Enhanced Nitinol Properties for Biomedical Applications

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Abstract: In recent years, Nitinol producers and medical products have experienced an exponential growth, driven by advanced manufacturing techniques and the use of progressively less invasive medical procedures. Concurrently, new processing techniques have been developed to further enhance the valuable properties of Nitinol used in medical devices; recent patents on these techniques include changing the composition of nickel and titanium, alloying the nickel-titanium with other elements, improving melting practices, heat-treating the alloy, and mechanical processing of the alloy. For example, alloying the nickel-titanium with ternary elements may widen the superelastic temperature operating window, maximize/minimize the stress-strain hysteresis, and improve the radiopacity of a Nitinol intraluminal device comparable to that of a stainless steel device of the same strut pattern coated with a thin layer of gold. Limiting to less than 30% the final cold work step (after a full anneal, and before the shape-setting step) may improve the Nitinol fatigue lifetime of about 37%, the fatigue lifetime being a primary factor limiting the performances of Nitinol endoluminal prosthetic implants. Local selective and differential thermo-mechanical treatments have also been devised to achieve different physical properties in different portions of a Nitinol medical device in order to improve its performance under expected operating conditions.

1. INTRODUCTION

In recent years, equiatomic or near-equiatomic inter-metallic compounds of nickel and titanium (commonly referred to as Nitinol or Nitinol alloys) have been used in a wide and growing variety of insertable and implantable medical devices, such as guide wires [1], cannulae [2], catheters [3], needles [4], introducer sheaths [5]; intraluminal filters [6], vascular (coronary and peripheral) and non vascular stents [7] and graft support systems [8]; dental instruments [9], endodontic files for use in the cleaning, shaping, and widening stages of root canal procedures [10]; surgical instruments [11], devices for occluding anatomical defects [12], manipulation [13] and retrieval [14] devices; components for binding together a pair of biological tissues [15], anchor devices [16], sutures [17], staples for bone fixation [18]; devices for correcting spinal deformities [19], orthodontic brackets [20] and archwires [21]; heart anatomy reshaping devices [22], valves [23]; these represent the most relevant applications and related recent patents.

These applications are made possible by the most celebrated superelastic and shape memory properties [24-26], as well as by a number of lesser-known and more specific properties properly reviewed in a series of papers and reports by Duerig and co-workers (see for example refs [27, 28]). These properties include elastic deployment, thermal deployment, kink resistance, biocompatibility, constant unloading stress, biomechanical compatibility, dynamic interference, hysteresis, MR compatibility, fatigue resistance, and uniform plastic deformation. The reference international

organizations and conferences, i.e., International Conference on Martensitic Transformations (ICOMAT), European Symposium on Marensitic Transformation (ESOMAT), and particularly International Conference/Organization on Shape Memory and Superelastic Technologies (SMTS), have chronicled over the years the tremendous progress in understanding these Nitinol properties and the success that Nitinol technology has recently experienced in the medical industry. Nevertheless, researchers involved in the field are still constantly discovering new and fascinating attributes of Nitinol, and some aspects of Nitinol have not yet been fully clarified, such as the ductility of the B2-phase as it relates to pseudo-twinning, unique observations of the R-phase, the stiffness of Nitinol during unloading, an unusual situation in which austenite can be stress induced from martensite, and an unusual deformation memory associated with subsequent modes of deformation [29].

New processing techniques have been developed since the early 1980's to further enhance the valuable properties of Nitinol. These techniques include changing the Ni/Ti compositional ratio in binary NiTi, alloying the nickel-titanium with other elements, improving melting practices, heat treating the alloy, and mechanical processing of the alloy. Examples of such techniques have been extensively reported in patents: Fountain *et al*. (1982, [30]) disclose processes for producing a shape memory Nitinol alloy having a desired transition temperature; DiCarlo and Walak (2000, [31]) disclose a process for improving ductility of Nitinol; Pelton and Duerig (1998, [32]) disclose cold working and annealing a Nitinol alloy to lower a transformation temperature; Thoma *et al*. (1989, [33]) describe a process for adjusting the physical and mechanical properties of a shape memory alloy member by increasing the internal stress level of the alloy through cold work and heat treatment; Simpson *et al*. (1988

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[34]), Mitose and Ueki (1999, [21]), Duerig *et al.* (1998, [35]), Boylan and Huter (2004, [36]) teach adding a ternary element to a nickel-titanium alloy to enhance engineering properties.

Recently, the availability of micro-tubing and high precision laser cutting, as well as the use of progressively less invasive medical procedures, have focused attention on the quickly growing and technologically demanding intraluminal applications, particularly on self-expanding stents. Accordingly, new and complex manufacturing and processing techniques have been developed to improve radiopacity, thermo-mechanical properties, and fatigue resistance of Nitinol intraluminal medical devices. New selective and differential themo-mechanical treatments have also been devised to spatially modulate the local mechanical properties of such devices, in order to improve their performances under expected operating conditions. In this paper we review some of the most relevant and recent patents related to these new techniques. The large field of Nitinol surface treatments is outside the scope of this paper and will be neglected. We begin with a brief introductory description of superelasticity, shape memory effect, and common Nitinol processing techniques.

2. NITINOL PROPERTIES AND PROCESSING TECHNIQUES

NiTi alloys having shape memory effect and superelastic properties generally have at least two phases: a martensitic phase (M) and an austenitic phase (A). Martensite is stable at relatively low temperatures, has a relatively low tensile strength, is soft and malleable, its structure is composed of self-accommodating twins, and can be easily deformed by de-twinning the structure via an applied stress. Austenite is stable at higher temperatures, has a relatively high tensile strength, is a strong and hard phase of the alloy, exhibiting properties similar to those of titanium, and is characterized by a B2 structure. The properties of the austenitic and martensitic phases of NiTi alloys have been deeply discussed by Otsuka and Ren in a recent review paper entitled "Physical metallurgy of Ti-Ni based shape memory alloys" [26]. The direct A→M (reverse M→A) martensitic phase transformation can be induced by a decrease (increase) in temperature or by the application (removal) of an external load. Shape memory and superelaticity are closely related to these different temperature-driven and stress-driven transformation modes, respectively.

2.1. Shape Memory

Conventionally, M_S and M_F indicate the martensite start and finish temperatures, at which the transformation from austenite to martensite begins and is completed, respectively, as the temperature decreases ($M_S > M_F$). Likewise, A_S and A_F indicate the austenite start and finish temperatures, at which the transformation from martensite to austenite starts and is completed, respectively, as the temperature increases ($A_S < A_F$). Since $A_S > M_F$ and $M_S < A_F$, a hysteresis loop is displayed when the percent austenite (or martensite) phase in the alloy is plotted as a function of the temperature for a thermal cycle involving the direct A→M and reverse M→A transformations.

Shape memory means that a metal alloy, plastically deformed in the martensitic phase, spontaneously returns to its previous undeformed shape ("remembered" shape) when heated to the austenitic phase. Shape memory effect is imparted by heat treating the alloy at temperature above A_F, at which the austenitic phase is stable (see paragraph 2.6 for the details of the imparting-memory treatment); the shape of the metal during this heat treatment is the shape "remembered". Fig. (**1**) illustrates the shape memory effect in a strain versus temperature (ε-T) plot. The heat-treated metal is cooled to a temperature below M_F at which the martensitic phase is stable, causing the austenitic phase to transform to the martensitic phase with no changes in the macroscopic shape of the alloy (1). The metal in the martensitic phase is then plastically deformed into a particular desired shape (2). With subsequent heating (3,4), the metal gradually reverts to its original shape as the martensite transforms to austenite (4). Ultimately, at a temperature above A_F, the material completes the return transformation to the austenitic phase and fully recovers the applied strain. The alloy may accommodate several percentage points of recoverable strain (8% in the example of Fig. (**1**).
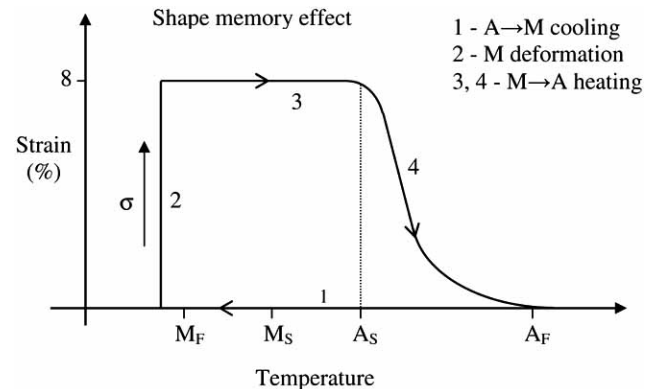

Fig. (1). Diagram of strain versus temperature illustrating the shape memory effect for an exemplary shape memory alloy.

2.2. Superelasticity

Superelasticity (or pseudoelasticity) refers to the ultra high elastic behavior of the alloy under stress: typical reversible strains of up to 10% elongation can be achieved in a superelastic Nitinol wire as compared to 0.5% reversible strain in a steel wire, for example. The superelastic behavior appears in the austenitic phase when stress is applied to the alloy and the alloy changes from the austenitic phase to the martensitic phase. This particular martensitic phase is more precisely described as stress-induced martensite (SIM), which is unstable at temperatures above A_F. As such, if the applied stress is removed, the stress-induced martensite reverts back to the austenitic phase.

Figure (**2**) illustrates an idealized stress-strain curve for a superelastic nickel-titanium alloy at a temperature above A_F. With applying an increasing stress, at first, the superelastic specimen deforms elastically until it reaches a particular stress level where the alloy undergoes a stress-induced phase transformation from the austenitic phase to the martensitic

phase. The line from point O to point B represents the elastic deformation of the nickel-titanium alloy. After point B the strain is no longer proportional to the applied stress and it is in this region between point B and point C that the stress-induced transformation of the austenitic phase to the martensitic phase begins to occur. As the phase transformation progresses, the alloy undergoes significant increases in strain with little or no corresponding increase in stress. The strain continues to increase while the stress remains essentially constant until the transformation of the austenitic phase to the martensitic phase is complete. This constant or plateau region C-D is known as the loading stress, since it represents the behavior of the material as it encounters continuous increasing strain. It is in this plateau region C-D that the transformation from austenite to martensite occurs. At point D the transformation to the martensitic phase due to the application of stress to the specimen is substantially complete. Thereafter, further increase in stress is necessary to cause further deformation. The martensitic metal first yields elastically upon the application of additional stress and then plastically with permanent residual deformation. In the figure, beyond point D, the martensitic phase begins to deform elastically, and beyond point E, the deformation is plastic or permanent.

If the load on the specimen is removed before any permanent deformation has occurred, the stress-induced martensite elastically recovers and transforms back to the austenitic phase, and the specimen returns to its unstrained state. The reduction in stress first causes a decrease in elastic strain until the martensite recovers its original shape, provided that there was no permanent deformation to the martensitic structure. The line from point E to point F represents the elastic recovery of the martensite. As stress reduction reaches the level at which the martensitic phase begins transformation to the austenitic phase, the stress level in the specimen remains essentially constant until the transformation to the austenitic phase is complete; i.e., there is significant recovery in strain with only negligible corresponding stress reduction. In the figure, at point F in the recovery process, the metal begins to transform from the stress-induced, unstable, martensitic phase back to the more stable austenitic phase. In the region from point G to point H, which is also an essentially constant or plateau stress region, the phase transformation from martensite back to austenite takes place. This constant or plateau region G-H is known as the unloading stress. After the transformation back to austenite is complete, further stress reduction results in elastic strain reduction. The line from point I to the starting point O represents the elastic recovery of the austenitic metal to its original shape.

This ability to incur significant strain at relatively constant stress upon the application of a load and to recover from the deformation upon the removal of the load is commonly referred to as "superelasticity" or "pseudo-elasticity", and sometimes "rubber-like" effect. Regarding the terminology, the authors believe that the term "pseudoelasticity" should be used when the closed loop of the stress-strain curve is due to "non elastic" physical phenomena such as SIM. This should help engineers to consider Nitinol properties as non-linear and strongly temperature dependent thermo-mechanical behaviours. From the practical

point of view, "superelasticity" or "pseudoelasticity" are synonyms for describing the stress-strain curve reported in Fig. (**2**).
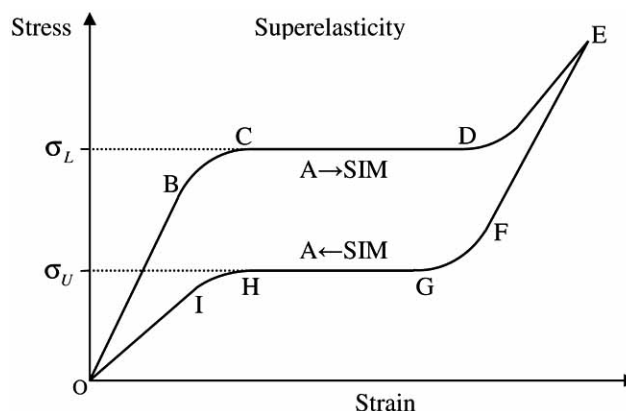

Fig. (2). Diagram of stress versus strain, at a temperature above the austenitic final temperature A_F, illustrating the superelasticity of an exemplary shape memory alloy.

As emphasized above, the pseudoelastic stress-strain curve is characterized by two regions of nearly constant stress, identified above as loading plateau stress C-D and unloading plateau stress G-H. The loading plateau stress represents the period during which martensite is being stress-induced in favor of the original austenitic crystalline structure. As the load is removed, the stress-induced martensite transforms back into austenite along the unloading plateau stress part of the curve. Naturally, the loading plateau stress σ_L always has a greater magnitude than the unloading plateau stress σ_U. The difference $\sigma_L - \sigma_U$ defines the stress hysteresis of the system.

2.3. Use of Superelasticity in Medicine

The superelastic effect is frequently utilized for delivery and deployment of medical devices that pass through very small openings inside the body and then elastically spring back into the desired shapes (elastic deployment) at the target site. For example, a self-expandable stent is typically maintained at a compressed diameter by a tubular delivery sheath which overlies the stent to facilitate the insertion and delivery within a blood vessel. When the constraining member (e.g., the delivery sheath) is removed and the stress is released, the martensite transforms to austenite and the stent recovers its deployed configuration. The stent may expand from the compressed diameter to an expanded diameter and come into contact with the vessel wall to support it. According to this embodiment, the nickel-titanium alloy has an austenite finish temperature A_F which is less than or equal to human body temperature (37°C) so that removal of the constraining member is sufficient to trigger the transformation to the austenitic phase.

The constant unloading stress exhibited by a Nitinol material over a large strain range is widely utilized in orthodontic and orthopedic devices. In contrast to stainless steel and other conventional appliances, a Nitinol device may

apply a constant optimized force over a wide range of shapes, i.e., over a very broad treatment time, without the need of continuous force adjustments. Even the hysteresis, commonly considered a drawback due to the reduced energy storage efficiency, may be a desirable feature in stent design, as will be discussed in paragraph 5.

A great number of medical devices are based on stress induced martensite. The most commercially important patents now pending for medical devices incorporating SIM alloys include the Jervis's series which is listed in Jervis patent [37].

2.4. Use of Shape Memory in Medicine

Besides superelasticy, the shape memory effect may be utilized to deliver and deploy the medical device comprising the nickel-titanium alloy. In other words, a change in temperature instead of an applied (removed) stress may control the transformation from martensite to austenite. For example, a stent may be deployed by heating instead of retraction of a delivery sheath. According to this embodiment, the nickel-titanium alloy has an austenite finish temperature (A_F) which is less than or equal to body temperature (37°C). The medical device is maintained at a temperature of less than A_S, prior to and during delivery of the device into the body, thereby maintaining a martensitic structure of the nickel-titanium alloy. The device transforms to the austenitic structure and thus deploys when warmed up to about body temperature. Cooling of the device during delivery is desirable to prevent the martensitic structure from prematurely transforming to austenite. As the device is being advanced in the body, the cooling may entail keeping the device at a temperature below A_S by, for example, flushing a cold fluid through the device or through a delivery system of the device itself. Preferably, the nickel-titanium alloy has a value of A_F of at least about 32°C, yet no higher than about 37°C.

2.5. Transformation Temperature Tuning

The A_F and the other transformation temperatures of Nitinol alloys can be fine-tuned within a desired temperature range by controlling the alloy composition and processing.

The transformation temperatures are very sensitive to small changes in the ratio of nickel to titanium. Increasing the proportion of nickel to titanium in the alloy provides a means of reducing the A_F temperature to a desired level, thus stabilizing austenite. For example, A_F is generally above 100°C for equiatomic NiTi, whereas it is generally around 100°C for slightly off-stoichiometric alloys including an excess of nickel (e.g., from about 50.6 to about 50.8 at. % Ni). As discussed above, Nitinol alloys, which are austenitic at and slightly below body temperature, are known to be useful for medical devices. Specifically, alloys including 50.6-50.8 at. % Ni and 49.2-49.4 at. % Ti are considered to be medical grade Nitinol alloys.

The transformation temperatures are also very sensitive to the presence of minute quantities of alloying elements or trace amounts of impurities. Additions of chromium, palladium, cobalt and/or iron may be effective in reducing A_F, whereas additions of vanadium and/or cobalt may be effective in reducing M_S. Thus, Nitinol's properties thus can

be tailored for specific applications by selecting the appropriate concentration, type, and combination of alloying elements. On the contrary, oxygen and carbon are contaminants which should be excluded from the system as they can affect the transformation temperature and reduce mechanical properties. Oxygen has the ability to tie up titanium by forming $Ti_4Ni_2O_x$ inclusions, thus depressing M_S. The exact impact of oxygen on Nitinol properties is still unclear. Excess oxygen concentrations may not significantly affect shape memory effect or superelasticity, but may negatively impact ductility and fatigue resistance. Carbon forms TiC inclusions which also tie up Titanium and depress M_S as a consequence. ASTM F 2063-05, the standard specification for wrought Nichel-Titanium Shape Memory Alloys for Medical Devices and Surgical Implants, accepts Oxygen and Carbon contents up to 500 ppm in NiTi compound.

2.6. Nitinol Processing Techniques

Nickel-titanium alloys have a variety of characteristics and behaviors depending on composition and processing conditions. Products made from Nitinol alloys nevertheless typically undergo a common series of processing steps. However, the following processing sequence may be generally employed to produce Nitinol alloys and Nitinol medical devices.

Melting

A melt incorporating the desired amounts of alloying elements is formed and then cooled into a solid (e.g., an ingot). High purity raw materials (usually Ti sponge and electrolytic grade Ni) are preferably melted in an inert gas or vacuum atmosphere: the constituent components are placed in a crucible, then induction heated or electrical arc heated in a vacuum induction melting (VIM) process or vacuum consumable arc melting (VAR) process, respectively. Remelting is generally desirable to obtain satisfactory microstructural homogeneity in the ingot. For example, successive VAR processes or a VIM/VAR double melting process may be employed. The Nitinol ingot after VIM/VAR processing has the desired general composition of nickel to titanium as well as trace elements of carbon, oxygen, iron, and other impurities.

Hot working

After the melting process, the Nitinol ingot has little ductility. The ingot may then be hot worked into a first shape (e.g., bar, rod, hollow tube, or plate) by extruding, hot rolling, or forging. Hot working is generally employed to refine the as-cast structure of the ingot and more specifically to achieve a microstructure that exhibits better workability. The hot working is generally carried out at temperatures in the range of approximately 700°C to 950°C, and may require multiple hot working and reheating cycles. The reheating may be carried out over an eight hour period. Preferably, the ingot undergoes a minimum deformation of about 90% during hot working in order to homogenize the as-cast, dendritic microstructure. Prior to hot working, it may be beneficial to carry out a solution heat treatment that involves soaking the ingot at an elevated temperature for a given time, followed by quenching. The solution heat treatment may aid in homogenizing the microstructure of the alloy, and

preferably, is carried out at temperatures in the range of approximately 1000°C to 1150°C.

Cold working

The Nitinol first shape is moved closer to the target component with the desired mechanical and physical properties by means of a series of cold working steps. Typically, the Nitinol receives cold working in the range of 30 to 50 % at each step, and is also annealed at about 600 to 800°C for stress release after each cold work step. The interspersed anneal cycles minimize work hardening of the Nitinol caused by the repeated cold work, through recrystallization and growth of the austenite grains. The cold working is typically performed by cold drawing for wires through a series of dies, cold rolling for tapes, and tube drawing with an internal mandrel for tubes.

Machining operations

Machining operations, such as drilling, cylindrical centerless grinding, or laser cutting may also be employed to fabricate the desired component. Other operations, such as wire braiding or winding, may also be carried out.

Shape Setting

A heat treatment is employed after the last cold work step to impart a "memory" of the desired final shape ("remembered" shape) and to optimize the shape memory, superelastic and mechanical properties of the component. Usually, shape setting involves annealing the component while constrained in a final shape at a temperature in the range of approximately 350 to 550°C. The number, duration and the temperature of the heat treatments may alter the transformation temperatures. In alloys having an excess of nickel atoms (e.g., from about 50.6 to about 50.8 at. % Ni), for example, the heat treatment described above may cause nickel-rich precipitates to form, thereby reducing the nickel content of the matrix and causing the transformation temperatures to increase. The precipitates may also improve the tensile strength of the nickel-titanium alloy. At this stage, the Nitinol component has been transformed into a standardized, nearly finished condition for consumption in the industry.

3. IMPROVED RADIOPACITY

Nickel-titanium alloys are commonly used for the manufacture of intraluminal biomedical devices, such as self-expandable stents, stent grafts, embolic protection filters, and stone extraction baskets. A distinct disadvantage with these self-expanding Nitinol devices is the fact that they are not sufficiently radiopaque as compared to similar structures made from gold or tantalum. As a result of this poor radiopacity, such devices may be difficult to visualize from outside the body using non-invasive imaging techniques, such as x-ray fluoroscopy. Visualization is particularly problematic when the intraluminal device is made of fine wires or thin-walled struts. Consequently, a clinician may not be able to accurately place and/or manipulate a Nitinol stent or basket within a human blood vessel.

Conventional approaches to improving the radiopacity of nickel-titanium medical devices include the use of radiopaque markers or coatings. For example, gold markers attached to ends of a stent may guide the positioning of the device and delineate its length during an x-ray procedure. Alternatively, a medical device may be plated, clad or otherwise coated with gold or another heavy metal to create a radiopaque surface or outer layer. In another approach, a heavy metal cylinder may be included within the lumen of a stent to produce a radiopaque core. These techniques to improving radiopacity, however, create a number of important complications such as material compatibility, galvanic corrosion, high manufacturing cost, coating adhesion or delamination, biocompatibility, increased delivery profile of the device, loss of coating integrity following collapse and deployment of the device, interference with the mechanical behavior of the device, etc.

Radiopacity can be appreciably improved by increasing the wall or strut thickness of the Nitinol self-expanding device. But increasing strut thickness detrimentally increases the stent chronic outward force, and decreases the flexibility of the device, which is a quality necessary for ease of delivery.

Radiopacity can also be improved by alloy addition. Some relevant and recent patents reviewed in the following paragraphs discuss alloying nickel-titanium with a ternary element, which increases Nitinol's radiopacity yet preserves its biocompatibility, its superelastic qualities and all the other associated properties that are advantageous for intraluminal biomedical applications.

3.1. Addition of Tungsten

A patent entitled "Thermoelastic and superelastic Ni-Ti-W alloy", published in January 2005 by Pelton [38], discloses a radiopaque NiTiW stent for implantation in any body lumen. The added tungsten in specified amounts improves the radiopacity of the Nitinol stent comparable to that of a stainless steel stent of the same strut pattern coated with a thin layer of gold. Furthermore, the stent retains its superelastic and shape memory behavior and further maintains a thin strut/wall thickness for high flexibility.

Composition

In order to achieve a sufficient degree of radiopacity while maintaining the superelastic engineering properties of a binary nickel-titanium, the radiopaque stent of the invention should include tungsten whose atomic percent is greater than or equal to 5 and less than or equal to 12. In various preferred embodiments, the atomic percent of the nickel is approximately 50.8, the atomic percent of the titanium is a maximum of approximately 40, and the atomic percent of the tungsten is approximately 10. A preferred method of fabricating the superelastic radiopaque stent is also indicated by the inventor, together with suggested temperature ranges for the A_F temperature of NiTiW ingot ($0 \leq A_F \leq 20$°C), NiTiW tubing ($-15 \leq A_F \leq 0$°C), and final laser cut NiTiW stent ($0 \leq A_F \leq 30$°C).

Properties

This invention provides a Nitinol stent with improved radiopacity and without the downside of increasing the stent wall thickness or strut thickness. As explained above, increasing wall or strut thicknesses detracts from the flexibility of the stent, which in turns is detrimental to deliver-

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