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December 1, 2000

Via Overnight Mail

Dr. Mary S. Wolfe
Executive Secretary
National Toxicology Program
111 T.W. Alexander Drive
Building 101
Room A322
Research Triangle Park, NC 27709

Re: 10th Report on Carcinogens Listing Recommendation for Metallic Nickel and Nickel Alloys

Dear Dr. Wolfe:

On behalf of Ultimate Wireforms, Inc., we strongly object to the proposed listing of "metallic nickel and certain nickel alloys" as "reasonably anticipated to be human carcinogens" in the *10th Report on Carcinogens* by the National Toxicology Program (NTP). 65 Fed. Reg. 61,352 (Oct. 17, 2000). The listing, as recommended in the *Draft Report on Carcinogens Background Document for Metallic Nickel and Certain Nickel Alloys (Background Document)*, if finalized would totally abdicate the application of sound scientific judgment in reviewing the available toxicological and epidemiological data, and ignore over 100 years of actual human experience using metallic nickel and nickel alloys with no significant adverse effects on human health.

I. BACKGROUND

Ultimate Wireforms manufactures precision orthodontic wire products made of stainless steel and nickel-titanium alloys, including orthodontic archwires, springs, and ligature wires. Accordingly, Ultimate Wireforms is very concerned about the potential listing of metallic nickel and nickel alloys in the *Report on Carcinogens*. The available evidence demonstrates that nickel metal and alloys are safe and valuable materials and are not associated with increased incidences of carcinogenicity.

The stainless steel and nickel-titanium orthodontic products manufactured by Ultimate Wireforms are regulated as Class I medical devices by the U.S. Food and Drug Administration and have been used safely by U.S. consumers for decades. Ultimate Wireforms' products also meet strict European CE standards mandated by the European Union. Stainless steel provides excellent

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corrosion resistance and desirable tensile strength, while nickel-titanium offers excellent corrosion resistance along with unsurpassed super-elastic properties. As such, these nickel alloys are highly valued in orthodontic applications.

Ultimate Wireforms adamantly objects to the recommended listing of nickel metal and certain nickel alloys as "reasonably anticipated" human carcinogens for the following reasons:

- (1) Associating metallic nickel and certain nickel alloys with cancer ignores over a century of human experience using nickel and nickel alloys safely;
- (2) The conclusions in the *Background Document* regarding metallic nickel and certain nickel alloys fail to reflect the application of sound scientific judgment, particularly considering that the alleged evidence of carcinogenicity in laboratory animals is associated with forms of the metal/alloys (powder) and routes of exposure that are not relevant to humans;
- (3) The data cited with respect to prosthetic implants comprised of nickel alloys does not support listing; and
- (4) Given the unique properties possessed by individual alloys, NTP should not broadly classify all nickel alloys in the same listing, but separately review each alloy.

These issues are discussed in detail in the comments submitted by the Specialty Steel Industry of North America (SSINA), which are hereby incorporated by reference. The comments set forth below focus on a particular concern of Ultimate Wireforms, specifically the suggestions in the *Background Document* that certain nickel alloys and medical implants are associated with increased cancer risks.

Listing metallic nickel and nickel alloys as "reasonably anticipated" human carcinogens would ignore the fact that nickel alloys such as stainless steel and nickel-titanium have been used for several decades and are universally recognized as being safe for use in a wide variety of consumer products, including orthodontic and other medical devices. Any classification of these benign nickel alloys as carcinogens would be entirely improper. The impact of such a gross misclassification upon the orthodontic industry could be devastating.

II. NICKEL ALLOYS HAVE BEEN SAFELY USED IN ORTHODONTIC APPLIANCES AND MEDICAL IMPLANTS FOR DECADES AND POSE NO CANCER RISK

A. Human Experience Indicates That Nickel Metal And Alloys Pose No Significant Risks To Health

NTP recognizes that metallic nickel and nickel alloys have been "[w]idely used in commercial applications for over 100 years." 65 Fed. Reg. at 61,354. Despite this heavy usage of nickel, the *Background Document* acknowledges that there is no sufficient evidence from humans associating nickel metal and nickel alloys with cancer. *Background Document* at 33-36. Similarly, the International Agency for Research on Cancer (IARC) found "inadequate evidence of carcinogenicity in humans" for nickel metal and alloys, as well as metallic implants. *Id.* at 33, 35.

Given the widespread usage of nickel metal and alloys in society, if nickel metal and alloys were truly associated with an increased cancer risk, one would expect to find significant statistical evidence of carcinogenicity associated with these substances in humans. The lack of any such evidence indicates that no significant risk exists. NTP should consider this extensive human experience with nickel metal and alloys when reviewing the listing recommendation.

B. Evidence Pertaining To Orthodontic And Other Medical Implants Does Not Support The Listing Of Nickel Metal And Alloys

Nickel alloy medical implants have been widely used in the United States for decades without accompanying reports of significant adverse effects. In 1988, over 6.5 million metallic orthopedic implants were in use in the United States (Sharkness *et al.*, 1993) -- a number that most likely is larger today -- but only 35 cases of tumors in the region of the implant had been reported over the past 30 to 40 years (McGregor *et al.*, 2000).¹

Numerous studies have established the biocompatibility of nickel alloy implants, particularly orthodontic appliances, that are in use today.² For example, nickel-titanium implants (which

¹ As explained in the comments submitted by SSINA, a number of factors other than the metallic content of the implants likely contributed to such tumors, including (1) non-specific local inflammatory responses to implanted foreign material; and (2) the presence of cancer risk factors such as rheumatoid arthritis.

² The *Background Document* does not assert that stainless steel medical implants are associated with increased cancer risks. Accordingly, these comments focus on nickel-titanium alloys
(continued...)

typically contain approximately 55 percent nickel by weight) have been the subject of numerous biocompatibility studies. See Attachment A.³ These studies have uniformly found that nickel-titanium orthodontic appliances are highly biocompatible; none have found any indication of cancer risk. Significantly, clinical studies by Fukuyo *et al.* (1990) and Lu (1990) found strong biocompatibility and indicated no tumorigenic responses among a series of subjects implanted with nickel-titanium alloys, with follow up periods ranging from several months to six years.^{4,5} In fact, stainless steel and nickel-titanium orthodontic appliances have been used safely in humans since at least the 1970s.

The lack of cancer risk associated with nickel-titanium alloys stands in stark contrast to the extraordinary statement in the *Background Document* that "[i]n general, alloys containing > 50% nickel were carcinogenic in [animal] implantation studies." *Background Document* at 51. Nickel-titanium alloys demonstrate that high nickel content alloys are not necessarily (if at all) carcinogenic, and that any generic classification of such alloys is scientifically unsound. Further, the *Background Document* presents no data suggesting that nickel-titanium alloys are associated with increased cancer risks. Other than nickel-titanium which is 55 percent nickel, to Ultimate Wireform's knowledge, no other high nickel content (greater than 50 percent nickel) alloys are used as implants in the United States today.

Accordingly, given that the available data on nickel-titanium alloys show no increased cancer risk and no other medical implants comprised of high nickel content alloys are known to be in use in the United States today, it would be legally and scientifically improper for NTP to list either

² (...continued)
which contain higher levels of nickel than stainless steel.

³ Attachment A contains a bibliography and several papers regarding studies on the biocompatibility of nickel-titanium alloys, including: Fukuyo *et al.*, *Shape Memory Implants, in Engineering Aspects of Shape Memory Alloys* 470 (1990); Lu, *Medical Applications of Ni-Ti Alloys in China, in Engineering Aspects of Shape Memory Alloys* 445 (1990); Barrett *et al.*, *Biodegradation of orthodontic appliances. Part I. Biodegradation of nickel and chromium in vitro*, 103 *Am. J. Orthod. Dentofac. Orthop.* 8 (1993); Bishara *et al.*, *Biodegradation of orthodontic appliances. Part II. Changes in the blood level of nickel*, 103 *Am. J. Orthod. Dentofac. Orthop.* 115, 118 (1993); Park and Shearer, *In vitro release of nickel and chromium from simulated orthodontic appliances*, 82 *Am. J. Orthod.* 156 (1983).

⁴ See Fukuyo *et al.* (1990); Lu (1990).

⁵ Another study found that nickel-titanium orthodontic appliances release nickel "in amounts significantly below the average dietary intake" of nickel. See Bishara *et al.* (1993). See also Park and Shearer (1983).

nickel alloy medical implants or high nickel content alloys generally as reasonably anticipated human carcinogens. If NTP is to make a listing, it must identify specific nickel alloys or medical implants that have demonstrated evidence of tumorigenic activity. Ultimate Wireforms does not believe that sufficient evidence exists to proceed with such a listing.

III. EACH ALLOY IS A UNIQUE SUBSTANCE AND SHOULD BE SEPARATELY REVIEWED

An alloy is a metallic material, homogeneous on a macroscopic scale, consisting of two or more elements so combined that they cannot be readily separated by mechanical means. Alloys are not simply mixtures in which the constituents retain their separate identities and can easily be separated. During manufacture the constituents are heated to very high temperatures, usually above their melting points. The constituents then react with, and dissolve into, each other to form alloys consisting of new crystalline structures and compounds with new properties that are retained during cooling to room temperature. The original elemental constituents can not be separated from each other by normal physical means.

As a result, the physical, chemical, and toxicological properties of an alloy are different from those of its elemental constituents. Accordingly, the carcinogenic potential of nickel alloys must be evaluated separately from that of metallic nickel. And, because of the unique properties that each alloy possesses -- which are influenced by a number of factors, including its chemical composition, history of melting and heat treatment, and any mechanical working to which it was subjected -- judgments regarding the carcinogenic potential of an alloy can not be made on the basis of the concentration of nickel or any other metal in the alloy.

Of particular significance in assessing cancer risk, the unique properties of each individual alloy affect the release rate and bioavailability of individual metal ions. Alloys that are more corrosion resistant, such as stainless steels and nickel-titanium, are expected to present lower biological risks.

In sum, because each alloy is essentially a separate substance with separate properties, NTP can not issue a generic listing of "nickel alloys." Rather, the agency must separately consider each alloy.

IV. CONCLUSION

Based on the foregoing comments, Ultimate Wireforms strongly believes that the recommendation in the *Background Document* to list metallic nickel and nickel alloys as "reasonably anticipated" human carcinogens is unsupported by the available evidence, contrary to sound scientific judgment, and at odds with decades of safe human experience with these materials. In particular, the evidence regarding nickel alloy medical implants neither supports the listing of

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metallic nickel and nickel alloys nor demonstrates that such alloys are associated with significant cancer risks.

When the available evidence is combined with general human experience, it should be clear that nickel alloy implants are not properly associated with increased cancer risks. Further, given the widespread usage of nickel alloy implants, which involve intimate human contact with nickel alloys and in some cases nickel metal released from the alloy, the available evidence indicates that nickel metal and alloys pose no significant cancer risk and should not be listed as "reasonably anticipated" human carcinogens. Any conclusion that would associate nickel alloys with increased cancer risk would be legally and scientifically unsupportable.

NTP decisions have significant downstream regulatory and economic impacts. Moreover, identification as a carcinogen by NTP -- or other agency classification decisions based on NTP conclusions -- has widespread social and economic impacts (*e.g.*, toxic tort litigation, consumer product deselection). Accordingly, NTP has a legal duty to ensure that its decisions are based on sound science and the product of reasoned decision making before stigmatizing a substance as a known or reasonably anticipated carcinogen. The available evidence for metallic nickel and nickel alloys in particular does not meet this standard.

If you have any questions or we may be of any further assistance, please do not hesitate to contact us.

Very truly yours,



Joseph J. Green
Counsel to Ultimate Wireforms, Inc.

Attachments

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ENGINEERING ASPECTS OF SHAPE MEMORY ALLOYS

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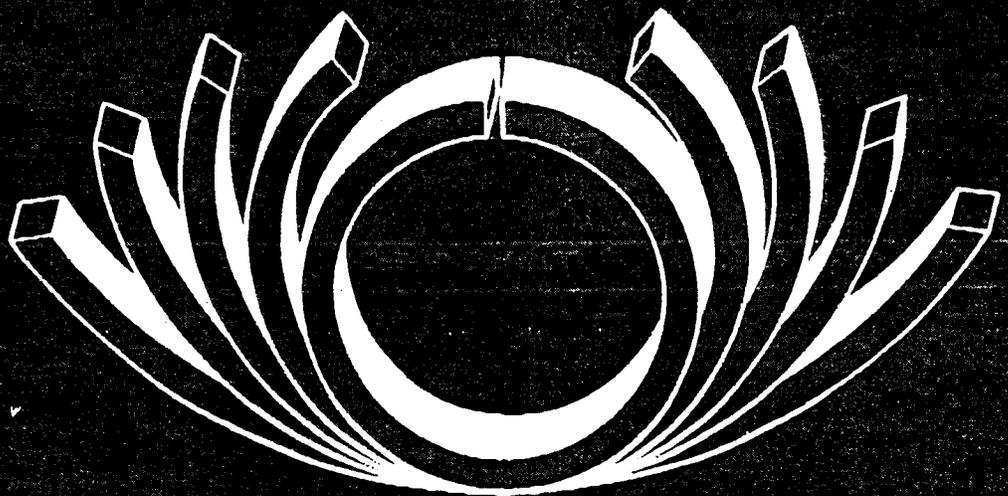


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Medical Applications of Ni-Ti Alloys in China

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Chairman and Professor of Orthopedic Department,
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Ni-Ti combines the unique characteristics of shape memory and superelasticity with excellent fatigue life, wear characteristics and corrosion resistance. Not only does it have many industrial applications; its good biocompatibility makes it an ideal biological engineering material, especially in orthopedic surgery and orthodontics. Its function cannot be compared to any of the conventional materials.

1. Fundamental Medical Studies

Ni-Ti alloys have been applied to the medical field in China for ten years. Before clinical applications, a series of fundamental medical studies were performed, such as corrosion resistance, cell growth inhibition, trace nickel analysis of hair and the tissue response to sample coupons implanted in animals.

1.1 Corrosion Tests

Corrosion testing was carried out by quantitative *in vitro* testing¹. Seven kinds of media were used, simulating the conditions in the mouth and human body. Specimens were put into the media and sealed at 37°C for 72 hours. The weight loss was measured on equiatomic Ni-Ti coupons with the dimensions of 19.38 x 0.63 x 14.87 mm using comparative standards of 316L stainless steel (Table 1).

Table 1: Corrosion Rates of Ni-Ti

Media	Mass corrosion rate (mm/y ²)	Corrosion Resistance Grade
Synthetic Saliva	2.9x10 ⁻⁵	A
Synthetic Sweat	2.8x10 ⁻⁵	A
Hank's Solution	0	A
1% sodium chloride sol.	5.5x10 ⁻⁵	A
1% Lactic Acid	5.7x10 ⁻⁵	A
0.05% hydrochloric Acid	0	A
0.1% sodium sulphate acid	6.9x10 ⁻⁵	A

An experiment to determine the corrosion of implanted Ni-Ti coupons in rabbits was also carried out² using coupons of 10x10x2 mm in size. The results are shown in Table 2.

Table 2: Corrosion of Ni-Ti Implanted in Rabbits

No.	Implanted time (Days)	Weight increase (g)	Corrosion rate (mm/yr.)
1	3	-9.1x10 ⁻⁵	5.6x10 ⁻³
2	7	-3.8x10 ⁻⁵	1.1x10 ⁻³
3	15	-2.4x10 ⁻⁵	3.1x10 ⁻⁴
4	30	-7.2x10 ⁻⁵	4.5x10 ⁻⁴
5	90	-3.4x10 ⁻⁵	6.7x10 ⁻⁵
6	180	-4.7x10 ⁻⁵	4.8x10 ⁻⁵
7	360	-4.2x10 ⁻⁵	2.4x10 ⁻⁵

1.2 *In Vitro* Toxicity³

In vitro toxicity was evaluated by cell growth inhibition tests, adhesion tests or cell adhesion, which had advantages of being short term tests and at the same time being highly repeatable and reliable. Mouse fibroblast L-cells were grown in Eagle's medium with the addition of 10% calf's serum. The Ni-Ti specimens were put into the culture chamber. A cell suspension was prepared and pipetted into the chamber containing a humidified carbon dioxide atmosphere at 37°C for 24 hours. Finally, they were fixed and compared with a negative control. The results showed that the cells grew well on the surface of the alloy.

1.3 Histological Observation⁴

In order to observe tissue tolerance to implants, 60 Ni-Ti specimens were implanted in the femur and subcutaneous area of rats for periods of 3 to 10 months. X-ray photographs taken after one week showed newly formed bone tissue in close contact with the Ni-Ti. Radiographic examination of the implants showed normal bone healing with no evidence of reaction and/or resorption of bone and no rejection phenomenon over a 10 month period.

The histological observations indicated that new formed bone tissue was already growing between the compact bone and the separated bone. After one week, part of the sponge tissue covered the Ni-Ti surface. After two weeks, the gap between the compact bone and Ni-Ti was nearly filled with newly formed bone. From 4 to 8 weeks, the amount of compact bone in contact with the Ni-Ti increased with time. After 8 weeks normal bone tissue was observed. Subsequent stages showed only an increase in the compactness of the bone. The tissue response consisted of a thin pseudo-membrane surrounding the test pieces; microscopic examination shows no inflammatory reaction, and the biocompatibility of Ni-Ti was good. As a result, it is considered that Ni-Ti is a valuable implant material for dental and medical applications.

1.4 The Analysis of Ni-Content in Dog Implant

Though a variety of alloys containing nickel are widely used in medicine, pure nickel has been demonstrated to be harmful to the human body. In order to investigate whether the nickel in the Ni-Ti implants may migrate to other parts of the body, a trace nickel analysis of dogs' hair was performed by means of X-ray spectrograph, both preimplantation and postimplantation.

Four young dogs were used: two for preliminary tests and two for formal tests. Three Ni-Ti disks were used per dog, each 7.5mm in diameter and 2mm in thickness. The specimens were embedded in the soft tissue of the dogs' right hind legs. The anterior

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dorsal region of the thorax was shaved to obtain the hair used for analysis. As a control, the hair was cut 1-3 days prior to implantation. When the hair grew postoperatively, it was shaved again for testing. The hair was cut from the same region after 6, 9, 12, 18 and 24 months. The results, given in Table 3, show that the nickel content in the dogs' hair increased only slightly after implantation. The surfaces and weight of the specimens changed very little.

Table 3: Nickel Contents in Dogs' Hair Pre- and Postimplantation

	Nickel content (ppm)
preimplantation	0.50-0.60
6 months	0.20-0.30
9 months	0.10-0.63
12 months	0.96-0.92
18 months	0.87-1.15
2 years	0.86-0.54

2. Clinical Applications

Since 1981 Ni-Ti devices have been used clinically in Beijing and Shanghai, in fields such as orthodontics, oral-maxillofacial surgery, orthopedic surgery, plastic surgery and gynecology.

2.1 Shape Memory Ni-Ti Clip for Tubal Sterilization

In 1981, a new tubal clip for femal sterilization was designed: it could be opened in ice water and closed at 40°C. Four rabbits were initially tested. A month after the application, the clips were found to be covered by a smooth serosal layer without any adhesion. From December 1981 to March 1985, these types of clips were applied to 325 women for sterilization with satisfactory results⁴.

The clips were 2 mm in width, either 15 or 17 mm in length, and had a space of 0.1 mm between the two arms to avoid cutting the tube and prevent fistula formation. The inner parts of the two arms were toothed. Their weight varied from 0.4 to 0.47 gm.

Minilaparotomy was done under local anesthesia and the uterine tube was traced out to the fimbriae routinely. With the isthmic and ampullary portions of the tube held up by Allis forceps, the opened clip was removed from ice water with mosquito forceps and placed directly over the isthmus 30 mm from the uterine cornu. The two arms closed spontaneously after 40°C warm saline was poured over the clip. Then the tube was replaced into the abdominal cavity. The total operative time was recorded from anesthesia to the end of the operation. Any feeling of discomfort during the application of clips was noted and recorded. Patient follow-up was done 6 months after the operation and yearly thereafter.

The average operation time was 14 minutes, with times ranging from 6 to 45 minutes. Patients did not complain of pain either during or after the operation. There was neither traumatic injury nor hematoma. In only one case was a mild infection of the abdominal incision noted.

One hundred and forty-four cases were followed for more than 2 years and 124 cases for more than 3 years. X-rays of the pelvis in 10 cases revealed a normal position of the clips without distortion. Hysterosalpingograms in 3 cases revealed blockages of the tubes at the position of the clips. Follow-up showed that 29 cases had very mild backache. One had irregular periods which diagnostic curettage proved to be functional uterine bleeding with cystic hyperplasia of the endometrium. Six had oligomenorrhea, and none had menorrhagia. Four women became pregnant 5-10 months after sterilization, all of whom were treated in the first 6 months of our project. On second operations performed on three women, the clips were found to be in correct positions, with fistula formation in one while in the other two, the tubes were very thick and large. The tubes were not excised or tied: the procedure brought about very little

trauma. There were 4 failures with preliminary unrefined clips made during the first six months of the project. No ectopic pregnancy was noted. Among these 4 failures, two cases were performed in the postmenstrual period giving a failure rate of 2/127 (1.63%), and two cases were postabortion (a failure rate of 6.4%). Postpartum and postabortion sterilizations yielded failure rates 2 to 5 times higher than that of postmenstrual cases, probably due to edema and congestion of the tissue after conception. In second operations, the clips were found to be 15 and 17 mm in length. Clamps with increased forces at the tips of two arms were designed (over 75 grams). During the last three years, 250 women were operated upon with no failures. In total, the failure rate was 1.23%.

In conclusion, the clips with a narrow width of 2 mm are conveniently clamped on the isthmic portion of the fallopian tube for sterilization. A more reliable reversal is possible by microsurgical reanastomosis.

2.2 Internal Fixation in Orthopedic Surgery Via Compressive Staples⁵

Since 1980, the shape memory characteristic of Ni-Ti has been used to manufacture an internal fixation staple. From 1981 onward these staples have been used in clinical cases with promising results. The alloy is Ni-44 wt %Ti. The most commonly used staple is 1.5 mm in diameter and consists of an undulated body and 2 pointed arms attached to each end of the body at an angle of 60 degrees. The undulated body can be straightened between 0 and 5°C. Once the pointed arms are inserted into the bone, body temperature and hot saline pads induce a recovery of the straightened staple to its original undulated shape, thereby exerting a compressive force on the bone ends. The recovery force (bending moment) has been measured to be 3 kg-mm after straightening the staple 5 mm in ice water and heating it to 37°C. If it is then heated to a higher temperature and then cooled again to 37°C, the recovery force increases to 5.5 kg-mm. In order to enhance the recovery force, the temperature of the saline pads should be above 37°C but well within the range that can be tolerated by the patient. The Ni-Ti shape memory alloy possesses a better wear resistance than the commonly used Ti-alloys and medical-grade stainless steel. It also possesses good tissue compatibility and can resist corrosion by body fluids.

From December 1981 to July 1985 Ni-Ti staples were used in cases of bone and joint operations, including fractures of the ankle, triple arthrodesis of the foot, arthrodesis of the wrist joint, arthrodesis of the hip joint, fracture of the patella, fracture of the olecranon, and metacarpal and phalangeal fractures. In addition to internal fixation with the staples, patient immobilization was used. All cases showed either bony union or sound ligament healing. With the exception of arthrodesis cases, functional recovery was also satisfactory. Follow-up examination of those patients retaining the staples for more than 2 years showed no signs of inflammation and no tenderness over the operated area. X-ray examination revealed solid bony union without loosening of the staples and without absorption of the fixed bones.

The compressive staple can be easily applied. It is only necessary to make a small incision on the periosteum and to drill a small hole through the incised periosteum in each bone fragment. The periosteum of the bone ends can be retained. Thus damage to the endosteum, as occurs during intramedullary nailing, and damage to the periosteum, as is produced during extensive stripping for plate fixation, can be obviated. The surgical trauma is minimized and favorable conditions for bone healing are provided. However, as the area thus fixed is rather limited as is the fixation force, external immobilization with a cast is necessary in the early post-operative period.

Histologically, in 8 cases no obvious foreign body reaction was detected in the soft tissues abutting the staples which were removed after bone union.

2.3 Shape Memory Pins in Oral-Maxillofacial Surgery⁶

Since November 1981, Ni-Ti pins have been used in oral-maxillofacial surgery, such as in the fixation of fractures of the mandible, in orthognatic surgery, in reconstructive

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surgery of maxillofacial bone defects, in iliac or rib bone transplantation post-mandibulectomy, etc. From clinical analysis and observations of 18 cases, a complete 100% success rate has been achieved. The results show that Ni-Ti is an excellent biomaterial for use in oral and maxillofacial surgery, and has bright prospects for medical applications.

2.4 Shape Memory Double-Cup Hip Prosthesis⁷

Double-cup total hip surface replacement has certain advantages, but its clinical application is limited due to postoperative complications such as loosening or displacement of the prosthesis, avascular necrosis of the femoral head or delayed fracture of the femoral neck. In the double-cup prosthesis now available, the diameter of the rim of the femoral component should be larger than that of the bottom. Otherwise, it cannot be positioned over the femoral head which is the main cause of loosening and displacement. Luck modified the femoral cup to a cylindrical form, so that it could prevent the cup from rotating into varus, but it required a wider trimming of the femoral head and neck. Perhaps this is the cause of delayed fracture of the femoral neck after replacement.

The lip of the femoral component (made of NT-2 shape memory alloy) is able to shrink by means of raising the local temperature after the component is applied to the femoral head. Over trimming of the femoral head can be avoided and the stability is thus significantly increased.

The design of the shape memory cup of the femoral head and its clinical trial in 16 cases (17 hips) is presented in the present work. The clinical indications were osteoarthritis, central dislocation, joint stiffness and pathological dislocation. The follow-up period was 4-48 months. All of these cases were found to have their femoral components in the proper position and no loosening or fracture of femoral neck was found. The femoral cup was cracked in one case after a bad fall two years after the operation. Another case had constant postoperative hip pain even though the cup still remained in place. The cups were removed one year after operation and a total hip replacement was then performed.

2.5 Intervertebral Artificial Joints⁸

The artificial joint is shaped from a Ni-Ti shape memory sheet 0.8 mm thick and 8 mm wide. The maximum distances between 2 arched arms are 13, 14, 15 and 16 mm. A two mm long inverted spur projects anteriorly and laterally on both the upper and lower arched arms. There is a vertical "resisting" plate over each end to prevent posterior slippage. The length of the plate is 6 mm with a central notch which is clamped by pliers. The depths of the concave arches are 16, 17, 18 mm, smaller than the average the sagittal diameter of the cervical vertebra in order to prevent compression of the spinal cord by protrusion into the vertebral canal.

There are five characteristics of the joint: its shape can be freely changed in 4 to 10°C water and recovered at normal body temperature (36-37°C); the loading capacity of the anterior opening of the joint prosthesis when compressed to half distance is 164 MPa - larger than the net weight of the skull; the fatigue lifetime of the alloy at 490 MPa is over 2.5×10^7 cycles, and the alloy exhibits good wear resistance; the alloy is non-toxic to the human body, not harmful to tissue, and corrodes slower than 0.001 mm/year; the magnetic conductivity of the alloy is less than 1.002.

In the operation, the artificial joint is pressed by a hemostat clamp in 5 to 10°C aseptic physiological saline solution to make the distance between upper and lower arched arms about half of the original distance, and to completely close the opening so that the artificial joint can be easily introduced by passing through the narrow outer opening of the intervertebral space into the deep part of the intervertebral space until the resisting plates are situated just lateral to the anterior margin of the vertebra. The implant then recovers rapidly to its original shape by warming to normal body

temperature. The implant, acting as a support, is prevented from slipping by means of the arched upper and lower arms and the inverted spurs. The patient is allowed to sit up with a plaster collar and to be ambulatory the day after the operation. Neck collar fixation is maintained for about six weeks. The movement of the cervical vertebral with the artificial joint is schematical.

Our patient mainly suffer from adult osteogenic cervical spondylosis and cervical fracture-dislocation complicated with compression symptoms of the spinal cord. The corresponding size of the joint is selected for the patient, and the patient should be examined again to determine spinal column mobility and to identify any hidden fractures that may be present. In all, 32 cases have been reported (24 male and 8 female) with ages ranging from 24 to 65 years (46.5 year average). Of these, 16 cases suffered from cervical fracture dislocation complicated with paralysis and 16 suffered from cervical spondylosis. In total there were 37 intervertebral space operations, in which 4 involved 2 vertebrae and one underwent two operations. As to the distribution of the vertebral levels, 6 cases were C4-5, 23 cases C5-6 and 8 cases C6-7. The operations were all quite smooth with surgery times ranging from 60 to 120 minutes.

The advantages of using the artificial joint are that bone grafting is not necessary, and that suffering and complications related to surgery can be prevented because the operation time is shortened. There were no complications due to inward or outward slippage, and no absorption of bone graft or pain over the bone graft donor area were observed. Mobility of the diseased vertebra is preserved (or increased) which follows with the human body's anatomical and physiological principles. The incidence of degenerative changes occurring in the neighboring vertebrae due to transmitted local movement after fusion-fixation of the diseased vertebra is reduced. The device also possesses a certain spreading action (the force is 8-16 kg when compressed to half its height, which exceeds the weight of skull). Thus it not only can prevent kyphotic deformities which often appear after resection of diseased bone, but it can also improve the original angular deformity (mostly seen in patients with vertebral trauma). Surgical procedures and manipulating techniques are simplified and fusion-fixation is not necessary after decompression.

Through clinical application, it is suggested that this kind of intervertebral joint prosthesis possesses articulating and supporting action; long term follow-up is necessary to observe the duration of its function and the reaction to the implantation.

2.6 Scoliosis Correction Rods²

The diameters of the Ni-Ti rods vary from 6.8 to 7.8 mm, and the lengths vary from 200 to 400 mm depending upon the individual. The shape recovery temperatures range from 35°C to 39°C. Three kinds of rod are available: straight, "L"-shaped and curved. The diameter of the fixation wire is 1 mm. The sterilized instruments are put into refrigerator preoperatively.

After exposure of the vertebral laminae and the articular process, the facet joint surface is destroyed bilaterally and parts of the articular processes are removed from the apex of the convex side to facilitate corrective manipulation. Two memory rods are fixed by wires using the sublaminar method. When the trunk is manipulated, hot saline solution moistened gauze (34 to 50°C) is spread over the rods. When the rods warm to A_s , they soon recover their original shape and produce a corrective force.

Throughout the manipulation period, the patient is monitored with spinal stimulating potentials. Facet joint fusion is then carried out by placing cancellous bone in the spaces of laminae and articular process. The incision is then washed and sutured - postoperative external immobilization is not required. The patient is kept in bed for 6 weeks.

Between 1982 and 1985, operations were carried out on 70 patients with idiopathic scoliosis. Of these, the preoperative Cobb's angles ranged from 35° to 105° with a mean of 53.8°. The postoperative Cobb's angles ranged from 9° to 67° with a mean of 25.8°, resulting in corrections ranging from 13° to 62° with a mean of 25.9°. In percentage, the angles were corrected 23.4% to 75% (a mean of 51.8%). The

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postoperative incremental increases in height ranged from 20 to 60 mm (mean of 39 mm). The lengths of the rods were from 22 to 40 cm, and the numbers of vertebrae which were fixed ranged from 5 to 13. The upper-ends of the rods protruded into the subcutaneous tissues in 2 cases, both because of insufficient wire fixation.

Shape memory scoliosis rods can offer an efficient corrective effect; the percentage of angle correction averaged 5.18% in patients treated in the above described way; Luque reported 65 cases of scoliosis (25 idiopathic, 40 paralytic), of which the percentages of angle correction were 53-72%. He employed traction, such as Holo traction pre-operatively, and observed only 15°-19° correction during operation. If preoperative correction was combined with the above procedure, the effect would be better. Fracture does not occur in the fulcrum: the fixation of memory alloy instrumentation is distributed over multiple laminae and spinous processes, so the force is dispersed. The shape memory rods are fixed with wire to the laminae, according to the curvature of the spinal deformity. Thus the forces generated during heating and the corrective forces on each segment of the spine are even. The above procedure need not employ a plaster body cast postoperatively. There has also been no corrective angle loss detected in follow-up observation. Kahn reported 42 cases: the corrective angles in Harrington's group were 40% six weeks after operation and 30% in Luque's group; after 19 months of follow-up the corrective angles were 29% in Harrington's group and 33% in Luque's. There has been no appearance of loss of correction in our cases; on the contrary a few cases have shown improvement.

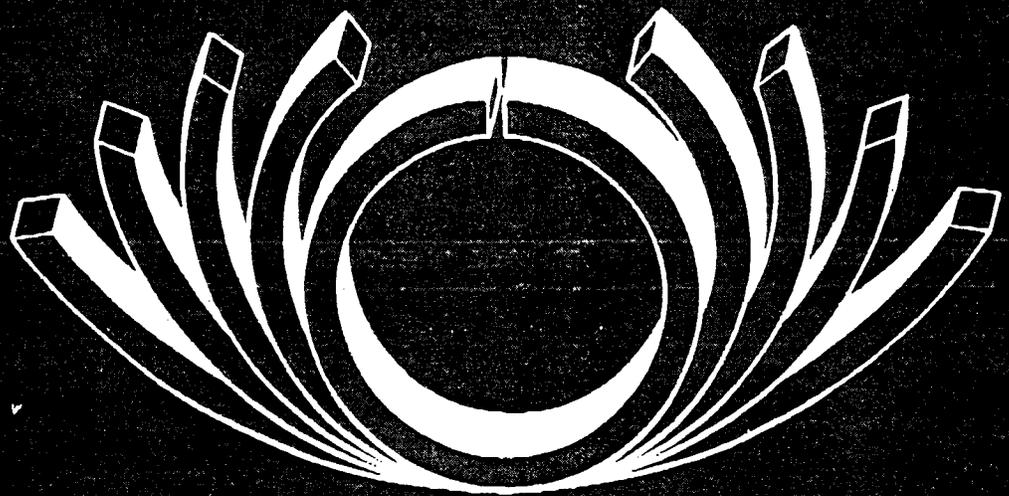
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ENGINEERING ASPECTS OF

ENGINEERING ASPECTS OF SHAPE MEMORY ALLOYS

(Conference 1990)



Shape Memory Implants

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The Shape memory implant (SMI) is a dental endosseous implant made of Ni-Ti shape memory alloy. The device was given official approval by the Ministry of Health and Social Welfare of Japan for use as a medical implant on June 1, 1985. In this paper, information regarding the biocompatibility of the device will be presented, as well as how the SMI is used in clinical operation, and the indications and advantages of the implant compared with the other dental implants.

1. Biocompatibility

Cell cultures were studied using L181 cells, which is anchoring-dependent cell from connective tissue from the rear leg of a rat. Figures 1 and 2 show low and high magnification enlargements of the Ni-Ti specimen; the L181 cell has clearly grown onto the base material. No toxicity of Ni-Ti is observed.

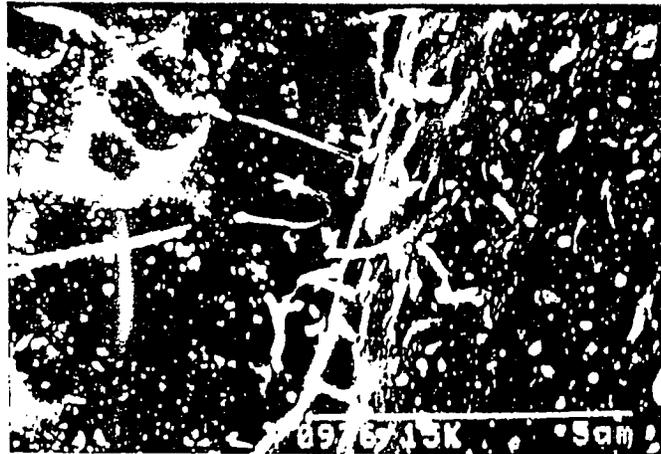


Figure 1: Low magnification SEM micrograph of Ni-Ti after implantation in a rat.

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Figure 2: High magnification SEM micrograph of Ni-Ti after implantation in a rat.

We have studied histology by implanted SMI's into the jawbones of Japanese monkeys and dogs. Figure 3 shows an X-ray photograph 6 months after such an operation and Figure 4 shows the apex of the SMI. Figure 5 shows the same part 6 months after operation. Newly generated bone tissue is observed surrounding the Ni-Ti shape memory implant. New bone contacted or attached tightly to shape memory implant and connective tissue is not observed. From these results, we conclude that the shape memory implant has good biocompatibility.



Figure 3: An X-ray of an SMI implant 6 months after installation.



Figure 4: An SEM photograph showing the apex of an implant.



Figure 5: An SEM photograph showing the body of an implant.

2. Design of the Shape Memory Implant

There are now two types of shape memory implants: single wing and double wing. Figure 6 shows the single wing type shape memory implant; part of the apex opens bucco-lingualy after insertion into jaw bone. Figure 7 shows double wing type; parts of the apex and vent opened as in the case of the single wing type. This effect has a very strong ability of mastication compared with the ordinary non-opening blade type implant.

The stresses in the implant were analyzed by the Finite Element Method. Figure 8 shows a cross-sectional cut of the ordinary blade implants. Bite forces of 60 kg from a vertical direction were supported before the implant was reduced to half its height. Figure 9 shows a similar analysis of the single wing SMI: here the height reduction at the same 60 kg load is half that of the ordinary implant. Figure 10 shows that the double wing SMI compresses only 1/4 as much as the ordinary implant.

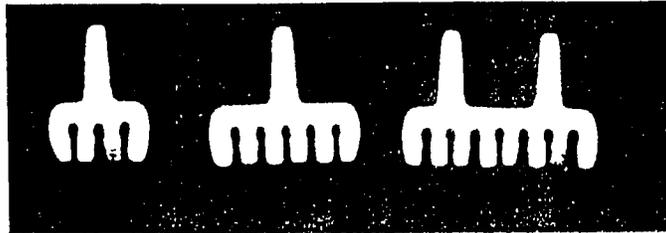


Figure 6: Photograph showing the single wing type of implant.

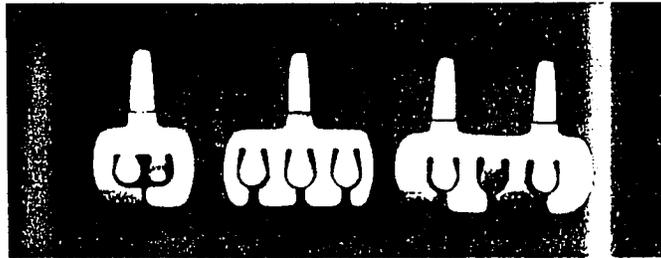


Figure 7: Photograph showing the double wing type of implant.

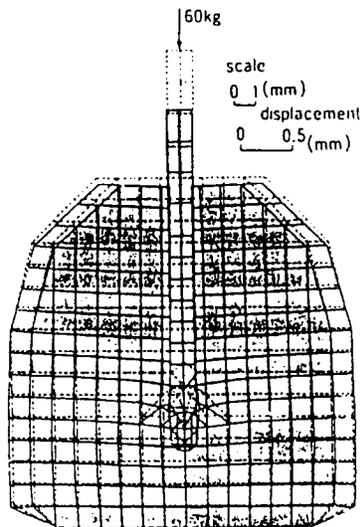


Figure 8: A finite element analysis of an installed conventional dental implant showing significant deflection under a 60 kg load.

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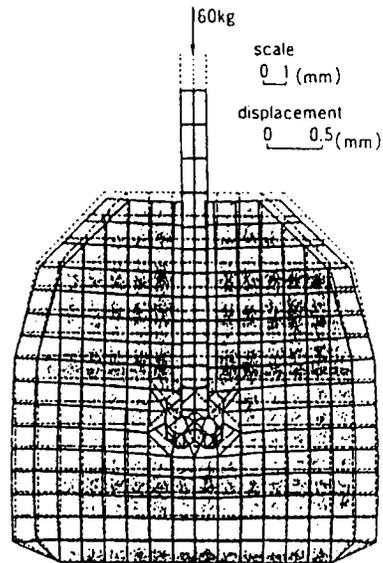


Figure 9: A finite element analysis of a single wing SMA implant showing a much smaller deflection than the conventional implant.

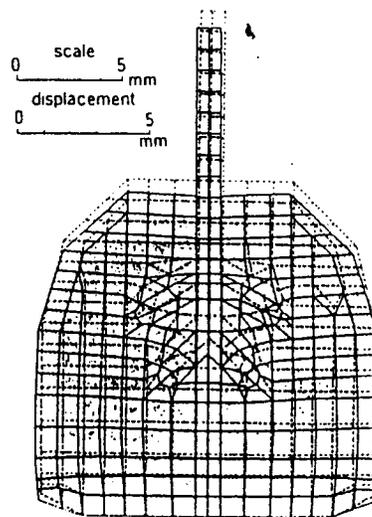


Figure 10: A finite element analysis of a double wing SMA implant showing still further reductions in deflection.

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3. Clinical Studies

Since 1985, there have been approximately 15,000 successful clinical applications of the SMI in Japan. Figure 11 and Figure 12 shows upper edentulous and lower bilateral cases 6 years after operation. Figure 13 and Figure 14 shows upper and lower bilateral cases 4 years after operation. Clinical results have shown good mastication.



Figure 11: X-ray showing an upper edentulous case 6 years after operation.



Figure 12: X-ray showing a lower edentulous case 6 years after operation.

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Figure 13: An upper bilateral case 4 years after operation.

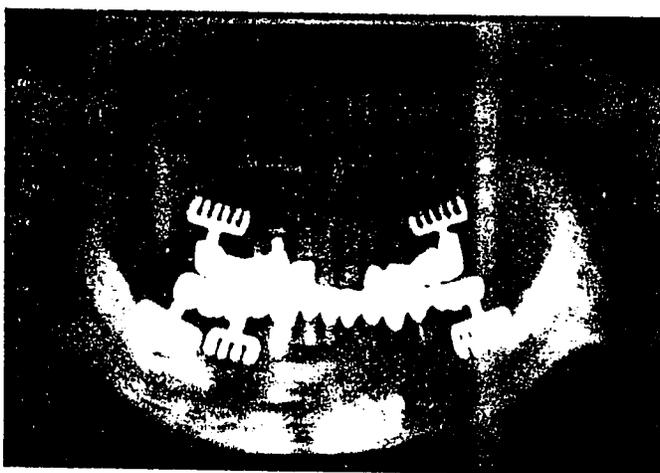


Figure 14: A lower bilateral case 4 years after operation.

The advantages of the shape memory implants are that they exert strong and continuous forces of mastication, have good initial fixation in jaw bone, are easily installed and require a simple operation, and that they have a good stress dispersion from the shape memory effect.

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ORIGINAL ARTICLES

Biodegradation of orthodontic appliances. Part I. Biodegradation of nickel and chromium in vitro

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The purpose of this study is to compare in vitro the corrosion rate of a standard orthodontic appliance consisting of bands, brackets and either stainless steel or nickel-titanium arch wires. The corrosion products analyzed were nickel and chromium. Evaluation was conducted with the appliances immersed for 4 weeks in a prepared artificial saliva medium at 37° C. Ten identical sets were used, each simulating a complete orthodontic appliance used on a maxillary arch with a full complement of teeth. Five sets were ligated to stainless steel arch wires, and the other five sets were ligated to nickel-titanium arch wires. Nickel and chromium release was quantified with the use of a flameless atomic absorption spectrophotometry. The analysis of variance was used to determine if differences existed between the nickel and chromium release according to arch wire type, as well as with time (days 1, 7, 14, 21, and 28). The results indicate that (1) orthodontic appliances release measurable amounts of nickel and chromium when placed in an artificial saliva medium. (2) The nickel release reaches a maximum after approximately 1 week, then the rate of release diminishes with time. On the other hand, chromium release increases during the first 2 weeks and levels off during the subsequent 2 weeks. (3) The release rates of nickel or chromium from stainless steel and nickel-titanium arch wires are not significantly different. (4) For both arch wire types, the release for nickel averaged 37 times greater than that for chromium. How much of these corrosive products are actually absorbed by patients still needs to be determined. (AM J ORTHOD DENTOFAC ORTHOP 1993;103:8-14.)

Orthodontic bands, brackets, and wires are universally made of austenitic stainless steel containing approximately 18% chromium and 8% nickel. In addition, nickel-titanium alloys used as orthodontic arch wires have been introduced in 1970s and present another source of patient exposure to metal corrosion products. Since the oral environment is particularly ideal for the biodegradation of metals because of its ionic, thermal, microbiologic, and enzymatic properties, some level of patient exposure to the corrosion products of these alloys could be assumed, if not assured. Presently, there is little information on the biodegradation of orthodontic appliances in vitro, and even less on how much of these biodegradation products are actually absorbed by the patient.

This project has been generously supported by the American Association of Orthodontists Foundation and the United States Air Force.

The views of the author(s) do not support or reflect the views of the United States Air Force or the Department of Defense.

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LITERATURE REVIEW

Human exposure sources. In general, the most significant human exposure to nickel, chromium, and titanium occurs through the diet,¹⁻⁶ atmosphere,^{1,3,4,7} drinking water,^{1,2,8} clothing fasteners,⁹ jewelry,⁹ and iatrogenic uses of articles containing these metals. The major dietary sources for these three metals are vegetables, grains, and cereals.^{1,3,4} The average dietary intake for these three metals has been estimated to be 200 to 300 µg/day for nickel,^{3,10} 280 µg/day for chromium,¹ and 300 to 2000 µg/day for titanium.²

Nickel concentrations in drinking water generally measure below 20 µg/L.⁸ Average chromium levels in drinking water have been reported as 0.43 µg/L.¹ Levels for titanium are reported to range from 0.5 to 15 µg/L.²

Clothing fasteners (metal buttons, zippers) and jewelry articles are common sources of nickel exposure. Sweat plays an important role in leaching the nickel from such metal objects.⁹ On the other hand, iatrogenic exposures to nickel, chromium, and titanium can occur from joint prostheses, dental implants, orthopedic plates and screws, surgical clips and steel sutures, pacemaker leads, prosthetic heart valves, dental alloys, and orthodontic appliances.^{3,6,11-49}

Nickel release from dental alloys have been reported as $4.2 \mu\text{g}/\text{cm}^2$ per day.¹² It has also been reported that the in vitro release rate for full mouth orthodontic appliances to be $40 \mu\text{g}/\text{day}$ for nickel and $36 \mu\text{g}/\text{day}$ for chromium.¹⁴ For heat-treated stainless steel orthodontic arch wires the release rate for nickel was found to be $0.26 \mu\text{g}/\text{cm}^2$ per day.¹⁵ Previous studies have not investigated the corrosion of nickel-titanium alloys when used in conjunction with stainless steel appliances, and most studies have not used artificial saliva solutions.^{12,14}

The purpose of this study is to compare in vitro the corrosion rate of a standard orthodontic appliance consisting of bands, brackets, and both stainless steel and nickel-titanium arch wires. The corrosion products analyzed were nickel and chromium. Evaluation was conducted with the appliances immersed for 4 weeks in a prepared artificial saliva medium at 37°C .

MATERIALS AND METHODS

The appliance. Ten identical sets of bands and brackets were used, each set simulating a complete orthodontic appliance used for a maxillary arch with a full complement of teeth. Each set comprised the following: two second molar bands with buccal tubes and welded lingual buttons, two first molar and second premolar bands with buccal twin brackets and welded lingual buttons, two each of first premolar, canine, lateral, and central incisor brackets used for direct bonding to enamel. Average size second premolar, first, and second molar bands were selected. The material from which the bands were constructed was American Iron and Steel Institute (AISI) type 305 stainless steel with type 316 for the brackets and tubes (Ormco Corp. [personal communication, 1989], Glendora, Calif.). Bondable brackets were made of type 303 and 304 stainless steel (GAC International Inc. [personal communication, 1989], Central Islip, N.Y.). All bands and brackets were used in the "as-received" condition.

No attempt was made in the present investigation to cover either the inner surfaces of the bands or the bonding surface of the brackets as was previously suggested.¹⁴ This was done to eliminate the introduction of any possible extraneous sources of nickel and chromium. In a clinical situation, the inner surfaces of bands would be coated with a cementing medium, and the mesh or bracket bases would be covered with a composite bonding material. Therefore it could be assumed that the surfaces available for biodegradation and metal release are approximately double what would be available clinically. The exposed surface area may be considered as equivalent to a full maxillary and mandibular fixed appliance after its placement.

Five sets of these appliances were ligated to rectangular stainless steel arch wires, and the other five sets were ligated to rectangular nickel-titanium arch wires (Nitinol-Unitek Corp., Monrovia, Calif.). Both types of arch wires were 12.5 cm in length and had a cross-sectional dimension of 0.017×0.025 inches. The arch wire length was determined

from an ideal typodont set-up and measured distally from the right second molar tube to the left second molar tube.

The stainless steel arch wires were idealized with canine and molar offsets, then heat-treated in an electric furnace at a temperature of 425°C for 5 minutes. This temperature setting is the midpoint of the heat treatment range of 370° to 480°C recommended by Phillips.¹⁶ Similarly, the time period used for heat treatment fell into the ranges reported by Phillips.¹⁶

The nickel-titanium arch wires were used in the "as-received" condition after being cut to the specified length. The teeth were ligated to the arch wires with standard 0.01-inch stainless steel ligation wires (AISI type 304).

A small bend was placed at each end of all arch wires to keep the second molar bands from sliding off. All appliances were then cleaned in acetone and dried.

Experimental conditions. Nickel and chromium release was tested by placing each of the 10 appliances in separate polyethylene screw-top bottles containing 100 ml of artificial saliva.

The simulated saliva medium consisted of 0.4 gm NaCl, 1.21 gm KCl, 0.78 gm $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$, 0.005 gm $\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$, 1 gm Urea [$\text{CO}(\text{NH}_2)_2$] and 1000 ml distilled and deionized water. The artificial saliva formula was a modification of that used by Gjerdet and Hero,¹⁷ the difference being that their formula included 0.795 gm of $\text{CaCl}_2 \cdot \text{H}_2\text{O}$ and only 0.4 gm of KCl. When the Gjerdet and Hero formula was employed, interferences occurred with the atomization of chromium in the atomic absorption spectrophotometer caused by the presence of the calcium ions. These interferences were of such a magnitude that they prevented the accurate measurement of chromium. As a result, it was decided to substitute calcium chloride with an equimolar amount (0.81 gm) of potassium chloride. Potassium chloride was chosen instead of sodium chloride because it more closely matches the corrosive properties of calcium chloride. Protein was initially added to the formula since the work of Brown and Merritt indicated an increased corrosion rate when saline solutions contained serum proteins.¹⁸ Albumin was selected as the protein component because of its presence in saliva and its ready availability.¹⁹ The albumin, derived from eggs, was found to be unsatisfactory because of its high endogenous concentration of nickel and was eliminated from the formula.

The pH of the artificial saliva was adjusted to 6.75 ± 0.15 with 10 N sodium hydroxide. The pH value coincides with that reported for human saliva.²⁰

The sample bottles were placed in an Environmental Incubator Shaker Model G-24 (New Brunswick Scientific Co., New Brunswick, N.J.) and agitated slowly at 37°C for 4 weeks. On days 1, 7, 14, 21, and 28 the entire 100 ml of artificial saliva solution was removed from each bottle and replaced with a fresh solution except on day 28 when the experiment was ended. The replacement of the solution was performed to avoid saturating the artificial saliva medium with corrosion products.

Nickel and chromium analyses were performed on the

Table I. Basic statistics for the rates of nickel release, in parts per billion, at days 1, 7, 14, 21, and 28 for orthodontic appliances with stainless steel (SS) and Nitinol arch wires

Day	Arch wire type	Mean	Standard deviation	Standard error of mean	Range	Significance ^a
1	SS	2.865	1.299	581	1,560-4,410	NS ^b
	Nitinol	4.290	1.423	636	2,620-5,760	
7	SS	7.518	1.473	659	5,805-9,060	NS
	Nitinol	8.408	1.274	570	7,680-10,680	
14	SS	5.220	1.773	793	2,895-7,860	Sig. ^c
	Nitinol	2.763	973	435	1,725-3,880	
21	SS	1.928	1.317	589	790-3,850	NS
	Nitinol	1.575	1,614	722	204-4,026	
28	SS	1.262	1,517	544	220-3,318	NS
	Nitinol	702	626	280	193-1,788	

^aSignificance determined by Duncan's multiple range test.

^bNS, not significant at alpha = 0.05.

^cSignificant at $p = 0.0264$.

solutions removed from each set at each experimental period. This resulted in a total of 50 samples available for analysis, 25 for the stainless steel arch wires, and 25 for the nickel-titanium arch wires.

In addition, four 100 ml artificial saliva samples were used as controls and placed in similar polyethylene bottles, but with no orthodontic appliances. These solutions were also slowly agitated at 37° C. Two of the control samples were analyzed after 1 week, whereas the other two control samples were analyzed at the end of 4 weeks.

Measurement technique. The analyses were performed with a flameless atomic absorption spectrophotometer (Scintrex Ltd, Ontario, Canada). Atomic absorption is a technique based on the unique spectrum of each element. For every element analyzed, characteristic wavelengths are generated in a discharge lamp (hollow cathode lamp) and in turn are absorbed by a cloud or vapor of that element. The amount of absorption is proportional to the concentration of the element that is vaporized into the light beam.³³

Commercially available nickel and chromium standard stock solutions were used to prepare working standards of 5, 10, 20, and 40 ng/ml with distilled and deionized water. Calibration plots were generated at the start of every run using freshly prepared working standards. All glassware was first cleaned with a 1:1:1 solution of sulfuric acid, nitric acid, and water and then stored in a solution containing 0.6 nitric acid. All water used in this study was deionized by a 5 stage Milli-Q plus water purification system (Millipore Corp., Bedford, Mass.) to remove any potential metal contamination from the glassware. Before use, all glassware was rinsed at least three times with deionized water, inverted, and allowed to dry.

Reliability of measurements. The analysis for all the samples was performed according to the *Application Manual for the Scintrex AAZ-2 Zeeman Modulated Absorption Spectrophotometer*.³⁴ Two specimens from each sample were analyzed for each metal, and the mean value was recorded. If the two readings for any sample differed by more than 10%

from the mean value, then additional specimens were analyzed until three values were recorded that fell within a 10% variation from the mean value.

Statistical analysis. The analysis of variance general linear models procedure including Duncan's multiple range test was used to determine if differences existed between the dependent variables, metal concentration for nickel and chromium, and the independent variables, arch wire type (stainless steel and nickel-titanium), as well as time (days 1, 7, 14, 21, and 28). Significance was predetermined at an alpha of 0.05.

FINDINGS

Cross observations. During the course of this study no rust-colored precipitates were noticed in any of the sample containers. Localized areas of rust-colored corrosion were apparent on a few brackets and bands. The corrosion occurred primarily at either the bracket-mesh base or bracket-band interface. This visible corrosion was evident on approximately 10% of total number of brackets and bands used in this study.

Changes in nickel concentration (Table I). A peak nickel concentration in the artificial saliva occurred on day 7, then steadily decreased during the subsequent 3-week period. The analysis of variance indicated a statistically significant difference in nickel concentrations released in the solution with time ($p = 0.0001$).

When the nickel release from appliances attached to stainless steel and nickel-titanium arch wires were compared, no significant differences were found, except at day 14 where nickel release was significantly greater from the stainless steel arch wires as compared with the nickel-titanium arch wires ($p = 0.0232$). In general, the overall pattern of nickel release was similar for the two appliances (Fig. 1).

Changes in chromium concentration (Table II). The

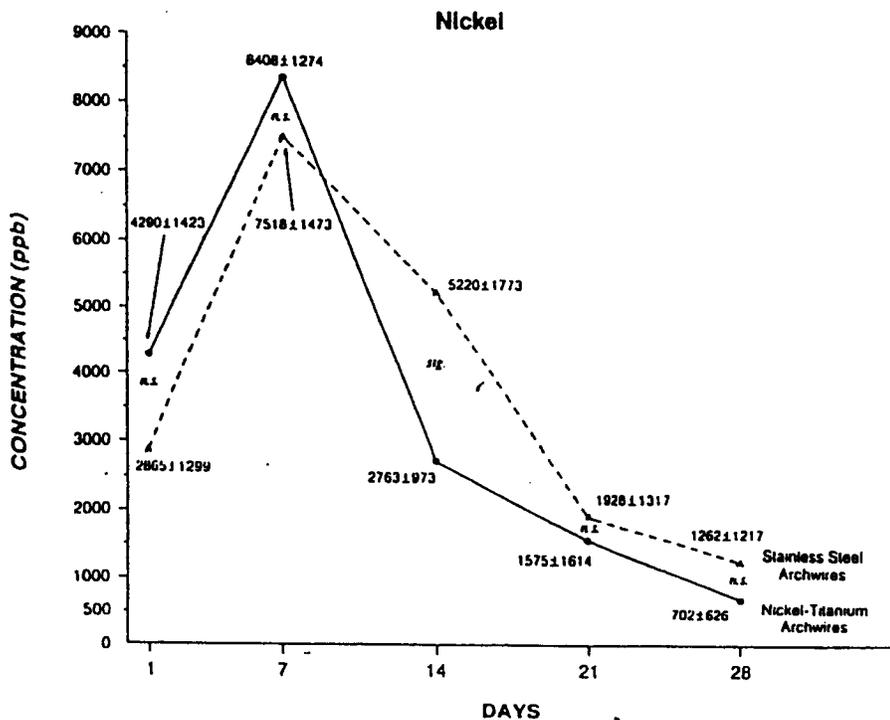


Fig. 1. Changes in nickel release rates for orthodontic appliances with stainless steel and nitinol arch wires.

Table II. Basic statistics for the rates of chromium release, in parts per billion, at days 1, 7, 14, 21, and 28 for orthodontic appliances with stainless steel (SS) and Nitinol arch wires

Day	Arch wire type	Mean	Standard deviation	Standard error of mean	Range	Significance ^a
1	SS	21.2	8.5	3.8	12.8-34.3	NS ^b
	Nitinol	16.4	7.3	3.3	8.0-27.8	
7	SS	23.7	12.6	5.6	12.1-43.2	NS
	Nitinol	43.6	24.7	11.1	14.1-79.4	
14	SS	125.5	159.8	71.5	20.5-405.0	NS
	Nitinol	154.1	71.7	32.1	26.0-191.0	
21	SS	132.4	80.9	36.2	60.5-264.0	NS
	Nitinol	102.3	48.9	21.9	16.3-137.0	
28	SS	233.1	250.4	112.0	68.5-672.0	NS
	Nitinol	126.9	111.3	49.7	13.1-252.0	

^aSignificance determined by Duncan's multiple range test.
^bNS, not significant at alpha = 0.05.

release of chromium into the artificial saliva solution showed the greatest increase through day 14. The release rate leveled off between days 14 and 21 and then increased moderately at day 28. As with nickel, the number of days, which had elapsed since the initiation of the experiment, did make a significant difference in the corrosion level of all appliance types ($p = 0.0065$).

When chromium levels released from the appliances constructed from stainless steel archwires were com-

pared with those of nickel-titanium arch wires, no significant differences were present ($p = 0.5456$). In other words, the overall pattern of chromium release was similar for both appliances (Fig. 2).

The interrelationship of nickel and chromium levels. The nickel concentration in the artificial saliva was at a significantly higher level than that of chromium at each time period ($p = 0.0001$). The smallest difference was recorded on day 28 where the nickel concen-

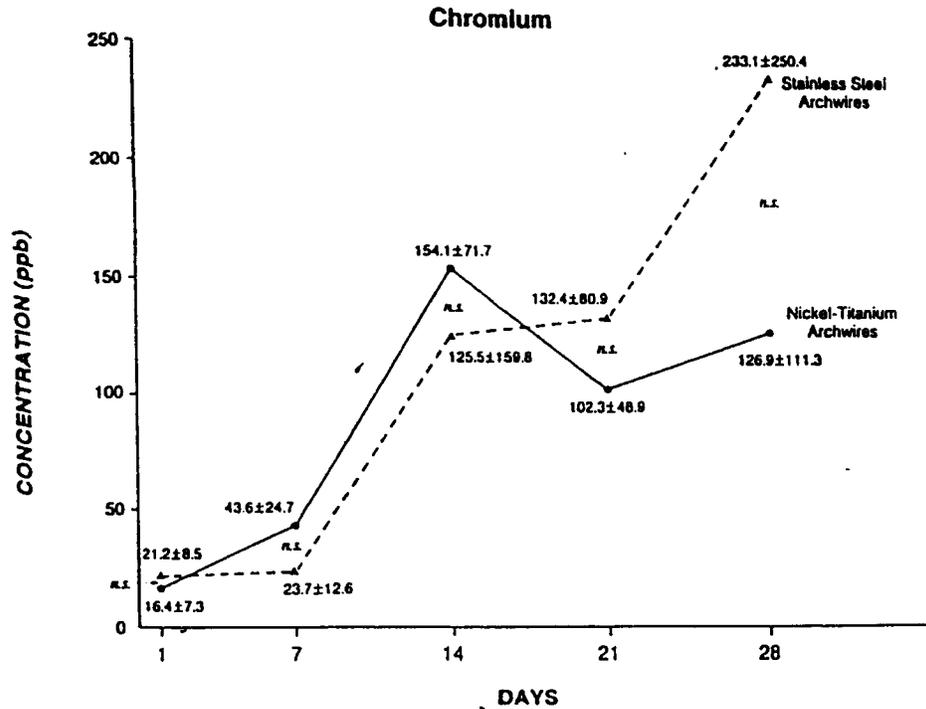


Fig. 2. Changes in chromium release rate for orthodontic appliances with stainless steel and nitinol arch wires.

tration averaged 5.5 times the chromium concentration. The greatest difference occurred at day 7 where the nickel levels were 236 times those of chromium. Over the total period tested, the nickel concentration averaged 37.3 times higher than the chromium concentration.

DISCUSSION

In the present study, no rust-colored precipitates were visible in the sample bottles, as was previously observed.¹⁴ However, it is possible that some insoluble precipitates containing nickel and chromium were present but were undetectable by visual examination. On the other hand, corrosion was visible at localized areas adjacent to the spot welds between the bracket and the mesh bases, as well as between the brackets and bands. No attempt was made to remove and examine these attached corrosion products.

Therefore all the results of the *in vitro* study are representative of the solubilized forms of nickel and chromium. It is of interest to note that Park and Shearer¹⁴ found that the precipitated corrosion products contained much higher amounts of chromium than nickel, whereas the solution itself contained more nickel than chromium. They also found that nickel was released primarily as soluble compounds, whereas chromium was released primarily as insoluble compounds.

Nickel. When the concentrations of nickel were measured at the various time intervals, a maximum level was found at day 7, and all subsequent concentration levels demonstrated a progressive decline. Park and Shearer¹⁴ and Menne et al.⁵⁵ also found that the corrosion of the appliances reached a plateau after 6 days and did not increase appreciably thereafter. Marek and Treharne had similar findings.⁵⁶

Two explanations for this behavior can be contemplated. First, the nickel present on the surface of the stainless steel may quickly corrode during the first 7 days of the experiment, then the rate of release drops off as the surface nickel is depleted. Second, corrosion products may have formed on the surface after 7 days slowing the corrosion of nickel. When the overall findings including those on chromium levels are taken into consideration, it seems that the first hypothesis is most likely.

Comparison of nickel release from the appliances with stainless steel arch wires to those with nickel-titanium arch wires revealed no significant differences in the nickel levels at all time periods except day 14. This is most likely a random occurrence, since at all other time intervals there were no significant differences between the two appliances.

The total release of nickel during the 4-week period of this study averaged 13.05 $\mu\text{g}/\text{day}$. Even if this figure

is doubled to simulate the equivalent release from a fully banded and bonded maxillary and mandibular appliances, the release rate of 26.1 $\mu\text{g}/\text{day}$ is approximately one tenth the reported average daily dietary intake of 200 to 300 $\mu\text{g}/\text{day}$.^{3,10} It needs to be remembered that these estimated levels are still higher than the anticipated clinical levels, since in the present study both the inside of the bands, as well as the bracket bases, were exposed to the artificial saliva.

Chromium. As with nickel, significant changes were found in the chromium levels at the various time intervals. The level of chromium released was found to increase up to day 14, at which point it leveled off. The differences in chromium release between the two arch wire types were not found to be significant.

Contrary to nickel, the rate of chromium corrosion did not decrease after day 7. As a result, it is unlikely that a buildup of corrosion products occurred at this time since such an occurrence would have made the concentrations of both metals decrease after day 7. As stated earlier, the more plausible assumption is that the nickel concentration on the surface of the appliances is being depleted at a faster rate than that for chromium.

The total release of chromium during the 4-week period averaged 0.35 $\mu\text{g}/\text{day}$. Doubling this figure to simulate orthodontic appliances placed on both dental arches would give a release rate of 0.7 $\mu\text{g}/\text{day}$. This is approximately 0.25% of the reported average daily dietary intake of 280 $\mu\text{g}/\text{day}$ for chromium.¹ As discussed earlier, this figure is also an over estimation of the chromium release rate from a fully banded and bonded orthodontic appliance.

CONCLUSIONS

From the results of the present investigation, the following can be concluded:

1. Orthodontic appliances release measurable amounts of nickel and chromium when placed in an artificial saliva medium.
2. The nickel release reaches a maximum after approximately 1 week, then the rate of release diminishes with time.
3. The chromium release increases during the first 2 weeks and levels off during the subsequent 2 weeks.
4. The release rates of nickel and chromium from stainless steel or nickel-titanium arch wires are not significantly different.
5. For both arch wire types, the release rate for nickel averaged 37 times greater than that for chromium.
6. The estimated release rates from full-mouth orthodontic appliances are less than 10% of the

reported average daily dietary intake for nickel and 0.25% of those reported for chromium.

7. How much of these corrosive products are actually absorbed by patients undergoing orthodontic treatment still needs to be determined.

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ORIGINAL ARTICLES

Biodegradation of orthodontic appliances. Part II. Changes in the blood level of nickel

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The purpose of this study is to determine whether orthodontic patients accumulate measurable concentrations of nickel in their blood during their initial course of orthodontic therapy. Blood samples were collected at three different time periods: before the placement of orthodontic appliances, 2 months after their placement, and 4 to 5 months after their placement. The study involved 31 subjects, 18 females and 13 males, who had malocclusions that required the use of a fully banded and bonded edgewise appliance. The age of the subjects in the study ranged between 12 and 38 years. The blood samples were frozen and shipped to a commercial medical laboratory for analysis by atomic absorption spectrophotometry. The three blood samples for each patient were analyzed in succession on the same day to eliminate equipment variance that could occur if blood samples were analyzed on separate days. A total of 93 blood samples were sent for analysis. From the findings in this study the following can be concluded: (1) Patients with fully banded and bonded orthodontic appliances did not show either a significant or consistent increase in nickel blood levels during the first 4 to 5 months of orthodontic therapy. (2) Orthodontic therapy using appliances made of alloys containing nickel-titanium did not result in a significant or consistent increase in the blood levels of nickel. The results obtained from both parts of this investigation indicate that orthodontic appliances used, in their "as-received" condition, corrode in the oral environment releasing both nickel and chromium, in amounts significantly below the average dietary intake. Furthermore, the biodegradation of orthodontic appliances during the initial 5 months of treatment did not result in significant or consistent increase in the blood level of nickel. (AM J ORTHOD DENTOFAC ORTHOP 1993;103:115-9.)

Nickel and chromium are two metals often used in the construction of various parts of most orthodontic appliances. The potential health effects from exposure to nickel and chromium and their compounds have been scrutinized for more than 100 years, and it was established that these metals could cause hypersensitivity, dermatitis, and asthma. In addition, a significant carcinogenic and mutagenic potential has been demonstrated for compounds containing these metals.

To assess the potential for any health effects that could be attributed to orthodontic appliances, a determination must be made to quantify three factors: the rate at which orthodontic appliances release potentially harmful metal compounds in the oral environment, the

degree humans absorb these metal compounds, and finally, the length these compounds are retained in the body.

The purpose of this study is to determine if an increase in the blood levels of nickel occurs in patients who undergo routine orthodontic therapy.

LITERATURE REVIEW

Chromium is known to be an essential element for human beings and animals.^{1,2} While nickel is essential for some animals,³ a similar role in human beings has not been conclusively identified.⁴

The predominant systemic effects in human beings from exposure to nickel or chromium compounds are allergy,^{3,5-29} dermatitis,^{*} and asthma.^{28,32-35}

The incidence for nickel allergy was reported to be 1% in male subjects and 10% in female subjects.^{8,9,11-13} On the other hand, the incidence for chromium allergy is estimated at 10% in male subjects and 3% in female subjects.¹⁹

Most causes for nickel and chromium allergies have

*References 5, 7, 8, 12, 14, 23-25, 27, 28, 30, 31.

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been attributed to dermatologic exposures to these metals or to compounds containing these metals. Pierced earrings and metal buttons in blue jeans have been found to be responsible for a significant number of nickel hypersensitivity cases in women.^{9,12,13} In men, the most common sources of sensitization to nickel are occupational exposures, wristwatches, and the metal buckles found on watchbands.¹⁰

Nickel and chromium carcinogenicity: The fact that nickel, chromium, and their compounds present a known cancer risk has been well documented in the literature.^{2,5,6,29,30,36-50} Nearly all the reported cases of nickel- and chromium-induced carcinoma have occurred from occupational exposures to inhaled metal compounds. The primary tumor locations are the lung and the nasal mucosa.* Not all nickel and chromium compounds have carcinogenic potential. For nickel compounds, risk is inversely related to its solubility in an aqueous media.³⁶ For chromium compounds, carcinogenic risk has only been identified with compounds in which the chromium is in a hexavalent oxidation state.^{43,44,46,49,50} There is no experimental evidence that nickel or chromium compounds are carcinogenic when administered by oral or cutaneous routes.^{6,29,30}

The average latency period from the time of exposure to these metal compounds to the development of cancer has been reported to be between 20 and 25 years.^{36,39,45,46,49}

Patch testing for nickel and chromium allergy. The most frequently used method to identify a person with an allergy is the epicutan test or Patch test. False negative reactions have been reported in testing for nickel allergies in known sensitive persons.²⁴ Such testing should not be used indiscriminately since these tests may induce sensitivity in persons who before testing were not sensitive.

Nickel and chromium concentrations in blood. Normal whole blood concentrations for nickel have been reported to be between 2.4 ± 0.5 ng/ml and 30 ± 19 ng/ml.⁵¹⁻⁵⁴ For chromium, the average values have been reported as 0.371 ng/ml and 1.4 ± 0 ng/ml.^{55,56}

Mechanisms for limiting the intestinal absorption of nickel^{3,57} and chromium,^{37,58} have been identified. The oxidation state of chromium uniquely affects its ability to be absorbed by a person, and only the hexavalent form (Cr VI+) is readily absorbed.³⁷ The primary route for elimination of absorbed nickel and chromium from the body is through the urine.

Corrosion of biomedical materials. Corrosion of dental and medical appliances must first occur for these

trace metal compounds to be absorbed by the patient. The corrosion rate is influenced by the composition of the material, the chemical and thermal environment of the material, the surface area, and the degree of surface smoothness. Several reports have documented that nickel-containing dental prostheses can be responsible for episodes of expressed nickel allergy.^{14-16,59,60}

Symptoms of allergic reactions of dental alloys have included severely inflamed hyperplastic gingival tissue surrounding crowns fabricated from a nickel-containing alloy,¹⁵ alveolar bone loss from a similar crown,¹⁶ and edema of the throat, palate, and gums.¹⁷ In addition, osteomyelitis was reported when stainless steel bone fixation wires were used in the jaws of a patient who was sensitive to nickel.¹⁸

Orthodontic appliances have also been found to produce reactions of hypersensitivity.¹⁹⁻²² Nickel allergy reactions to orthodontic appliances have been reported after the use of facebows and neck straps^{19,20,22} and also after the insertion of nickel-titanium orthodontic arch wires.²¹ At present, there is no direct evidence that the intraoral use of nickel-containing alloys will induce a hypersensitive state in a previously nonsensitized person.⁶

In Part I of this study,⁶¹ as well as other in vitro studies⁶²⁻⁶⁵ on the corrosion of orthodontic appliances, the findings indicated that both nickel and chromium are liberated as corrosion products in an artificial saliva medium.⁶¹ Commercial recycling of orthodontic brackets, heat treating, or silver soldering of arch wires all increased the corrosion rate of these appliances.⁶³⁻⁶⁵

How much of the nickel and chromium that are released from the biodegradation of orthodontic appliances is actually absorbed by the body has not been documented.

The purpose of this study is to determine whether orthodontic patients accumulate measurable concentrations of the nickel in their blood during their initial course of orthodontic therapy. Blood samples were collected at three different time periods: before the placement of any orthodontic appliances, 2 months after their placement, and 4 to 5 months after their placement.

MATERIALS AND METHODS

This study involved 31 subjects, 18 females and 13 males, who had malocclusions that required the use of a fully banded and bonded edgewise appliance. Of the 55 persons who were asked to participate, 32 initially accepted. The age of the subjects in the study ranged between 12 and 38 years.

An explanation of the research project was given both verbally and in writing, a consent form and demographic information were obtained. In addition, an allergy questionnaire was completed to identify any existing allergies, particularly allergies to metal.

*References 2, 5, 29, 36, 41, 42, 48-50.

Table I. Blood level concentrations in parts per billion (ppb) for nickel in 18 female patients

Patient number	Time 0	Time 1	Time 2
1	0.4	<0.4	0.4
2	0.4	<0.4	<0.4
3	<0.4	0.8	0.4
4	<0.4	<0.4	<0.4
5	<0.4	<0.4	<0.4
6	<0.4	0.4	<0.4
7	<0.4	<0.4	<0.4
8	<0.4	<0.4	1.3
9	<0.4	<0.4	<0.4
10	0.5	<0.4	<0.4
11	<0.4	<0.4	<0.4
12	<0.4	<0.4	<0.4
13	<0.4	0.5	<0.4
14	<0.4	<0.4	<0.4
15	<0.4	0.8	<0.4
16	<0.4	<0.4	0.5
17	0.9	<0.4	<0.4
18	<0.4	<0.4	<0.4

Time 0, Before orthodontic appliance placement; Time 1, approximately 2 months after orthodontic appliance placement; and Time 2, approximately 4 to 5 months after orthodontic appliance placement.

A baseline blood sample was taken through standard venipuncture techniques, in acid-washed, trace element vacutainer blood collection tubes. The tubes contained 143 USP units of sodium heparin as an anticoagulant (Becton-Dickinson Type 6527, Rutherford, N.J.). The baseline samples were obtained before the fitting or cementation of any bands or bonds. Another blood sample was taken in the same manner after orthodontic appliances had been in place for approximately 2 months. During this time period, nickel-titanium arch wires were primarily used. A third blood sample was collected after appliances have been in place for at least 4 to 5 months. At which time, stainless steel arch wires were predominantly being used.

It was not possible to obtain the third blood sample on a female subject, and therefore she was excluded from the study.

The blood samples were frozen and shipped to a commercial medical laboratory for analysis by atomic absorption spectrophotometry (Smith, Kline, and Beecham Medical Laboratories, Van Nuys, Calif.). The three blood samples for each patient were analyzed in succession on the same day to eliminate equipment variance, this could occur if blood samples for the same patient were analyzed on separate days. A total of 93 blood samples from 18 female and 13 male subjects were sent for analysis.

FINDINGS

Allergic predispositions. The allergy questionnaires completed by the 31 subjects revealed a suspected positive allergy to metal in five subjects, all females. An incidence of 28.8% for females. All symptoms were in

Table II. Blood level concentrations in parts per billion (ppb) for nickel in 13 male patients

Patient number	Time 0	Time 1	Time 2
19	<0.4	<0.4	<0.4
20	<0.4	<0.4	<0.4
21	0.8	<0.4	<0.4
22	<0.4	1.0	<0.4
23	0.4	<0.4	<0.4
24	<0.4	<0.4	<0.4
25	<0.4	<0.4	<0.4
26	<0.4	<0.4	0.4
27	<0.4	<0.4	<0.4
28	<0.4	<0.4	<0.4
29	<0.4	<0.4	<0.4
30	<0.4	<0.4	<0.4
31	<0.4	<0.4	<0.4

Time 0, Before orthodontic appliance placement; Time 1, approximately 2 months after orthodontic appliance placement; and Time 2, approximately 4 to 5 months after orthodontic appliance placement.

response to wearing earrings and included red, itchy, or flaky skin at the location of the earrings.

Blood levels. The detailed results of the blood level analysis for nickel are presented in Tables I and II. These findings indicate that no demonstrable increase in the blood level of nickel occurred during the 5-month course of orthodontic treatment. Of the 93 blood samples analyzed, 77 (82.8%) were below the detection limit of 0.4 ppb. Ten (10.8%) were either 0.4 or 0.5 ppb and only six (6.4%) had higher values ranging between 0.8 and 1.3 ppb. The occurrence of levels at or above the detection limit were equally distributed in each of the three sampling time periods. In other words, there was no detectable pattern in the increase in the blood level of nickel over the time periods evaluated.

For the five subjects who acknowledged allergic reactions to metal earrings, only 3 of their 15 blood samples (20%) were at or above the detection limit for nickel, and all of these occurred at the 2-month time period. The three measureable levels were 0.4, 0.5, and 0.8 ppb.

No statistical analysis of this data was deemed appropriate since the majority of these values was not different from zero.

DISCUSSION

When the blood samples were sent for analysis, the request included determinations for the levels of both nickel and chromium. Unfortunately, the levels of chromium in frozen whole blood could not be determined with the equipment presently available at the commercial laboratory. It was explained that the proteins present in whole blood interfered with the determination of

the chromium levels and that the analysis of chromium would have required the use of blood serum instead of whole blood. The original choice to use whole blood was because chromium is selectively bound to the red blood cells. Once whole blood was frozen it became practically impossible to extract the serum component. In any event, the use of blood serum samples would have provided only a partial indication of the changes in the chromium blood levels during orthodontic therapy.

Nickel levels in the blood: The present results indicate that only 17.2% of the blood samples contained a nickel level that was at or above the detection limit of 0.4 ppb. The occurrence of detectable levels of nickel in the blood was distributed randomly over the three time periods observed in this study, and at no time exceeded 1.3 ppb. Actually 16 patients (8 males and 8 females) had no detectable nickel levels at any of the three periods, and another 5 patients (2 males and 3 females) had a reduction in the blood level after treatment was initiated (Tables I and II).

Several possibilities exist for the random and infrequent occurrence of higher values, these include: (1) Contamination from the stainless steel venipuncture needle. This could occur if a small piece of stainless steel from the needle was carried into the venipuncture tube during the drawing of the blood sample. (2) The higher blood levels may correspond with the consumption of foods containing a high trace level of nickel.

Regardless of the source, all the blood levels of nickel found in these subjects were below the normal levels previously reported in the literature (2.4 ± 0.5 ppb,⁵² 4.8 ± 1.3 ppb,⁵⁴ 6.0 ± 1.0 ppb,⁵³ and 30 ± 19 ppb⁵¹). Thus, none of the subjects in the present study displayed blood levels for nickel which were greater than normal.

In the five subjects who were identified through the allergy questionnaire as being sensitive to metal earrings, there was no evidence that their nickel blood levels were any higher than those of other persons.

CONCLUSIONS

From the findings in this study, the following can be concluded:

1. Patients with fully banded and bonded orthodontic appliances did not show a significant increase in the nickel blood levels during the first 4 to 5 months of orthodontic therapy.
2. Orthodontic therapy using appliances made of alloys containing nickel-titanium did not result in a significant increase in the blood levels of nickel.

The results obtained from the first part of this investigation, as well as those obtained from the present

findings, indicate that orthodontic appliances used in their "as-received" condition corrode in the oral environment releasing both nickel and chromium, but in amounts significantly below the average dietary intake.⁶¹ Furthermore, the biodegradation of orthodontic appliances during the initial 5 months of treatment does not result in an increase in the blood level of nickel in patients undergoing orthodontic treatment.

We express our appreciation to the American Association of Orthodontists Foundation and the United States Air Force for their generous support of this project.

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In vitro release of nickel and chromium from simulated orthodontic appliances



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The purpose of this experiment was to measure the amounts of nickel and chromium released from a simulated orthodontic appliance incubated in 0.05 percent sodium chloride solution. The average release of metals was 40 μg nickel and 36 μg chromium per day for a full-mouth appliance. This was well below the average dietary intake of nickel and chromium consumed by Americans. However, the clinician should be aware that release of nickel and chromium from orthodontic bands might sensitize patients to nickel and chromium and may cause hypersensitivity reactions in patients with a prior history of hypersensitivity to these metals.

Key words: Corrosion, stainless steel, nickel, chromium, orthodontic bands

The austenitic stainless steels commonly used for orthodontic bands and wires contain approximately 18 percent chromium and 8 percent nickel. Nickel is the most common cause of metal-induced allergic contact dermatitis in man and produces more allergic reactions than all other metals combined.¹ Second in frequency is chromium. In a study in which cultured human cells were used, nickel was recently reported to be moderately cytotoxic while chromium was considered to have little cytotoxicity.² Injury to the skin from mechanical, physical, or chemical agents followed by intimate contact with sensitizing allergens favors the development of allergic eczematous dermatitis.¹ Corrosion of various stainless steel orthopedic implants has been shown by several authors to occur and has been associated with metal hypersensitivity.^{3, 4} There is, therefore, the possibility that nickel and chromium released from stainless steel orthodontic bands, brackets, and wires might elicit an allergic reaction. To our knowledge, there are no quantitative data on the amounts of nickel and chromium released from orthodontic appliances. The aim of the research described here was to provide such data.

MATERIALS AND METHODS

Ten simulated orthodontic appliances were constructed for half of a mandibular arch from similarly sized first and second molar bands, first and second premolar bands, and canine, lateral incisor, and central incisor brackets (Fig. 1). The bands were American Iron and Steel Institute (A.I.S.I.) Type 304 with Type 303Se brackets. Bondable brackets were Type 303Se

with Type 304 mesh pads. A lingual button was welded to the second molar band; all other bands and brackets were used in the as-received condition. Bands were filled with clear, cold-cure orthodontic acrylic, and the mesh backs of the brackets were filled with orthodontic bonding resin. Bands and brackets were held securely in place to a 2.8 inch, 0.0195 by 0.025 inch standard rectangular arch wire by elastomeric units. Ten simulated controls contained only equivalent pieces of clear cold-cure acrylic, bonding resin, and elastomeric units.

Nickel and chromium release was tested by placing each of the ten experimental and ten control appliances in separate polyethylene screw-top bottles containing 100 ml. 0.05 percent sodium chloride and two drops of toluene (preservative) at 37° C. On days 3, 6, 9, and 12, a 4 ml. sample of the solution in each bottle was removed for subsequent nickel and chromium analyses and an equivalent amount of fresh 0.05 percent sodium chloride was added back to each bottle. At the end of the 12-day experiment, the rust-colored precipitates in the experimental sample bottles were collected by centrifugation, washed three times with 0.05 percent sodium chloride, dried overnight at 85° C., and solubilized in concentrated nitric acid. Nickel and chromium were analyzed in the solubilized precipitates and the solutions from the bottles by atomic absorption spectrophotometry.⁵

RESULTS

Significant amounts of both nickel and chromium were solubilized from the simulated orthodontic appliances into 0.05 percent saline solution (Fig. 2). Approximately three times more nickel was solubilized than chromium, and the cumulative amounts of nickel

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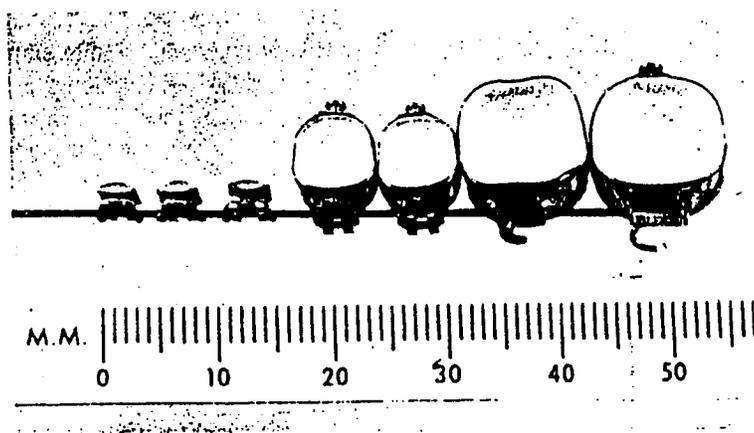


Fig. 1. Simulated mandibular half-arch used to measure the in vitro release of nickel and chromium.

and chromium released reached a plateau after 6 days. After 12 days, total cumulative release of soluble nickel was 121 μg and total release of soluble chromium was 40 μg (Table I).

A rust-colored precipitate was observed in the experimental sample bottles at about day 3 and appeared to increase with time. Analysis of the nitric acid-soluble fraction of this 12-day accumulation of precipitate revealed appreciable quantities of chromium, 72 μg (Table I).

Initial signs of corrosion on the experimental appliances were noted in most samples at day 3. Macroscopic examination of the appliance revealed that corrosion occurred at the weld sites of the bands and, once initiated, became progressively severe. There was no macroscopic evidence of corrosion on the bondable brackets. No important macroscopic changes in the control appliances were noted.

The total average cumulative release of both soluble and precipitated nickel and chromium from one quadrant of the simulated orthodontic appliances was 125 μg nickel and 112 μg chromium.

DISCUSSION

The data presented clearly indicated that both nickel and chromium were released from stainless steel orthodontic appliances into 0.05 percent sodium chloride solution at 37° C. The bulk of the nickel released remained in solution, while a greater portion of the released chromium was present in the precipitate which formed during corrosion. The amount of chromium analyzed in the precipitate was eighteen times greater than the amount of precipitated nickel. Release of nickel and chromium into soluble and insoluble fractions has also been observed in earlier studies with stainless steel endodontic pins.^{6, 7} Chromium has been implicated as a source of dark green stains associated

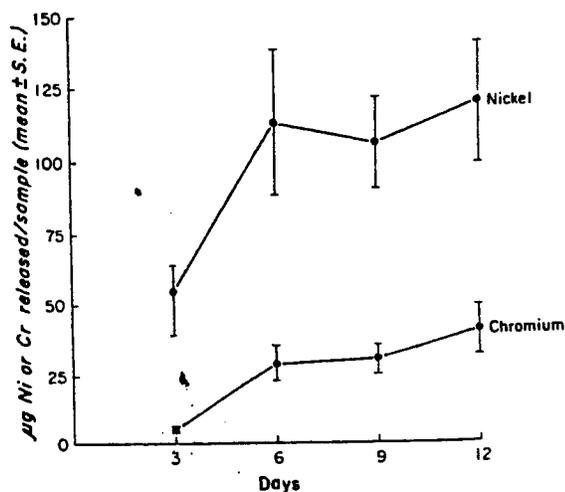


Fig. 2. Cumulative release of soluble nickel and chromium from simulated orthodontic appliances into 0.05 percent sodium chloride as a function of time.

with stainless steel brackets. Elemental analysis in a scanning electron microscope equipped with an x-ray analyzer revealed two chromium peaks, but no peak for nickel.⁸ A recent report⁹ also indicates the presence of insoluble chromium compounds in black/green stains found in association with the corrosion of stainless steel brackets.

The present study indicates that nickel is released primarily as a soluble compound, while chromium is released primarily in an insoluble form with corrosion of the simulated orthodontic appliances. Earlier clinical reports^{8, 9} also indicate that chromium is released in an insoluble form.

The general mechanism for the corrosion and subsequent release of metal ions from stainless steel involves the loss of the passivated layer consisting of chromium oxide and chromium hydroxide which forms

Table I. Cumulative amounts of nickel and chromium released from mandibular half-arch orthodontic appliances after 12 days in 0.05 percent sodium chloride

Form of nickel or chromium	Nickel (μg)	Chromium (μg)
Soluble	121 \pm 69*	40 \pm 28
Precipitated	4 \pm 2	72 \pm 40
Total	125 \pm 22	112 \pm 18

*Mean \pm S.E. (n = 10). No measurable quantities of nickel or chromium were released from control appliances.

on the surface of stainless steel upon contact with oxygen. A number of factors facilitate the corrosion of stainless steel. Crevice corrosion is an intense local attack which occurs in shielded areas on a metallic surface. Stainless steel is especially susceptible to this form of corrosion and has been implicated as the mechanism involved in the corrosion of orthodontic brackets.⁸ Halide ions, especially chloride, cause pitting corrosion. Mechanical distortion and excessive cold working promote corrosion by making the distorted portion of the wire or band more anodic. The alloy then behaves electrochemically as if two alloys were present. The presence of dissimilar metals or alloys, such as silver solder, amalgams, or gold, may lead to galvanic corrosion. Heating between 400° and 900° C. makes stainless steel more susceptible to intergranular corrosion because of loss of chromium carbide at the grain boundaries. In this experimental design, our observations indicate that intergranular corrosion is the probable type of corrosion, as evidenced by the presence of rust-colored precipitate at weld sites. The conditions of this study did not allow for further evaluation of the other mechanisms of corrosion.

In the oral cavity such factors as temperature, quantity and quality of saliva, plaque, pH, protein, physical and chemical properties of food and liquids, and general and oral health conditions may influence corrosion by a combination of the mechanisms discussed above. In vitro studies using artificial saliva may give a more realistic picture of nickel and chromium release. However, because of possible contamination and technical difficulties, it was decided to use 0.05 percent sodium chloride, which is the average chloride concentration in saliva,¹¹ rather than an artificial saliva as a test solution.

Nickel and chromium are normally present in the foods consumed by man. The dietary intake of nickel was reported to be 300 to 500 μg per day, while chromium intake varied from 5 to more than 100 μg per day.¹² Our experiment measured nickel and chromium

release from one quadrant (Table I) but, on the basis of four quadrants, our results showed release of 40 μg nickel and 36 μg chromium per day for a simulated full-mouth appliance. These values are thus well below the normal daily intake of these two metals and may not be of clinical significance in most patients. However, the clinician should be aware that the release of the metal ions may cause a local hypersensitivity reaction at oral soft-tissue sites. Characteristic lesions of contact stomatitis vary from barely visible, mild erythema to a fiery red color with or without edema. Symptoms may include loss of taste, numbness, burning sensation, and soreness of the involved area, often accompanied by angular cheilitis. Itching is not a frequent symptom. Although it is more difficult to provoke contact stomatitis than contact dermatitis,¹² severe gingivitis associated with orthodontic therapy may be a manifestation not only of poor oral hygiene but also of a contact hypersensitivity reaction to nickel and/or chromium ions released during the corrosion of stainless steel. The possibility of such a reaction occurring has been noted earlier in the dental literature.^{14, 15}

Further research is required to determine the short-term and long-term biocompatibility of the soluble and insoluble nickel and chromium compounds released with the corrosion of orthodontic stainless steel appliances. We also need to determine whether these compounds are of clinical significance in sensitizing patients or eliciting a contact hypersensitivity reaction in patients who have a prior history of contact hypersensitivity to nickel and/or chromium.¹⁶

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SESSION III: BIOLOGICAL RESPONSES (BIOCOMPATIBILITY AND CORROSION) OF NITINOL ALLOYS

iii1o **Biocompatibility of Nitinol**

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This review adjusts the recent knowledge on the biocompatibility of Nitinol. The fundamental aspects of biological responses to Nitinol and its alloy components are clarified. The clinical advantages of using this functional biomaterial are evident. Although most studies support the good biocompatibility of Nitinol there are a lot of open questions. The long-term in vivo performance of this material is not well demonstrated and the host-Nitinol interactions at the cell and molecular levels are mostly unknown. However, the experimental and clinical data strongly support Nitinol as a safe biomaterial and indicate that it is at least as good as stainless steel or titanium alloys.

iii2o **Corrosion of Nitinol**

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Nitinol is a very attractive material for manufacturing minimally invasive therapy devices and tools because of its unique superelasticity and shape memory properties. While several studies have shown it possesses good biocompatibility, its high nickel content and possible dissolution during corrosion still remains a concern. However, passivation and electropolishing can significantly decrease nickel dissolution from Nitinol by forming a corrosion resistant titanium oxide surface layer. In general, passivated and electropolished Nitinol exhibits equivalent, if not better, static corrosion behavior and ability to resist and repassivate (repair) surface damage when compared to 316L stainless steel. Combining Nitinol with stainless steel, titanium, and tantalum does not significantly affect its corrosion behavior. However, combining Nitinol with gold, platinum, and platinum-iridium alloys can result in an order of magnitude increase in corrosion rate. Nickel release from Nitinol decreases from well below dietary levels to nearly non-detectable levels in the first few days following immersion in a physiological media. Finally, in vivo studies indicate minimal corrosion of Nitinol during implantation with released nickel concentration in surrounding tissues or organs being equivalent to that released by 316L stainless steel.

On Methods Used for Corrosion Testing of NiTi

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Results of studies on the corrosion characteristics of NiTi alloy have ranged from "it behaves much like titanium" to "its corrosion resistance is either low or unpredictable". But, a wide variety of methods have been used: linear or reverse polarization at a variety of scan rates, E_{corr} monitoring, and rapid repassivation tests like F746 or mechanical scratching. There is also a variety of conditions used: saline, Hanks', Ringers, saliva, protein solutions, cell culture media or sweat; air, O₂ and 5% CO₂, or N₂. In an effort to develop an ASTM standard for corrosion testing of NiTi devices such as stents, these issues and some lab results will be reviewed.

iii40 **Degradation of Stentor Devices after Implantation in Human Beings**

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The Stentor® device is, since its modification 1996, not available any longer. It was one of the most applied devices world-wide and is one of the only devices, which has reached a duration of implantation in human beings exceeding 3 years. The examination of explants reveals material deficiencies which must be known by those performing patient follow-up and give us the opportunity to learn about long-term endurance of components which are also present in most other, still available devices. Among 33 endovascular grafts, retrieved 5 to 43 months after implantation, the majority were 18 MinTec® devices (17 Stentor®, 1 Cragg®). These 18 explants were examined by endoscopy, stereomicroscopy (SM), scanning electron microscopy (SEM) and energy dispersive x-ray analysis (EDAX). The textile coating showed holes along the longitudinal seam. Several ligatures in-between the stent frames busted, allowing the frames to dislocate. Occasional fractures of the stent wire accompanied by surface alterations on the wire were seen by SM. Here SEM revealed signs of pitting corrosion with bizarre map-shaped holes, dynamic stress crack corrosion and fractures of the wire. EDAX measured a scarification of nickel on the ground of the pits. The exclusion of an aneurysm from pressurisation is presumably the life-time purpose of the graft covering. Since the ingrowth of the polyester coating seems not to be comparable with conventional grafts the stability of the stent is irresistible to hold the covering in place. Distention of the frame weakens the device. The stent wire fractures are worrying since Nitinol is known to be highly resistant to corrosion. The origin of the Nitinol used in Stentor® devices is not known to us yet. Nitinol is available in various qualities. We are performing further studies concerning the corrosion of various Nitinol qualities.

iii50 / **Blood Compatibility of Nitinol Compared to Stainless Steel**

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Because of its superelasticity, shape memory, corrosion resistance and biocompatibility, nitinol is now becoming very popular for the manufacturing of minimally invasive device such as endoluminal stents. Despite several studies on in vitro or in vivo biocompatibility of NiTi, few studies have been conducted on the interactions on the interactions of the material with blood. The chemical properties, charge, energy and topography of the surface regulate the amount and the nature of adsorbed proteins, which modulate the platelets adhesion. Thus, stent surface composition is believed to play a key role in thrombus formation following stent implantation. The aim of this study was to investigate the hemocompatibility of nitinol stents in comparison to stainless steel stents. To achieve this goal, an exvivo AV shunt porcine model was used to measure fibrinogen adsorption as well as platelet adhesion on the devices. Based on our results, nitinol exhibit a lower acute thrombogenicity than stainless steel under the test conditions used in this study. Indeed, the amount of labeled fibrinogen and platelet deposition after 15 min. of perfusion was significantly lower for nitinol stents.

iii6o The Corrosion Behavior of NiTiTa Shape Memory Alloy

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Due to its enhanced X-ray visibility, good thermal stability and excellent shape memory effect, NiTiTa shape memory alloy has been recognized as a potential candidate for biomedical applications. Nevertheless, up to the present time, no research addresses the corrosion characteristics of the alloy. In the present study, the corrosion behavior of the Ni₄₆Ti₄₄Ta₁₀ alloy in a simulated body fluid was investigated using X-ray diffractometer, DSC, SEM (with EDS) and atomic absorption spectroscopy. The corrosion rate of the NiTiTa alloy was carefully measured. Comparisons were made between NiTiTa, binary NiTi alloy and 316 stainless steel. The results indicate that (1) in the beginning of the test (less than 48 hours), binary NiTi alloy releases more nickel into the solution than NiTiTa alloy and 316 stainless steel. After 48 hours, the nickel release rate decreases to about the same level in binary NiTi and stainless steel. The minimum nickel release rate was detected in NiTiTa alloys.

iii7o Surface and Corrosion Aspects of NiTi Alloys

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New data on surface conditions of NiTi alloys treated in various manners are presented. Designed surfaces having a uniform structure, thickness, phase and elemental compositions do not show pitting corrosion for up to 1200 mV (possibly higher). The healing ability of designed surface films was studied using corrosion scratch tests. The advantages of the developed material are discussed in terms of biocompatibility. An evaluation of the toxicity level of various metals used in common implants is presented. Nickel dose effect, nickel uptake by media in vitro, and nickel release in vivo are discussed based on this new understanding.

iii8o Studies of Apoptosis of Smooth Muscle Cells after Implantation of NiTi Self-Expand Stent

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Implantation of vascular stents is the most important achievement in therapy of cardiovascular disease. A stent can prevent restenosis, but it can't reduce the proliferation of smooth muscle cells. Now, most methods of treating restenosis aimed at inhibiting proliferation of SMCs. We, from the viewpoint of apoptosis, analyzed the effects of apoptosis in the restenosis after stent implantation. 20 rabbits were studied and 20 NiTi stents were implanted in the normal abdominal aorta. TUNEL and electron microscope were used to determine the apoptosis cells. The experimental results showed that apoptosis cells appeared in the wall of stenting segment from 24hr to 8 weeks, the peak between 3-6 weeks, while the neointimal was formed completely and covered by a single layer cells — endotheliocyte. The apoptosis cells were both in the neointimal and media. It can be concluded that after stent implantation, the SMC not only proliferated but also died (apoptosis), this kind of death may play an important role in maintaining the number of SMCs. Increasing apoptosis cells may reduce restenosis after stenting.

iii9p Plasma Source Ion Implanted Nickel Titanium for Biomedical Applications

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Plasma source ion implantation (PSII) is used as a surface modification technique to improve the biocompatibility of NiTi without negatively affecting its mechanical behavior. In the stent application, for example, the biocompatibility of NiTi is strongly dependent on its surface characteristics which influences thrombosis and affects vessel repair mechanisms. PSII of NiTi sheets with argon at 50k V and a dose of 3E17 ions/square cm resulted in a higher Ti:Ni ratio leaving fewer free Ni ions on the surface. The argon implantation only slightly altered the transformation stress of the material. Additionally, subsequent cyclic mechanical testing had no negative effect on the Ni surface concentrations measured.

iii10p In Vivo Results of Porous Nitinol Shape Memory Metal Alloy: Bone Response and Growth

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Porous nitinol implant were machined to 5 x 5 x 7 mm block. Pore structure analysis were carried out by Hg-porosimetry and scanning electron microscope. Fifteen New Zealand White rabbits were used. Sterile porous nitinol implants were implanted in the defects of proximal tibial metaphysis. Limbs of five rabbits were harvested respectively at 2, 4 and 6 weeks post implantation. Each specimen was embedded in PMMA. Embedded specimen was sectioned into 300 μ m thickness with isomet-diamond saw. Quantitative histomorphometric analysis was performed within each implant. The pore sizes of porous nitinol were $323 \pm 89 \mu$ m. Porosity was $55.3 \pm 6.7\%$. Microscopic examination showed the bone growth in the pore spaces of all implants. The bone growth into the pore space of porous nitinol, percent ingrowth (bone tissue hits/total implant hits in overlaid grid), was excellent (at 6 week, $78.3 \pm 9.7\%$) and increased as the harvest time increased and was excellent. In vivo response of porous nitinol could be used as an ideal bone substitute. Also porous nitinol have many advantages for bone substitute such as its controllable porosity, pore size and stiffness and superelasticity. Using porous nitinol, we are now devising and developing the various designs of bone substitute.

iii11p Surface Corrosion and Trace Metal Determination of NiTi in Biological Environment after Long Term Implantation

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NiTi shape memory alloy is a potential material for orthopedic surgery. Because of the high nickel content of NiTi it is possible that nickel may dissolve from the material due to corrosion and cause unfavorable effects. The purpose of this work was to determine the surface corrosion properties and systemic release of trace metals from NiTi in vivo after a maximum follow-up of 60 weeks. Femoral osteotomies of 40 rats were fixed with either NiTi or stainless steel (StSt) intramedullary nails. The rats were killed at 2, 4, 8, 12, 26 and 60 weeks. The corrosion of the retrieved implants was analyzed by electron microscopy (FESEM). Determination of trace metals (Ni, Cr, Fe) from several organs at 26 and 60 weeks (brain, liver, kidney, spleen, muscle) was done by graphite furnace atomic absorption spectrometry (GF-AAS) or inductively coupled plasma-atomic emission spectrometry (ICP-AES). The FESEM assessment showed surface corrosion changes to be more evident in the StSt implants. There were no statistically significant differences in nickel concentration between the NiTi and StSt groups in any of the organs. NiTi appears to be an appropriate material for further intramedullary use, because its corrosion behavior seems to be satisfactory in vivo for long-term implantation.

Ryhänen, Jorma, Biocompatibility evaluation of nickel-titanium shape memory metal alloy

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Abstract

The shape memory effect, superelasticity, and good damping properties, uncommon in other implant alloys, make the nickel-titanium shape memory metal alloy (Nitinol or NiTi) a fascinating material for surgical applications. It provides a possibility to make self-locking, self-expanding and self-compressing implants. The purpose of this work was to determine if NiTi is a safe material for surgical implant applications.

The primary cytotoxicity and the corrosion rate of NiTi were assessed in human osteoblast and fibroblast cell cultures. Comparisons were made with 316 LVM stainless steel (StSt) and pure titanium. The metal ions present in the media were analyzed using atomic absorption spectrometry (GFAAS). Despite the higher initial nickel dissolution, NiTi induced no toxic effects, decrease in cell proliferation or inhibition in the growth of cells in contact with the metal surface.

The general soft tissue responses to NiTi were compared to corresponding responses to StSt and Ti-6Al-4V alloy in rats during a follow-up of 26 weeks. The muscular tissue response to NiTi was clearly non-toxic and non-irritating, as were also the neural and perineural responses. The overall inflammatory response and the presence of immune cells, macrophages and foreign body giant cells were similar compared to the other test materials. At 8 weeks, histomorphometry showed that the capsule membrane of NiTi was thicker than that of stainless steel, but at 26 weeks the membrane thicknesses were equal.

A regional acceleratory phenomenon (RAP) model was used to evaluate new bone formation, bone resorption and bone (re)modeling after periosteal implantation of NiTi, StSt or Ti-6Al-4V in rats using histomorphometry. Maximum new woven bone formation started earlier in the Ti-6Al-4V group than in the NiTi group, but also decreased earlier, and at 8 weeks the NiTi and StSt groups had greater cortical bone width. Later, no statistical differences were seen. NiTi had no negative effect on total new bone formation or normal RAP during a 26-week follow-up.

The ultrastructural features of cell-NiTi adhesion were analyzed with scanning electron microscopy (FESEM). Cell adhesion and focal contacts showed a good acceptance of NiTi.

Femoral osteotomies of rats were fixed with either NiTi or StSt intramedullary nails. Bone healing was examined with radiographs, peripheral quantitative computed tomography (pQCT) and histologically. The maximum follow-up was 60 weeks. There were more healed bone unions in the NiTi than the StSt group at early time points. Callus size and bone mineral density did not differ between the NiTi and StSt groups. Mineral density in both groups was lower in the osteotomy area than in the other areas along the nail. Density in the nail area was lower than in the proximal part of the operated femur or the contralateral femur. Bone contact to NiTi was close, indicating good tissue tolerance. Determination of trace metals from several organs was done by GFAAS or inductively coupled plasma-atomic emission spectrometry (ICP-AES). There were no statistically significant differences in nickel concentration between the NiTi and StSt groups in distant organs. The FESEM assessment showed surface corrosion changes to be more evident in the StSt implants.

On the basis of this study, the biocompatibility of NiTi seems to be similar to or better than that of stainless steel or Ti-6Al-4V alloy. NiTi appears to be suitable for further use as a biomaterial, because its biocompatibility is good. When NiTi is intended to be used in long-term implants, optimal surface treatment must consider.

Keywords: NiTi, biocompatible materials, bone and muscle response, corrosion