the addition of sodium oxalate, fluoride, or bicarbonate. A similar trend is noted in samples containing sodium sulfate. On the other hand, the pyruvic acid content increases rapidly in the presence of sodium iodoacetate, and apparently more slowly at the equivalent concentration of sodium chloride. It is probable, therefore, that the temporary stabilizing effect of iodoacetate added to oxalated blood, as observed by Bueding and Wortis, is due to a balance between the reactions which increase and those which remove pyruvic acid. In the absence of any added salts, i.e. without the addition of anticoagulants or “preservatives,” fresh blood may be held for as long as 3 minutes in a cool syringe without any indication of loss or gain of pyruvic acid.

Despite this apparent stability of the fresh untreated blood, the results of analyses are almost always lower (from 0.05 to 0.15 mg. per cent) than those obtained from samples which contain iodoacetate or iodoacetate plus
oxalate. Such a difference, immediately after withdrawal, has never been noted with any salts except the iodoacetate. The discrepancy may be due to conversion of some of the iodoacetate into keto acid, such as occurs spontaneously in solutions of trichloroacetic acid. On the other hand, it may be the result of reactions which occur at the time of withdrawal of the sample from the blood vessel. It is limited to this time because no apparent further change occurs for at least 1 minute thereafter. Therefore, it is due either to an extremely rapid removal of pyruvic acid from the untreated blood or to an equally rapid conversion of preformed precursors into pyruvic acid, catalyzed by the iodoacetate, in the “preserved” blood.

We prefer the procedure described in this paper because of its simplicity and convenience. Although measurement of the sample by means of a syringe is not as accurate as the measurement by means of a pipette, the error is within the limit of error of the analytical methods. Since the sample is measured and the proteins immediately precipitated, the errors introduced by the addition of iodoacetate and other salts are eliminated. Lactic acid is determined more accurately, and the lactic-pyruvic ratios are more constant (see, for example, the results from W. H., Table I), in the freshly collected untreated samples of blood than in those samples which contain monoiodoacetate.

SUMMARY

Blood is withdrawn from the vein by means of a cool, dry, clean 2 or 5 cc. syringe. The volume of the sample is adjusted to the mark and the contents are expelled in a fine stream through the needle into 5 volumes of trichloroacetic acid. The entire operation requires from 30 to 45 seconds. The error of measurement of blood by means of syringes is within the limits of error of the methods for the determination of pyruvic and lactic acids. Application of a tourniquet for a period of 2 minutes, and continued application during collection of the sample from the vein, did not noticeably affect the results. Although moderate stasis has no apparent effect, it is recommended that the tourniquet be released as soon as the needle has entered the vein.

Fresh untreated blood, when held at room temperature in cool syringes for varying periods of time up to 3 minutes, did not gain or lose pyruvic acid.

Sodium bicarbonate, sodium fluoride, sodium oxalate, or sodium sulfate when added to blood brought about a loss of pyruvic acid. The rate of loss was greatest with the bicarbonate and least with the sulfate. On the other hand, a rapid increase of keto acid was noted in the samples to which sodium monoiodoacetate was added. In two out of three experiments, a distinct increase of pyruvic acid was noted following the addition of
sodium chloride. The apparent "stabilizing" effect of sodium fluoride and iodoacetate added to oxalated blood is probably due to a balance between many reactions, some of which result in a loss and others in a gain of pyruvic acid. The simple and convenient procedure described by the authors completely eliminates the errors resulting from the addition of salts.

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