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Clindamycin hydrochloride monohydrate and its ethanol solvate

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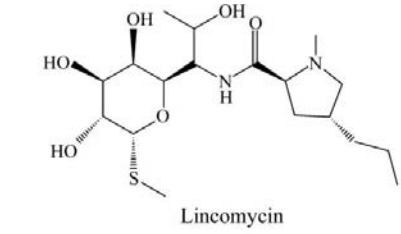
Clindamycin hydrochloride, an antibiotic of the lincomycin family, was crystallized as the monohydrate, namely (2*S*,4*R*)-2-(*N*-{(1*S*,2*S*)-2-chloro-1-[(3*R*,4*S*,5*R*,6*R*)-3,4,5-trihydroxy-6-(methylsulfanyl)perhydropyran-2-yl]propyl}aminocarbonyl)-4-propylpyrrolidinium chloride monohydrate, $C_{18}H_{34}ClN_2O_5S^+\cdot Cl^-\cdot H_2O$, (I), and as the monohydrate ethanol solvate, $C_{18}H_{34}ClN_2O_5S^+\cdot Cl^-\cdot H_2O\cdot C_2H_6O$, (II). The conformation of the clindamycin molecule in both crystal structures is the same and is found to be similar to that in enzyme-bound clindamycin. The simultaneous presence of free chloride ions and water molecules in (I) and of additional ethanol molecules in (II) provides an interesting network of hydrogen bonds. The significance of this study lies in the interactions in these structures and the aggregations occurring *via* hydrogen bonds in the hydrated and solvated crystalline forms of the title compound.

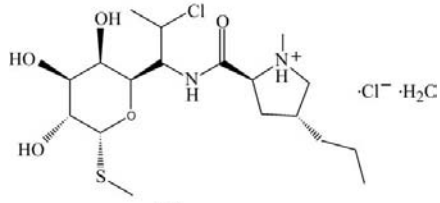
Comment

Clindamycin is a lincosamide antibiotic. It is usually used to treat infections with anaerobic bacteria but can also be used to treat some protozoan diseases, such as malaria. It is a common topical treatment for acne, and can be useful against some methicillin-resistant *Staphylococcus aureus* (MRSA) infections (Daun, 2007). Clindamycin is also used in veterinary medications. It is marketed under various trade names, including Dalacin, Clindacin, Cleocin, and Evovlin (clindamycin by itself), Duac, BenzaClin and Arcanya (in combination with benzoyl peroxide), and Ziana (with tretinoin). Clindamycin is a semisynthetic derivative of lincomycin, a natural antibiotic produced by the actinobacterium *Streptomyces lincolnensis*. It is obtained by 7(*S*)-chloro-substitution of the 7(*R*)-hydroxy group of lincomycin. We report here the crystal structures of clindamycin hydrochloride monohydrate, (I), and its ethanol solvate, (II), as part of our ongoing studies of the structural characterization of drug molecules.

The clindamycin molecule consists of a derivative of the amino acid *trans*-L-4-*n*-propylhygrinic acid joined to a sulfur-containing octose derivative. Views of the molecules of (I) and (II), showing the atom labelling, are presented in Figs. 1(*a*) and 1(*b*). The bond distances and angles in (I) and (II) are in the normal ranges (Allen *et al.*, 1987) and are comparable with the corresponding values observed in lincomycin hydrochloride (Rajeswaran & Srikrishnan, 2004) and clindamycin 2-phosphate hydrate (Leban *et al.*, 1994). An earlier initial study of clindamycin hydrochloride monohydrate reported only the unit-cell dimensions were reported [a = 9.47 Å, b = 9.91 Å, c = 13.50 Å, β = 104.5° and V = 1226.6 Å^3, monoclinic space group $P2_1$; Cambridge Structural Database (CSD; Allen, 2002) refcode DECLMY (Duchamp, 1967)], which are similar to those of (I).



Lincomycin



(I)
(II) = (I)·EtOH

In both (I) and (II), the propyl side chain is disordered; in (I), atoms C15/C16/C17 are disordered over two sites with occupancies of 0.760 (6) and 0.240 (6), and in (II), atoms C16/C17 are disordered over two sites with occupancies of 0.709 (8) and 0.291 (8). Additionally, the ethanol solvent molecule (atoms C19/C20/O6) in (II) is disordered over two sites with occupancies of 0.709 (8) and 0.291 (8).

The central amide linkage plays an active role in the solid-state conformation and governs the overall shape of the clindamycin molecule in (I) and (II). It is planar and in an extended conformation (Fig. 2). Atom N2 of the terminal pyrrolidine ring is protonated to form the pyrrolidinium cation in both (I) and (II). Fig. 2 shows an overlay of the clindamycin molecules of (I) and (II) with the extracted clindamycin ligand from the crystal structure of the complex of clindamycin bound to the G2099A mutant 50S ribosomal subunit of *Haloarcula marismortul* [Tu *et al.* (2005); Protein Data Bank (PDB; Berman *et al.*, 2000) entry 1YJN], clindamycin 2-phosphate hydrate and lincomycin. It can be seen that the clindamycin molecules prefer to adopt the same configuration and similar conformations in spite of having significant sites for drug activation.

In the structures of both (I) and (II), the pyranoside ring is of the galactopyranose stereochemistry with a $^4C_1$ chair form, with configuration 1a2e3e4a5e (a = axial and e = equatorial), where 1, 2, 3, 4 and 5 represent atoms C2, C3, C4, C5 and C1, respectively. A similar conformation has been observed in the

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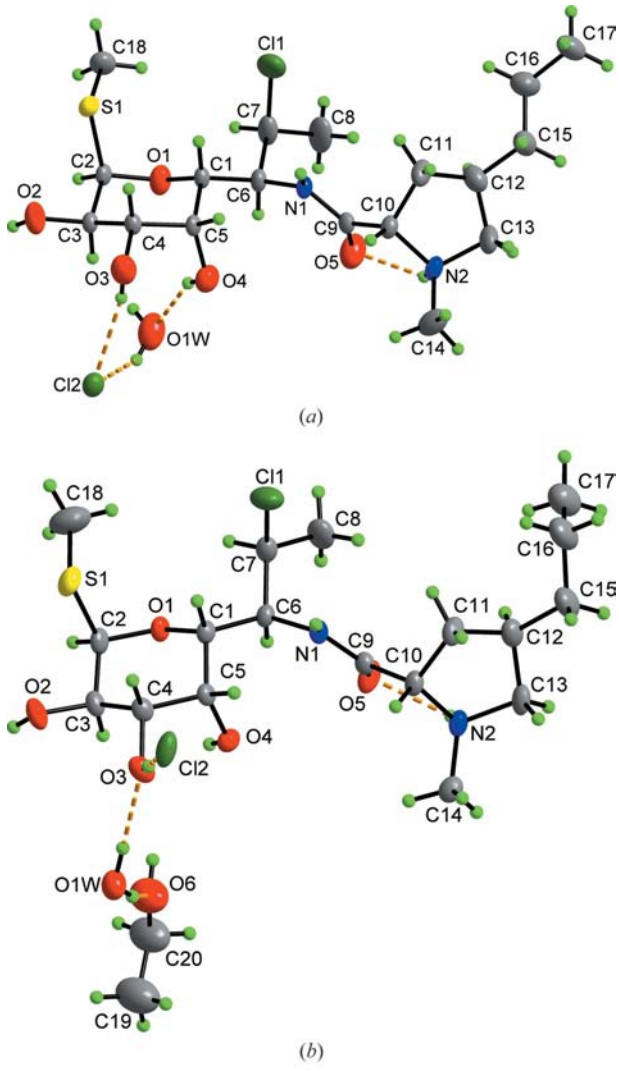

Figure 1
Views of (*a*) clindamycin hydrochloride monohydrate, (I), and (*b*) clindamycin hydrochloride monohydrate ethanol solvate, (II), showing the atom-numbering schemes. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii. Dashed lines indicate hydrogen bonds. Only the major parts of the disordered atoms of the propyl side chains [C15/C16/C17 in (I) and C16/C17 in (II)] and of the ethanol solvent molecule (C19/C20/O6) in (II) are shown.

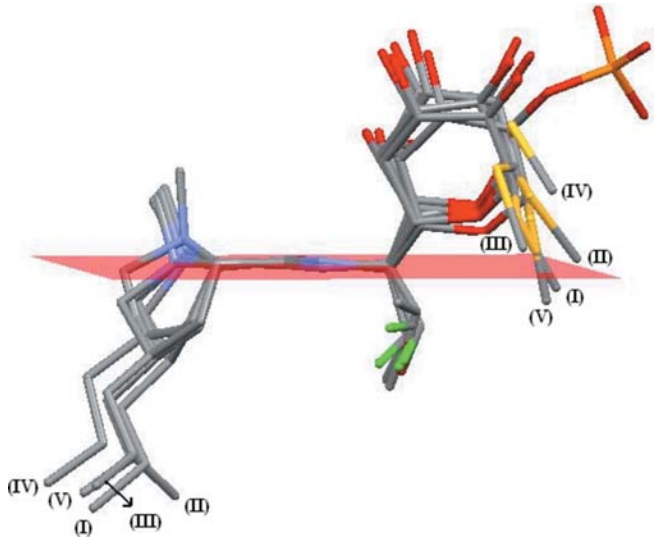

Figure 2
A superposition of the molecular conformations of clindamycin molecules, showing the planar central carboxamide groups. The overlay was made by making a least-squares fit through the planar carboxamide atoms of (I). The labels and r.m.s deviations (Å) of the carboxamide atoms are as follows: clindamycin hydrochloride monohydrate ethanol solvate, (II), 0.025; 1YJN, (III), 0.050; lincomycin hydrochloride, (IV), 0.025; clindamycin 2-phosphate hydrate, (V), 0.091 (even though there are three molecules in the asymmetric unit and their overlay is almost exact, only one molecule is represented here). Disordered atoms C151/C161/C171 of (I) and C161/C171 of (II) and all H atoms have been omitted for clarity.

structures of lincomycin hydrochloride and clindamycin 2-phosphate hydrate.

The pyrrolidinium ring in both structures is in an envelope conformation, with C12 being the flip atom. The flip angle of the envelope, defined as the dihedral angle between the planes of atoms N2/C10/C11/C13 and C11/C12/C13, is 38.0 (2)° in (I) and 38.7 (2)° in (II). On the other hand, even though the pyrrolidine ring is in an envelope conformation in the structures of lincomycin hydrochloride, clindamycin 2-phosphate hydrate and 1YJN, it is observed that the atom corresponding to C13 occupies the flip position. The sum of the bond angles around the pyrrolidinium N2 atom (ΣN2) is 335.5 (2)° in (I) and 335.1 (2)° in (II), and this atom tends to be coplanar with the central carboxamide plane [deviation of N2 = 0.001 (2) Å in (I) and 0.179 (3) Å in (II)]. We believe that this tendency towards coplanarity of atom N2 may be related to the antibacterial activity, since N2 bears a positive charge facilitating binding at the active site. The corresponding deviations of N2 found in lincomycin hydrochloride, clindamycin 2-phosphate hydrate and 1YJN are 0.173, 0.068/0.802/0.087 (three molecules in the asymmetric unit) and 0.035 Å, respectively.

The crystal packing in (I) and (II) is influenced by the presence of the free chloride ion and the single water molecule, which appears to be crucial for crystal formation. As observed in the crystal structures of small-molecule hydrates (Jeffrey & Saenger, 1991), the water molecule in (I) is four-coordinated, with each molecule acting as a donor in two hydrogen bonds and an acceptor in two (Table 1). Thus, the water molecules and the free chloride ions (Cl2) connect the three moieties (pyrrolidinium, amide and pyranoside) of the clindamycin molecules and form an intricate three-dimensional intermolecular hydrogen-bond network (Fig. 3). The presence of an additional ethanol molecule in (II) supports the water molecule in hydrogen bonding (Table 2). The water molecule of (II) is three-coordinated, with each molecule acting as a donor to two hydrogen bonds and an acceptor to just one. Similarly, the ethanol molecule also acts as a donor and an acceptor. Thus, the water molecules, mediated by the ethanol molecules and free chloride ions, connect the three moieties of the clindamycin molecules to form a complex three-dimensional intermolecular hydrogen-bond network (Fig. 4). It is interesting to note that pyranoside atom O1, bonded atom Cl1 and carboxamide atom O5 (excluding its

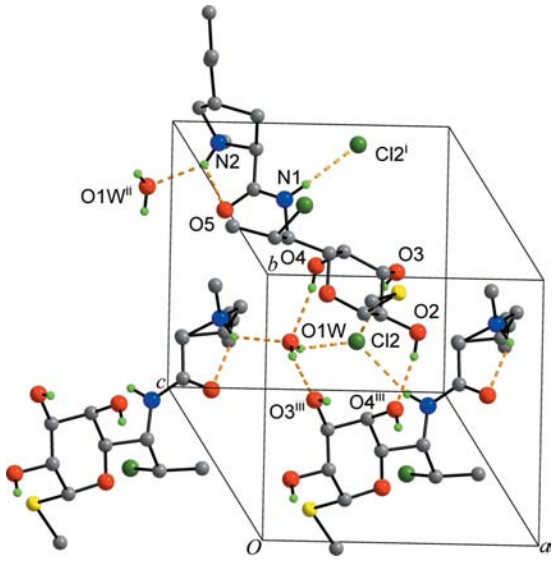

Figure 3
Part of the crystal packing of (I), illustrating the intricate hydrogen-bond network. Hydrogen bonds are shown as dashed lines and H atoms not involved in hydrogen bonding have been omitted for clarity. Only the major parts of the disordered atoms of the propyl side chain (C15/C16/C17) are shown. Selected atoms of the molecules present in the asymmetric unit are labelled, primarily to provide a key for the coding of the atoms. [Symmetry codes: (i) $-x+1, y+\frac{1}{2}, -z+1$; (ii) $-x, y+\frac{1}{2}, -z+1$; (iii) $-x+1, y-\frac{1}{2}, -z+1$.]

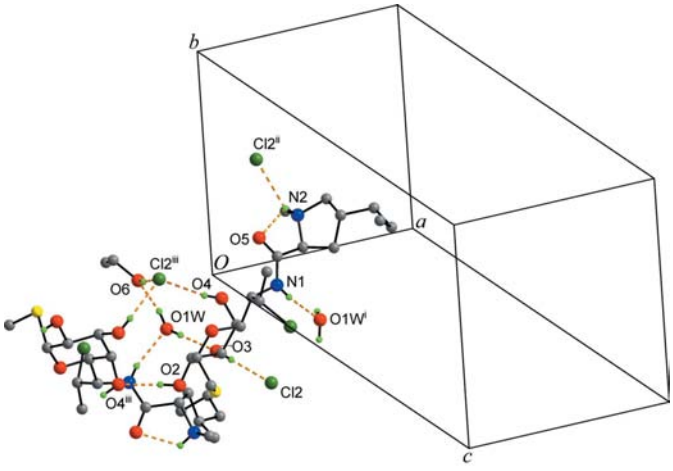

Figure 4
Part of the crystal packing of (II), illustrating the complex hydrogen-bond network. Hydrogen bonds are shown as dashed lines and H atoms not involved in hydrogen bonding have been omitted for clarity. Only the major parts of the disordered atoms of the propyl side chain (C16/C17) and of the ethanol solvent molecule (C19/C20/O6) are shown. Selected atoms of the molecules present in the asymmetric unit are labelled, primarily to provide a key for the coding of the atoms. [Symmetry codes: (i) $x+\frac{1}{2}, -y-\frac{1}{2}, -z$; (ii) $x, y+1, z$; (iii) $x-\frac{1}{2}, -y-\frac{1}{2}, -z$.]

intramolecular hydrogen bonding) do not participate in the hydrogen-bonding network in either structure. This may provide some insight into the nature of drug-binding interactions at the enzyme active site. In (I), nonclassical C—H···O, C—H···Cl and C—H···S interactions are observed, while in (II) only a C—H···O interaction is observed.

In conclusion, this structural analysis can facilitate the understanding the solid-state features of the drug and its hydrogen-bonding interactions in hydrated and solvated environments.

Experimental

Clindamycin hydrochloride (Pharmacology Department, IICT, Hyderabad) (50 mg) was dissolved in a mixture of ethanol (5 ml) and water (2 ml). After 4 d, crystals of (I) and (II) were obtained and were distinguished by their distinct crystal habits, *viz.* needles and plates, respectively. After 8 d it was observed that the plate-shaped crystals of (II) turned opaque. Hence, for (II), data were collected on a crystal sealed in a vial with mother liquor solution.

Compound (I)

Crystal data

$C_{18}H_{34}ClN_2O_5S^+\cdot Cl^-\cdot H_2O$
$M_r = 479.45$
Monoclinic, $P2_1$
$a = 9.4669$ (6) Å
$b = 9.9255$ (6) Å
$c = 13.4949$ (8) Å
$\beta = 104.601$ (1)°
$V = 1227.08$ (13) Å^3
$Z = 2$
Mo $K\alpha$ radiation
$\mu = 0.38$ mm^{-1}
$T = 294$ K
0.15 × 0.10 × 0.06 mm

Data collection

Bruker SMART APEX CCD area-detector diffractometer
11796 measured reflections
4321 independent reflections
4211 reflections with $I > 2\sigma(I)$
$R_{int} = 0.016$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.031$
$wR(F^2) = 0.084$
$S = 1.05$
4321 reflections
323 parameters
68 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max} = 0.26$ e Å^{-3}
$\Delta\rho_{min} = -0.20$ e Å^{-3}
Absolute structure: Flack & Bernardinelli (1983), with 2022 Friedel pairs
Flack parameter: 0.02 (5)

Compound (II)

Crystal data

$C_{18}H_{34}ClN_2O_5S^+\cdot Cl^-\cdot H_2O\cdot C_2H_6O$
$M_r = 525.52$
Orthorhombic, $P2_12_12_1$
$a = 9.9630$ (16) Å
$b = 10.6998$ (17) Å
$c = 26.324$ (4) Å
$V = 2806.2$ (8) Å^3
$Z = 4$
Mo $K\alpha$ radiation
$\mu = 0.34$ mm^{-1}
$T = 294$ K
0.13 × 0.11 × 0.05 mm

Data collection

Bruker SMART APEX CCD area-detector diffractometer
27108 measured reflections
4937 independent reflections
4748 reflections with $I > 2\sigma(I)$
$R_{int} = 0.027$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.050$
$wR(F^2) = 0.119$
$S = 1.18$
4937 reflections
364 parameters
125 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max} = 0.45$ e Å^{-3}
$\Delta\rho_{min} = -0.19$ e Å^{-3}
Absolute structure: Flack & Bernardinelli (1983), with 2123 Friedel pairs
Flack parameter: 0.00 (7)

Table 1
Hydrogen-bond geometry (Å, °) for (I).

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1N···Cl2^{i}	0.88 (2)	2.53 (2)	3.3540 (19)	157.2 (19)
N2—H2N···O1W^{ii}	0.85 (3)	2.23 (3)	2.897 (3)	136 (2)
N2—H2N···O5	0.85 (3)	2.02 (3)	2.616 (2)	126 (2)
O2—H2O···O4^{iii}	0.82 (3)	1.97 (3)	2.763 (2)	164 (3)
O3—H3O···Cl2	0.82 (2)	2.44 (2)	3.2403 (17)	166 (2)
O4—H4O···O1W	0.78 (3)	2.02 (3)	2.744 (2)	153 (3)
O1W—H1W···Cl2	0.87 (2)	2.36 (3)	3.094 (2)	142 (4)
O1W—H2W···O3^{iii}	0.89 (2)	2.08 (3)	2.910 (2)	155 (4)
C5—H5···Cl2^{i}	0.98	2.75	3.712 (2)	167
C14—H14B···O2^{i}	0.96	2.58	3.484 (4)	158
C15—H15B···S1^{iv}	0.97	2.83	3.763 (5)	162

Symmetry codes: (i) $-x+1, y+\frac{1}{2}, -z+1$; (ii) $-x, y+\frac{1}{2}, -z+1$; (iii) $-x+1, y-\frac{1}{2}, -z+1$; (iv) $x-1, y+1, z$.

Table 2
Hydrogen-bond geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1N···O1W^{i}	0.81 (3)	2.14 (3)	2.917 (4)	161 (3)
N2—H2N···Cl2^{ii}	0.84 (2)	2.59 (2)	3.253 (3)	137 (3)
O2—H2O···O4^{iii}	0.87 (2)	1.89 (2)	2.738 (3)	165 (4)
O3—H3O···Cl2	0.81 (4)	2.28 (4)	3.082 (3)	175 (3)
O4—H4O···Cl2^{iii}	0.85 (2)	2.26 (2)	3.104 (2)	169 (4)
O6—H6A···Cl2^{iii}	0.82	2.23	3.046 (9)	173
O61—H6B···Cl2^{iii}	0.82	2.45	3.26 (3)	170
O1W—H1W···O3	0.85 (2)	2.04 (2)	2.863 (4)	163 (4)
O1W—H2W···O6	0.89 (2)	1.91 (3)	2.741 (9)	156 (5)
O1W—H2W···O61	0.89 (2)	2.07 (3)	2.94 (2)	169 (5)
C10—H10···O3^{i}	0.98	2.35	3.298 (4)	162
C14—H14B···O2^{i}	0.96	2.44	3.206 (4)	137

Symmetry codes: (i) $x+\frac{1}{2}, -y-\frac{1}{2}, -z$; (ii) $x, y+1, z$; (iii) $x-\frac{1}{2}, -y-\frac{1}{2}, -z$.

The site-occupancy factors of disordered atoms C15/C16/C17 (propyl group) of (I) refined to 0.760 (6) and 0.240 (6), while those of atoms C16/C17 (propyl group) and C19/C20/O6 (ethanol solvent molecule) of (II) refined to 0.709 (8) and 0.291 (8). The anisotropic displacement parameters and bond distances of the major and minor components of the disordered atoms were restrained to be similar using SIMU and SAME instructions (*SHELXL97*; Sheldrick, 2008). The C—C distances of the disordered groups were restrained to be 1.55 (2) Å and the C—O distances to be 1.45 (2) Å. Except for the disordered ethanol solvent molecule in (II), all N-bound H atoms, O-bound H atoms and water H atoms of (I) and (II) were located in difference Fourier maps and their positions were refined subject to O—H distance restraints of 0.89 (2) Å for O1W—H1W, O1W—H2W and O3—H3O of (I) and for O1W—H1W, O1W—H2W, O2—H2O and O4—H4O of (II), an H1W···H2W distance restraint of 1.55 (2) Å for (I) and an N2—H2N distance restraint of 0.82 (2) Å for (II). The isotropic displacement of these H atoms were set at U_{iso}(O) = 1.5U_{eq}(N,O). The O-bound H atom of the disordered ethanol solvent molecule in (II) was found in a difference Fourier map and subsequently placed in an idealized position, with O—H = 0.82 Å and U_{iso}(H) = 1.5U_{eq}(O). All other H atoms were located in difference density maps, positioned geometrically and included as riding atoms, with C—H = 0.96–0.98 Å and U_{iso}(H) = 1.5U_{eq}(C) for methyl or 1.2U_{eq}(C) for the other H atoms. The methyl groups were allowed to rotate but not to tip. The absolute configuration of the procured material was known in advance and was confirmed by unambiguous refinement of the absolute structure parameter (Flack & Bernardinelli, 2000).

For both compounds, data collection: *SMART* (Bruker, 2001); cell refinement: *SAINT* (Bruker, 2001); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *DIAMOND* (Brandenburg & Putz, 2005) and *Mercury* (Macrae *et al.*, 2008); software used to prepare material for publication: *SHELXL97*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SF3125). Services for accessing these data are described at the back of the journal.

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