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19-Nortestosterone for Male Fertility Regulation

ULRICH A. KNUTH

HERMANN BEHRE

LUTZ BELKIEN

HINRICH BENTS

EBERHARD NIESCHLAG

It has long been known that administration of gonadal steroids may impair spermatogenesis.[10,11,15] Testosterone alone or androgens in combination with gestagens have been tested for their potential as agents for male fertility regulation (for review see Patanelli and colleagues[17]). To date, no treatment schedule nor any combination of hormones has been able to induce azoospermia in 100% of participating volunteers. Even in men responding with complete disruption of spermatogenesis, testosterone esters have to be given at least every 10 to 12 days to maintain azoospermia because of the relatively short half-life of available preparations.[23]

THE NEED FOR LONG-ACTING ANDROGEN PREPARATIONS WITHOUT INITIAL SERUM PEAK FORMATION AFTER INJECTION

Data from nonhuman primates suggest that testosterone alone may be sufficient to maintain or reinitiate spermatogenesis even in the absence of detectable gonadotropin values.[3,16] One could speculate that peak values of serum testosterone, reached after injection with available testosterone esters, may be high enough to maintain spermatogenesis to a certain extent. Intratesticular testosterone levels under substitution therapy are likely to be much lower than physiologic concentrations. Binding to the androgen receptor is not a linear function of testosterone concentrations, however. Because binding follows a sigmoid curve or logarithmic function, even low concentrations of testosterone may cause sizable receptor occupancy during peaks of serum testosterone concentrations with consequent maintenance of spermatogenesis. To avoid this, a slow-release formulation of an androgen devoid of high-peak concentrations after injection would be required for male fertility control.

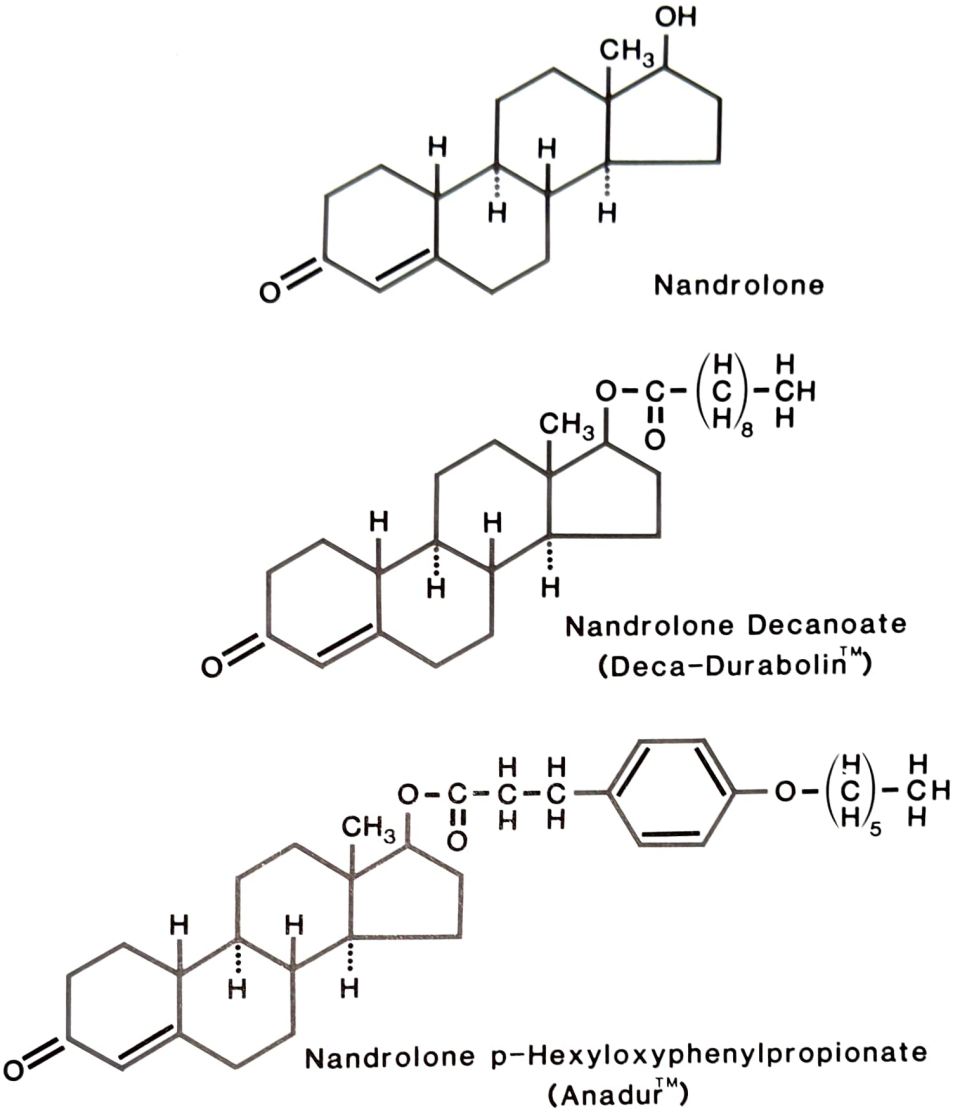

FIG. 29-1. 19-Nortestosterone and its esters.

THE SEARCH FOR AN APPROPRIATE ANDROGEN

Since commercially available testosterone preparations do not provide this characteristic, we looked for other androgenic substances already available on the market.[20,22] In the course of this search, our attention was called to nandrolone (19-nortestosterone, 19NT) and its esters (Fig. 29-1). Since their synthesis and initial testing, they have been used widely as anabolic substances and proved to be without toxic side-effects during many years of clinical use.[6]

PHARMACOKINETIC STUDIES

To characterize commercially available nandrolone esters most suitable for the intended purpose, pharmacokinetic studies with nandrolone hexyloxyphenylpropionate (Anadur; 19NT-HPP) and nandrolone decanoate (Deca-

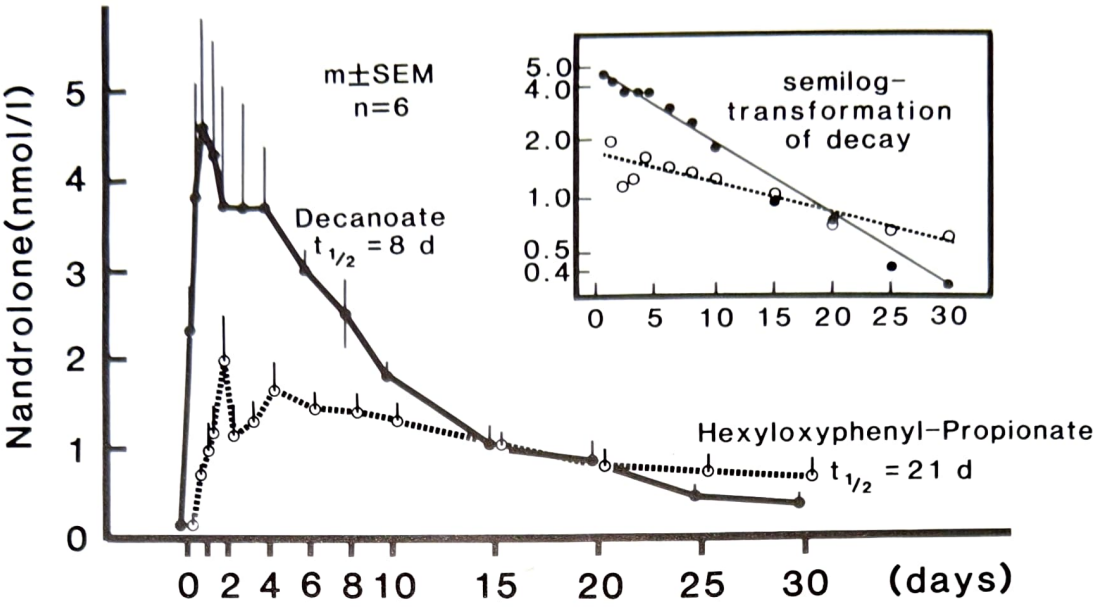

FIG. 29-2. Nandrolone serum levels after IM administration of 50 mg nandrolone decanoate or nandrolone hexyloxyphenylpropionate in a group of six volunteers. (Redrawn after Belkien L, Schürmeyer T, Hano R *et al.*: Pharmacokinetics of 19-nortestosterone esters in normal men. J Steroid Biochem 22:623–629, 1985)

Durabolin; 19NT-D) were conducted using HPLC separation in combination with a specific radioimmunoassay for detection of 19NT in serum.[1] Both preparations led to rapidly increasing levels of 19NT in the peripheral blood after intramuscular injection. Peak levels were reached within 8 hours of 19NT-D administration, whereas 19NT-HPP injections caused a considerably slower release from the injection site; 24 hours were required to reach maximal serum concentrations of nandrolone (Fig. 29-2). Magnitude of peak serum levels showed an inverse relation with a pronounced peak following 19NT-D injection and a more blunted increase after the 19NT-HPP treatment. In five out of the six volunteers tested in a crossover design, the elimination of 19NT was slower after administration of 19NT-HPP compared to 19NT-D. The mean half-life (±SD) of 19NT-HPP was 21 ± 12 days versus 8 ± 5 days for the decanoate. Based on these data for half-life and peak formation, 19NT-HPP was chosen as the androgen ester suitable for further use in clinical trials for a male antifertility agent.

ANDROGENIC PROPERTIES OF NANDROLONE

Although considered to be mainly an anabolic steroid, the parent compound, nandrolone (19NT), exerts a strong inhibitory effect on gonadotropin secretion. Compared to testosterone, nandrolone binds to the androgen receptor with 54% higher affinity and possesses some gestagenic activity.[5,19,24,25] Like testosterone, 19NT is metabolized by 5-alpha-reductase to the reduced compound, dihydronandrolone (DHNT). In contrast to dihydrotestosterone (DHT), binding affinity of DHNT to the androgen receptor is considerably lower (Fig. 29-3). Binding data imply stronger androgenic activity in all target

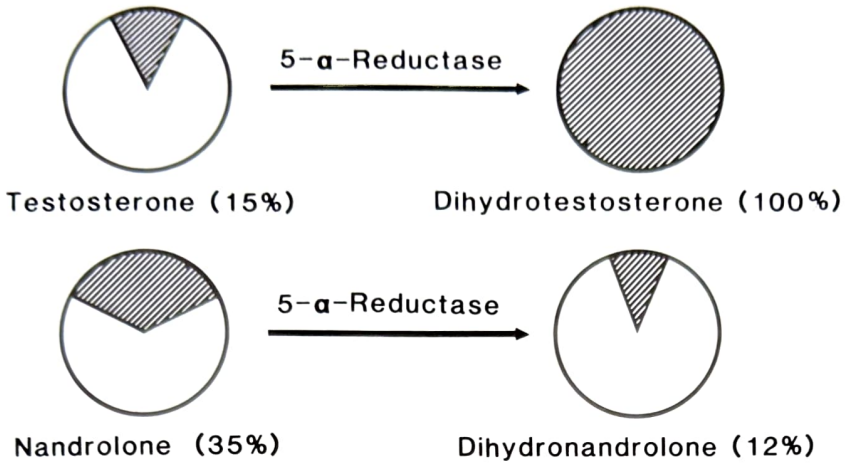

FIG. 29-3. Relative binding of testosterone, nandrolone, and their metabolites to the androgen receptor. (Redrawn after Toth M, Zakar T: Relative binding affinities of testosterone, 19-nortestosterone and their 5-alpha-reduced derivatives to the androgen receptor and to other androgen binding proteins: A suggested role of 5-alpha-reductive steroid metabolism in the dissociation of "myotropic" and "androgenic" activities of 19-nortestosterone. J Steroid Biochem 17:653–660, 1982 and from Toth M, Zakar T: Different binding of testosterone, 19-nortestosterone and their 5-alpha-reduced derivatives to the androgen receptor of the rat seminal vesicle: A step toward the understanding of the anabolic action of nortestosterone. Endokrinologie 80:163–172, 1982)

tissue without 5-alpha-reductase activity and very low androgenic activity in organs with DHT dependence.

PREVIOUS STUDIES WITH ANABOLIC STEROIDS

In view of the favorable pharmacokinetic background, it is surprising that 19NT has not been tested previously for its potential as a male antifertility agent. To our knowledge, no clinical studies have been performed by other groups. Anabolic steroids alkylated in position 17 have been studied for their effects on gonadotropin and testosterone production, but detailed studies on spermatogenesis are virtually nonexistent.[2,4,13,18] A case report has appeared, and a significant reduction in sperm density after 1 and 2 months of daily treatment with methandienone was reported by Holma.[13] In this study three out of fifteen men became azoospermic,[12,14] however treatment time was too short to allow a comprehensive analysis.

CLINICAL TRIALS

PILOT STUDY

To test the potential of 19NT-HPP as a male antifertility agent in more detail, we conducted a pilot study in a small number (n = 5) of volunteers.[21] All of them engaged in heavy physical exercise to improve muscle mass and they

expected additional improvement of strength by the anabolic action of the substance to be used.

Participants received 100 mg/week IM injections of 19NT-HPP for 3 weeks, followed by 200 mg/week for the subsequent 10 weeks. Follow-up continued until sperm density again reached more than 20 mil/ml.

During treatment, despite testosterone levels in the range of orchidectomized men, none of the volunteers reported a loss of libido or potency. Azoospermia was first observed in one subject after 7 weeks of treatment (Fig. 29-4). By week 13, all participants were azoospermic. Azoospermia persisted for 4 to 14 weeks after treatment. Seminal measurements returned to normal 8 weeks after treatment in one subject, 14 weeks in another, and 20 weeks in two. In the fifth volunteer normalization of seminal parameters took more than 24 weeks, when sperm density was still below 1 mil/ml. During week 30, however, all parameters returned to normal.

During treatment, body weight increased from 87.5 ± 0.9 kg to 94.0 ± 1.9 kg, whereas testicular size was reduced by 50%, lagging behind the fall in sperm count. Since all participants were involved in heavy weight lifting during the study period, it is difficult to decide whether the increase in weight was caused by the anabolic steroid alone or was attributable to an increase in muscle mass consequent to extreme training.

The absence of impaired libido and impotence in spite of severely reduced testosterone values proved the androgenic potency of 19NT-HPP. Since no other side-effects became apparent, a certain potential of 19NT as a male antifertility agent seemed to be established.

LONG-TERM STUDY

Because of the promising results of the pilot study, the antifertility potential of 19NT-HPP was investigated in greater detail in a larger group of normal volunteers. To exclude bias by extreme exercise and related habits of bodybuilders, only men with average physical activity, who were not interested in increasing their strength, were recruited for a second study.

Twelve volunteers received 200 mg/wk of 19NT-HPP IM for 7 weeks to allow gradual accumulation of effective 19NT serum levels in a minimum of time. After this initial phase, injection intervals varied between 1 and 3 weeks in an effort to maintain effects on serum gonadotropin values and spermatogenesis at a lower dose of nandrolone administration. Total treatment lasted 25 weeks, succeeded by follow-up examinations for 17 additional weeks. The regimen was supplemented by a final test at week 52. Possible changes in general well-being and sexuality were monitored by standardized tests and specially designed protocols.[7]

Differences in injection intervals during the second half of the treatment phase did not influence any of the parameters measured, except 19NT serum levels themselves. This demonstrates the advantageous influence of the long half-life of the ester used.

As in the pilot study, 19NT treatment generally suppressed serum gonadotropins below detection limits. This was followed by testosterone levels well in the castrate range. Complete suppression persisted up to week 28.

The subsequent inhibition of spermatogenesis caused azoospermia in two volunteers as early as 9 weeks after the first injection of 19NT-HPP, with an

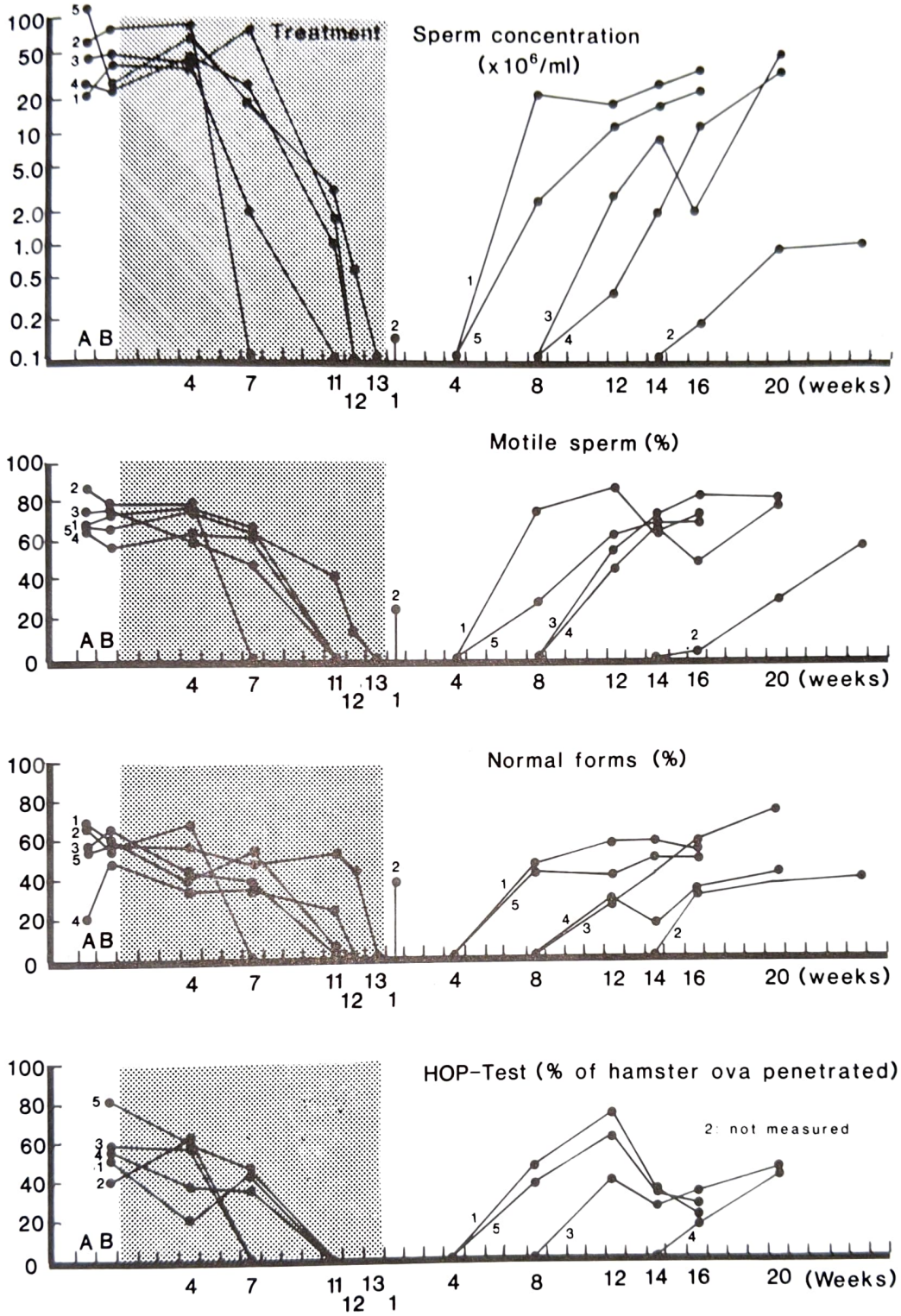

FIG. 29-4. The effect of 19-nortestosterone administration on sperm parameters in five volunteers. Treatment phase of 13 weeks is indicated by shaded area. A and B represent pretreatment control values. (Redrawn after Schürmeyer TH, Knuth UA, Belkien L *et al.*: Reversible azoospermia induced by the anabolic steroid 19-nortestosterone. Lancet i:417–420, 1984)

increasing number of men throughout the following treatment period. Twenty-one days after the last injection, 27 weeks after the start of treatment and theoretically the point at which a maximal impact of treatment could be expected, six volunteers presented with azoospermia; two additional volunteers showed only single sperm in the sediment of the ejaculate, and two had sperm counts below 5 mil/ml. Only two out of twelve men treated with 19NT-HPP revealed sperm counts in the normal range above 20 mil/ml with unimpaired motility, representing a failure rate of 17%. One of them, however, had been azoospermic after 9 and 12 weeks of treatment, with a recovery of sperm counts thereafter.

Normalization in the other participants with sperm concentrations above 20 mil/ml occurred as early as 15 weeks after the last injection and was complete in eleven of the twelve men after 28 weeks of follow-up. The volunteer with sperm counts below 5 mil/ml at week 52 presented with normal values 8 weeks later.

In contrast to the study in body-builders, no significant weight increase occurred. In spite of low testosterone concentrations, no effect on libido or potency became apparent when weekly protocols on several parameters of sexual activity, desire, and functions were evaluated. Complaints about impaired somatic functions or reduction of general well-being were not reported by any of the volunteers.

Administration of 19NT-HPP did not affect liver enzymes, creatinine, uric acid, serum electrolytes or serum lipids; however, hemoglobin, erythrocytes, hematocrit, and mean corpuscular volume (MCV) were significantly elevated following 13 weeks of treatment when compared to pretreatment values. They did not exceed the range considered normal by our laboratory standards, however.

EVALUATION

Both studies presented here provide evidence that 19NT may be used to suppress spermatogenesis in men while its androgenic property is strong enough to maintain libido and potency.

The ideal result of complete azoospermia in all participants at the end of the treatment phase during the small pilot study (with body-builders undergoing extreme physical exercise) could not be achieved in a larger number of men.[21] Nevertheless, the rate of 83% of azoospermia or severe oligospermia with sperm concentrations below 5 mil/ml observed at the end of treatment compares favorably to results achieved with testosterone esters at more frequent injections (for review see Patanelli and colleagues[17]). Because of its long half-life, 19NT-HPP offers a considerable advantage over available testosterone esters, since azoospermia can be maintained in a large number of men with longer intervals between single injections.

Besides the long half-life of the 19NT-ester used and its slow release without pronounced peak levels after injection, the effectiveness of 19NT as a potential male antifertility agent (compared to testosterone) seems to depend greatly on the unique binding characteristics of the parent substance and its reduced metabolite to the androgen receptor already discussed above. We

have yet not tried to find the minimal effective dose, but it is to be expected that the psychosexual effect on libido and potency as well as the inhibitory effect on gonadotropin secretion is still maintained at lower concentrations of 19NT. This effect is probable because mediating central brain areas are devoid of 5-alpha-reductase activity and the higher endogenous androgenic activity of nandrolone compared to nonreduced testosterone is of influence.

A potential antifertility agent used by a healthy person has to be beyond the possibility of any adverse effect on general health and well-being, especially when taken for extended periods. In contrast to 17-alkylated steroids, no changes in liver function have been reported with 19NT. Our studies to date also demonstrate the lack of liver toxicity since transaminases were unchanged throughout the entire periods under investigation.

Considering the suppressive action of testosterone on HDL and stimulating effects on LDL (for review see Goldberg and associates[8]) with the consequence of an increased risk of cardiovascular problems, it is of special interest to note that 19NT at doses used did not alter serum triglycerides, cholesterol, or LDL and HDL concentrations.[9]

In summary, one can conclude that 19NT-HPP seems to offer advantages over available testosterone esters as a male antifertility agent. Ongoing and future studies using different dose regimens or the combination with other substances will reveal whether 19NT-HPP will maintain its position in the front line of potential methods for male fertility regulation.

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