Nalmefene enhances LH secretion in a proportion of
oligo-amenorrheic athletes

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The influence upon LH secretion of doses of nalmefene, an orally effective congener of naloxone, and a placebo was compared in nine oligo-amenorrheic athletes with that in five regularly menstruating non-athletic women as a test for periodic elevations in hypogalamic opioid tone. After a 360-min control period, LH levels were followed for an additional 360 min following ingestion of the medications in random order approximately six weeks apart. 10-min blood sampling being employed throughout. The mean amplitude post-nalmefene in the athletes was significantly greater than pre- (p<0.05), although there were no differences in the frequency of LH pulses after placebo or nalmefene ingestion. Subjects were labelled as “responders” if their peak AUC after treatment exceeded their pretreatment AUC for LH by more than 1.96 so (p<0.05). There were no placebo responders, but 5/9 of the athletes and 1/5 of the menstruating controls were classified as nalmefene responders (p<0.05). In addition, a variable proportion of the athletes (but none of the controls) experienced symptoms suggestive of narcotic withdrawal 1–4 h after ingesting nalmefene and again 12–18 h later. It appears that demonstrable increases in opioid tone occur at least transiently in a proportion of oligo-amenorrheic athletes.

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Rigorous physical training is accompanied by a variety of menstrual disorders. Acute exercise elevates circulating levels of endogenous opioid peptides. Also tonic levels of plasma β-endorphin, a compound that depresses LH secretion, have been shown to be slightly increased in athletes (1). Moreover, resting values of β-endorphin are significantly higher in amenorrheic than in eumenorrheic athletes (2), suggesting that augmented endogenous opioid peptide tone may play a role in the associated menstrual dysfunction. However, while endogenous opioid peptide neurons exist in close proximity to GnRH neurons, it is not known whether increments in the concentration of hypothalamic opioids accompany increases in peripheral endogenous opioid peptide levels. To test the hypothesis that endogenous opioid tone is periodically elevated in women engaged in vigorous exercise, we studied the clinical effects of a single dose of nalmefene, an orally effective long-acting congener of naloxone, and a placebo in nine oligo-amenorrheic athletes who experienced 0–1 menstrual periods per year, and compared its influence on LH secretion with that of a placebo in five normally ovulating and menstruating non-athletic women.

Methods and materials

Subjects
Nine oligo-amenorrheic athletes with a mean chronologic age of 26.1 years and a mean gynecologic age (number of years elapsed since the menarche) of 11.8 years, and five normally ovulating and menstruating non-athletic controls with a mean chronologic age of 23.6 years and a mean gynecologic age of 10.6 years gave written informed consent to participate in the study, which had been approved by the Hospital’s Ethics Committee. The duration of oligo-amenorrhea ranged from 1 to 7 years (mean 3.5 years).

Screening
A complete history, general physical and pelvic examination, vaginal maturation index, biochemical and hematologic profiles and an endocrine profile were obtained on each subject to exclude other causes of amenorrhea. Vaginal maturation indices were converted to scores as an index of estrogen effect, parabasal cells being rated as 0, intermediate cells as 0.5, and superficial cells as 1.0, according to the technique of Meisels (3). The normal
control group consisted of college women who participated in the usual school activities but who had not engaged in aerobic training for at least six months. Besides normal biochemical, hemato logic and endocrine profiles they had a history of regular ovulatory menstrual cycles with normal luteal function as judged by menstrual calendars (limits of cycle duration 25–35 days), biphasic temperature patterns and mid-luteal serum progesterone levels of at least 16 nmol/L. In both groups, the residual lung volume for each subject was established by the nitrogen dilution method and total body fat was computed by the formula of Siri (4) from body density obtained by hydrostatic weighing. All of the endocrine indices were normal in the control women, and in none of the athletes was there clinical or biochemical evidence of other causes of amenorrhea (values not shown).

**Experimental protocol**

Normal control subjects were studied during the follicular phase (days 2–8); all subjects were tested on two occasions at least one month apart (mean 6 weeks; range 4–14 weeks). They entered the Clinical Research Center on the evening prior to each test, consumed a standardized dinner at 18.00, and slept from 23.00 to 07.00. At 07.00, a plastic cannula was inserted into an antecubital vein and kept patent with small volumes of normal saline solution. At 08.00, blood sampling at 10-min intervals was begun and continued until 20.00. Nalmefene 20 mg or an identically appearing placebo (randomly assigned) was administered orally at the midpoint (14.00) of each test. The subjects consumed five small meals over the 12-h period. Each meal consisted of 20% of a diet calculated to supply basal energy expenditure + 50% (composition: carbohydrate, 50%; protein, 15%; and fat, 35%). Side effects (anorexia, nausea, fatigue, dizziness and insomnia) were recorded by the subjects in a diary throughout the study and for five days thereafter. All data were coded numerically and evaluated by a statistician in a blinded fashion.

**Hormonal measurements**

Plasma LH levels were measured by means of an established double antibody radioimmunoassay (5). All samples for a given subject were run in a single assay, the second IRP-HMG being employed as the reference preparation. Highly purified human pituitary LH provided by the National Hormone and Pituitary Program of the National Institute of Diabetes, Digestive and Kidney Diseases was iodinated, using previously established techniques. Replicate controls were run for each assay in low, intermediate and high ranges: the within-assay errors were 7.6%, 7.2% and 6.3% for the corresponding control pools, respectively. The overall between-assay error was 8.7%. All LH measurements were made in quadruplicate and the results evaluated by means of the log-logit program of Rodbard et al. (6). Screening values for estradiol, progesterone, androstenedione and DHEA-S were obtained by solid phase radioimmunoassay (Diagnostic Products Corporation). Thyroxine and TSH levels were measured by standard radioimmunoassays.

**Statistical analysis**

Continuous demographic variables for oligo-amenorrheic athletes and controls (Tables 1A and 1B) were compared by t-tests.

Assessments of possible effects of nalmefene or placebo administration were performed on changes in the area under the LH peaks (AUC). Pulsar, a standard peak identification program (7), was employed to detect LH pulsations. The pulsar defaults specified by the authors were employed in the main. cutoff limits selected being 3.80 for one value, 2.60 for two, 1.90 for three, 1.50 for four and 1.20 for five values above the moving average. The peak split cutoff was set at 2.70. The sensitivity of the assay was set at 0.30 and the smoothing time was 7.20 min. A maximum of six iterations was permitted.

Subjects were labelled as “responders” if their peak AUC after treatment (nalmefene or placebo) over the subsequent 6 h exceeded their pretreatment AUC for LH by more than 1.96 sp (p<0.05). McNemar’s test for related samples was used to compare nalmefene with the placebo responses.

A two-way analysis of variance was performed on the number and mean amplitude of pulses with factors for drug treatment and time plus their interaction (Table 2). Post hoc assessments were made using the Newman-Keuls method of multiple comparison. In addition, the relationship between the nalmefene response (magnitude change in mean LH value) and various parameters was examined using Pearson correlation (continuous variables) and logistic regression (categorical variables).

McNemar’s test for related samples was employed to detect significant differences in the number of subjects experiencing any of the five adverse symptoms (e.g. nausea) following the ingestion of nalmefene as against ingestion of the placebo (Table 3). The proportion of subjects who experienced at least one side effect was similarly evaluated.

All tests were two-tailed with the significance set at the p≤0.05 level.

**Results**

Key characteristics of the subjects are listed in Tables 1A and 1B. In the oligo-amenorrheic group, exercise constantly exceeded recreational levels, although there was considerable variation in the types of exercise selected by the subjects. Running was the principal sport in 8/9, although swimming was important in 5/9 and significant participation in such vigorous games as soccer, basketball and lacrosse was listed by 5/9. Vaginal
### Table 1A. Characteristics of the oligo-amenorrheic athletes.

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>Chronological age (years)</th>
<th>Gynecological age (years)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>% ideal body weight relative to height&lt;sup&gt;a&lt;/sup&gt;</th>
<th>% fat</th>
<th>Duration of oligo-amenorrhea (years)</th>
<th>Months amenorrheic before testing</th>
<th>Self-reported weekly exercise</th>
<th>Vaginal maturation index (%)</th>
<th>Nalinefene responder</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>23</td>
<td>8</td>
<td>161.0</td>
<td>57.0</td>
<td>+5.2</td>
<td>28.2</td>
<td>5</td>
<td>60</td>
<td>Running 50 km/week</td>
<td>0</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>11</td>
<td>168.0</td>
<td>55.0</td>
<td>-6.0</td>
<td>17.0</td>
<td>7</td>
<td>84</td>
<td>Running 110 km/week</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>33</td>
<td>19</td>
<td>173.4</td>
<td>60.1</td>
<td>-3.1</td>
<td>21.5</td>
<td>4</td>
<td>24</td>
<td>Running 65 km/week Cycling 160 km/week Swimming 3-5 km/week</td>
<td>0</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>21</td>
<td>6</td>
<td>165.7</td>
<td>51.9</td>
<td>-8.9</td>
<td>21.7</td>
<td>3</td>
<td>36</td>
<td>Running 95 km/week Cycling 160 km/week Swimming 3-5 km/week</td>
<td>0</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>14</td>
<td>163.2</td>
<td>51.9</td>
<td>-6.5</td>
<td>22.0</td>
<td>1</td>
<td>8</td>
<td>Running 40 km/week Swimming 10 km/week Nautilus 30 min/week</td>
<td>0</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>29</td>
<td>16</td>
<td>159.5</td>
<td>51.5</td>
<td>-1.1</td>
<td>23.5</td>
<td>1.25</td>
<td>2</td>
<td>Aerobic dancing 4 1/2 hr/week Running stairs 2 hr/week Weight lifting 2 hr/week</td>
<td>0</td>
<td>75</td>
</tr>
<tr>
<td>7</td>
<td>25</td>
<td>12</td>
<td>160.0</td>
<td>54.0</td>
<td>+0.7</td>
<td>23.5</td>
<td>4</td>
<td>48</td>
<td>Running 55-65 km/week Swimming 10-15 km/week</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>8</td>
<td>25</td>
<td>11</td>
<td>165.4</td>
<td>48.5</td>
<td>-14.6</td>
<td>23.2</td>
<td>5</td>
<td>60</td>
<td>Running 40 km/week Walking 25 km/week Stationary bicycling 90 min/week Nautilus 75 min/week</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>9</td>
<td>22</td>
<td>9</td>
<td>173.0</td>
<td>53.3</td>
<td>-13.6</td>
<td>26.1</td>
<td>1</td>
<td>9</td>
<td>Running 70-80 km/week</td>
<td>0</td>
<td>85</td>
</tr>
</tbody>
</table>

Mean: 26.1 11.8 165.5 53.7 -5.3 23.0 3.5 36.8

<sup>a</sup> Standard of Sargent (30).  
Normal build: ±7.5% of standard.  
Slender build: -7.5 to -15% of standard.
Table 1B. Characteristics of the normally menstruating control subjects.

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>Chronological age (years)</th>
<th>Gynecological age (years)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>% ideal body weight relative to height*</th>
<th>% fat</th>
<th>Vaginal maturation index (%)</th>
<th>Nalmefene responder</th>
<th>Day of cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>26</td>
<td>14</td>
<td>153.7</td>
<td>52.1</td>
<td>+4.0</td>
<td>32.8</td>
<td>0</td>
<td>60</td>
<td>3</td>
</tr>
<tr>
<td>11</td>
<td>20</td>
<td>7</td>
<td>161.5</td>
<td>56.4</td>
<td>+3.5</td>
<td>29.7</td>
<td>0</td>
<td>70</td>
<td>4</td>
</tr>
<tr>
<td>12</td>
<td>20</td>
<td>7</td>
<td>167.0</td>
<td>55.7</td>
<td>-3.6</td>
<td>20.1</td>
<td>0</td>
<td>90</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>30</td>
<td>17</td>
<td>168.0</td>
<td>54.2</td>
<td>-7.4</td>
<td>20.7</td>
<td>0</td>
<td>55</td>
<td>5</td>
</tr>
<tr>
<td>14</td>
<td>22</td>
<td>8</td>
<td>166.4</td>
<td>53.7</td>
<td>-6.6</td>
<td>20.8</td>
<td>0</td>
<td>80</td>
<td>3</td>
</tr>
<tr>
<td>Mean</td>
<td>23.6</td>
<td>10.6</td>
<td>163.3</td>
<td>54.4</td>
<td>-2.4</td>
<td>24.8</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Standard of Sargent (30).
Normal build: ±7.5% of standard.
Slender build: −7.5 to −15% of standard.

Table 2. LH pulse characteristics following placebo and nalmefene administration (mean ±SEM).

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Nalmefene</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>Frequency</td>
<td>6.1±1.0</td>
<td>6.4±0.5</td>
</tr>
<tr>
<td>Amplitude</td>
<td>15.3±2.4</td>
<td>15.4±2.0</td>
</tr>
</tbody>
</table>

b p<0.05.

Maturation indices were normal in all of the menstruating control subjects and 8/9 of the athletes. One of the latter (Subject No. 2, who had the highest running mileage) exhibited mild vaginal atrophy and had 10% parabasal cells in the smear. The mean maturation index scores of the normally menstruating women were higher than those of the athletes (p<0.05). There were no significant differences between the athletes and the controls with respect to chronologic age, gynecologic age, percent ideal body weight relative to height, or percent body fat.

The LH pulsatility patterns for the athletes who were classified as “responders” and “non-responders” to nalmefene are depicted in Figs. 1 and 2, respectively; those for the normally menstruating controls, four of whom were classified as “non-responders” and one as a “responder”, are shown in Fig. 3. If the pulsatility patterns during the first 6 h before the ingestion of either nalmefene or the placebo are examined, it is clear that the pulse frequencies and amplitudes during the control period are by no means constant. A particularly striking demonstration of pulsatility occurred in Subject No. 9 (Fig. 2).

In 5/9 of the oligo-amenorrheic athletes and 1/5 of the menstruating controls, a significant LH response to nalmefene occurred (p<0.05). Moreover, the number responding to nalmefene significantly exceeded those responding to the placebo by McNemar’s test in the oligo-amenorrheic group (p=0.025). No such significance was found in the control group (p>0.05). No correlation could be demonstrated between a nalmefene response and the mileage run on the day prior to the test by the athletes, the pattern of habitual exercise, the percent of ideal body weight relative to height, the basal levels of LH, or the incidence of side effects.

Analysis of variance disclosed no difference in the frequency of pulses between placebo and nalmefene tests (Table 2). Likewise, no difference was detected between pre- and post-placebo trials. However, the pre/post treatment-by-time interaction was significant (p = 0.03) for the mean amplitude of the LH pulses, and post hoc determinations showed that the mean amplitude of LH pulses was significantly greater than pre- (p < 0.05) after nalmefene treatment.

None of the athletes experienced any side effects following ingestion of the placebo, and none of the controls experienced side effects after the ingestion of

Table 3. Incidence of side effects following the ingestion of nalmefene or a placebo.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Nalmefene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia</td>
<td>0</td>
<td>3/9 (33%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>5/9 (56%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>2/9 (22%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Insomnia</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

At least one side effect

| p-value | 0.10 | 0.05 | 0.10 | 0.005 | 0.10 | 0.001 |

8/9 (89%)
either the placebo or nalmefene. However, after nalmefene 8/9 of the athletes complained in varying degrees of symptoms (anorexia, nausea, dizziness, fatigue and insomnia) suggestive of opiate withdrawal (Table 3). These symptoms appeared 1 h after ingestion of the drug and lasted from 1 to 4 h. Most runners experienced a second wave of side effects 12–18 h after nalmefene ingestion which persisted, in a few instances, up to 36 h.

Discussion

Clinical characteristics

A frequently elicited feature of the menstrual history was the annual occurrence of a single episode of scanty vaginal staining, unaccompanied by molimina or cramps. It tended to be associated with increased dietary...
intake, as during convalescence from injuries, vacation trips or holidays ("Christmas menses"). From this fact and the high maturation values it was apparent that the athletes were "just" amenorrheic rather than "very" amenorrheic, according to the terminology of the late JSL Browne. "Just" amenorrheic denotes a labile suppression of menstrual function that is quick to disappear once physiologic circumstances improve. "Very" amenorrheic refers to a persistent suppression of menses that is refractory to an amelioration of circumstances adverse to the subject.

**Unstimulated LH pattern**

Day-to-day variation in the unstimulated LH pulse frequency patterns of women has been little studied. Cumming et al. (8) noted marked inter-subject variations in LH pulsatility in eumenorrheic athletic women. Other investigators have observed great inter-subject differences in LH pulsatility among seemingly similar subjects with hypothalamic amenorrhea (9, 10). Reame et al. (11) obtained a repeat LH pulsatility pattern in 3 women with hypothalamic amenorrhea over an interval of 3–6 months. In one patient there was no change in pulse frequency; in another there was a moderate increase; in a third there was a pronounced decrease in the performance of the GnRH pulse generator, with occasional higher frequencies too ephemeral to reinitiate ovarian function. Our finding of control period variations in LH patterns over time in several subjects suggests that although these women remained amenorrheic for long periods, their LH secretory pattern likely varied from quiescent to normal circhoral pulsatility.

**Nalmefene response pattern**

Nalmefene, a congener of naloxone and naltrexone, is an orally active narcotic antagonist with a long half-life (T1/2 = 17 h). It is rapidly absorbed from the gastrointestinal tract and passes into the entero-hepatic circulation, which may account for the second wave of side effects that we observed. Nalmefene has approximately four times the affinity of naloxone for μ/E receptors and twice the binding affinity for delta and kappa receptors (12). The role of μ/E receptors in modulating LH secretion in rats and human beings is well established. However, data regarding a putative role of kappa receptors in
regulating LH secretion in male rhesus monkeys and men are thus far negative; those in rats are meager and contradictory. (13, 14).

This study extends an observation by McArthur et al. (15) that naloxone administration was followed by enhanced LH release in one of three athletes with amenorrhea of long standing, normal body composition and low basal levels of gonadotropins. It is uncertain whether the apparently higher proportion of responders to nalmefene in the present study is fortuitous or is related to differences in the properties of the two antiopioid compounds.

Negative responses to naloxone infusion were reported in seven athletes with amenorrhea of comparatively short duration and unsuppressed basal levels of LH (16, 17). However, as noted by Van Vugt et al. (18), the effectiveness of injected naloxone in releasing LH is correlated with pre-injection LH levels: low levels are associated with significant naloxone-induced LH release, whereas high levels are associated with an absence of
response. An hypothesis advanced by these workers to account for such observations is that endogenous opioid secretion is episodic. Elevated pre-injection LH concentrations may be the result of periodic reductions in opioid activity, at which time antagonism by anti-opioid agents has no effect on LH secretion. Increased opioid activity, on the other hand, may be associated with reduced pre-injection LH levels and a significant response to opioid blockade. Supporting evidence for this hypothesis has been presented by Nappi et al. (19). While they did not engage in naloxone testing, these investigators have demonstrated that plasma LH levels are negatively correlated with cerebrospinal fluid $\beta$-endorphin concentrations. Grossman and Besser (20) induced a significant rise in LH in a professional dancer by infusing naloxone. Moreover, Russell et al. (21) challenged four eumenorrheic swimmers with a naloxone infusion and observed a significantly higher peak LH response in the oligomenorrheic group. Samuels et al. (22) failed to find significantly elevated LH blood levels in either six eumenorrheic or six amenorrheic athletes after opioid blockade at rest or during exercise. However, the authors suggest that small group sizes and heterogeneity within groups, as in the present study, may have obscured differentiation. In addition, administration of naloxone as a loading bolus, followed by a 25-min infusion in the subjects at rest, and a presumably briefer infusion in subjects beginning treadmill exercise after the loading bolus, may not have sufficed to elicit a maximal LH response.

In a recent abstract, Loucks et al. (23) reported a stimulating effect of naloxone on LH pulse frequency in cycling athletes as compared to sedentary controls, but not in amenorrheic athletes: an infusion of metaclopromide exerted a converse influence. Lacking information regarding the duration of absent menses in the amenorrheic athletes, the normalcy of luteal function in the menstruating athletes, and the estrogen effect in both groups, we cannot assess their resemblance to our subjects.

Factors contributing to our failure to differentiate the 5/9 responders in the oligo-amenorrheic group from 1/5 in the normally menstruating control group include very small sample sizes and the large dose of nalmefene employed, which evoked a significant rise of LH in Subject No. 14 on day 7 of her cycle (Fig. 3). Using 16 mg doses of naloxone, Grossman et al. (24) elicited positive LH responses in normal young women tested between days 2 and 7. The associated degree of estrogen effect in our subject would have sufficed for the elaboration of low levels of hypothalamic $\beta$-endorphin secretion, demonstrable with large doses of opioid blocking agents.

Endocrine abnormalities resembling those in amenorrheic athletes are being reported by investigators studying patients with hypothalamic amenorrhea, in a proportion of whom exercise appears to be the key initiating factor. Quigley et al. (10) found that half of a group of patients with hypothalamic amenorrhea attri- butable to emotional stress responded with LH and prolactin increases to the administration of naloxone and half to the administration of metoclopramide. LH responsiveness to naltrexone has also been found to be enhanced in hypothalamic amenorrhea attributable to weight loss, oral contraceptive withdrawal and physical exertion by Wildt et al. (25). Sauder et al. (26), Peters et al. (27) and by Khoury et al. (28). Wildt et al. (29) employed naltrexone to treat 75 patients with luteal insufficiency, anovulation and amenorrhea attributed to increasing degrees of hypothalamic-ovarian failure (no information regarding a possible role of exercise in these cases is available). Sixty-five patients responded temporarily in varying degrees to naltrexone, and pregnancy occurred in 18/50 desiring to conceive.

The heterogeneity of LH response to nalmefene in our group of athletes is conceivably due to transient variations in endogenous opioid peptide tone. Reference to the fluctuations in resting levels of LH has already been made, and the period elapsing between the last vaginal staining and nalmefene testing varied from 2 to 84 months (Table 1A). Indeed, heterogeneity of LH pulse patterns following naloxone administration has characterized virtually every study of hypothalamic amenorrhea. Since nalmefene blood levels were not measured, we cannot exclude the possibility that differences in the bioavailability of nalmefene account for the heterogeneity. However, this seems unlikely in view of previous studies of nalmefene pharmacodynamics following oral administration.

Our results indicate that in some athletes with exercise-associated oligo-amenorrhea who cannot be prospectively identified by presently available methods, opioid receptor blockade with the $\mu$- and $\kappa$-receptor antagonist nalmefene increases serum levels and the amplitude of LH secretory episodes, and elicits symptoms of narcotic withdrawal. Taken together, these observations suggest that the probability of at least transient increases of heightened hypothalamic opioid tone in such individuals.

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References


References


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