

Parasitological and Clinical Aspects of Muscle Pathology in Trichinellosis

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Abstract

Muscle pathology in trichinellosis is presented in the light of selected parasitological and clinical topics.

The parasitological problems discussed include the start and development of muscle invasion and distribution of *T. spiralis* larvae in various groups of muscles. Among numerous clinical problems the frequency and clinical manifestation of the muscle system involved in the course of trichinellosis, biochemical disturbances and bioelectric alterations, noted at the acute and late stages of trichinellosis are discussed. Attention is drawn to the value of muscle biopsy for evaluating *T. spiralis* invasion and its sequelae.

Key words: Trichinellosis, invasion intensity, electromyography, biochemical alteration, muscle biopsy.

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The pathophysiology of the muscular phase of trichinellosis is complex and reflects the interaction of multiple factors. The development of muscle lesions is caused by contact with larvae, the penetration of these in muscle cells, growth, development and finally encapsulation of the larvae. The mature Nurse-cell-infective larva complex can remain stable, as long as the host remains alive and does not calcify it [5]. Invasion results in morphological, ultrastructural, biochemical and bioelectric changes in the muscle tissue, which form the pattern of trichinellosis pathology [10, 11, 18, 24, 3, 38, 40]. The sequence and intensity of lesions in muscles in the course of trichinellosis are determined by a) intestinal invasion, b) the immunological reaction of the host.

Changes in the intestinal invasion by direct destruction of the mature intestinal *Trichinella* forms or, indirectly, by various external means, able to alter the local or systemic defences of the host, may modify the course and sequelae of muscle invasion. In the course of trichinellosis, the principal pathomechanism role in the development of muscle lesion is played by phenomena such as antigen release by the parasite, production of antibodies, early type hypersensitivity reaction, sequelae due to release of mediators, participation of cytokines and increase in the blood eosinophil level. These phenomena represent local and systemic host responses both at early and later stages of

invasion. They are responsible for the induction of multi-organ pathology.

In the review, the most important parasitological and clinical aspects of muscle pathology encountered in the course of trichinellosis are presented. It is based on our own clinical observations and experimental studies and on comparison of these with results of other authors.

Parasitological aspects of muscles pathology

When discussing the parasitological aspects of muscle pathology in the trichinellosis the following problems have to be considered: 1. the beginning and development of muscle invasion, 2. distribution of *T. spiralis* larvae in various groups of muscles.

In human suffering from trichinellosis, the beginning of muscle invasion is difficult to determine or cannot be determined at all.

In small experimental rodents (mouse, rat) muscle invasion by *Trichinella spiralis* larvae starts as early as the 5th-6th day after infection, i.e. when *Trichinella* reaches sexual maturity in the small intestine and the second generation (newborn) larvae begin to migrate [16]. Parasitological studies in large experimental animals, i.e. on *Macaca mulatta* and *Macaca irus* [23, 26] are important for examining the problem since multiple biopsies to define the kinetics of *Trichinella* invasion in the muscle can be per-

formed. In *Macaca mulatta* infected with 2500 larvae, the beginning of the invasion was noted at the 12th day after infection; on days 42 to 68 of disease the number of larvae had rapidly increase and afterwards the invasion decreased in the intensity till day 190 of observation. In *Macaca irus* infected with 150 larvae/kg body weight, i.e. with a higher invasive dose, muscle invasion involved a rapid increase in the number of larvae between the 23rd and 39th day after infection, followed by a slow decrease in the intensity of invasion up to 101st day after infection. Correlation between developing muscle invasion on the one hand and increasing clinical manifestations in the animals: increasing level of eosinophils in blood and increasing levels of antibodies in serum, on the other merit particular attention since they indicate the involvement of an immunologic pathomechanism in trichinellosis [27].

In animals and in humans the invasive dose, species or strain of *Trichinella* play an essential role in the intensity and dynamics of muscle invasion.

In view of present knowledge species of *Trichinella spiralis* and the different pathogenic potential in various geographic regions evaluation of the integrity of about the invasion in muscle tissue requires another approach. This is associated with history of observation, made in Africa, in Kenya and Senegal [9, 15] and later in various regions of Russia [32] and in New Zealand [41, 35]. Descriptions of epidemic foci of trichinellosis by the above authors indicate various sources of infection in the wild environment (African river pig, brown bear, polar bear, wild boar) and demonstrate that the clinical pattern and course of the disease are not exclusively shaped by the intensity of invasion in patients' muscles but are also influenced by the species or strain of *Trichinella* involved. The set of performed studies at the Istituto Superiore di Sanità in Rome [36, 37, 1] has definitely proven that 5 well-defined separate species can be distinguished within the genus *Trichinella*.

In humans distributions and intensity of invasion in individual groups of skeletal muscles have been recognized in a few cases from autopsy material studies [20, 14, 33, 12]. As demonstrated by studies by Gerwel et al. [12], parasitological examination (by digestion in artificial gastric juice) of various muscle group sections of patients who died from very severe course of trichinellosis yielded the following number of *Trichinella* larvae per gram muscle tissue: m. pectoralis 355 larvae, mm. intercostales 353 larvae, m. quadriceps femoris 338 larvae, m. deltoideus 292 larvae, a lower numbers 258, in m. gastrocnemius and the lowest number, 250 larvae in the diaphragm muscle; 277 larvae per g were found in orbital muscles.

Studies of *Trichinella sp.* larvae distribution in various muscle groups of large experimental animals, i.e. *Macaca irus* indicated a different invasive character from that noted at autoptic examination of humans. Examination [26] showed that the most intense invasion was in masseter muscles (1096 larvae/g) followed by the tongue muscle (792 larvae/g). It was two-fold less intense in arm muscles

(319 larvae/g) lower in mm. quadriceps femoris (296/g), intercostal muscles (183 larvae/g) and very low in diaphragm muscle (51 larvae/g).

According to Gould [14] the concept of larvae preference for some muscle groups, advanced by numerous investigators, beginning with the second half of the last century has till now not been corroborated or been supported by pathophysiological or biochemical evidence corresponding to parasitological findings. Recently, however, some authors [19] have suggested, on grounds of experimental studies, that the different intensity of larval invasion in selected groups of muscles in various hosts was related to the intensity of exercise involving the specific group of muscles.

Clinical aspects of muscle pathology in trichinellosis

The clinical aspects of muscle pathology in trichinellosis involve the following problems: 1. the clinical manifestation of muscle system involvement in the trichinellosis process, 2. the clinical course of trichinellosis and relation to intensity of muscle invasion, 3. biochemical disturbances as an exponent of muscle injury, 4. bioelectric disturbances in the muscular system in early and late period of trichinellosis, 5. diagnostic value of muscle biopsy.

Since striated skeletal muscles represent the main site pathology in trichinellosis at the acute and at the later stages of the disease the muscle symptoms dominate both. However, muscle system disturbances cannot be considered in isolation to other symptoms, particularly at the acute stage of the disease.

Frequency and intensity of clinical symptoms in trichinellosis including muscle pains, are related to multiple variables in the invasive dose, the *Trichinella* species, intensity of muscle invasion, timing of use of antihelmintics, and glucocorticoids and immunomodulators [29]. At the late stage or at certain times after experiencing trichinellosis muscle pains depend upon the gradual eradication of *Trichinella* larvae by delayed type response in muscle tissue.

Frequency of muscle pains at the acute stage of trichinellosis varies depending on the individual epidemic foci of the disease in the world. Several authors suggest that muscle pains appear in a relatively high proportion of patients, 78% to 97% [33, 39, 31, 21, 25, 30]. In these last years, Bourée et al. [4] have noted muscle pains during epidemics in France in only 50% cases while neurologic disturbances were present in as many as 60% patients. Authors from Italy [2, 35] have found that muscle pains were most frequent symptom in the group of monitored patients but, were only noted in 67% and 68.9%. According to studies [41] on 4 foci in the Canadian Arctic, muscle pains were observed in 25% to 60% patients and muscle weakness in 25% to 50% patients. In one trichinellosis foci the authors did not detect any periorbital oedema and the dominating symptom was diarrhoea which was present in all cases. At the acute stage of trichinellosis muscle pains gradually become increasingly severe (for a few days) and

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are usually accompanied by fever. The symptoms include periorbital oedema, weakness, headaches, conjunctivitis or alimentary tract disturbances which may frequently precede myalgia. In some patients with severe invasion, muscle pains are substituted by adynamia as the most important symptom [33]. Very early, eye ball pains in occipital muscles and in the muscles of the extremities appear. In severe cases, the pain also involves muscles of the trunk. Muscle pains, particularly in the extremities appear during movement while spontaneous pains are very rare. Some clinicians [20, 33], regard muscle pains at rest as a sign of a severe attack of the disease. Others find that they accompany complications such as thrombophlebitis. Movement sparing, due to pains associated with movement, leads to contractures in the knee and elbow joints in particular, to spurious nuchal rigidity, difficulty in opening the mouth and, occasionally, to trismus. Upon recovery, contractures subside very slowly and their disappearance is promoted by massage and physiotherapy.

Observation by many authors [33, 7, 25, 28, 30] have shown no relation between the increase in eosinophilia on the one hand and the intensity of muscle invasion on the other. This is particularly noted in patients with very severe disease and a very low number of eosinophils in the blood and very intense muscle invasion, usually accompanied by immunosuppression [28].

Studies on the relation of the clinical course of trichinellosis and the intensity of muscle invasion

The relation is evaluated after the acute symptoms of the disease subside or retrospectively, a long time after suffering from the disease [13, 25, 30]. Intensity of the invasion is defined according to the classification recommended by Hall and Collins in 1937 and quoted by Gould [14]. Depending upon the clinical pattern and course of the disease, trichinellosis is defined as a very severe, severe, moderately severe, mild, abortive or symptomless. The classification [22] reflects the presence of typical trichinellosis signs and symptoms and their intensity and duration in time. In abortive trichinellosis the individual signs and symptoms are only noted, when accompanied by eosinophilia. The asymptomatic course is diagnosed on the

grounds of epidemiologic anamnesis, presence of eosinophilia and a positive serological test with *Trichinella* antigen.

Results of parasitologic studies on muscle biopsies in 43 patients with acute clinical trichinellosis are shown in Table I.

Data in the table indicate that higher numbers of *Trichinella* larvae in muscle tissue are frequently noted in patients with a severe case of trichinellosis, less frequently in moderately severe disease. In no patient of the latter group were there more than 500 larvae detected in 1 gram muscle tissue while in patients with a severe case more than 500 larvae per gram was found in 3 cases. In no patient with mild disease were more than 100 larvae detected per 1 gram of muscle tissue.

The severity of the clinical course of trichinellosis depending on the intensity of invasion in muscles and the magnitude of the invasive dose can be best illustrated by the case [28] of W.B. 42 years old, a male patient. The patient died from severe trichinellosis after consuming a large amount of wild boar meat, heavily infected with *Trichinella spiralis* larvae. The course of the diseases involved swelling of the entire body, central nervous system signs and symptoms, renal insufficiency accompanied by low eosinophilia (100 to 300 cell per mm³) and negative serological test with *Trichinella* antigen. Treatment of trichinellosis was hampered by patient unconsciousness and renal insufficiency. Autopsy revealed a very intense invasion of the muscles (2806 larvae of *Trichinella* per g diaphragm muscle, 4900 larvae per g tongue muscle, 4050 larvae per g thigh muscles). The authors stressed that the severe course of the disease was due to a high invasive dose of *Trichinella*, massive invasion of the patient's muscles and the highly invasive strain of *Trichinella* originating from a forest environment.

Biochemical disturbances as an index of muscle injury in trichinellosis

Biochemical disturbances in trichinellosis are mainly manifested by muscle enzyme release in the serum. In both experimental studies [17, 34] and human trichinellosis [3, 30], an increase in serum activities was noted in the case

Table I. Invasion intensity and acute clinical course of trichinellosis in 43 patients.

Intensity of invasion (number of larvae per g muscle)	clinical course, number and percent of patients in parenthesis		
	severe	moderate	mild
	16	17	10
0	1 (6.2)	3 (17.6)	0 (0.0)
1 - 10	1 (6.2)	3 (17.6)	5 (50.0)
11 - 100	3 (18.8)	8 (47.0)	5 (50.0)
101 - 500	8 (50.0)	3 (17.6)	0 (0.0)
501 - 1000	1 (6.2)	0 (0.0)	0 (0.0)
> 1000	2 (12.5)	0 (0.0)	0 (0.0)

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of creatinine phosphokinase (CPK), lactate dehydrogenase (LDH), 1,6-diphosphofructoaldolase (1,6 ALD), aspartate aminotransferase (AspAT). Increase in serum CPK activity is the most characteristic feature of human trichinellosis. Between the 2nd and 5th weeks after the onset of the disease 76% to 90% patients had increased activity levels. The origin of the increased serum CPK activity in general and in the activities of LDH₄, LDH₅ isoenzymes were noted in 50% patients at the early stage of invasion, i.e. the 1st and 6th weeks of the disease, which was earlier than the peak values observed in immunological test [3]. The authors have suggested that for this reason the biochemical tests should have diagnostic value in the first weeks of invasion. Nevertheless, in two epidemics [3] no correlation was observed between the clinical course of trichinellosis and total serum activity of LDH. Results of estimating CPK and LDH activities in another trichinellosis focus [30] caused by consuming infected wild boar meat (27 cases) are listed in Table II.

The data presented are those showing that the increase in CPK activity (as compared to normal value of 80 - 120 IU) has a variable correlation with the severity of the clinical course in patients with moderate or mild trichinellosis. Testing of serum LDH activity in 9 patients revealed an elevated activity, compared to the normal value (250 IU), which was more pronounced in 4 patients with moderate disease than in 5 patients with mild disease.

Bioelectric disturbances in the muscular system due to trichinellosis

Bioelectric disturbances in the muscular system in the course of trichinellosis are expressed by the changes in the electromyographic (EMG) record. The alterations in EMG records have been observed both in experimental animals infected with *T. spiralis* [42, 43, 23] and in trichinellosis patients at various stages of the disease [8, 18, 24, 21].

Electromyographic changes noted at the acute stage of trichinellosis and in the late phase of invasion allows one to evaluate muscular system function. Evaluation of bioelectric disturbances at the acute stage of trichinellosis can be exemplified by studies performed on 24 patients hospitalized in the Clinic of Parasitic and Tropical Diseases, University of Medical Sciences in Poznan. The studies were performed between the 18th and 47th days of invasion and between the 5th and 35th days of clinical symptoms.

The following muscles were chosen for examination in each case: m. interosseus I, m. tibialis anterior and triceps surae. The type of trace during rest and during maximum effort against resistance was evaluated in each record. In evaluation of motor unit potential the following parameters were considered: shape, amplitude duration of potential and number of phases during free contraction of muscles were investigated.

Table III shows that in 15 patients the EMG record pointed to primary muscular damage, including 11 severe cases of disease and the course of moderate severity and

Table II. Results of creatinine phosphokinase (CPK) and lactate dehydrogenase (LDH) activity in serum of patients in the acute phase of trichinellosis. From Kociecka et al. 1992.

clinical course and number of patients		severe n = 1	moderate n = 11 n = 14	mild n = 1	abortive
CPK U/l	n = 27	n = 1 17090	I group n = 5 336.2 ± 195.3 II group n = 3 794.7 ± 111.3 III group n = 3 2812 ± 1948	I group n = 12 223.9 ± 84.3 II group n = 2 1511 3275	n = 1 303
LDH U/l	n = 9	ND	I group n = 4 583.5 ± 222.9	I group n = 5 367.4 ± 137.9	ND

ND - not done

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significant intensity of invasion. In group I there were 196 to 1130 *Trichinella* larvae per g of muscle tissue. In group II patients with a less intense invasion there were 30 to 76 larvae per g. A slight pathological record was noted in 4 cases including 2 patients with mild trichinellosis. In 5 patients the EMG record was normal.

The group of records of primary muscle damage included traces where the number of polyphasic potentials was over 20% and the shortest duration of motor unit potentials was over 1 millisecc., with poor effort tracings and low amplitude potentials. In the slightly pathologic record, the traces were less accentuated.

Table III. Electromyographic studies in the acute phase of trichinellosis (24 patients). From Kaczmarek et al. 1975.

Groups	No. of patients	larvae/ 1 g muscle	Clinical course			EMG tracing			Mean duration of motor units potentials
			severe	moderate	mild	i.p.m.d.	s.pathologic	normal	
I	7	196 - 1130	4	3	-	6	1	-	-0.6 to -3.6
II	4	30 - 76	1	3	-	3	1	-	-7.7 to -2.3
III	4	1 - 9	-	-	4	1	-	3	0 to -1.5
IV	9	-	-	4	5	5	2	2	-0.9 to -3.7

s.pathologic - slightly pathologic

i.m.d.p. - indicating primary muscle damage

Table IV. EMG tracing related to the clinical course in the acute phase of invasion 60 person with 3 - 8 years history of trichinellosis. From Kociecka et al. 1975.

EMG tracing	Clinical course			Number of patients
	severe	moderate	mild	
indicating primary muscle damage	1	6 (60%)	3 (30%)	10
slightly pathologic	-	7 (46%)	8 (53%)	15
normal	-	7 (20%)	28 (80%)	35
number of patients	1	20	39	60

Table V. EMG tracing related to the intensity of invasion. 51 person, 3 - 8 years history of trichinellosis. From Kociecka et al., 1975.

	EMG tracing			Number of patients
	normal	s.pathologic	i.p.m.d	
0 - 10 larvae/g muscle	20	7	4	30
12 - 96 larvae/g muscle	10	6	5	21

s. pathologic - slightly pathologic

i.p.m.d. - indicating primary muscle damage

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Abnormalities of EMG tracings in patients during the acute phase of the disease are myogenous in character and not pathognomic of trichinellosis. They disappear within a few months parallel with improvement in the clinical status and with regression of histologically detectable changes in muscle tissue.

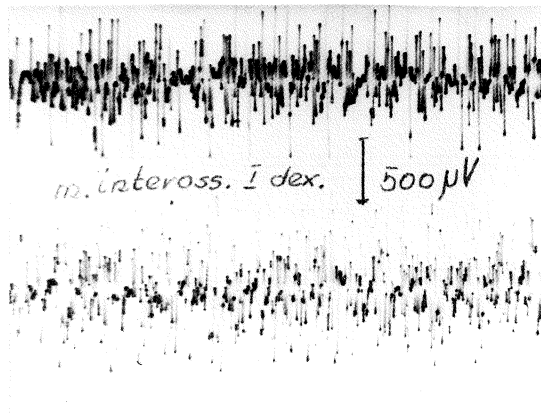


Figure 1. EMG tracings in patients with acute stage of trichinellosis.

Electromyographic studies after past experience of trichinellosis are indications which determine the extent of bioelectric disturbances representing invasion sequele. In our Clinic of Parasitic and Tropical Diseases in Poznan electromyography performed in a group of 60 persons with 3 to 8 years history of trichinellosis [24] a normal EMG tracing was obtained only in 35 cases (58.3%). Tracing

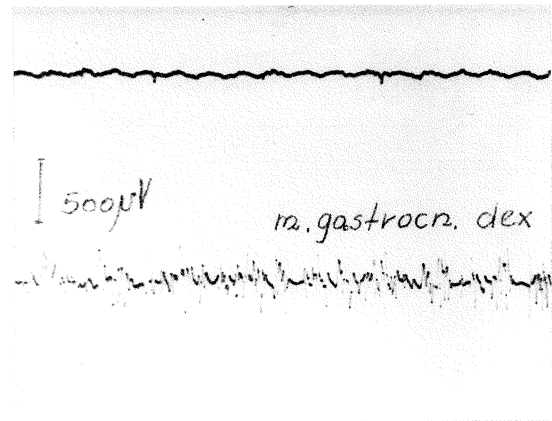


Figure 2. EMG tracings in patients after past experience of trichinellosis.

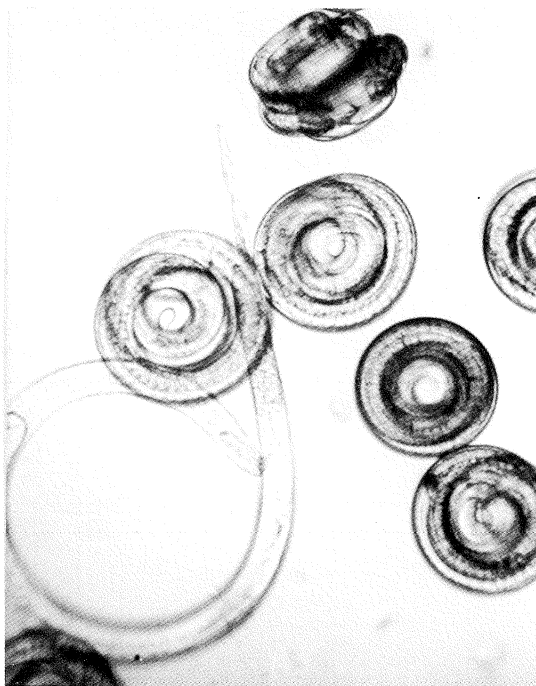


Figure 3. *Trichinella spiralis* larvae obtained from muscle sample by digestion method.



Figure 4. Trichinoscopy of muscle sample taken from patient with trichinellosis. Seen encapsulated larva of *Trichinella* sp. 80 x magnification.

indicated primary muscle damage in 10 cases (16.6%) and slightly abnormal damage in 15 cases (25%) was also found (Table IV).

In a group of 51 examined patients (Table V) no marked relation was found between the character of the electromyographic tracing and the intensity of invasion (0-96 larvae per 1 g muscle) nor histologically detectable lesions in the muscle. Persons with basophilic transformation in muscle fibers, cellular infiltrates and enlarged nuclei of muscle cells occasionally had a normal EMG tracing. No distinct correlation could be noted between the character of the EMG tracing some years after suffering from the disease and the clinical course at the acute stage of the disease.

Fig 1 and 2 shows the EMG tracings in patients with acute stages of trichinellosis and after past experience of trichinellosis.

Diagnostic value of muscle biopsy in trichinellosis

The value of studying muscle biopsies obtained from trichinellosis patients has been stressed for many years. Muscle biopsy permits: a) evaluation of invasion intensity and spread of lesions in muscles, b) facilitates prognosis as a sequel of trichinellosis.

Muscle biopsy studies are also important for retrospective evaluation of patients who suffered from the disease in the past [13]. They are also indispensable in diagnostically doubtful cases as well as in sporadic cases of the disease. Most frequently muscle biopsy is performed on the first case in a given focus of trichinellosis (index-case).

Muscle biopsy samples are examined by parasitologic and histologic techniques. Parasitologic examination allows definition the number and stage of development of *Trichinella* larvae (uncoiled, coiled, encapsulated) Fig. 3. and 4.

Histologic studies on muscle biopsies not only aim at detecting *Trichinella* larvae and determining the extent of their settling in muscles but also at detection of indirect indices of the invasion i.e. presence of basophilic transformation of muscle cells, cell infiltrates and estimation of intensity of the latter around the involved muscle fibers [10, 11, 40]. The lesions confirm *Trichinella* invasion also in cases of low intensity, in which direct demonstration of larvae may present difficulties.

Biopsies performed at the late stage of trichinellosis or at a much later time have clinical significance. The relevant literature is scarce. In our Clinical Center the group of authors [13], on the grounds of the studies have concluded that muscle biopsy is an important qualitative and quantitative evaluation method in retrospective analysis of trichinellosis. Using trichinoscopy and digestion techniques larvae can be detected in every case when the invasion intensity is over 10 larvae per 1 gram and in the majority of cases even with a less intense invasion. In the studied material calcification of capsules surrounding *T. spiralis* larvae was observed beginning about six years after invasion and involved only some of the capsules. Histopathological examination showed lesions in the muscles which

permits evaluation of the host reaction to *T. spiralis* larvae. The examination also helps to establish diagnosis in cases of muscle disease not linked to trichinellosis but displaying some common clinical features. Moreover, histologic examination performed as late as 8 years after infection occasionally revealed cellular infiltrates around the larvae and basophilic transformation of muscle tissue [10]. The findings are of fundamental importance both for the diagnostic and evaluation of individual cases.

At present, the possibility of determining the species of *Trichinella* in muscle biopsy material using contemporary taxonomic techniques, including molecular test [1, 6, 36, 37] represents a significant progress in diagnosing trichinellosis.

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