Altered thermal sensitivity in injured and demyelinated nerve
A possible model of temperature effects in multiple sclerosis

FLOYD A. DAVIS AND SAMUEL JACOBSON
From the Department of Neurology, Rush-Presbyterian-St. Luke’s Medical Center, Chicago, Illinois, U.S.A.

SUMMARY Electrophysiological studies were performed on frog and guinea-pig peripheral nerves to determine the effect of temperature on conduction at the site of pressure and demyelinating lesions. An increased susceptibility to thermally-induced conduction blockade has been demonstrated. In pressure-injured frog and guinea-pig nerves, conduction blocks occur at temperatures approximately 6°C lower than in normal nerves. A similar phenomenon occurs in guinea-pig demyelinated nerve (experimental allergic neuritis) and in some cases at temperatures around 15°C lower than in controls. It is suggested that these effects are the result of a critical lowering by temperature of an already markedly depressed conduction safety factor. In support of this, it has been shown that calcium ion depletion, which would be expected to increase the conduction safety factor by lowering the threshold for excitation, counteracts the increased thermal sensitivity of frog pressure-injured nerve. These findings are discussed in relation to well-known temperature effects in multiple sclerosis. They add support to an earlier proposed hypothesis that the changes in signs and symptoms with a change of body temperature in multiple sclerosis may be caused by an effect of temperature on axonal conduction.

It was recently reported that scotomas, nystagmus, and oculomotor paresis in patients with multiple sclerosis (MS) are improved by infusions of sodium bicarbonate, disodium edetate (Na₂ EDTA), and also by hyperventilation, procedures which have in common the ability to lower the concentration of serum ionized calcium (Davis, Becker, Michael, and Sorensen, 1970). The testing of these procedures was suggested by electrophysiological studies on pressure-injured and demyelinated nerves in animals. These experiments and their theoretical clinical implications are reported here.

Signs and symptoms in MS are believed to be due to impaired conduction in demyelinated axons of the central nervous system (Charcot, 1877; Namerow, 1968; Namerow and Kappl, 1969). It is well known that clinical findings in MS worsen with small elevations in body temperature while cooling can produce a dramatic improvement (Simons, 1937; Brickner, 1950; Guthrie, 1951; Edmund and Fog, 1955; Nelson, Jeffreys, and McDowell, 1958; Boynton, Garramone, and Buca, 1959; Nelson and McDowell, 1959; Watson, 1959). Since the phenomenon can occur with the central scotoma and medial longitudinal fasciculus syndrome, findings indicative of pure tract lesions, it would appear that it is the axonal conduction abnormality in MS that is labile and capable of being modified in both a favourable and unfavourable manner. In attempting to understand the mechanism responsible for this temperature phenomenon, the following working hypothesis was proposed. The ratio of the action current generated by a nerve impulse to the minimum amount needed to maintain conduction is known as the conduction safety factor (Tasaki, 1953). Tasaki found a value around 5-7 in myelinated toad axons (Tasaki, 1953). This ratio reflects the net effect of many variables such as action potential amplitude and duration, membrane threshold, axoplasmic resistance, etc, which are involved in the maintenance of axonal conduction. If the safety factor is decreased by injury or disease to a level that just barely permits conduction to occur, the smallest additional insult

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could produce a conduction block even though similar changes do not block normal nerve. On the other hand physical and chemical agents that can increase the safety factor might improve conduction in diseased or injured axons. If, in MS, some nerve fibres traversing a plaque are in such a precarious state, it might be possible that a small change in temperature could upset this delicate balance such that conduction occurs at one temperature but not at one slightly higher. Indirect support for this hypothesis was previously obtained in experiments on isolated, single lobster axons (Davis, 1970). It was shown that the conduction block caused by a focal, pressure, or thermal lesion is remarkably sensitive to small changes in temperature. Conduction is restored by cooling the nerve, while on rewarming the block returns; less than a 1°C change determines whether or not conduction can occur. It was suggested that cooling may increase the conduction safety factor, enabling the impulse either to jump over or conduct through the injured region.

In this study a similar phenomenon has been demonstrated in demyelinated guinea-pig peripheral nerve as well as in pressure-injured frog and guinea-pig peripheral nerves. It has also been found that lowering the concentration of calcium ions bathing an injured nerve, a procedure that would be expected to enhance the conduction safety factor by lowering the threshold for excitation, markedly improves conduction.

MATERIALS AND METHODS

1. In vitro frog nerve preparation a. Electrical recording With the apparatus shown in Fig. 1, it was possible to stimulate and record from opposite ends of an excised frog (Rana pipiens) sciatic nerve trunk while the temperature and/or ionic environment of a middle, injured segment was varied. Stimuli consisted of single, supramaximal, 0-1 msec, rectangular pulses from a Grass S-8 Stimulator and Stimulus Isolation Unit. These were delivered to the thicker proximal end of the nerve by the stainless steel or platinum electrodes 1 and 2, anode and cathode respectively. Compound action potentials were recorded monophasically at the stainless steel or platinum electrodes 5 and 6 by crushing the nerve proximal to the latter electrode. The preparation was grounded at electrode 3. Potentials were displayed on a Tektronix Dual Beam 561A Oscilloscope after amplification with a Tektronix FM 122-Low Level Preamplifier and were photographed with a Polaroid Camera.

As shown in Fig. 1, a short segment of nerve located approximately midway between the stimulating and recording electrodes was submerged in a Ringer-filled cavity in a cork block which was thermally insulated from two adjacent polystyrene foam blocks by 1·5 mm air gaps. The temperature of the Ringer’s solution was controlled by a closed water-circulating system and was monitored with a Yellow Springs Model 44 Tele-Thermometer and Thermistor Probes. Segments of the nerve lying outside the Ringer-filled cavity (including the portions traversing the air gaps) were carefully encased in petroleum jelly to prevent drying. The segments of nerve at the stimulating and recording sites were shown to remain at room temperature when the Ringer temperature was varied. The Ringer’s solution was adjusted to pH 7·5 and had the following composition in millimoles/litre: NaCl-115, KCl-2·5, CaCl$_2$-1·8, NaHCO$_3$-2·4, TRIS buffer-1·0. Calcium-free Ringer’s solution differed only by the absence of CaCl$_2$. Room temperature ranged from 23°C to 25°C and did not vary more than 0·5°C during an experiment.

b. Pressure lesion Pressure lesions were made in the middle of the segment of nerve submerged in the Ringer-filled cavity according to the method of Lorente de Nó (Lorente de Nó, 1947). A lesion, 1 mm long, was made by gently squeezing the nerve with flexible eye forceps; the pressure was gradually increased until the maximum amplitude of the compound A spike was decreased approximately 60–80%. Lorente de Nó has shown that if the lesion is not too wide and the continuity of the nerve fibres is not disrupted some axons continue to conduct because the safety factor enables impulses to “jump across” the lesion. His observation that these pressure-injured fibres conduct impulses at a decreased velocity (Lorente de Nó, 1947) have been confirmed in our studies (Fig. 2) and indicate that his technique has been satisfactorily reproduced.

2. In vivo guinea-pig experiments a. Experimental allergic neuritis (EAN) EAN was induced in unselected, adult male and female guinea-pigs by the method of

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FIG. 1. Frog stimulating-recording apparatus. The sciatic nerve rests on the stainless steel (or platinum) electrodes numbered 1-6. Stimulating and recording electrodes are 1, 2 and 5, 6 respectively. The mid-segment of the nerve rests on the ground electrode 3 and is submerged in a cavity filled with Ringer’s solution. The temperature of the Ringer’s solution is controlled by means of a closed water-circulating system (not shown) at the bottom of the cavity. Exposed parts of the nerve are covered with petroleum jelly (not shown).
The proximal portion of the sciatic nerve was stimulated through silver electrodes while action potentials were recorded with platinum electrodes placed along the peroneal nerve. A ground electrode was inserted under the sciatic nerve approximately midway between the stimulating and recording electrodes. Stimulus parameters and recording techniques were the same as those described above for the frog except for occasional substitution of monophasic by diphasic recording.

The mineral oil bathing the sciatic nerve at the site of the ground electrode was partitioned off by muscle and fascia to form an isolated pool. This resulted in the formation of three separate mineral oil pools, one for each pair of stimulating and recording electrodes and a middle pool at the site of the ground electrode. The length of sciatic nerve coursing through the latter pool was approximately 1 to 2 cm. The mineral oil in this middle pool was heated by means of a narrow beam of light from an infra-red heat lamp. As an added precaution against heating the stimulating and recording regions aluminium foil reflectors were draped over these areas. The temperatures of the heated pool and stimulating-recording areas were continually monitored by thermistors. Even when the temperature of the middle pool was increased by 20°C the temperatures of the stimulating and recording sites did not appreciably change.

d. Histological methods Some of the nerves studied electrophysiologically were later fixed for at least one week in 10% formaldehyde-saline, dehydrated and embedded in paraffin. Sections were stained with the luxol fast blue-cresyl fast violet method for myelin. Haematoxylin and eosin was also used as a general tissue stain.

RESULTS

1. Effect of temperature on conduction in pressure-injured frog nerve Pressure lesions were made in the segment of nerve submerged in the Ringer-filled cavity as described in the Material and Methods section, and action potentials were recorded as the temperature was gradually increased. The graph in Fig. 3 compares control and experimental nerves. The ordinate represents the relative area subtended by the monophasic A potential (measured with a planimeter directly from the original Polaroid photographs). This measurement is directly related to the number of conducting fibres. The area at 20°C was arbitrarily assigned a unit value. Note that the control nerves did not appreciably change until around 32°C when decreases occurred.

*This value cannot be assumed to be directly proportioned, since it is unlikely that each axon contributes an equal share to the area of the compound action potential.
that rapidly progressed to nearly complete block by 34-36°C. These blocks were reversible if the higher temperatures were not maintained longer than one to two minutes.

These blocking temperatures are similar to those reported for *Rana temporaria* (Bremer and Titica, 1946). In *Rana esculenta* (Bremer and Titica, 1946) and *Rana catesbiana* (Treonar, Lambert, and Herrick, 1953) heat block occurs at higher temperatures. The pressure-injured nerves blocked at much lower temperatures. Conduction block began around 26°C, and by 30°C there was approximately a 50-60% decrease in action potential area. In contrast with the control nerves, this effect was reversible when exposure to the blocking temperature was maintained for 10 to 15 minutes. Recovery was occasionally characterized by a hysteresis such that lower temperatures were needed to restore original values.

These results indicate that the injured axons, while capable of conducting impulses, have a heightened susceptibility to thermal block. The block usually begins about 6°C lower in injured than in normal nerve; however, in several experiments even more marked effects were seen. In the experiment shown in Fig. 4 the action potential began to decrease at 23°C and is nearly completely blocked by 30°C. In this experiment reversal occurred without a hysteresis.

2. EFFECT OF TEMPERATURE ON CONDUCTION IN PRESSURE-INJURED AND DEMYELINATED GUINEA-PIG NERVE. a. Pressure lesions Pressure lesions were made in the segment of sciatic nerve running through the middle mineral oil pool (see Materials and Methods section) and supramaximally stimulated compound action potentials were recorded as the temperature in this pool was gradually increased. Figure 5, I and II, depicts typical results with control and experimental nerves, respectively. The compound action potential of the uninjured control, Fig. 5, I, nearly completely blocked by 48°C and recovered when the temperature was lowered to 45°C. In 10 control preparations a similar degree of block

![Figure 3](http://jnnp.bmj.com/)

**Fig. 3.** Comparison of thermally induced conduction block in 12 frog nerves, six normal and six pressure-injured. A decrease in the action potential area (ordinate) indicates a decrease in the number of conducting fibres. Note that conduction block occurs at lower temperatures in the pressure-injured nerves.

![Figure 4](http://jnnp.bmj.com/)

**Fig. 4.** Increased sensitivity of pressure-injured frog nerve to temperature elevation. There is a progressive decrease in the amplitude of the compound action potential indicating a conduction block in many fibres. In contrast, normal nerves do not block at temperatures below 30°C; see Fig. 3.
FIG. 5. Effect of temperature elevation on conduction in normal (I), pressure-injured (II), and demyelinated (III) guinea-pig nerves. Conduction blocks, reflected by a decrease in the action potential amplitude, occur at lower temperatures in the injured and demyelinated nerves; reversal is frequently characterized by a hysteresis. Note that conduction block in the experimental nerves can occur at temperatures close to the normal rectal temperatures (38-39°C) for the guinea-pig.
occurred at 46·6 ± 1·6°C. In the pressure-injured nerves block occurred at much lower temperatures (Fig. 5, I1). In six pressure-injured nerves block occurred at 40·8 ± 1·2°C. As noted in the frog, recovery was occasionally associated with a hysteresis such that lower temperatures were needed to restore original values.

b. Demyelinating lesions (Experimental allergic neuritis, EAN) Nineteen guinea-pigs were injected with the rabbit sciatic nerve emulsion. Five animals appeared to be unaffected and were not studied. Of the remaining 14, one severely involved animal died before being studied. The rest developed moderate to severe limb paresis most marked in the hind limbs beginning approximately three weeks after the injections. All of the latter animals were studied. Since these animals can develop lesions within the central nervous system in addition to nerve roots and peripheral nerves, a correlation between the electrical findings and clinical picture is not feasible. As previously reported by Cragg and Thomas (1964) some affected animals had normal or only slightly abnormal appearing action potentials. This was observed in eight animals all of which demonstrated a normal response to temperature elevation. However, four of the five animals with moderate to marked action potential attenuation and dispersion demonstrated a marked increase in sensitivity to thermal block.

The results in two nerves from different animals are shown in Fig. 5, III (I and 2). In (I), the compound action potential markedly decreased as the temperature was elevated to 40°C. The effect reversed with a hysteresis qualitatively similar to that seen in frog and guinea-pig pressure-injured nerves. Figure 6 shows a longitudinal section taken from the segment of this nerve traversing the middle mineral oil pool and stained for myelin with the luxol fast blue-cresyl fast-violet method. Many of the fibres in the upper portion have a normal reticulated appearance and contrast with the lower fibres which show demyelinated segments and areas of myelin degeneration; the axis cylinders appear to be intact.

In Fig. 5, III(2) the action potential displays two peaks. Note that the amplitude of the second peak decreases as the temperature is raised while the first peak remains unchanged. The first peak finally went on to block at 45°C which is similar to the blocking temperature of normal nerve. The first peak may represent normally or minimally diseased fibres, while the second peak represents slower conducting, more severely demyelinated fibres. Cragg and Thomas arrived at the same conclusion based on the differential response of double-peaked compound action potentials in EAN to repetitive stimulation (Cragg and Thomas, 1964). Histological examination of the segment of this nerve traversing the middle mineral oil pool revealed many scattered areas of demyelination.

These experiments demonstrate that pressure-injured and demyelinated guinea-pig nerve fibres have a heightened susceptibility to thermal block even at temperatures close to the normal temperature (38-39°C). In the one preparation that responded normally to temperature elevation in spite of a markedly dispersed and attenuated compound action potential, histological examination of the heated segment revealed very mild pathological changes. It is possible that many of the lesions responsible for the marked conduction abnormalities were by chance situated in segments of the nerve outside the heated, middle mineral oil pool.

3. Effect of calcium ion depletion on conduction in pressure-injured frog nerve If, as postulated, temperature elevation blocks pressure-injured and demyelinated nerve due to a further lowering of an already markedly depressed safety factor, then agents that enhance the safety factor should counteract the thermal block. Bathing a nerve in calcium-free Ringer's solution is well known to decrease the threshold for excitation (Misske, 1930; Brink, Bronk, and Larrabee, 1946). Theoretically, this effect should increase the safety factor by lowering the minimal amount of action current needed to maintain conduction.

The effect of lowering calcium at the site of a pressure lesion in frog nerve is shown in Fig. 7. The stimulating-recording apparatus shown in Fig. 1 was used. Supramaximal stimuli were delivered through electrodes 1 and 2; compound action potentials were recorded at electrodes 5 and 6. At 1 mm pressure-injured lesion was made in the segment of nerve traversing the Ringer-filled pool. The epineurium of this segment had previously been removed in order to facilitate calcium removal. Figure 7, A, 1-4, demonstrates the previously described effect of temperature on a pressure-injured nerve with the pool containing Ringer's solution. Note the progressive decline of the amplitude of the compound action potential as temperature increased. Within two minutes after replacing the Ringer's solution with calcium-free Ringer's solution, there was a marked increase in the amplitude of the action potential as seen in Fig. 7 A, 5 (compare with A, 2). In Fig. 7 A, 6-10, the temperature of the calcium-free Ringer's solution was gradually increased. In contrast with the previous response of this same nerve when in Ringer's solution, the action potential amplitude did not decrease.
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FIG. 6. *Horizontal section of sciatic nerve from guinea-pig with experimental allergic neuritis (EAN) stained for myelin with the luxol fast blue-cresyl fast violet method. Section taken from same nerve studied electrophysiologically in Fig. 5, III (I). Many of the fibres in the upper half of this field have a relatively normal appearance with a prominent neurokeratin network. In marked contrast, the lower portion shows demyelinated segments and areas of myelin degeneration.*

until higher temperatures were reached; compare Fig. 7 A, 2-4, with Fig. 7 A, 5-7.

In Fig. 7B another pressure-injured nerve demonstrates the marked increase in action potential amplitude caused by bathing the lesion in calcium-free Ringer's solution. Note that the temperature is maintained at 30°C throughout. The effect is reversible and is completed within two to three minutes after changing solutions. Similar but less marked effects occurred with Ringer's solution containing 0.45 mM calcium (25% of the normal Ca concentration). This effect is too large to be explained by a change in temporal dispersion and must be due to an increase in the number of conducting fibres. However, it is not known whether this is due to restoration of conduction in blocked fibres, ephaptic transmission, or both. Although spontaneous nerve activity can be induced by calcium ion depletion, none was observed in these experiments.

**DISCUSSION**

This study demonstrates that there is an increased susceptibility to thermally induced conduction block in pressure-injured and demyelinated nerve. The same phenomenon has been previously reported in pressure and thermally injured, single lobster axons. This seemingly ubiquitous response of
damaged and demyelinated nerve to temperature adds support to the earlier proposed hypothesis that the change in signs and symptoms with a change of body temperature in multiple sclerosis may be caused by an effect of temperature on axonal conduction (Davis, 1970). Thus the dramatic worsening of a central scotoma with hyperthermia might be due to a blocking of conduction in some demyelinated
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optic nerve fibres, while the improvement with cooling might be due to a restoration of conduction in blocked axons.

The precise mechanism for this temperature phenomenon is not known and might even vary in different preparations. However, it is reasonable to consider that it may be related to alterations in specific conduction parameters—that is, action potential amplitude and duration, excitation threshold, axoplasmic resistance, nodal current density, etc.—which have in common the ability to lower the conduction safety factor. In his classic studies on myelinated nerve, Tasaki emphasized that the nerve impulse is characterized by a safety factor which enables conduction to occur in the presence of adverse conditions (Tasaki, 1953). Thus, a localized axonal lesion may destroy the impulse-producing mechanism without blocking conduction if the current that is generated by the action potential and spreads to the other side of the injured region is strong enough to induce a threshold depolarization. The impulse will, in effect, jump over the blocked segment. Tasaki has shown that a myelinated nerve fibre continues to conduct even though two adjacent nodes of Ranvier are inactivated (Tasaki, 1953). Although the safety factor concept was derived from studies on peripheral nerve fibres it is likely that it is also relevant to impulse conduction in CNS axons.

The effects of heating and cooling on conduction reported here might be due to a decrease and increase, respectively, of an already critically depressed conduction safety factor. In a like manner, the improvement seen with cooling in multiple sclerosis might be due to an increase in the safety factor which enables an impulse to 'jump over' a short blocked segment. However, it is also possible that cooling restores conduction in the blocked segment. Theoretically, either or both might occur, depending on the nature of the block. If the excitability of the blocked segment is totally and irreversibly destroyed, restoration of conduction could occur only by jumping the lesion. This would not occur if the blocked segment were too long. On the other hand, if a lesion blocks conduction due to a reduction of the safety factor below the critical value of 1, cooling might restore conduction in the blocked segment by increasing the safety factor. This effect would not be limited by the size of the lesion. Many variables can affect the safety factor. From Tasaki’s studies it is clear that the safety factor decreases with a decrease in amplitude of the action potential (Tasaki, 1953). Also, the higher the threshold for excitation the more action current is needed to stimulate the nerve; this would decrease the safety factor. Alterations in axoplasmic resistance, through which the action current flows, are also important. Thus, a constriction along an axon would be expected to increase resistance and thereby lower the safety factor. Many of these parameters are affected by changes in temperature. It is well established that the duration of the action potential is characterized by a relatively large negative temperature coefficient (Gasser, 1931; Schoepfle and Erlanger, 1941; Bremer and Titeca, 1946; Tasaki and Fujita, 1948; Hodgkin and Katz, 1949). Thus, with rising temperature the duration decreases, while with cooling an increase occurs. This might be expected to produce a decrease and increase, respectively, in the safety factor. Findings concerning the effect of temperature on the amplitude of the action potential vary. Positive coefficients have been found in frog and toad nerve (Gasser, 1931; Tasaki and Fujita, 1948) while a negative coefficient has been reported in the squid giant axon (Hodgkin and Katz, 1949). The effects of temperature on threshold are complex and can vary with the characteristics of the stimulus. In lobster axons the rheobase is decreased while the threshold for short duration stimuli is increased as the temperature is lowered (Wright, 1958). Tasaki reported a decrease in the excitability of toad nerve with cooling below 20°C (Tasaki, 1949). In unpublished studies we have seen the same phenomenon in frog nerve but also found quite unexpectedly that the threshold increases with heating above 20°C. In the case of axoplasmic resistance which is inversely related to temperature, the decrease with temperature elevation would tend to enhance the safety factor.

No doubt there are many ways in which temperature can alter the conduction safety factor and this may vary in different types of nerves and in different species. Whether or not conduction occurs under the experimental conditions reported in this paper would appear to be due to the net effects of these and perhaps other variables on the conduction safety factor. The details of these relationships remain to be elucidated.

The idea that the safety factor may be decreased in injured and demyelinated axons is not new. Lorente de Nô suggests that conduction is slowed in pressure-injured nerve because of a decrease in the safety factor (Lorente de Nô, 1947). Kaeser and Lambert (1962) have suggested that the decreased conduction velocity in segmentally demyelinated nerve may be due to a decrease in nodal current density which implies a decreased safety factor. Hall (1967) and McDonald (1963) have expressed similar ideas.

Although the safety factor concept can give only a limited explanation for the temperature effects reported in this study, it has considerable heuristic
value. For example, it suggests that an increase in the conduction safety factor might improve conduction in diseased nerves. This led to the experiments with low calcium solutions. In contrast with the role of sodium and potassium ions as current carriers in the generation of an action potential, many observations suggest that calcium ions may be associated with permeability changes. It is well known that nerves bathed in a low calcium Ringer’s solution develop an increased excitability (Misske, 1930; Brink, Bronk, and Larrabee, 1946). In frog nerve calcium depletion causes a depolarization associated with an increased permeability to sodium ions (Stämpfli and Nishie, 1956). In addition, voltage clamp experiments in the squid giant axon have shown that a five-fold reduction of external calcium concentration affects the system controlling sodium and potassium conductance in a manner similar to a 10-15 mV depolarization (Frankenhaeuser and Hodgkin, 1957). Since calcium ion depletion lowers the threshold for excitation, it might be expected to increase the safety factor and thereby improve conduction in injured nerve. This prediction has been borne out in the calcium depletion experiments in pressure-injured frog nerve reported in this paper. A similar effect might be expected in demyelinated nerve if, as believed, it is also characterized by a decreased conduction safety factor.

These ideas have been tested in patients with multiple sclerosis by the use of procedures believed to produce a reduction in serum ionized calcium. It was found that marked improvement in scotomas, nystagmus, and oculomotor paresis occurs with intravenous infusions of sodium bicarbonate or disodium edetate (Davis, Becker, Michael, and Sorensen, 1970). These effects are transient, lasting less than an hour after the infusions are stopped. Although these chemicals do not, in any way, constitute a form of therapy, they do demonstrate that signs in multiple sclerosis can be favourably altered by chemical means and point to a new approach to a search for symptomatic therapy in multiple sclerosis and perhaps other demyelinating diseases. Accordingly, the animal models reported in this study would appear to be useful in studying the pathophysiology and pharmacological modification of conduction relevant to these clinical problems.

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