Environmental Health Perspectives
Vol. 26, pp. 89-95, 1978

Clinical Expression of Neurotoxic Injury and Diagnostic Use of Electromyography

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The clinical features of neurological damage produced by acrylamide, lead, organophosphates, hexacarbon solvents, and methylmercury are described, and the differences in effects of these compounds are stressed. The characteristic pattern of electrophysiological changes for each group of substances are described and correlated with pathological findings.

Each group of neurotoxic substances has its own particular effect on the nervous system, producing a typical clinical disorder, pathological changes which are often distinctive in type and distribution and resulting in a characteristic pattern of electrophysiological abnormalities. This paper discusses examples of substances producing peripheral neuropathy which illustrate these points. There are often sound reasons for deciding which particular electrophysiological technique would be most appropriate for screening exposed populations to determine whether subclinical or minimal clinical nerve damage has occurred.

Acrylamide

Acrylamide has been known to be neurotoxic since the early 1950's, but the clinical features of acrylamide toxicity to man have been well recognized only for the past 10 years (*1*). Although the substance is now extensively used in industry, less than 50 human cases have been described in the literature (*2*). Nevertheless the increasing pollution of the environment by this substance makes it essential that toxic effects are widely appreciated. A formidable body of experimental work is in progress to elucidate the underlying mechanism of the neuropathy.

In elucidating the cause of peripheral neuropathy, recognition of symptoms and signs other than those directly related to the peripheral nerves may be diagnostically important. In acrylamide poisoning, the hands usually become red, and the palms peel and excessive sweating occurs. Weight loss can occur early. Acrylamide never produces toxic symptoms after a single exposure however massive, but high level exposure for a short time causes clinical evidence of CNS involvement, often before the development of peripheral neuropathy. Drowsiness is common; in a family, described by Igisu and colleagues (*3*), whose well water became severely contaminated with acrylamide, frank encephalopathy developed. Affected subjects developed drowsiness, memory disturbances, confusion, ataxia and hallucinations at least two weeks before any evidence of peripheral neuropathy. With lesser exposure evidence of peripheral neuropathy alone may develop slowly. The nerve lesion involves motor and sensory fibers. Cramps occur early. Distal numbness and paraesthesiae follow, with distal weakness developing about the same time or a little later. As the condition progresses motor involvement is more marked than sensory loss. All reflexes are lost early, an uncommon finding in toxic neuropathies. When exposure ceases recovery is complete in mild cases, but slow improvement for a year or more, with slight residual abnormalities is to be expected in those severely affected.

Conduction velocity studies in acrylamide poisoning in rats (*4*), baboons (*5*), and man (*6*) have consistently shown some fall in maximal nerve conduction velocity. When muscle action potentials are recorded from the small foot muscles following stimulation of the motor nerves at the ankle and in the thigh, as described in acrylamide poisoned rats

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by Fullerton and Barnes (*4*), conduction velocity in the most rapidly conducting nerve fibers in the leg can be calculated. Figure 1 shows that a reduction of about 20% occurred in a group of poisoned rats compared with controls and that velocity recovered after clinical recovery.

Consideration of pathological changes in the nerves is important in interpreting these findings. Acrylamide causes a dying-back type of neuropathy in which nerve fiber degeneration begins at the distal ends of the fibers and spreads proximally as illustrated in Figure 2. Increasingly severe involvement of nerve fibers can be seen as sections are examined more distally. Figure 3 shows the fiber diameter distribution in nerves of two control rats, three acrylamide-poisoned rats, and one during recovery from acrylamide poisoning. Large diameter fibers are predominantly affected. The increased number of small diameter fibers in the recovering animal is probably due to the presence of regenerating fibers, which are all initially of small diameter. Conduction velocity is correlated with fiber diameter and so loss of large diameter fibers will cause a reduction in maximal conduction velocity while smaller, more slowly conducting fibers continue to conduct normally. In acrylamide poisoning there is no evidence of a conduction abnormality in fibers which have not degenerated completely.

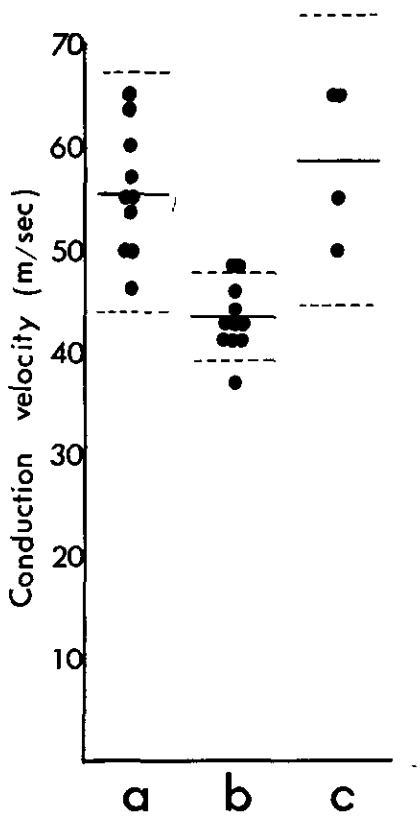

FIGURE 1. Maximal nerve conduction velocity in motor fibers to small foot muscles in (*a*) healthy adult rats, (*b*) rats which had been on a diet containing 200 ppm acrylamide for six months or 400 ppm acrylamide for two to three months, (*c*) rats which had been severely affected and returned to a normal diet five to nine months previously. Solid lines indicate mean conduction velocities; dotted lines are two standard deviations from the mean. From Fullerton (*4*).

Lead

The situation in experimental lead poisoning is quite different. Experimental poisoning is used as

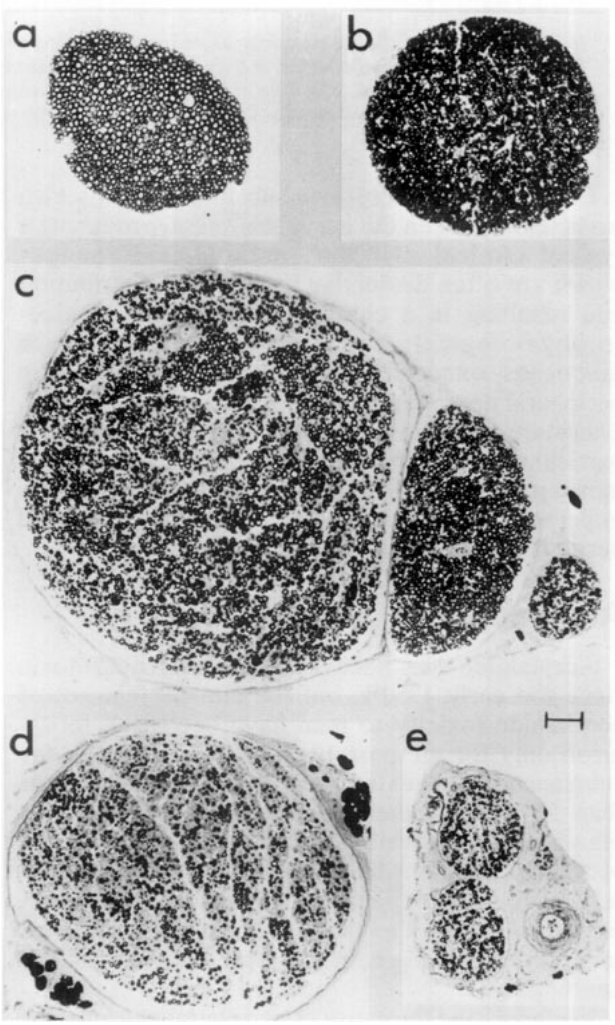

FIGURE 2. Transverse sections of nerves fixed in Flemming's solution and stained by the modified Weigert method from a rat which had received a diet containing 200 ppm acrylamide for six months: (*a*) lumbar ventral root, (*b*) lumbar dorsal root, (*c*) sciatic nerve in thigh, (*d*) posterior tibial nerve above ankle, (*e*) sural nerve in mid calf. Calibration: 100 μm. From Fullerton (*4*).

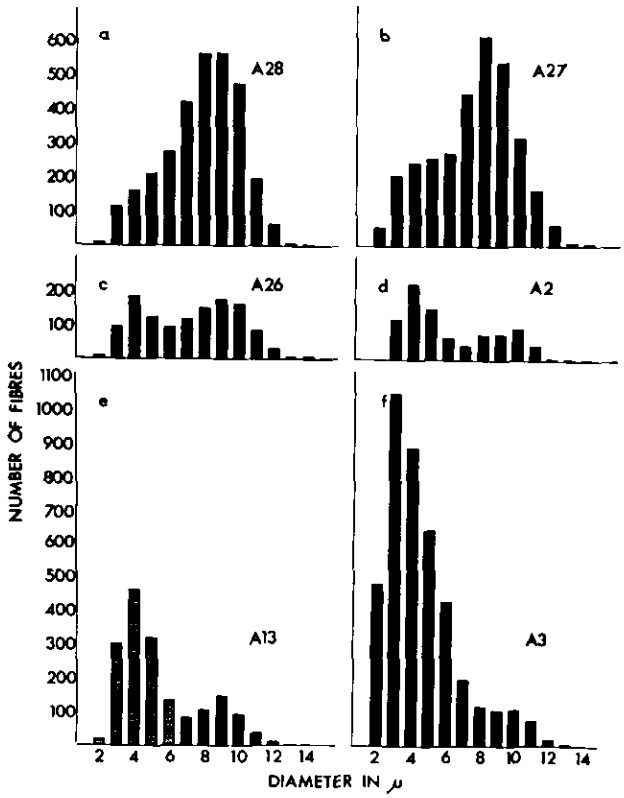

FIGURE 3. Histograms showing distribution of myelinated fiber diameters in posterior tibial nerves of rats on the following diets: (*a*), (*b*) healthy adult rats (*c*) 400 ppm acrylamide for 2 months, (*d*) 300 ppm acrylamide for 4 months, (*e*) 200 ppm acrylamide for 6 months, (*f*) 300 ppm acrylamide for 4 months followed by normal diet for 6 months. From Fullerton (*4*).

an example because frank lead neuropathy in man is rare today and severe neuropathy in man has not been studied using modern techniques. In lead-poisoned guinea pigs, severe reduction in conduction velocity may occur (*7*) (Fig. 4). It should be asked whether such velocities could be associated with normal conduction in surviving small fibers. Consideration of Figure 5 makes this unlikely. Figure 5 shows action potentials recorded from the foot muscles of a control and lead-poisoned guinea pig (GPC 27) following stimulation at the ankle (S1) and in the thigh (S2). The action potential in the poisoned animal starts after the direct muscle response is over in the control animal. The late potential in the control animal is of reflex origin. Thus, no normal fibers conduct at the velocity of fibers in the poisoned animal, indicating that pathological slowing of conduction can occur in individual fibers. Pathological examination of single fibers shows a different process from the axonal degeneration that occurs in acrylamide neuropathies. Myelin degeneration occurs without degeneration

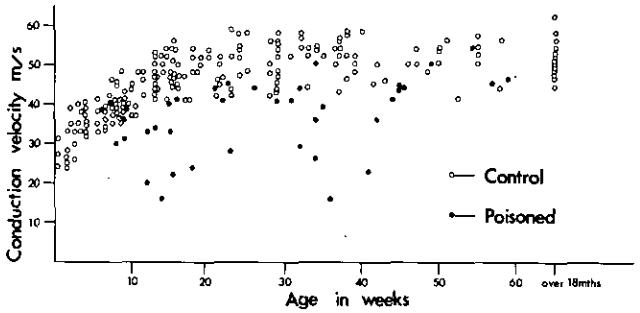

FIGURE 4. Maximal motor nerve conduction velocity in relation to age in control guinea-pigs and guinea-pigs which had received repeated doses of 50% lead acetate orally for up to 2 years. From Fullerton (*7*).

of the axons, producing segmental demyelination. Although conduction can still occur in many abnormal fibers, it does so at a reduced rate through the abnormal regions. There is no firm evidence that segmental demyelination occurs in lead poisoning in man and marked slowing of conduction, such as occurs in rats, has never been described in man. This may be because suitable subjects have not been investigated or because the pathological process is different. Species differencies in the effects of other toxic agents on the nervous system are known.

Organophosphates

Some organophosphates produce peripheral neuropathy and comparison of the clinical, elec-

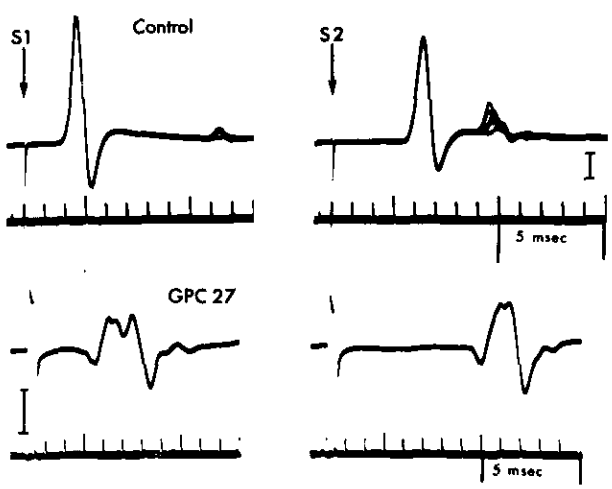

FIGURE 5. Muscle action potentials recorded from plantar muscles of guinea-pigs following supramaximal nerve stimulation at ankle (S1) and in thigh (S2). GPC27 had received repeated oral doses of 50% lead acetate. Calibration: 1 mV for control, 500 μV for GPC27. From Fullerton (*7*).

trophysiological, and pathological features with those produced by acrylamide illustrate how each toxic substance produces its own characteristic findings. Practically all organophosphorus compounds inhibit cholinesterase and acute toxic effects depend on this action. Sweating, salivation, vomiting, weakness, fasciculation, and meiosis occur. The latter two signs are of particular diagnostic importance. Most deaths that have occurred from organophosphate exposure have been the result of this effect. In treatment, atropine will control cholinergic effects, and pralidoxime has a more directly curative effect in reversing cholinesterase inhibition.

Peripheral neuropathy, which occurs after exposure to some OP compounds, is quite distinct from the acute effect, and the work of Johnson (*8*) suggests that it depends on inhibition of another specific esterase. Most of the organophosphorus compounds used as insecticides do not inhibit "neurotoxic" esterase, do not cause ataxia in hens, and are most unlikely to produce peripheral neuropathy in man. Our knowledge of the clinical features of organophosphorus neuropathy has largely resulted from cases of tri-*o*-cresyl phosphate (TOCP) poisoning (*9*).

Peripheral neuropathy can, and usually does, occur after a single exposure, but there is a characteristic latent interval of 10 days to 3 weeks before neurological symptoms develop. These then progress rapidly. The clinical features differ in many ways from those of acrylamide neuropathy. Sensory symptoms and signs are often minimal or absent even in severe cases. Weakness is even more restricted to the distal muscles than in acrylamide neuropathy. There may be no power at all in the small hand muscles when power in muscles above the wrist is normally or minimally reduced (personal observation). Widespread loss of reflexes, particularly at an early stage, does not occur, and ankle jerks alone may be absent. Pyramidal tracts are frequently affected, again unlike the effects of acrylamide. Clinical evidence of spinal cord involvement may be masked by peripheral neuropathy initially, but as the peripheral nerves recover, spasticity may become more evident. Since central nervous tissue recovers much less well than peripheral nerve, more permanent disability can follow OP neuropathy than follows exposure to toxic substances whose effects are limited to the peripheral nerves.

In contrast to acrylamide neuropathy in which a small reduction in maximal motor nerve conduction velocity is characteristic, experimental studies in baboons have shown that in TOCP neuropathy no reduction in maximal velocity occurs even when weakness is severe (*10*). This is illustrated in Figure 6, in which the conduction velocity findings in baboons with TOCP neuropathy studied by Hern (*10*) are contrasted with those of Hopkins and Gilliatt (*5*) in acrylamide neuropathy. Similarly, in acute organophosphorus neuropathy in man, normal motor nerve conduction velocity has been found in the median nerve supplying grossly weak and wasted thenar muscles (Flowler, personal communication).

Organophosphorus neuropathy is a dying-back disorder superficially similar to acrylamide neuropathy. However, when fiber diameter histograms of affected nerves were examined in baboons, it could be seen that there was an overall reduction in fiber number, but the fibers of largest diameter were not selectively affected (*11*). Thus one would expect maximum conduction velocity to be unaffected, since this value depends on conduction in the largest surviving fibers. From this it can be predicted that estimation of motor nerve conduction velocity would be an inappropriate screening test for subclinically or minimally affected subjects. Conversely, in a patient with severe weakness and wasting due to peripheral neuropathy, normal velocity findings are unusual and might at least raise the possibility of OP toxicity as a cause. Although clinically OP neuropathy predominantly affects motor nerves in man, pathological and electro-

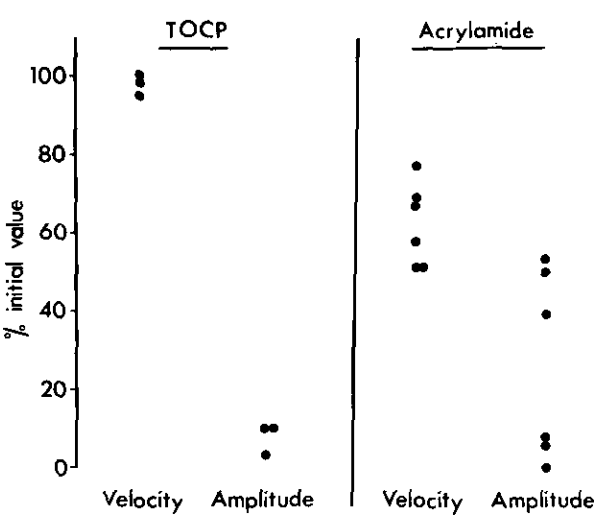

FIGURE 6. Maximal motor nerve conduction velocity in leg and amplitude of muscle response recorded from extensor digitorum brevis in baboons with TOCP and acrylamide neuropathy. Results are expressed as percentages of preintoxication values. Results for TOCP compiled from data of Hern (*10*) and for acrylamide from data of Hopkins and Gilliatt (*5*).

physiological studies indicate that sensory fibers are involved. Sensory potentials may be abnormal, when sensation is clinically normal (Fowler, personal communication). Since, for technical reasons, measurement of the amplitude of sensory nerve action potentials as a more sensitive indicator of abnormality than the amplitude of muscle action potentials, one is in the paradoxical situation of suggesting that, to screen for organophosphorus neurotoxicity, sensory and not motor fibers should be studied, even though the clinical disorder is predominantly motor. To decide on the appropriate electrophysiological investigation would not be possible without a thorough understanding of the pathological basis of the disorder and the results of experimental studies.

Hexacarbons

Another type of peripheral neuropathy of toxic origin has recently been defined with its own characteristic clinical, pathological, and electrophysiological features. This neuropathy is caused by certain hexacarbon solvents and the most important neurotoxic ones that have been identified are *n*-hexane and methyl butyl ketone. Many cases of peripheral neuropathy have been reported from Japan resulting from exposure to glues in which *n*-hexane was the solvent (*12*). Peripheral neuropathy has been a recognized hazard in the Italian shoe industry for many years, but it is only recently that *n*-hexane, again in the glue, has been identified as the causative agent (*13*). The most severely affected individuals that have been described with this disorder have been glue-sniffing addicts (*14*). Methyl butyl ketone was responsible for many cases of peripheral neuropathy in a coated fabrics plant (*15*).

During development of neuropathy following exposure to hexacarbons, sensory symptoms usually occur first, but are mild. Weakness then develops and progresses more rapidly than sensory loss. In any but the mildest cases, the condition appears to be a predominantly motor neuropathy. Even when severe, weakness remains distal. Ankle jerks are lost, but other reflexes are usually preserved. When sensory signs do occur, superficial modalities of light touch, fast pain and temperature are affected much more than position sense and deep pain.

In many clinical descriptions of this condition it has been stressed that deterioration may continue for weeks, or in one instance up to 3 months (*14*) after exposure ceased. It is important to be aware of this, because otherwise the diagnosis may be questioned during the period of deterioration following cessation of exposure. During the subsequent year, or longer, substantial recovery may be expected.

Maximal motor nerve conduction velocity has been estimated in many of the reported patients with hexacarbon neuropathy (*14, 15*). It has often been found to be substantially reduced, and values considerably lower than those found in patients with acrylamide poisoning have been reported. In the motor nerves in the lower limbs some patients have been described in whom maximal velocity was between 25 and 30 m/sec (*14, 15*). The lower limit for the control range for maximal velocity in the lower limbs is approximately 38 m/sec. There is no evidence to suggest that the slowest conducting motor fibers in healthy subjects conduct at a velocity as low as 25 m/sec. Values of this order are usually seen only when segmental demyelination is present.

Pathological changes have been described in experimental hexacarbon neuropathy in animals (*16, 17*) and following nerve biopsy in man (*14*). The changes have been similar. Giant axonal swellings filled with neurofilaments develop at intervals along the nerve fibers. Secondary myelin changes occur at the site of the swelling. These often occur in the paranodal region and are associated with myelin retraction from the node. Myelin thinning may be seen over other swellings. Thus, although this seems to be the first instance of a primary axonal neuropathy associated with substantial reduction in conduction velocity, this can probably be related to secondary structural changes in the myelin sheath, since the properties of the myelin sheath are of prime importance in determining conduction velocity.

In a condition such as this, in which marked slowing of conduction occurs in clinically severely affected patients, measurement of maximal motor nerve conduction velocity would be an appropriate electrophysiological investigation to apply to groups of exposed individuals. In subclinically affected individuals, velocity would probably fall within the control range but it is likely that differences would become apparent if a subclinically affected group was compared with a control group of subjects.

Methylmercury

One of the earliest effects of methylmercury in rats is damage to dorsal root ganglian cells, resulting in degeneration of sensory fibers in peripheral nerves (*18*). The earliest symptoms in man consist

of paraesthesiae in the fingers and toes and frequently around the mouth and on the tongue. From this one might predict that electrophysiological studies on peripheral nerve sensory fibers would give an objective measure of the severity of the disorder. The amplitude of sensory nerve action potentials can be measured accurately. With loss of fibers or slowing of conduction in individual fibers producing dispersion of the potential, amplitude will fall.

However in this instance there is a marked difference in the effect of the compound, methylmercury, on different species.

As already described, methylmercury in man initially causes paraesthesiae. These are followed by ataxia and visual disturbances (*19*). Only in very severely affected subjects are there more widespread effects on the nervous system. Abnormal movements, myoclonus, disturbances of consciousness and motor involvement occur at an advanced stage of poisoning. Ataxia is due to affection of the granular cells in the cerebellum (*20*). Gait and truncal movements are affected to a greater extent than individual limbs. The visual disturbance is due to involvement of cells in the occipital cortex, and characteristically there is concentric constriction of the visual fields with preservation of normal acuity in a small central field of vision (*19, 20*). This combination of symptoms does not occur in any other disease or condition and these clinical features are, thus, diagnostic of methylmercury poisoning.

Methylmercury poisoning in man has occurred in two distinct situations. One has occurred as a result of inorganic mercury in industrial waste being discharged into the sea or rivers. Small aquatic organisms convert the mercury to an organic form which becomes concentrated in larger fish which are then eaten by man. This occurred in Minamata and Niigata in Japan, and much of our knowledge of organic mercury poisoning has come from the study of patients affected in these episodes (*21*). Other large outbreaks have occurred as a result of people accidentally eating grain treated with methylmercury as a fungicide. This occurred in a large episode in Iraq in 1971 (*22*). Instead of sowing the grain, which would have produced a nontoxic crop, the grain was eaten. At least 6500 people were affected, with 459 recorded deaths.

Electrophysiological studies were carried out on 19 of the Iraqi subjects, all of whom had clinical evidence of moderate or severe organic mercury poisoning (*23*). All had had some sensory disturbance, most had had paraesthesiae, and 13 still had abnormal sensory signs in the limbs when the tests were carried out four months after the onset of symptoms. No abnormality of conduction velocity or of sensory nerve action potential amplitude was found in any of the patients and no differences could be detected between the results for the whole group and a group of age matched control subjects. If the sensory symptoms and signs had been due to involvement of peripheral nerve fibers, then abnormalities would have been present. With this poison one can say that electrophysiological tests have shown that peripheral nerves are not affected in man, and that sensory symptoms must be due to abnormalities of the central nervous system; the effect of the poison in man is in some ways different from that in the rat.

I am grateful to the editor of *British Journal* of *Industrial Medicine* for permission to publish Figs. 1, 2 and 3 and to the editor of *Journal of Neuropathology* and *Experimental Neurology* for Figs. 4 and 5.

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