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WORKSHOP REPORT*

NON-DYSTROPHIC MYOTONIAS AND PERIODIC PARALYSES

A European Neuromuscular Center Workshop held 4–6 October 1992, Ulm, Germany

INTRODUCTION

Our understanding of the pathology of the non-dystrophic myotonias and the periodic paralyses has profited immensely from the use of modern electrophysiology (three microelectrode voltage clamp, patch-clamp techniques) and molecular biology (candidate gene approaches in contrast to reverse genetics in other neuromuscular diseases). In the past few years it has become clear that—apart from the not yet understood pathomechanism of myotonia in myotonic dystrophy—there are two clearly distinct pathomechanisms discernible for the non-dystrophic myotonic disorders: with a mutation in either the gene encoding the skeletal muscle Cl^- channel (CHLCN1) or the gene encoding the α-subunit of the adult skeletal muscle Na^+ 'channel (SCN4A). Several mutations exist in each gene.

As a consequence of this new knowledge the terms of skeletal muscle Cl^- channel diseases (chloride channelopathies) and skeletal muscle Na^+ channel diseases (sodium channelopathies) were coined [1, 2] and the workshop (organized by Frank Lehmann-Horn and Reinhardt Rüdel) was structured accordingly. The participants of the workshop approved of this classification and suggested that the Editor of *Neuromuscular Disorders* be asked to adopt it for his Table of Gene Locations.

Muscle sodium channel diseases:

Hyperkalemic periodic paralysis (MIM 170500);
Normokalemic periodic paralysis (MIM 170600);
Paramyotonia congenita (MIM 168300);
Myotonia fluctuans.

Muscle chloride channel diseases:

Myotonia congenita (Thomsen) (MIM 160800);
Recessive generalized myotonia (Becker) (MIM 255700).

The pathomechanism of the very rare Schwartz–Jampel syndrome (SJS) has not yet been sufficiently clarified. Classification is therefore not possible and the syndrome was not discussed much during the workshop. There are, however, plans for a future ENMC workshop on Schwartz–Jampel Syndrome and the authors of this report call for signs of interest!

In hypokalemic periodic paralysis, the most common form of the periodic paralyses (which is never associated with myotonia), the mutated gene, has not yet been localized. Electrophysiological evidence suggests that a K^+ channel might be altered in this disease, and there is a recent report where the authors excluded linkage to SCN4A [3]. For these reasons the disease is different from the mainstream of the workshop and was not a matter of discussion.

The participants agreed unanimously that it was desirable to use clear abbreviations for the different forms of periodic paralysis and decided on HyperPP, NormoPP and HypoPP for hyperkalemic, normokalemic and hypokalemic periodic paralysis, respectively. Paramyotonia congenita is often abbreviated to PC.

Professor Emery suggested that the participants form an international consortium with Professor Rüdel as chairman. It was agreed that it was desirable to convene again after about 2 yr.

MUSCLE SODIUM CHANNEL DISEASES

For many years clinicians have argued as to whether the two major members of this group, paramyotonia congenita and hyperkalemic periodic paralysis, are separate diseases or

*The authors dedicate this report to Professor Peter Emil Becker who will celebrate his 85th birthday in the autumn of 1993.

comprise a nosological entity. This problem can be regarded as solved, as it is now clear that various mutations of the SCN4A gene exist and that each mutation causes a typical clinical picture. The term "adynamia–paramyotonia complex", coined by King Engel, making use of the original name given by Gamstorp to HyperPP, thus seems to be a fortunate clinical designation for the muscle Na^+ channel diseases. Two sessions and a general discussion were devoted to this subject. The first session with Walter Stühmer in the chair, dealt with genomic organization, gene expression and protein structure of the human skeletal muscle Na^+ channel. Two groups (Andrea McClatchey, Al George) reported on their completion of the identification of the exon/intron structure of the human SCN4A gene encoding the α-subunit of the adult skeletal muscle Na^+ channel. The gene contains 24 exons distributed over about 30 kb of chromosome 17q23. As with many genes, the genomic structure becomes more condensed towards the 3′ end, with the last 30% of the coding sequence appearing in a single exon [4, 5].

Data on other Na^+ channel genes (different mammalian species and different human tissues) were presented for comparison by Al George and John Caldwell. About ten different, but closely related, Na^+ channel α-subunit genes are known, most of which are expressed in brain, peripheral nerves and muscle [4, 6, 7]. While hSkM1, the TTX-sensitive SCN4A product, is only expressed in adult human skeletal muscle, another two distantly related α-subunits, both with low TTX sensitivity, were found in fetal and denervated skeletal muscle and in adult cardiac muscle (hH1), as well as in myometrium and fetal skeletal muscle (hH2) [8]. No diseases have so far been linked to any Na^+ channel gene other than to SCN4A, but it was suggested that there might be such diseases.

The expression of the human Na^+ channel α-subunit or its equivalent in the rat, rSkM1, in Xenopus oocytes has been successful but the expression system was not satisfactory because of an abnormally slow inactivation of the normal channel (Al George). When hSkM1 was transfected into mammalian cells, e.g. human embryonic kidney cells (HEK), inactivation was about normal. Introduction of the equivalent of the C2111T and A4774G mutations into the rat construct and its expression in HEK cells resulted in an altered mode of gating with repetitive re-openings producing a persistent Na^+ current (Stephen Cannon [9], Louis Ptáček). Walter Stühmer pointed out that the S5/S6 segment region in each channel repeat may be involved in channel inactivation. He then took one of the shaker related K^+ channels as an example to discuss how much the channel open probability can be reduced by low extracellular K^+.

The second session, chaired by Thomas Deufel, dealt with the genotypes, electrophysiology, and phenotypes of muscle Na^+ channel diseases. Several groups presented new SCN4A mutations and described their relation to various clinical pictures. Four of the mutations were related to paramyotonia congenita or atypical myotonia (Frank Lehmann-Horn, Andrea McClatchey, Louis Ptáček), another was associated with paramyotonia congenita with cold- and potassium-induced stiffness (Roland Heine), two further ones were related to hyperkalemic periodic paralysis (Frank Lehmann-Horn) and the last was linked to a family with the symptoms of hyperkalemic periodic paralysis and cold-induced weakness. This family shows incomplete penetrance (Andrea McClatchey). These new mutations bring the number of known human SCN4A mutations to 13, all causing either cold-induced stiffness or potassium-induced paralysis or atypical myotonias. All mutations result in the change of a single amino acid in the Na^+ channel protein (Table 1) altering its function, and are transmitted as dominant traits. Many of the amino acid changes are located either within the intracellular loop connecting repeats III and IV, the supposed inactivation gate of the channel, or at the intracellular side of the S5/S6 interlinker, a region hypothesized to act as an acceptor of the inactivation gate (Fig. 1).

Patch clamping of native muscle preparations from patients with hyperkalemic periodic paralysis or paramyotonia congenita, revealed an increase in the time constant of fast Na^+ channel inactivation (Frank Lehmann-Horn). The number of late Na^+ channel openings was also much higher than the controls [13, 20]. Resealed fiber segments showed long-lasting trains of action potentials which came to an end at a reduced resting potential. In muscles from PC patients the reduced resting potential was at about -60 mV, with the fibers still excitable, or at -40 mV, at which point the fibers were inexcitable. In muscles from HyperPP patients, the runs usually ended around -40 mV. Computer simulation of action potentials

Table 1. Genotype/phenotype correlation in patients with a muscle Na^+ channel disease (lines 1–13), and silent amino acid substitutions found in healthy controls (lines 14–19). Note that a Phe 1421 Leu substitution was found for Quarter horses [10]

Genotype	Channel part	Predicted substitution	Exon	Phenotype	Reference
C2188T*	$IIS5_i$	Thr704Met	13	HyperPP	11
C2411T	$IIS6_i$	Ser804Phe	14	PC	5
G3466A	$(IIIS4/5)_i$	Ala1156Thr	19	HyperPP	5
G3917T	$(III/IV)_i$	Gly1306Val	22	PC	12
G3917A	$(III/IV)_i$	Gly1306Glu	22	Myotonia permanens	13
G3917C	$(III/IV)_i$	Gly1306Ala	22	Myotonia fluctuans	13
C3938T	$(III/IV)_i$	Thr1313Met	22	PC	12
A4078G	IVS1	Met1360Val	23	HyperPP	†
T4298G	IVS3	Leu1433Arg	24	PC	14
C4342T	IVS4	Arg1448Cys	24	PC	15
C4343A	IVS4	Arg1448His	24	PC	15
G4765A	$IVS6_i$	Val1589Met	24	PC	16
A4774G	$IVS6_i$	Met1592Val	24	HyperPP	17
607A/G	IS3	203Met/Val	4	Normal	4
2578G/A	$(II/III)_i$	860Glu/Lys	14	Normal	4
2580G/T	$(II/III)_i$	860Glu/Asp	14	Normal	18
2794G/C	$(II/III)_i$	932Asp/His	14	Normal	14
4126G/A	$IVS1/S2_e$	1376Asp/Asn	23	Normal	16
4817A/G	$IVS6_i$	1606Glu/Gly	24	Normal	19

I–IV = number of repeats in the Na^+ channel protein.
S1–S6 = number of the transmembrane segment within each repeat.
i = intracellular loop or "inactivation-gate acceptor" at the intracellular pore lining.
e = extracellular loop.
* = corresponding to C2111T in [11]; 2188 is correct in relation to other numbers.
† = reported by Lehmann-Horn for a HyperPP family with cold-induced weakness without stiffness.

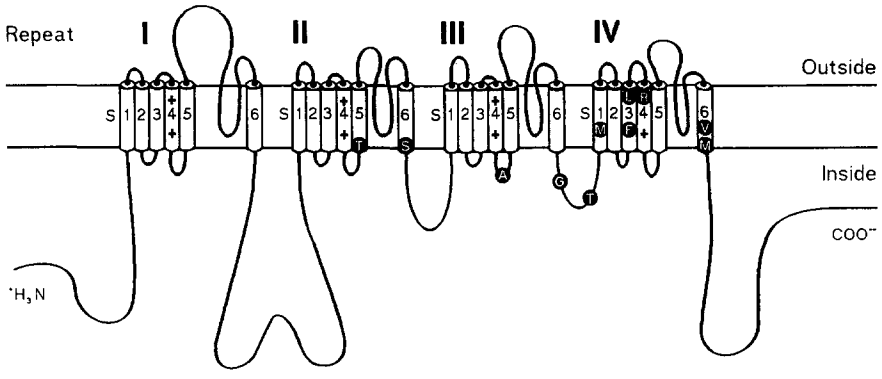

Fig. 1. Diagram of the sodium channel protein showing the locations of the amino acids that are replaced in patients with diseases of the adynamia–paramyotonia complex.

demonstrated that the failure of inactivation of a small proportion (less than 2%) of Na^+ channels can cause repetitive activity ending in a variable degree of stable depolarization (Stephen Cannon). Accumulation of K^+ within the T tubules was a necessary feature of the computer model for repetitive activity to occur [21, 22].

A novel dominant mutation in the homologous horse gene was shown to be the molecular basis of periodic paralysis in Quarter horses [10]. This horse disease was inadvertently disseminated by breeders, as the mutation causes the desirable muscle hypertrophy. Up to 5% of this popular breed (3,000,000 currently registered in the U.S.A.) are affected (Eric Hoffman).

The discussion focused on additional linkage studies (Bertrand Fontaine) and on genotype/phenotype correlations (Louis Ptáček, Eric Hoffman, Frank Lehmann-Horn). Each mutation causes either HyperPP or PC. Thr704Met seems to be the most frequent amino acid substitution (6 out of 17 German HyperPP families). This mutation results in a HyperPP subtype characterized by drug resistance and permanent weakness of mainly late onset. The same mutation was found in a family diagnosed as having normokalemic periodic paralysis on the basis of the original clinical criteria [23]. Furthermore, a clinically convincing potassium-induced paralysis family from Yugoslavia was presented which did not show linkage to the SCN4A gene: this was the first example of genetic heterogeneity within hyperkalemic periodic paralysis (Eric Hoffman). In addition, dinucleotide

haplotype/mutation correlations (Andrea McClatchey, Eric Hoffman) and normal polymorphisms were discussed (see Table 1).

MUSCLE CHLORIDE CHANNEL DISEASES

The low chloride conductance theory of myotonia was first proposed in the 1960s by Shirley Bryant, on the basis of electrophysiological studies on goats with autosomal dominant myotonia congenita. It explains the hyperexcitability as a direct consequence of a reduced Cl^- conductance in the T system of myotonic fibers. Later voltage clamp studies showed that this theory applies to myotonia in all Becker myotonia patients. Surprisingly, in several of the patients characterized by dominant inheritance, the Cl^- component conductance was normal. In addition, abnormalities in the properties of the Na^+ channels were noted in muscles from both Thomsen and Becker patients. It was not until 1992 that linkage to the gene coding for the muscle Cl^- channel was proven for both Becker and Thomsen myotonia [24].

The first of two sessions on the "muscle chloride channel diseases", chaired by Manuela Koch, was devoted to the molecular biology of the muscle Cl^- channel, the CHLCN1 gene product. Muscle Cl^- channels are members of a family of voltage-gated Cl^- channels that are completely different from the Cl^- channels which are altered in cystic fibrosis [25]. They provide 4/5 of the Cl^- conductance of the muscle fiber membrane. Klaus Steinmeyer reported that the CHLCN1 protein consists of 991 amino acids and that its molecular weight is 110 kDa. The mRNA contains 4–5 kb. In the rat, its expression greatly increases within the first 30 days of postnatal development.

The report was preceded by a short review on the myotonic ADR mouse by Harald Jockusch. Similar to the role the myotonic goat played for the elucidation of the electrophysiological basis of Cl^- channel myotonia, the mutation *adr* and some other allelic mutations played an important role in the discovery of human recessive myotonia as a Cl^- channel disease. The adr locus, and later the Chlcn1 gene, were shown to be linked to the T cell receptor β (Tcrb) and the Hox loci on chromosome 6 [26, 27]. A transposon of the ETn family was found to be inserted into the adr allele that destroys its coding potential for several membrane-spanning domains, in accordance with the sizable lack of Cl^- conductance [27]. In two other mouse mutants the Chlcn1 genes are inactivated by point mutations (Gronemeier M, Prosser J, Steinmeyer K, Jentsch Th, Jockusch H. Nonsense and missense mutations in the muscular Cl^- channel gene Chlcn1 of myotonic mice. In preparation).

The molecular genetics of human congenital myotonia was presented by Manuela Koch. In 1992, a partial cDNA of the human CLC-1 channel was cloned and physically localized on chromosome 7q32-ter. Linkage was shown to the TCRB locus supporting the mouse–human homology map for this chromosomal region [24]. Tight linkage between Thomsen myotonia and the TCRB locus was shown by a Canadian group [28] and, at the same time, linkage to this locus was found for German Thomsen and Becker families [24]. An unusual restriction site in the CHLCN1 genes of two Becker myotonia families revealed a T-to-G transversion predicting a phe-to-cys substitution in the 8th of the putative 12 transmembrane domains. The molecular genetic data suggest that different mutations in the CHLCN1 gene may cause dominant or recessive myotonia.

The second session on muscle Cl^- channel diseases was chaired by Erich Kuhn, with electrophysiology as the main subject. In spite of many attempts in several laboratories around the world, the Cl^- single-channel activity has not been consistently recorded from native muscle preparations, although it can be easily measured in myoballs cultured from normal individuals and myotonia patients. Christoph Fahlke reported that the single-channel conductance of the most frequent ("intermediate") Cl^- channel in myoballs was reduced to 50% for patients with Becker myotonia [29]. While this myoball channel has not yet been conclusively shown to be expressed in adult skeletal muscle, Erhard Wischmeyer presented data on Cl^- channels found in lipid-supplemented vesicles prepared from the sarcolemmal fraction of adult skeletal muscle of rabbit [30] and mouse. An indanyloxyacetic acid-sensitive and partially rectifying Cl^- channel was only present in the wild-type but not in the ADR mouse, and is, therefore, a candidate for the product of the Chlcn1 gene.

In the final portion of the workshop, secondary changes in the gating of Na^+ channels in "muscle chloride channel diseases" were discussed by Paul Iaizzo. The problem of

the patients with dominant myotonia and normal Cl^- conductance [31] was solved in part when it was recognized that myotonia fluctuans is a Na^- channel disease. There is, however, still the unexplained problem that some Thomsen patients had normal Cl^- conductance and slowed inactivation of the Na^+ channels.

The electrophysiological data were also contrasted to those observed for Schwartz–Jampel syndrome as "food for thought".

The workshop closed with a discussion, led by Reinhardt Rüdel, on the multimeric structure of the Cl^- channel and the possible disturbance of function caused by the mutations. As a last point, the secondary abnormalities in the Cl^- channel diseases were brought up. The abnormal K^+ and Na^+ conductances already reported by Bryant for the myotonic goat are unexplained, as are the Na^+ channel abnormalities in Becker and Thomsen patients mentioned above. In the myotonic ADR mouse, symptomatic treatment with the Na^+ channel blocker tocainide, partially reversed electrophysiological and biochemical alterations.

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List of participants

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ENMC

M. R. Rutgers (Baarn).

INTERNATIONAL ABBREVIATIONS USED

SCN4A	Gene encoding the human adult skeletal muscle Na^+ channel;
hSkM1	human adult skeletal muscle Na^+ channel (product of the SCN4A gene);
rSkM1	rat adult skeletal muscle Na^+ channel;
hH1	gene encoding the human cardiac, fetal and denervated skeletal muscle Na^+ channels;
hH2	gene encoding the human myometrium and fetal skeletal muscle Na^+ channels;
adr	adr gene;
ADR	phenotype of the mouse mutant carrying two adr alleles;
Chlcn1	mouse muscle Cl^- channel gene;
CHLCN1	human muscle Cl^- channel gene;
Clc-1	probe and locus for the mouse muscle Cl^- channel gene;
CLC-1	probe and locus for the human Cl^- channel gene;
RFLP	restriction fragment length polymorphism;
Tcrb	mouse T cell receptor β;
TCRB	human T cell receptor β.

DIAGNOSTIC CRITERIA

Since the genes and the gene products are known in the principal diseases of non-dystrophic myotonias and periodic paralyses, and since an increasing number of molecular biological laboratories have the relevant genetic markers available, an exact diagnosis will, in future, be made by the identification of the mutation. At present, many laboratories are engaged in correlating the clinical symptoms of their individual families with the various mutations and, therefore, a precise statement of the clinical diagnostic criteria remains useful.

It is important to state that myotonia, i.e. muscle stiffness, is a *symptom* that can be present in both muscle Cl^- and Na^+ channel diseases (and, of course, also in myotonic dystrophy and Schwartz–Jampel syndrome). The myotonia is best assessed as *myotonic runs* in the electromyogram. Diagnostic differentiation of the various diseases on the mere basis of these runs is not dependable. Muscle biopsy is usually not helpful for establishing the diagnosis.

The class of Cl^- channel diseases comprises dominant myotonia congenita (Thomsen) and recessive generalized myotonia (Becker). The term of *myotonia congenita* should only be reserved for these Cl^- channel diseases.

The class of Na^+ channel diseases encompasses all clinical variants of the "adynamia–paramyotonia complex". Although the key symptoms, namely attacks of muscle weakness and episodes of muscle stiffness, are known to overlap to various degrees, it makes sense from a clinical point of view to maintain the differentiation between hyperkalemic periodic paralysis (identical with Gamstorp's adynamia episodica hereditaria) and paramyotonia congenita (Eulenburg) because preventive measures are different for the two symptoms. HyperPP also implies a possible prognosis of progressive permanent weakness that is not a feature of PC.

Dominant myotonia congenita

The usual (but very rare) form is Thomsen's disease. There is also a form that is distinguished by very mild myotonia (DeJong's myotonia levior). It remains to be discovered whether this is caused by an allelic mutation.

Family history. Autosomal dominant inheritance; 100% penetrance.

Age of onset. From birth to early childhood.

Clinical signs. Muscle stiffness, particularly after rest, muscle function improving with continuing exercise (warm up). Myotonia fluctuates only slightly during lifetime; no progression. Frequent muscle hypertrophy.

Clinical signs that must not be mistaken. There are cases of Na^+ channel disease having myotonia without any weakness. The myotonia may exist without cooling. Before the advent of molecular biology, these cases were often misdiagnosed as forms of myotonia congenita.

Although patients with myotonia congenita, when asked, often state that their stiffness increases in the cold, this cannot be substantiated with objective measurements of muscle relaxation times.

Recessive generalized myotonia

At least two mutations must exist causing the same clinical picture. (There is one mutation detected in several unrelated families, but other investigated families do not show this mutation.)

Family history. Autosomal recessive inheritance. Some of the heterozygous carriers show myotonic runs in the EMG. Such cases must not be confused with dominant myotonia, and sometimes molecular biology is required to differentiate from myotonic dystrophy.

Age of onset. Occasionally present in early childhood, usually first decade of life, in some cases not before the end of the second decade and even progression of symptoms into the third decade of life.

Clinical signs. Muscle stiffness, particularly after rest, muscle function improving with continuing exercise (warm up). In many patients marked transient weakness after rest which improves during several minutes of continued exercise. Weakness is more pronounced in the upper extremities, stiffness is more pronounced in the legs. In many cases hip and leg muscles are hypertrophied. The signs are usually progressive for a few years after their first appearance and then remain stable for the rest of the life.

Clinical signs that must not be mistaken. The well-known phenomenon of anticipation in myotonic dystrophy may lead to a familial constellation suggesting recessive inheritance and, as a consequence, may lead to the spurious diagnosis of recessive generalized myotonia. On the other hand, misinterpretation of the transient weakness may lead to the spurious diagnosis of myotonic dystrophy. In older patients with recessive generalized myotonia muscle biopsies may show a morphologic pattern that can be misdiagnosed as muscular dystrophy.

Paramyotonia congenita

The classical form was described by Eulenburg and independently by Rich. Several mutations in the Na^+ channel gene result in the classical clinical picture.

Family history. Autosomal dominant inheritance; 100% penetrance.

Age of onset. From birth.

Clinical signs. Muscle stiffness increasing with exercise (paradoxical myotonia). In many families paramyotonia is dramatically increased when the muscles are exercised in the cold. Transition from stiffness to local weakness when muscles are extensively exercised in the cold. Recovery from weakness may last several hours. Cave: Some families present consistently cold- and exercise-induced stiffness without

weakness. These are often misdiagnosed as having myotonia congenita!

Variability of signs. There are families where affected members present with the classical symptoms of paramyotonia congenita and also often experience attacks of hyperkalemic paralysis. The presentation of both sets of symptoms in severe form was termed paralysis periodica paramyotonica (PPP) by P. E. Becker, however, a continuum seems to exist, with PPP families and families having "pure" paramyotonia congenita presenting the two extremes. The severity of stiffness is not the same in all paramyotonia families.

Clinical signs that must not be mistaken. Permanent weakness is not observed in paramyotonia congenita.

Hyperkalemic periodic paralysis

Several mutations in the Na^+ channel gene may lead to the classical clinical picture.

Family history. Autosomal dominant inheritance; complete penetrance, but severity is very variable.

Age of onset. Early childhood to second decade of life.

Clinical signs. Attacks of weakness, usually in the morning, lasting from 10 min to 1 h or so, very rarely up to 1–2 days. Some patients experience only a few attacks of weakness in their lifetime, others have attacks of generalized weakness almost every day. During the attacks, serum K^+ is elevated to upper norm or above. Myotonic stiffness is not observed. Rest after exercise, fasting, or oral intake of K^+ are very efficient in precipitating attacks (provocative tests). Some patients always show slight signs of myotonia between and at the beginning of attacks, others show signs of paramyotonia, in a third category myotonic signs are absent.

Clinical signs that must not be mistaken. At the end of a paralytic attack, serum K^+ can fall below the normal level. A blood sample taken during this time can suggest hypokalemic periodic paralysis.

Normokalemic periodic paralysis

Very few families have been described. Attacks can last several days without an increase of the serum K^+ concentration. Since it was shown for one family that the Na^+ channel gene is mutated at a locus that causes HyperPP, in other families (Thr704) we suggest that the form of periodic paralysis without hyperkalemia is a variant of the adynamia–paramyotonia complex.

Myotonia fluctuans

Three families have been studied. Linkage to the Na^+ channel gene is established.

Family history. Autosomal dominant inheritance.

Age of onset. Early childhood.

Clinical signs. Severe generalized stiffness without weakness following exercise and/or K^+ loading. Rest after exercise leads to "delayed-onset myotonia". Cold does not induce stiffness or weakness.

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