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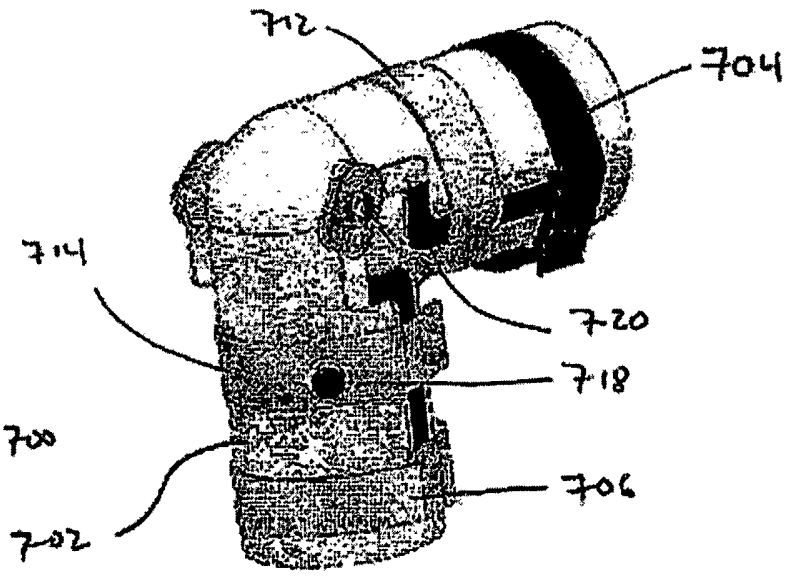

(57) Abstract: The invention relates to methods and apparatus for therapeutically treating connective tissue or increasing vascularization in tissue using ultrasound. More particularly, the present invention relates to methods and apparatus which use ultrasound to stimulate growth or healing, or to treating pathologies, of connective tissue, or to increase vascularization in ischaemic or grafted tissue using ultrasound.

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METHOD AND APPARATUS FOR ULTRASOUND TREATMENT OF CONNECTIVE TISSUE

CROSS-REFERENCE TO RELATED APPLICATION

This application claims priority to U.S. Serial No. 10/131,784 entitled "Method and Apparatus for Connective Tissue Treatment" filed on April 24, 2002 in the U.S. Patent and Trademark Office.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to methods and apparatus for therapeutically treating connective tissue and/or increasing vascularization in tissue using ultrasound. More particularly, the present invention relates to methods and apparatus which use ultrasound to stimulate growth or healing, or to treating and/or preventing pathologies of connective tissue, or to increase vascularization in ischaemic or grafted tissue using ultrasound.

2. Description of the Related Art

The use of ultrasound to therapeutically treat and evaluate bone injuries is known. Impinging ultrasonic pulses having appropriate parameters, e.g., frequency, pulse repetition, and amplitude, for suitable periods of time and at a proper external location adjacent to a bone injury has been determined to accelerate the natural healing of, for example, bone breaks and fractures.

U.S. Patent No. 4,530,360 to Duarte describes a basic non-invasive therapeutic technique and apparatus for applying ultrasonic pulses from an operative surface placed on the skin at a location adjacent to a bone injury. To apply the ultrasound pulses during treatment an operator must manually hold the applicator in place until the treatment is complete.

The Duarte patent as well as U.S. Patent No. 5,520,612 to Winder et al. describe ranges of RF signal for creating the ultrasound, ultrasound power density levels, ranges of duration for each ultrasonic pulse, and ranges of ultrasonic pulse frequencies.

U.S. Patent No. 5,003,965 to Talish et al. relates to an ultrasonic body treatment system having a body-applicator unit connected a remote control unit by sheathed fiber optic lines. The signal controlling the duration of ultrasonic pulses and the pulse repetition frequency are

generated apart from the body-applicator unit. Talish et al. also describes a mounting fixture for attaching the body-applicator unit to a patient so that the operative surface is adjacent the skin location.

While the systems described in these patents relate to therapeutic methods and apparatus for ultrasonic treatment of hard and soft issue injuries and defects, there is a need for ergonomically configured signal generators and transducers for the treatment of cartilage and/or osteochondral injuries and/or defects and/or for the treatment of cartilage/degenerative joint diseases, such as osteoarthritis (OA). Further, a need exists for an apparatus which optimizes the treatment of cartilage and/or osteochondral injuries and/or defects and/or the treatment of cartilage/degenerative joint diseases, such as osteoarthritis.

A cartilage and/or osteochondral injury and/or defect and/or degenerative joint disease, such as osteoarthritis, typically involves damage to the cartilage which lines articulating bones (articular cartilage), such as the bones of the knee, elbow, shoulder and ankle. Osteochondral injuries can be treated by chondral and/or osteochondral drilling causing blood flow at the site. The aim of chondral drilling is to stimulate cartilage regeneration as part of the healing process. However, the resulting nonhyaline or fibrocartilage produced is biomechanically inferior to articular cartilage, does not have comparable proteoglycan content, and may consist primarily of a thin unorganized layer of collagen. Further, it has been observed that degeneration of the new tissue generally occurs over time, requiring the need for additional reconstructive surgical treatment.

Other methods of treatment include: the transplantation of non-weight bearing cartilage to the injury and/or defect site; inducing a fracture at the injury and/or defect site; placing a carbon fiber matrix to induce cartilage formation; and autologous chondrocyte implantation (ACI). ACI entails removing chondrocytes capable of regenerating hyaline-like cartilage from the body and culturing them for several weeks. During the culture process, the number of cells increases approximately 15 times that of the original tissue sample. The cultured cells are then transplanted through an arthrotomy. A small piece of periosteum, the skin covering a bone, is taken from the patient's tibia. The periosteum is then sutured over the defect to provide a protective cover for the cultured cells. The cultured cells are injected under the periosteum into the defect where they will continue to multiply and produce a durable repair tissue. However, ACI increases the healing time since the chondrocytes need to be cultured before they are transplanted to the patient.

Therefore, there is a further need for a method and apparatus to stimulate cartilage regeneration which produces a repair tissue that is fibrocartilage or hyaline-like, and which is

equivalent to articular cartilage in mechanical properties. There is also a need for repair tissue that is generally superior in mechanical properties to that generated using conventional techniques, as described above. Further still, a need also exists for an apparatus which stimulates cartilage regeneration and where the regenerated cartilage does not degenerate over time requiring additional treatment or reconstructive surgery. Further, there is a need for an apparatus which stimulates cartilage regeneration and significantly reduces the healing time.

For treatment of degenerative joint diseases such as osteoarthritis, some combination of symptom-modifying drug, physiotherapy with nonsteroidal antiinflammatories (NSAID's), bracing, weight loss, and/or reduced activity are initially used. However, while these approaches may control symptoms, they do not effectively address the underlying damage to connective tissue, such as cartilage. Moreover, the drugs used may cause severe side effects in some patients, which can result in hospitalization and, in some cases, death. It has been reported that an estimated 20,000 OA patients die each year in the United States from gastrointestinal complications associated with NSAID use. If symptoms remain after these treatments, then more invasive treatment methods are often used, such as injection of viscoelastic materials, arthroscopic surgery, or total joint replacement. There remains a need for additional methods and apparatus that treat and repair connective tissue damage, e.g. damage to cartilage, rather than simply control symptoms of osteoarthritis, and that do not have the side effects and/or tolerance problems associated with current pharmaceutical therapies.

However, injuries and pathologies of cartilage are not the only conditions of connective tissue requiring treatment that involve significant healing time. When ligament and tendons rupture the patients have pain and laxity of the joint or muscle. The current repair options available to the surgeon are to replace or reconstruct the damaged tissue with autograft or allograft tissue, augmentation of the tear surfaces with a device, or by fixation of the tissue with devices such as sutures or anchors, or to simply treat symptoms such as pain and inflammation, without resolving the underlying problem. Because of the risks associated with surgery, treatment options that do not necessarily involve surgery would be desirable. In addition, the repaired tissue is often not as strong as the original undamaged tissue, so that methods to increase repair tissue strength and decrease rehabilitation time would also be desirable. The success of therapies involving replacement or reconstructed tissue is often dependent on the body's ability to vascularize the tissue. Increased vascularization will lead to improved, faster healing, while insufficient vascularization can lead to necrosis of the tissue. Thus, methods for increasing vascularization in surgically repaired tissues would be advantageous.

In addition, in allograft or autograft replacement, the graft dies off and is subsequently repopulated and remodeled by infiltrating cells. This is a lengthy process during which time the graft loses strength and is at risk of rerupture or damage. This leads to lengthy rehabilitation times (e.g., a minimum of 6 months for anterior cruciate ligament (ACL) reconstruction). Inhibiting cell death within the graft via stimulation of blood vessel and tissue in-growth would therefore be desirable. This will lead to a faster and stronger repair and reduced rehabilitation time thus the patients will return to full function faster. The phenomenon of "bone tunnel widening" can often present a problem. Improved integration of bone/tissue/ligament interfaces would help to avoid the "windshield wiper effect" posited as a mechanism for bone tunnel widening.

Surgical methods are also typically required to repair menisci in the knee, for example. Increased vascularization of the avascular "white zone" of the menisci is desirable due to the stimulation in healing that results.

As explained above, the current treatments for many or most of these connective tissue injuries/pathologies are either surgical procedures including repair, reconstruction, augmentation, fixation and tissue resection, or the use of drug therapies that reduce the pain and inflammation. These procedures are usually followed by (or combined with) rehabilitation including physiotherapy which will include a series of stretching exercises with a gradual increase in range of motion and loading on the repair tissue. However, physiotherapy is inconvenient, time consuming and relatively expensive, which can lead to problems with patient compliance. There is thus a need in the art for methods of speeding healing and increasing vascularization that lend themselves to use by the patient at home, and do not require a significant amount of time each day.

It is often desirable to address problems such as laxity of joints by modifying tissues such that the collagenous components of connective tissues (joint capsules, tendons, ligaments) are induced to contract, a procedure often termed capsulorrhaphy. Applying thermal energy to collagen can cause an alteration of the molecular configuration resulting in shrinkage. This results in a shorter structure and a "tighter" joint. However, the thermal energy incidentally may also damage the tissue resulting in loss of viability of cells, loss of blood supply and reduced mechanical integrity of the structure. Tissue shrinkage procedures have thus had difficulties resulting from decreased biomechanical integrity and long rehabilitation times due to slow healing. This has resulted in the 'modified' tissue being stretched back out prior to its healing and reestablishment of normal biomechanical strength, resulting in the loss of the benefit of the shrinkage procedure. This damage represents a significant disadvantage and has

inhibited the use of capsulorrhaphy and related tissue shrinkage procedures. Faster post-shrinkage repair of tissue would minimize these difficulties and make the technique more widely applicable.

Tissue engineering involves the growth of cells on a scaffold in vitro (outside the body) to produce a graft for the repair of tissues within the body. One of the shortcomings of this approach is that it is not possible to grow a tissue-engineered material (implant, graft or organ) with a vascular supply in vitro. When the tissue-engineered material is placed into the body and stimulated with ultrasound functional blood vessels are stimulated to grow into the tissue-engineered material from the hosts own blood supply. This is a means of vascularization of this implanted material thus retaining the function and viability of the grafted material. There remains a need for methods and apparatus to achieve this vascularization of tissue engineered material.

SUMMARY OF THE INVENTION

The method and apparatus of the invention resolve many of the difficulties associated with conventional therapies described above. In one embodiment, the invention relates to a method for stimulating growth or healing, or treating pathologies, of connective tissue in mammals in need thereof, by subjecting the affected connective tissue to noninvasive, low intensity ultrasound of a frequency and duration sufficient to stimulate growth, healing, or repair of the connective tissue.

In another embodiment, the invention relates to a method for increasing vascularization in ischaemic or grafted tissue (not limited to connective tissue) in mammals in need thereof, by subjecting the affected tissue to noninvasive, low intensity ultrasound of a frequency and duration sufficient to stimulate an increase in vascularization in the ischaemic or grafted tissue.

In another embodiment, the invention relates to an apparatus for effecting the treatment method described herein. The apparatus includes a placement module adapted to secure one or more transducers thereto in a plurality of configurations. The placement module is then secured to a site near the tissue in need of treatment, for example, at the knee, hip, ankle, shoulder, elbow, or wrist, and the transducers actuated to emit ultrasound sufficient to stimulate healing or repair, or to increase vascularization. Further, the present invention also provides an embodiment having a placement module which contains a locking structure for locking in a particular position the articulating bones of a joint undergoing treatment. This embodiment

prevents the patient from moving his limbs, for example, moving the femur with respect to the tibia, during treatment.

In another embodiment, the invention relates to an apparatus for positioning one or more ultrasonic transducers with respect to a joint for delivery of ultrasonic therapy thereto, having a covering member adapted to cover at least a portion of the joint or adjacent body members and be secured thereto in a fixed position, wherein the covering member comprises one more receiving areas adapted to receive and hold one or more ultrasonic transducer assemblies in one or more fixed positions relative to the joint or adjacent body member.

Because of the broad applicability of utility of the invention in promoting healing, the method and apparatus described herein are useful in treating patients with a broad range of problems, such as trauma, tissue insufficiency, pain, post-surgical healing, degenerative conditions such as osteoarthritis, and other problems. Moreover, because the invention is portable, does not require prolonged treatment times, and is designed for ease of use and positioning of the ultrasonic transducers, patients will be more likely to use the technique properly and sufficiently to benefit therefrom.

According to the invention there is provided an apparatus for positioning one or more ultrasonic transducers with respect to a joint for delivery of ultrasonic therapy thereto, comprising: a covering member adapted to cover at least a portion of the joint or adjacent body members and be secured thereto in a fixed position, wherein the covering member comprises one or more receiving areas adapted to receive and hold one or more ultrasonic transducer assemblies.

Also, according to the invention there is provided a method for stimulating growth or healing, or treating pathologies, of connective tissue in mammals in need thereof, comprising: covering at least a portion of a joint or adjacent body members with a covering member adapted to cover at least a portion of the joint or adjacent body member and be secured thereto in a fixed position; and subjecting the affected connective tissue to noninvasive, low intensity ultrasound of a frequency and duration sufficient to stimulate growth, healing, or repair of the connective tissue; further characterized in that the covering member comprises one or more receiving areas adapted to receive and hold one or more ultrasonic transducer assemblies.

BRIEF DESCRIPTION OF THE DRAWINGS

Specific embodiments of the invention are descried below with reference to the drawings, which are described as follows:

Fig. 1 is a perspective view of a patient wearing one embodiment of a portable ultrasonic treatment apparatus suitable for carrying out the method of the invention having a main operating unit or controller and a placement module;

Fig. 2A is an exploded view of the placement module of the portable ultrasonic treatment apparatus illustrated by Fig. 1;

Fig. 2B is a rear underside view of the placement module of the portable ultrasonic treatment apparatus illustrated by Fig. 1;

Fig. 3 is a cross-sectional view illustrating a transducer assembly according to one embodiment of the invention impinging ultrasonic waves to connective tissue within the knee, with an ultrasonic conducting gel positioned between the transducer assembly and the patient's knee;

Fig. 4 is a block diagram of one embodiment of the circuitry for one embodiment of an ultrasonic transducer assembly;

Fig. 4A is a block diagram of an alternative embodiment of the circuitry for the ultrasonic transducer assembly;

Fig. 5 is a perspective view of a second embodiment of the portable ultrasonic treatment apparatus, illustrating a main operating unit controller and a placement module for treating connective tissue injuries or pathologies within the elbow region;

Fig. 6 is a perspective view of a third embodiment of the portable ultrasonic treatment apparatus, illustrating a main operating unit controller and a placement module for treating connective tissue injuries or pathologies within the shoulder region;

Fig. 7 is a perspective view of a fourth embodiment of the portable ultrasonic treatment apparatus illustrating a main operating unit controller and a placement module;

Fig. 8 is a perspective view of the portable ultrasonic treatment apparatus illustrated by Fig. 7 mounted on a patient's ankle;

Fig. 9 is a perspective view of a fifth embodiment of the portable ultrasonic treatment apparatus, illustrating a main operating unit or controller and a placement module for treating connective tissue injuries or pathologies within the knee region;

Fig. 10A is an exploded view of the portable ultrasonic treatment apparatus illustrated by Fig. 9;

Fig. 10B is a perspective view of a support member of the portable ultrasonic treatment apparatus illustrated by Fig. 9;

Fig. 11A is a side view of an alternative embodiment of a placement module according to the invention;

Fig. 11B is a rear perspective view of the placement module of Fig. 11A;

Fig. 11C is a front view of the placement module of Fig. 11A and 11B;

Fig. 12A is a left perspective view of another alternative embodiment of a placement module according to the invention;

Fig. 12B is a right perspective view of the placement module illustrated in Fig. 12A;

Fig. 12C is an expanded perspective view of the placement module illustrated in Fig. 12A and 12B;

Fig. 12D is a top view of the placement module illustrated in Fig. 12A through 12C;

Fig. 13A is a left perspective view of another alternative embodiment of a placement module according to the invention;

Fig. 13B is a right perspective view of the placement module illustrated in Fig. 13A;

Fig. 14 shows an embodiment of the placement module of the invention suitable for treating the shoulder area. Fig. 14A is a schematic view of a placement module adapted to cover the torso area. Fig. 14B and 14C are close up schematic views of open (14B) and closed (14C) transducer ports;

Fig. 15A shows a schematic view of another embodiment of the placement module of the invention in the form of an adjustable shoulder brace. Fig. 15B and 15C are close up schematic views of open (15B) and closed (15C) transducer ports;

Fig. 16 is a schematic view illustrating an embodiment of the placement module of the invention, wherein the covering member is a shoe or sneaker;

Fig. 17A is a schematic view of another embodiment of a placement module similar in application to that of Fig. 16, but wherein the covering member is an elastic or stretchable. Fig. 17B is a close up schematic view of the transducer port or assembly;

Fig. 18A is a schematic view of an embodiment of a placement module according to the invention suitable for application of ultrasound to the wrist or hand area. Fig. 18B is a schematic exploded view of the transducer port or assembly;

Fig. 19 is a schematic view of an embodiment of a placement module according to the invention suitable for application of ultrasound to the elbow area.

Fig. 20A is a photomicrograph of ovine tendon graft after 3 weeks without treatment according to the invention;

Fig. 20B is a photomicrograph of ovine tendon graft after 3 weeks of ultrasonic treatment according to the invention;

Fig. 21A is a photomicrograph of ovine tendon graft after 6 weeks without treatment according to the invention;

Fig. 21B is a photomicrograph of ovine tendon graft after 6 weeks with ultrasonic treatment according to the invention;

Fig. 21C is a photomicrograph of an intra-articular section of the ovine tendon graft shown after 6 weeks with ultrasonic treatment according to the invention;

Fig. 21D is a photomicrograph of bone marrow near an ovine tendon graft after 6 weeks with ultrasonic treatment according to the invention;

Fig. 22A is a photomicrograph of an intra-articular section of ovine tendon graft after 12 weeks without treatment;

Fig. 22B is a photomicrograph of an intra-articular section of ovine tendon graft after 12 weeks with ultrasonic treatment according to the invention;

Fig. 22C is a photomicrograph of ovine tendon graft after 12 weeks without treatment;

Fig. 22D is a photomicrograph of ovine tendon graft after 12 weeks with ultrasonic treatment according to the invention.

Fig. 23A is a photomicrograph of tissue from an ultrasound treated knee joint in a guinea pig having osteoarthritis.

Fig. 23B is a photomicrograph of tissue from a control knee joint in a guinea pig having osteoarthritis.

Fig. 24 shows the histological scoring for the presence of vascularisation (neo-angiogenesis) in treated tissue compared to controls.

Fig. 25 shows the bone ingrowth at interface in treated tissue compared to controls.

Fig. 26 shows the peak load to failure for treated tissue compared to controls.

Fig. 27 shows the energy required to make the grafts fail compared to controls.

Fig. 28 shows the stiffness of the repaired tissue compared to controls.

Fig. 29A shows an unoperated (native) insertion.

Fig. 29B shows an ultrasound treated repair.

Fig. 29C shows a control repair tissue.

Fig. 30 shows the presence of vascularity for a treated tissue.

Fig. 31 shows tissue organization for a treated tissue.

Fig. 32 shows macroscopic grading in a treated tissue compared to untreated.

Fig. 33 shows cellularity in a treated tissue compared to untreated.

Fig. 34 shows vascularity in a treated tissue compared to untreated.

Fig. 35A shows a control defect.

Fig. 35B shows an ultrasound treated defect.

DETAILED DESCRIPTION OF SPECIFIC EMBODIMENTS

The ultrasonic treatment apparatus and method of the present invention involves the non-invasive use of low intensity, ultra high-frequency acoustic energy (ultrasound) to treat injuries, defects, or pathologies of connective tissue, or to increase vascularization of ischaemic or grafted tissue. It will be recognized that in treating connective tissue, increased vascularization will likely result and contribute to healing, but that the use of the method and apparatus to increase vascularization is not limited to treatment of connective tissue, but extends to grafted tissues, organs, or engineered tissue that has been produced ex vivo.

As described above, in one embodiment, the invention relates to an apparatus and method for the treatment of injuries and pathologies, and the stimulation of healing, of connective tissues. The method may be used as an adjunct to surgical repair, in order to speed healing, or in some cases can be used alone to heal tissue injuries without surgery (e.g., for degenerative diseases such as osteoarthritis, tendonosis, and tendonitis). The apparatus and method of the invention are particularly suitable for use in treatment of connective tissues associated with joints, such as those in the hand or foot, wrist, ankle (Achilles tendon), knee (e.g., anterior cruciate ligament, posterior cruciate ligament, meniscofemoral ligament, lateral or collateral ligaments, tendon of quadriceps, gracilis tendon, sartorius tendon, semitendinosis tendon, popliteus tendon, adductor magnus tendon, medial or lateral meniscus), elbow (lateral, collateral, or annular ligaments), hip, shoulder (e.g., supraspinatus tendon/rotator cuff/glenoidal labrum), back and neck.

Nonlimiting examples of conditions or situations in which treatment according to the invention is suitable include degenerative diseases such as osteoarthritis, ligament, tendon, spinal disc and meniscus injuries, ligament and tendon pathologies, surgical repair or modification (including modification procedures such as capsulorrhaphy (shrinkage), and procedures for shrinkage of the spinal disc (for example the Idet procedure), and for the treatment of ischaemic tissues (such as a myocardially infarcted heart) to increase vascularization by inducing a vascular supply (in-growth of new blood vessels) into these tissues (used herein to refer to tissues that have either a restricted blood flow or a lack of adequate vascular supply). The invention could also be used to increase vascularization in a grafted tissue/organ or into a tissue engineered graft that has been produced ex vivo.

The invention can be used as an adjunct to the surgical repair of ruptured ligament and tendons (for example rotator cuff tendon repair, anterior cruciate ligament, posterior cruciate, lateral collateral ligament, medial collateral, flexor or extensor repairs, Achilles tendon, surgical tendon transfers or tendon weaves).

The invention is suitable for treatment of a number of different tendoniopathies and/or overuse injuries, including without limitation lateral or medial epicondylitis (tennis elbow), carpal tunnel syndrome, plantar fascitis, Achilles tendonitis, and the like, as either an adjunct to surgery, or without surgery.

The invention can also be used to increase the rate, quality and vascularity of connective tissue that is regenerated on, and/or grows into, a scaffold which is implanted into the body to support connective repair/regrowth. The term "scaffold" as used herein means a three dimensional, at least partially porous structure, and having sufficient porosity to allow cell infiltration. The scaffold surface allows cell adhesion and growth such that cell proliferation and extracellular matrix (ECM) generation can occur and tissue can be laid down and remodel.

The scaffolds can be formed from bioresorbable or non-bioresorbable materials. Suitable bioresorbable materials include bioresorbable polymers or copolymers including, for example, polymers and/or copolymers formed from the following monomers or mixtures thereof: hydroxy acids, particularly lactic acid, glycolic acid; caprolactone; hydroxybutyrate; dioxanone; orthoesters; orthocarbonates; and/or aminocarbonates. The bioresorbable materials may also contain natural materials such as collagen, cellulose, fibrin, hyaluronic acid, fibronectin, chitosan or mixtures of two or more of these materials. The bioresorbable materials may also contain devitalised xenograft and/or devitalised allograft material. Bioresorbable ceramics, such mono-, di-, octa-, a-tri-, b-tri and tetra-calcium phosphate, hydroxyapatite, fluoroapatite, calcium sulphate, calcium fluoride, calcium oxide or mixtures of two or more of these materials, may also be used as scaffold material.

Suitable non-bioresorbable materials for use in scaffolds include polyesters, particularly aromatic polyesters, such as polyalkylene terephthalates, like polyethylene terephthalate and polybutylene terephthalates; polyamides; polyalkenes such as polyethylene and polypropylene; poly(vinyl fluoride), polytetrafluoroethylene carbon fibres, silk (natural or synthetic), carbon fibre, glass and mixtures of these materials.

Scaffolds may also be formed from materials that include hydrogels. Examples of suitable hydrogel materials include: poly(oxyethylene)-poly(oxypropylene) block copolymers of ethylene diamine, polysaccharides, chitosan, poly(vinyl amines), poly(vinyl pyridine),

poly(vinyl imidazole), polyethylenimine, poly-L-lysine, growth factor binding or cell adhesion molecule binding derivatives, derivatised versions of the above, e.g. polyanions, polycations, peptides, polysaccharides, lipids, nucleic acids or blends, block-copolymers or combinations of the above or copolymers of the corresponding monomers; agarose, methylcellulose, hydroxypropylmethylcellulose, xyloglucan, acetan, carrageenan, xanthan gum/locust bean gum, gelatine, collagen (particularly Type 1), PLURONICS™, POLOXAMERS™, poly (N-isopropylacrylamide) and N-isopropylacrylamide copolymers.

Structurally, the scaffold may be a woven, non-woven (fibrous material), knitted, braided or crocheted material, a foam, a sponge, a dendritic material, or a combination or mixture of two or more of these.

Following surgery, the ultrasound device is applied non-invasively to the outside of the body (e.g., coupled to the skin with coupling media, such as a gel) after surgery in the region of the repaired tissue, and is operated to transmit ultrasound, desirably in the form of pulses, into the tissue in need of treatment, or at the interface with the uninjured tissues. Exposure to the ultrasound stimulates a faster, better quality repair of the tissue. At a bone interface, the ultrasound will also stimulate bone repair and bone in growth into the repair or graft tissue. This gives rise to a faster, stronger repair and improved integration of the interface between, e.g., tendon, ligament and bone.

The method and apparatus of the invention may also be used to non-invasively treat pathologies of connective tissues, such as osteoarthritis, ligament and tendon conditions, without the need for a surgical procedure. Such conditions include, as examples, osteoarthritis, acute tears, chronic overuse injuries, and tendon pathologies including tendonosis and tendonitis. In these cases the device would be applied to the skin in the region of pain above the injured or degenerative tendon or ligament. The ultrasound would then propagate in to the defective tissue and stimulate the tissue to remodel and repair without the requirement for surgery. The treatment thus would improve the in-vivo function of the tissue with respect to mechanical load bearing, and avoid the risks and disadvantages associated with surgery, as described above.

As described above, the method and apparatus of the invention is also particularly suitable for stimulating repair of damaged menisci. This could be done after surgical repair to stimulate the healing process, or as a possible alternative to surgery. Without being bound by any theory, the invention appears to be particularly useful because it stimulates healing of the avascular 'white zone' of the meniscus by stimulating in-growth of blood vessels and their concomitant cell populations, which are capable of healing the damaged tissue. More

particularly, the meniscal cartilage is partially vascularized in the external periphery of the tissue and has an avascular inner region. If the vascular region is damaged, it usually heals or can be repaired due to the presence of a blood supply. If the avascular region is damaged, it does not heal and cannot be easily repaired because of the absence of blood supply. As a result, damaged avascular regions often must be resected, which can lead to post meniscectomy arthritis. However, using the method and apparatus of the invention repair of the avascular region becomes possible due to the ability of the invention to stimulate vascularization.

However, the method and apparatus of the invention is not limited to increasing vascularization of damaged menisci, but can also be used to treat general ischaemic tissues which have restricted blood flow and/or a lack of adequate vascular supply. For instance, the method and apparatus of the invention can be used to induce a vascular supply and in growth into a grafted tissue or organ, or into a tissue engineered graft that has been produced ex vivo and lacks a vascular supply. The invention could also be used to treat tissues with a partial vascular supply to stimulate repair of tissues in the avascular region of the tissue.

In addition to surgical and nonsurgical treatment of tissue injuries, defects, or pathologies, the method and apparatus of the invention can also be used as an adjunct to tissue modification treatments, such as capsulorrhaphy, or shrinkage of the spinal disc and related or similar tissue shrinkage procedures, to significantly increase the success rate and benefit to the patient of undergoing such procedures. As described above, the use of thermal energy to alter the configuration of connective tissue and thereby eliminate joint laxity is associated with problems relating to tissue damage. Loss of cell viability, loss of blood supply, and reduced mechanical integrity can result in loss of many of the benefits associated with the tissue shrinkage procedure.

The method and apparatus of the invention provides a means to address these potentially adverse effects by stimulating revascularization and cell repopulation, resulting in repair and return to normal biomechanical integrity. The invention adds to the ability to shrink the tissue the ability to also rapidly heal it in its shortened configuration, and as a result offers a new treatment option that was previously difficult to achieve. This invention thus makes practical a new treatment method having the significant benefits associated with a reduced surgical procedure, i.e. a less invasive and traumatic procedure, for otherwise difficult to treat cases. The reduction in healing time obtainable with the method and apparatus of the invention means that that the chances of the weakened tissue being stretched are reduced. The reduction in rehabilitation time allows the patient to return to normal

activities more quickly. The combination of a minimally invasive procedure using radiofrequency tissue shrinkage technology in combination with the method and apparatus of the invention provides a procedure offering dramatically reduced rehabilitation time and an opportunity to treat a broader range of patients and disorders without surgery.

The method and apparatus of the invention can be combined with pharmacological treatment modes, and these combinations also form a part of the invention. For instance, the method of the invention can be used in conjunction with known growth factor therapies, including but not limited to, the Transforming Growth Factor β superfamily, including: TGFβ's, Bone Morphogenetic Proteins (BMP's, e.g. BMP2, BMP4), Cartilage Derived Morphogenic Proteins (CDMP's e.g. CDMP-1, CDMP-2) and Growth Differentiation Factors (e.g. GDF5), angiogenic factors (angiogenin), platelet-derived cell growth factor (PD-ECGF), Platelet Derived Growth Factors (PDGF), Vascular Endothelial Growth Factor (VEGF), the Epidermal Growth Factor family, e.g. EGF, Transforming Growth Factor Alpha (TGFα), Platelet Derived Growth Factors, e.g. PDGF-A, PDGF-B, PDGF-BB, Fibroblast Growth Factors, e.g. BFGF, Hepatocyte Growth Factors (HGF), Insulin-like Growth Factors, e.g. IGF-1, IGF-II, Growth Hormones (GH), Interleukins (e.g. IL-1, IL-11), Connective Tissue Growth Factors (CTGF), Parathyroid Hormone Related Proteins (PTHrp), autologous growth factors (such blood and platelet derived factors), and mixtures of at least two of these materials. In conjunction with growth factor therapies, the method and apparatus of the invention provide a faster, better quality repair. Appropriate dosages of such growth factors are those known in the art for use in therapy without ultrasound treatment.

As described in more detail below, the apparatus of the invention contains one or more ultrasound treatment heads that direct ultrasonic energy to the site of the tissue to be treated through the overlying tissues. Without being bound by any theory, it is believed that the ultrasonic energy provides a mechanical stimulus that induces tissue repair and also stimulates blood vessel in growth and blood flow to the tissue which aids the healing or repair process. This stimulation appears to be the result of a molecular mechanism related to vascularity through an increase in growth factor and biological molecules known to be vital for angiogenesis, matrix production and cellular proliferation. The pathway may be mediated through signal transduction molecules that regulate cellular function.

The ultrasound is generally a low intensity ultrasound having a frequency ranging between about 1 and about 2 MHz, more particularly about 1.5 MHz. The ultrasound desirably is pulsed, having a pulse width ranging from about 10 to about 2,000 microseconds,

more particularly about 200 microseconds, with a repetition frequency ranging from about 0.1 to about 10 KHz, more particularly about 1 KHz.

The ultrasonic energy is emitted by one or more transducers. Multiple transducers are often desirable, in particular for treating some types of ligament injury, and when present can be configured into arrays to properly place them adjacent to areas to be treated. For example ACL surgical repairs can be treated with multiple transducers, each in a separate treatment head. One treatment head is applied to the outside of the knee in the region of the tibial bone tunnel; another treatment head is applied to knee in the region of the mid section of the graft and another treatment head is applied to knee in the region of the femoral bone tunnel. Multiple transducers can also be set to emit energy simultaneously (e.g., in simultaneous pulses) or in a phased fashion, such that they emit pulses sequentially.

One embodiment of the apparatus of the invention includes an ergonomically constructed placement module having a strap or other fastening means for securing it and the attached transducer or treatment head adjacent to the part of a patient's body in need of treatment. At least one ultrasonic transducer assembly is attached or imbedded within the placement module and properly positioned on the various anatomical regions in proximity to the desired treatment site. Different types of ultrasonic transducers and signals can be provided, such as those described and schematically depicted in U.S. Patent No. 5,520,612 to Winder et al. Particularly, the transducers and arrangements schematically depicted by Figs. 7-11 of the patent in which at least one transducer is used to provide acoustic energy to the site of the injury. The apparatus may also utilize a portable, ergonomically constructed main operating unit (MOU), which may be worn by the patient, and which provides control signals to the ultrasonic transducer(s). An example of a suitable MOU is that described in U.S. Patent No. 5,556,372 to Talish et al.

Turning to the figures, in particular Fig. 1, one embodiment of the portable ultrasonic treatment apparatus 10 useful in accordance with the invention is shown. The ultrasonic treatment apparatus 10 includes a MOU 12, a placement module 14, and ultrasonic transducer assembly or treatment head 16.

The placement module 14 comprises a placement support 20 which includes at least two or three channels 22 each having an extension 24 mounted therein. Each extension has a transducer pocket 26 at one end or holding one ultrasonic transducer assembly 16. It is contemplated for each extension 24 to have several ranges of movements besides longitudinal motion, such as articulating to the longitudinal motion.

The placement module 14 further includes a placement band 28 cooperating with slot 30 for securing the placement support 20 to the patient. The placement band 28 is configured to firmly secure the placement module 14 to the patient. A sponge-like material 32 can be used to line the inner surface of the placement support 20 for providing comfort to the patient (Figs. 2A and 2B). The placement support 20 may be constructed of hard plastics which may be custom molded for a particular body part of the patient.

With reference to Figs. 2A and 2B, the extensions 24 are mounted to the placement support 20 via screws 33 and thumb screws 34. The screws 33 are passed through slots 35 and holes 36 on the extensions 24 and are threaded to the thumb screws 34. The extensions 24 can be moved to different positions to accommodate patients of all sizes by unthreading the thumb screws 34 and shifting the screws 33 along the slots 35 and threading the screws 33 to the thumb screws 34 at the new position.

The transducer assembly 16 may include circuitry, schematically illustrated by Figs. 4 and 4A and described below, for exciting the least one transducer therein and is coupled to the MOU by cable 37 and wires 39. The wires 39 are coupled to the placement support 20. The cable 3 is preferably a multiconductor cable capable of transmitting relatively low frequency RF or optical signals, as well as digital signals. The cable 37 may include coaxial cable or other types of suitable shielded cable. Alternatively, the cable 37 may include fiber optic cable for transmitting optical signals. The signals may be transmitted continuously or as a series of pulses.

In operation, the placement module 14 is positioned and secured to the patient's body as shown by Fig. 3, such that each transducer assembly 16 lies over the treatment site. A locating ring such as the one disclosed in U.S. Patent Application No. 08/389,148, may be used for determining the location of injured bone, if the patient desires to have one of the transducer assemblies overlying a bone injury, before the placement module 14 is secured to the patient. Once the placement module 14 is properly positioned, the transducer within the transducer assembly 16 is excited for a predetermined amount of time. An ultrasound conducting gel 38 is positioned between the transducer assembly 16 and the injured part of the patient's body to prevent attenuation of the ultrasonic waves as they travel to the connective tissue 40, as shown by Fig. 3.

It is also contemplated that one or more transducers can be converted to receive reflected diagnostic data from the treatment site. This permits real time evaluation of the injury site and healing process.

With reference to Fig. 4, a block diagram of one embodiment of the ultrasonic transducer assembly circuitry is shown. The transducer assembly circuitry 17 includes a receiver/RF oscillator 50 which receives the signals transferred by a signal generator within MOU 12 via cable 37. The receiver/RF oscillator 50 is connected to transducer driver 52 which excites transducer 16. An alternative embodiment of the transducer assembly circuitry 17 is shown in Fig. 4A. In this embodiment, the ultrasonic transducer assembly 16 includes an internal battery 60 which supplies power to the components within the transducer assembly 16. For example, battery 60 supplies power to signal monitoring circuit 62 and signal driver 66. The signal monitoring circuit 62 provides, preferably, a digital output signal 68 which represents the waveform characteristics of the output of transducer driver 70. These characteristics can be displayed on a digital display and may include, for example, the frequency, pulse repetition frequency, the pulse width and the average output power of the transducer 16. The output signal 68 of signal monitoring circuit 62 is transferred to the signal generator within MOU 12 via driver 66 and cable 37. The signal generator may include a processor and a switch for regulating the signal characteristics. Control signals from the MOU 12 are received by receiver 72 via cable 37. Safety or fixture interlock 74, which may include switches on the outer surface of the placement module 14 or transducer assembly 16, ensures that the placement module 14 is properly positioned before providing power to the internal components of the transducer assembly 16.

A second embodiment of the portable ultrasonic treatment apparatus of the present invention is illustrated by Fig. 5 and designated generally by reference numeral 200. The treatment apparatus 200 includes MOU 12 and transducer assemblies 202 affixed to a placement module 204 via extensions 206 for ultrasonically stimulating the repair or healing of tissue in the elbow region. Each transducer assembly 202 includes a power transducer 212 connected to the MOU 12 by cable 218. An ultrasonic conducting gel 212 is positioned between the transducer assemblies 202 and the treatment site to prevent attenuation of the ultrasonic waves as they travel to the tissue being treated. In order to accommodate various patients, the extensions 206 can be adjusted to several positions by unthreading thumb screws 220. The circuitry for each transducer assembly 202 may be similar to that disclosed for the first embodiment and schematically illustrated by Figs. 4 and 4A.

It is envisioned that the placement module 204 b constructed from suitable conductive plastics, such as conductive ABS plastics with either carbon, stainless steel, nickel or aluminum fibers to forego the use of wires for connecting the transducer assemblies 202 to the cable 218.

In such an embodiment, the conductive placement module 204 would be used to electrically connect the transducer assemblies 202 to the MOU 12 via cable 218.

With reference to Fig. 6, a third embodiment of the portable ultrasonic treatment apparatus of the present invention is illustrated. In this embodiment, the treatment apparatus 300 includes a MOU 12, a placement module 304, and ultrasonic transducer assemblies 306. The placement module 304 is configured for placement on the shoulder region and includes a placement band 310 and a placement support 312. Each transducer assembly 306 is connected to the MOU 12 by cable 318 to power transducer assembly circuit within each assembly 306. The circuitry (not shown) may be similar to that disclosed for the first and second embodiments and schematically illustrated by Figs. 4 and 4A.

In operation, transducers within transducer assemblies 306 are excited for a pre-determined period of time to impinge ultrasonic waves to articular cartilage within the shoulder region.

A fourth embodiment of the portable ultrasonic treatment apparatus of the present invention which is primarily suitable for the treatment of connective tissue is illustrated by Figs. 7 and 8. In this embodiment, the apparatus 400 includes at least one ultrasonic transducer assembly 402 positioned within pockets 404 on a strip 406. The transducer assemblies 402 may be arranged in a plurality of configurations within pockets 404 to accommodate many patients' anatomical differences. The strip 406 is secured in proximity to the desired treatment site as shown by Fig. 8 by a self-tieing material 405. The strip 406 is connected is wires 407 and cable 408 to a MOU 12 which contains circuitry for exciting the at least one ultrasonic transducer assembly 402 affixed to the strip 406.

In operation, at least one transducer assembly 402 is excited to impinge ultrasonic waves to the treatment site as shown by Fig. 8. It is contemplated that during treatment an ultrasonic conducting gel is positioned between the strip 406 and the patient's body to prevent attenuation of the ultrasonic waves.

It is also contemplated to manufacture the strip 406 from suitable conductive plastics such as conductive, ABS plastics with either carbon, stainless steel, nickel or aluminum fibers to forego the use of wires for electrically connecting the at least one ultrasonic transducer 402 to the cable 408.

A fifth embodiment of the portable ultrasonic treatment apparatus of the present invention which is primarily suitable for the treatment of connective tissue is illustrated by Figs. 9-10B. In this embodiment, the apparatus 500 includes a MOU 12 and three ultrasonic transducer assemblies 502 positioned within pockets 504 on an inner surface of a concave plate

506 as shown by Fig. 10B. The concave plate 506 is positioned at one end 30 of a vertical bar 508 having a slot 509 at a lower portion. The apparatus 500 further includes a locking support module 510 having a thigh support 512 and a leg support 514.

As shown by the exploded view of Fig. 10A, the high support 512 includes a thigh support plate 516, a securing band 518, and two horizontal locking extensions 520 affixed to the thigh support plate 516 by crews 522 and thumb screws 524. The leg support 514 includes a leg support late 526, a securing band 528, and two vertical locking extensions 530 affixed to the leg support plate 526. The vertical bar 508 is configured to mount within a channel 532 on the leg support 514. The vertical bar 508 is secured to the channel 532 by screw 534 and thumb screw 536. The vertical bar 508 can be moved vertically along the channel 532 by unthreading the thumb screw 536 to accommodate various patients.

The thigh support 512 and the leg support 514 are locked to each other by locking the horizontal locking extensions 520 and the vertical locking extensions 530 by screws 538 and thumb screws 540 to prevent the patient from moving the thigh with respect to the leg during treatment and to ensure that the transducer assemblies 502 remain fixed in their proper positions. The transducer assemblies 502 are connected via a cable 542 which is plugged in to hole 544 to the MOU 12 which contains circuitry for exciting the ultrasonic transducer assemblies 502. It is contemplated that during treatment an ultrasonic conducting gel is positioned between the transducers 502 mounted in concave plate 506 and the patient's body to prevent attenuation of the ultrasonic waves.

Alternative embodiments of the placement module described above also form a part of the invention, and are illustrated in Fig. 11-19. These embodiments of placement module generally contain a covering member, which covers or surrounds a part of the joint or associated limbs or other adjacent anatomical structures, and provides attachment points for ultrasonic transducers or assemblies containing ultrasonic transducers. The covering member, while adjustable, is intended to remain in a fixed position once disposed on or around the joint, and its attachment points provide a frame of reference for appropriately positioning the ultrasonic transducer or assembly to direct the ultrasound toward the treatment site. While the embodiments illustrated herein are specifically adapted for use with the human knee, and more specifically adapted to provide ultrasound therapy to the ACL area, it will be recognized that these embodiments are not so limited in application, and can be readily used or adapted for use with other joints, or to treat other connective tissue within the knee.

Figs. 11A, 11B, and 11C illustrate an embodiment of placement module 600 having covering member 602 secured to the underside of the knee by upper and lower securing straps

604 and 606, respectively. Covering member 602, which may be flexible (e.g., a fabric) or rigid (e.g., a plastic) contains receiving areas 608, 610, which are adapted to receive ultrasonic transducer assemblies 612, 614. These are illustrated as straps containing ultrasonic transducer ports 616, 618, and which can be secured to covering member 602 by hook-and-loop fabric (e.g., VELCRO). As used herein, the term "ultrasonic transducer assembly" means an assembly capable of receiving and holding an ultrasonic transducer, with or without the transducer attached thereto. By positioning the transducer assemblies properly at their attachment points on the covering member, the ultrasonic transducers will be appropriately positioned to direct ultrasound to the area of the surgery or discomfort.

Figs. 12A, 12B, 12C, and 12D illustrate another embodiment of placement module 700 according to the invention. Covering member 702, which may be either rigid or flexible covers the front of the knee, and is secured to the legs by straps 704 and 706. Covering member 702 contains receiving areas 708, 710, which are adapted to receive ultrasonic transducer assemblies 712, 714, which contain ultrasonic transducer ports 716, 718. In the embodiment illustrated, placement module 700 also contains rigid strut 720, which adjusts to hold the joint in a predetermined position. As best seen in Fig. 12C, rigid strut 720 can be provided with adjustability by locking hinge or pivot 722, which is fitted with lockout gears 724, as well as with optional D-ring 726, which allows for the use of an optional strap for added security or an additional ultrasonic transducer assembly. As with the placement module illustrated in Fig. 11, the ultrasonic transducer assemblies 712, 714 are straps that, like the securing straps 704, 706 are secured to the covering member with hook and loop closures.

Figs. 13A and 13B illustrate yet another embodiment of placement module 800 having covering member 802, made from a flexible, elastic fabric that surrounds the knee and surrounding portions of the leg. Receiving areas 808, 810 are disposed in the fabric itself, so that an ultrasonic transducer can be inserted directly therein. The elastic material holds the transducers in position and directs the ultrasound toward the ACL treatment site.

Fig. 14A illustrates another embodiment of placement module 900, illustrated as a fabric shirt (forming covering member) 902 that can be worn over the torso. The shirt has a transducer port 904 (one is illustrated, but multiple ports may be present). Fig. 14B is a schematic diagram showing a close-up view of transducer port 904, wherein transducer port cap 908 is in the closed position. Fig. 14C is a schematic diagram showing transducer port cap 908 in the open position, so that transducer 906 is visible (similar ports can be used with the embodiments shown in the other figures). The covering member or fabric shirt 902 can be

made from an elastic or stretchable fabric, such as Spandex or the like, to hold the transducer port next to the skin of the patient.

Fig. 15A illustrates another embodiment of placement module 900 in the form of an adjustable shoulder brace. Covering member 902 can be made of an elastic or stretchable material to hold transducer port 904 firmly against the skin. Covering member 902 can be secured in place by retaining strap 910, which can be disposed around the torso and secured via one or more attachment point, 912. Retaining strap 910 and covering member 902 may form an integral piece that wraps around the body, or may be formed from two separate pieces of fabric having two attachment points. As with the embodiment shown in Fig. 14, the shoulder brace shown in Fig. 15A is well adapted to provide ultrasonic treatment to connective tissue in the shoulder area. The embodiment of transducer assembly or port 904 illustrated in Fig. 15B and Fig. 15C is described above with respect to Figs. 14B and Fig. 14C.

Fig. 16 illustrates an embodiment of placement module 900, wherein the covering member 902 is a shoe or sneaker having transducer assembly or port 904 attached thereto. As illustrated, the placement module 900 is particularly adapted to supply ultrasound to tissue in the area of the ankle, e.g., for repair or healing of Achilles' tendon injuries. However, transducer assembly or port 904 could be readily placed in other areas of the shoe or sneaker to apply ultrasound to other parts of the ankle or foot.

Fig. 17A illustrates another embodiment of placement module 900, similar in application to that of Fig. 16, but wherein the covering member 902 is an elastic or stretchable fabric holding transducer port or assembly 904 in place firmly against the skin. As with the embodiment shown in Fig. 16, placement of the transducer port or assembly can be varied to apply ultrasound to different tissues in the foot or ankle. The embodiment of transducer assembly or port 904 illustrated in Fig. 17B is described above with respect to Fig. 14C.

Fig. 18A illustrates an embodiment of placement module 900 suitable for application of ultrasound to the wrist or hand area. Covering member 902 forms an adjustable strap that encircles the wrist and holds transducer port or assembly 904 against the skin of the patient. The embodiment of transducer assembly or port 904 illustrated in Fig. 18B is described above with respect to Fig. 14C.

Fig. 19 illustrates an embodiment of placement module 900 suitable for application of ultrasound to the elbow area. Covering member 902 is an elastic or stretchable fabric holding transducer port or assembly 904 in place firmly against the skin. Although illustrated disposed on the outer side of the elbow, the transducer port or assembly 904 can be disposed along the inner surface of the elbow if desired.

EXAMPLE 1

An ovine model of soft tissue graft (digital extensor tendon) reconstruction of the ACL was utilized to allow for assessment of the method and apparatus of the invention. A modified ACL reconstruction was performed on 21 animals in three groups of 7 animals. Control groups of 2 animals (provided with no ultrasound treatment), and experimental groups of 5 animals (provided with ultrasound treatment for 20 minutes continuously each day) were harvested at the end of 3, 6, and 12 weeks.

The right hind limb was operated on in all animals. The anterior cruciate ligament (ACL) was visualized and removed at the insertion site through an antero-medial arthrotomy. The ACL reconstruction was performed using a digital extensor tendon graft. The tendon graft was harvested from the same limb by 2 stab incisions. The graft was whip stitched using # 2 Ethibond and prepared using the Acufex Graftmaster. The graft was doubled and passed through 4.5mm tunnels in the tibia and femur. Endobutton fixation was used on the femoral side with tibial fixation over a bony post. The surgical incisions were then closed using standard suturing techniques. The animals were then recovered and ultrasound treatment was initiated on the members of the experimental group one day following surgery.

The animals in the treatment groups were treated with pulsed low intensity ultrasound (1.5 MHz, pulsed at 1 KHz, 200μs burst width) for 20 minutes per day for the duration of the study. Ultrasound devices having two ultrasound transducers were used. One transducer was coupled to the skin (wool was shaved) over the femoral bone tunnel containing the graft, while the other was coupled to the skin over the tibial attachment tunnel. The transducers were held in place during treatment with strapping.

Animals were sacrificed at 3, 6 and 12 weeks following surgery with an intravenous lethal injection of anesthetic. The right hind limb of each was stripped of soft tissue and muscle and fixed in 10 % phosphate buffered formalin for a minimum of 72 hours with changes every 24 hours. The femoral and tibial bone tunnels were isolated using a saw and decalcified in 10 % formic acid – formalin solution. The femur and tibial tunnels were sectioned into 2-3 mm slices from the joint space to the outer cortex and placed into cassettes for paraffin embedding. Five-micron thick sections were cut on a microtome and stained with hematoxylin and eosin for microscopic analysis.

After 3 weeks of ultrasound treatment there are marked differences visible between histology images of tissue from the control animals (Fig. 20A) and the ultrasound-treated

animals (Fig. 20B). In the ultrasound-treated grafts there is cellular infiltration of fibrous tissue into the tendon in between the tendon fascicles. There is neo-angiogenesis/vascularity shown in the 20x magnification image, indicated by the arrows. The graft is highly cellular and the cells are plump active (matrix producing) cells. By contrast, the control samples (Fig. 20A) show no evidence of vascularity, the cells within the graft are necrotic, and the tendon is starting to degenerate.

After 6 weeks of ultrasound there is extensive neo-angiogenesis in the graft, as shown in Fig. 21B. The black dots in the 2x magnification picture are all new blood vessels. The red blood cells within these vessels can be seen in the 10x magnification image. At 20X magnification there are viable cells throughout the graft and there is new bone deposition and Sharpey's fibres at the interface of the graft and the bone tunnel. The Sharpey's fibres are spicules of bone that anchor the graft into the bone tunnel. By contrast, the control histology images shown in Fig. 21A show very little evidence of vascularity. The cells within the tendon body are very sparse and there is little evidence of Sharpey's fibres at the bone tendon interface. After six weeks of ultrasound treatment the angiogenic response is very pronounced that the intra –articular section of the graft and the bone marrow contained new blood vessels, as shown in Fig. 21C and 21D, respectively.

At 12 weeks, the intra-articular section of the graft in the control group, shown in Fig. 22A is essentially dead, with very few cells and blood vessels. By contrast, the ultrasound treated graft, shown in Fig. 22B, is highly cellular and contains functional blood vessels containing red blood cells. Photomicrographs of the treated graft show that there is a mature tissue at the bone tendon interface with healthy active cells after ultrasound treatment, shown in Fig. 22D. There are many Sharpey's fibres infiltrating the graft, which will provide increased strength. By contrast, photomicrographs of the control graft, Fig. 22C show few cells, which are producing a loose fibrous tissue, and few Sharpey's fibres at the bone tendon interface.

The histology sections were scored in a blind fashion by 2 independent observers for the presence of vascularisation (neo-angiogenesis). The data is shown in Fig. 24. At all timepoints there is significantly more vascularity with the pulsed low intensity ultrasound (Cartogen) as compared to controls.

The histology sections were scored in a blind fashion by 2 independent observers for the presence of bone in growth at the bone tendon interface. The data is shown in Fig. 25. At all timepoints there is significantly more bone in growth with the pulsed low intensity ultrasound (Cartogen) as compared to controls.

A further ovine study of soft tissue graft reconstruction was performed on 48 animals, which were split into groups of 8. There were 8 control and 8 treated animals at 3, 6 and 12 weeks. The surgical procedure and ultrasound treatment were as described above. At sacrifice the right limb of each animal was stripped of soft tissue and the knee joint dissected of all ligaments and tendons but leaving the intact ACL. The quality of the repair tissue/reconstruction was then tested to failure using an Instron tensile testing machine. The Figs. 26 to 28 shows that the pulsed low intensity ultrasound treatment increases the peak load to failure Fig. 26, the energy required to make the grafts fail Fig. 27 and the stiffness of the repaired tissue Fig. 28. Moreover the failure mode Table 1 is influenced by the treatment. The predominant failure mode for the control samples is pullout form the femoral tunnel, in contrast the pulsed low intensity ultrasound treated samples fail in the intra-articular region. This indicates that the treatment is able to stimulate superior integration in the bone tunnels, which is the weak link in the early reconstruction process.

	Failure Mode Femoral pullout	Failure Mode Intra-articular
Cont 3wks	8	0
Cont 6wks	8	0
Cont 12wks	2	6
US 3wks	8	0
US 6 wks	4	4
US 12wks	0	8

Table 1: Failure Mode

EXAMPLE 2

Hartley strain guinea pigs that spontaneously develop osteoarthritis (OA) were used for this study. This strain develops an arthropathology that mimics human OA between the age of 6 and 12 months of age. The OA is confined to the medial tibia plateau in the early stages of the disease.

Eight animals were utilized for this study. The animals were 2 months of age when the study was initiated. The left legs of the animals were treated with pulsed low intensity ultrasound (1.5 MHz, pulsed at 1 KHz, 200μs burst width) for a period of 4 months. The ultrasound was applied for 20 minutes per day, for 5 days per week. The ultrasound transducer was coupled to the skin with gel on the media side of the left knee after first

shaving the knee joint. The transducers were held in place during treatment with strapping. The animals were terminated at 6 months of age after 4 months of treatment.

The ultrasound treated (Fig. 23A) and control (Fig. 23B) knee joints were dissected and decalcified in 10 % formic acid – formalin solution. The knee joints were then embedded in paraffin. Five-micron thick sections were cut on a microtome and stained with toluidine blue for microscopic analysis. After 4 months of ultrasound treatment there was a marked difference in the degree/severity of OA between the treated and control knees. The cartilage on the media tibia plateau of ultrasound treated knee remained intact, as shown in Fig. 23A, whereas the cartilage on the control knee showed signs of degeneration, as shown in Fig. 23B. This observation (cartilage thinning, defects and surface irregularities) was consistently observed in animals that developed OA by 6 months of age.

EXAMPLE 3

An ovine model of unilateral patellar tendon reconstruction using 2 suture anchors was used. There were 21 animals in total with 5 pulsed low intensity ultrasound treated animals and 2 control animals at 3, 6 and 12 week timepoints. This model is used to represent that of a flat tendon to bone similar to the repair of the rotator cuff in the shoulder of humans.

The knee was approached through a 2 cm incision of the anteromedial aspect at the level of the tibial tubercle. The surgical procedure entailed dividing and reattaching the patella tendon at the tibial insertion. The tibial tuberosity was denuded of all tendon, insertion fibrocartilage and periosteum with a high-speed burr under irrigation. Two Smith & Nephew suture anchors (2.7 mm) were inserted into the bone and the suture used in a whip-stitch fashion to reapproximate the tendon back to the bone. The wounds were closed in layers using 3-0 Dexon. The treated animals received pulsed low intensity ultrasound (200 μsec burst of sine waves at 1.5 MHz repeated at 1 kHz, 30 mW/cm2) daily for 20 minutes until sacrifice. The ultrasound was applied adjacent to the repair tissue on the medial aspect joint.

Histological analysis:

The patella tendon – proximal tibia was harvested and fixed in formalin for 48 hours. The samples were decalcified in formic acid – formalin solution until complete. The proximal insertion was divided into 4 sections labelled 1-4 from lateral to medial. The

sections were labelled 1-4 from lateral to medial, paraffin embedded and sectioned on a Leica Microtome.

At three weeks, the tendon-bone interface was filled with poorly organized, highly cellular, less density soft tissues in non-treated animals. The ultrasound treated animals presented a more active interface similar to that observed at 3 weeks in the intraarticular model in the sheep knee. Islands of active new bone formation were evident in the ultrasound treatment group with an overall impression of a more active interface. New vascularity at the interface was also noted to a greater extent in the ultrasound treated samples compared to controls.

At six weeks, ultrasound treated groups showed increased organization of collagen fibres and newly formed matrix at the tendon-bone interface while the control sections showed mainly high density of soft tissues with an immature less organised interface. The cells in the ultrasound treated group were plump, indicative of active cells. Vascularity at the tendon-bone interface was present in both the control and ultrasound treated groups but again the treated group appeared to have increased vascularity based on qualitative assessment. Activity on the bone itself was also noted in the ultrasound group away from the tendon-bone interface.

At 12 weeks, there was a clear broad zone of transition from fibrous to cartilaginous tissues and to mineralised bone in the ultrasound treated groups while the control samples show a disorganised repair tissue. The pulsed low intensity ultrasound treatment produced a more organised, vascular and mature tissue Fig. 29B which had a similar morphological appearance to the unoperated (native) insertion site Fig. 29A compared to controls Fig. 29C. Sharpey's fibres and interdigitation between the tendon and bone was re-established in the treated samples see Fig. 29B, compared to control Fig. 29C. Note, this level of maturity was not observed in the non-treated repaired samples.

The organisation and vascularity of the repair tissue at the tendon-bone interface was scored in a blind fashion by 2 independent observers. The pulsed low intensity ultrasound treated samples had significantly higher scores for vascularity and tissue organisation as shown in the graphs of Figs. 30 and 31.

EXAMPLE 4

Two ovine models of meniscal repair were utilised. In the first model bilateral surgery was performed on 10 adult sheep. The knee was approached through a 2cm incision of the

anteromedial aspect. The knee was flexed to 90^{O} and a 8mm full thickness incision was created in the circumferential direction in the anteromedial menisci of each knee. The tears were then fixed with the Smith & Nephew Fast-Fix meniscal repair device. The wounds were closed with 3-0 Dexon.

In the other model similar bilateral surgery was performed on 10 adult sheep however instead of a 8mm tear a full thickness cylindrical defect was created in the anteromedial menisci of each knee. The treated animals received pulsed low intensity ultrasound (200 μsec burst of sine waves at 1.5 MHz repeated at 1 kHz, 30 mW/cm2) on the right knee, daily for 20 minutes until sacrifice. The ultrasound was applied adjacent to the repair tissue on the medial aspect joint. At harvest the operated menisci were dissected out and fixed in formalin for 48 hours. Then processed in wax and histologically sectioned and stained.

The meniscal tear model samples were scored for macroscopic evidence of repair, for the extent of cellularity and for the presence of vascularity. Figs. 32 to 34 show that the pulsed low intensity ultrasound gives rise to superior (higher) scores in the right treated menisci as compared to the untreated control in relationship to macroscopic grading Fig. 32, cellularity Fig. 33 and vascularity Fig. 34.

The cylindrical defects of the pulsed low intensity ultrasound stimulated some filling of the meniscal lesions with new repair tissue Fig. 35B. This filling was not observed in any of the untreated lesions see Fig. 35A. Indicating the stimulation of meniscal repair with ultrasound treatment.

WHAT IS CLAIMED IS:

1. An apparatus for positioning one or more ultrasonic transducers with respect to a joint for delivery of ultrasonic therapy thereto, comprising:
a covering member adapted to cover at least a portion of the joint or adjacent body members and be secured thereto in a fixed position, wherein the covering member comprises one or more receiving areas adapted to receive and hold one or more ultrasonic transducer assemblies.

2. The apparatus of claim 1, further characterized in that the covering member comprises a flexible fabric layer.

3. The apparatus of claim 2, further characterized in that the fabric layer comprises an elastic material surrounding the joint or adjacent body member.

4. The apparatus of claim 1, further characterized in that the ultrasonic transducer assembly is held in one or more fixed positions relative to the joint or adjacent body member.

5. The apparatus of claim 1, further characterized in that the receiving area comprises one or more transducer receiving ports disposed within the covering member and/or one or more covering member attachment areas adapted to secure the ultrasonic transducer assembly.

6. The apparatus of claim 5, further characterized in that the ultrasonic transducer assembly comprises a strap comprising a port adapted to receive an ultrasonic transducer and one or more strap attachment areas adapted to securely attach to a covering member attachment area, whereby the ultrasonic transducer port is securely positioned relative to the joint or adjacent body member.

7. The apparatus of claim 6, further comprising a rigid strut adapted to secure the joint in a fixed position during treatment.

8. The apparatus of claim 7, further characterized in that the rigid strut comprises an adjustment mechanism for varying the strut orientation or position.

9. The apparatus of claim 8, further characterized in that the adjustment mechanism comprises a lockable pivot or hinge.

10. The apparatus of claim 1, further characterized in that the joint is the knee, and the ultrasonic transducer assemblies are positioned relative to the interarticular space or the cruciate ligament bone tunnels.

11. The apparatus of claim 1, further comprising an ultrasonic transducer.

12. A method for stimulating growth or healing, or treating pathologies, of connective tissue in mammals in need thereof, comprising:
covering at least a portion of a joint or adjacent body members with a covering member adapted to cover at least a portion of the joint or adjacent body member and be secured thereto in a fixed position; and
subjecting the affected connective tissue to noninvasive, low intensity ultrasound of a frequency and duration sufficient to stimulate growth, healing, or repair of the connective tissue;
further characterized in that the covering member comprises one or more receiving areas adapted to receive and hold one or more ultrasonic transducer assemblies.

13. The method of claim 12, further characterized in that the low intensity ultrasound has a frequency of between about 1 and about 2 MHz.

14. The method of claim 12 or 13, further characterized in that the low intensity ultrasound has a frequency of around 1.5 MHz.

15. The method of claim 12, further characterized in that the low intensity ultrasound is pulsed.

16. The method of claim 15, further characterized in that the pulsed low intensity ultrasound has a pulse width of between about 10 and about 2,000 microseconds.

17. The method of claim 15 or 16, further characterized in that the pulse width is about 200 microseconds.

18. The method of any of claims 15 to 18, further characterized in that the pulse has a repetition frequency of about 0.10 to about 10 KHz.

19. The method of claim 18, further characterized in that the repetition frequency is about 1 KHz.

20. The method of claim 12, further characterized in that the connective tissue comprises tissue that has undergone or is undergoing degeneration as the result of osteoarthritis, tendonosis, or tendonitis, or a combination thereof.

21. The method of claim 12 or 20, further characterized in that healing is stimulated without surgical repair or modification of the tissue.

22. The method of claim 12, further characterized in that the connective tissue undergoing treatment has been subjected to surgery on or near the connective tissue.

23. The method of claim 22, further characterized in that the surgery comprises repair of flexor or extensor tendons, implantation of a scaffold capable of supporting tissue repair or regrowth, and/or repair of fibrocartilage.

24. The method of claim 22 or 23, further characterized in that the surgery comprises surgical transfer of a ligament or tendon or a ligament or tendon weave.

25. The method of claim 23, further characterized in that the scaffold comprises a material having a structure sufficiently porous to allow cell infiltration, and having a surface sufficient to allow cell adhesion and growth.

26. The method of claim 23, further characterized in that the fibrocartilage is selected from the group consisting of damaged lateral or medial meniscus, mandibular meniscus, spinal disc cartilage, and rib cartilage.

27. The method of claim 12. further characterized in that the connective tissue undergoing treatment comprises one or more ligaments, one or more tendons and/or fascia.

28. The method of claim 27, further characterized in that the connective tissue undergoing treatment is in the human knee, elbow and/or foot.

29. The method of claim 28, further characterized in that the one or more ligaments include the anterior cruciate ligament, posterior cruciate ligament, a genual ligament and/or a meniscofemoral ligament.

30. The method of claim 28, further characterized in that the one or more ligaments include a lateral or collateral ligament.

31. The method of claim 27, further characterized in that the tendon is one or more of the tendon of quadriceps, gracilis tendon, sartorius tendon, semitendinosis tendon, popliteus tendon, or adductor magnus tendon.

32. The method of claim 27, further characterized in that the tendon is in the human shoulder.

33. The method of claim 32, further characterized in that the tendon is the supraspinatus tendon.

34. The method of claim 28, further characterized in that the connective tissue undergoing treatment comprises the lateral or medial meniscus.

35. The method of claim 12, further characterized in that the ultrasound is applied to connective tissue following a tissue shrinkage procedure.

36. The method of claim 35, further characterized in that the tissue shrinkage procedure is selected from the group consisting of capsulorrhaphy and spinal disc shrinkage.

37. The method of claim 12, further characterized in that the connective tissue pathology is tendonitis or tendonosis.

38. The method of claim 12 or 37, further characterized in that the connective tissue has suffered an acute tear or chronic overuse injury.

39. The method of claim 28, further characterized in that the pathology is tennis elbow.

40. The method of claim 28, further characterized in that the pathology is plantar fascitis.

41. The method of claim 12, further comprising administering a pharmacological agent.

42. The method of claim 41, further characterized in that the pharmacological agent is a drug or growth factor.

43. The method of claim 42, further characterized in that the growth factor is administered in sufficient dosage to increase the rate of repair, the quality of repair, or both.

44. The method of claim 42 or 43, further characterized in that the growth factor is selected from the group consisting of the Transforming Growth Factor β superfamily, Bone Morphogenetic Proteins, Cartilage Derived Morphogenic Proteins and Growth Differentiation Factors, angiogenic factors, platelet-derived cell growth factor (PD-ECGF), Platelet Derived Growth Factors (PDGF), Vascular Endothelial Growth Factor (VEGF), the Epidermal Growth Factor family, Transforming Growth Factor Alpha (TGFα), Platelet Derived Growth Factors, e.g. PDGF-A, PDGF-B, PDGF-BB, Fibroblast Growth Factors, e.g. BFGF, Hepatocyte Growth Factors (HGF), Insulin-like Growth Factors, Growth Hormones (GH), Interleukins, Connective Tissue Growth Factors (CTGF), Parathyroid Hormone Related Proteins (PTHrp), autologous growth factors, and mixtures of at least two of these materials.

45. The method of claim 12, further characterized in that the ultrasound is generated by a plurality of ultrasonic transducers placed in the vicinity of the skin the tissue to be treated.

46. The method of claim 45, further characterized in that the ultrasonic transducers emit ultrasound simultaneously or sequentially.

47. The method claim 12, further characterized in that subjecting the tissue to the noninvasive, low intensity ultrasound results in an increasing vascularization in connective tissues, ischaemic tissues or grated tissue in mammals in need thereof .

48. The method of claim 12, further comprising administering to the mammal a therapeutic treatment for promoting angiogenesis.

49. The method of claim 48, further characterized in that the therapeutic treatment for promoting angiogenesis comprises administering endothelial cell growth factor (EGF), fibroblast growth factor (FGF), angiogenin, transforming growth factor beta (TGF beta), or prostaglandins.

50. The method of claim 48 or 49, further characterized in that the therapeutic treatment comprises prophylactic treatment of a connective tissue to promote angiogenesis to increase the speed of recover, repair, or both, post injury.

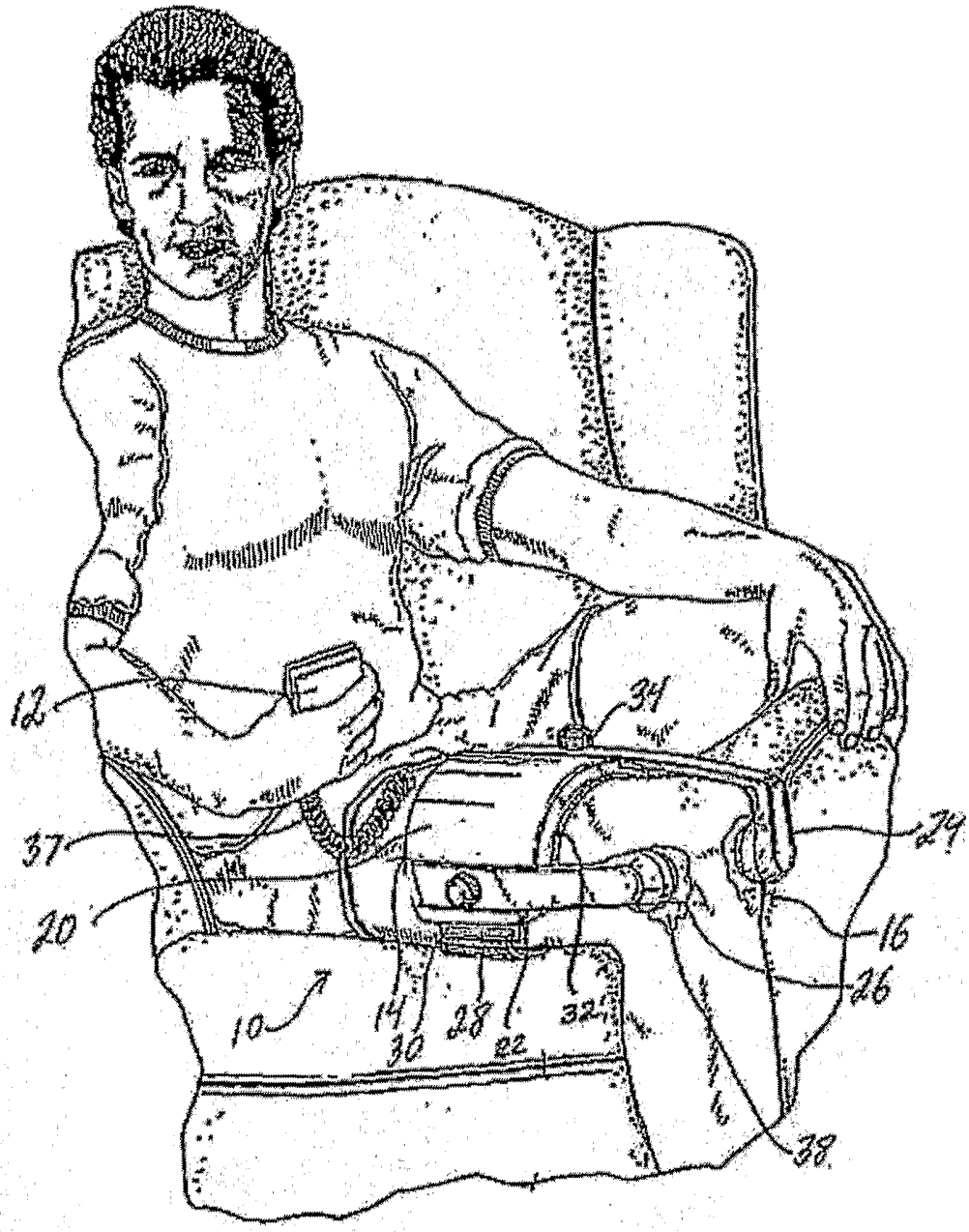
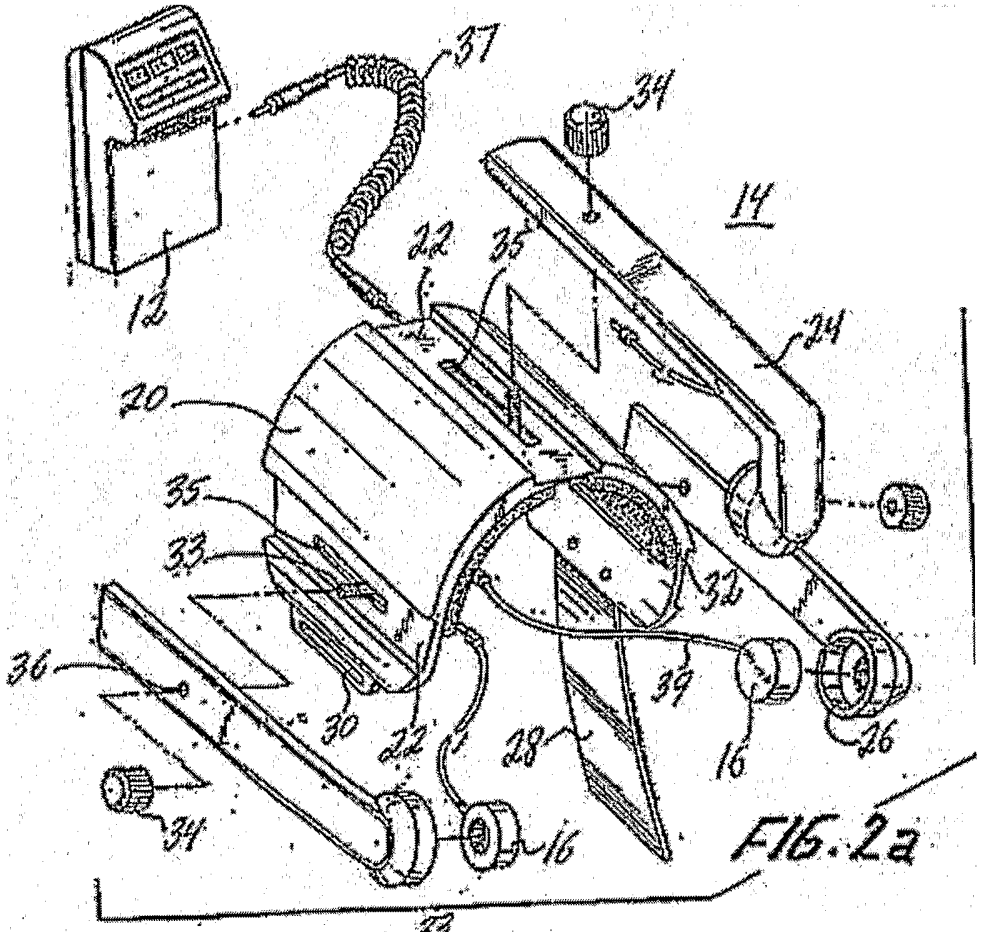


FIG. 1


37
34
14
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12
24
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26
34
16

FIG. 2a

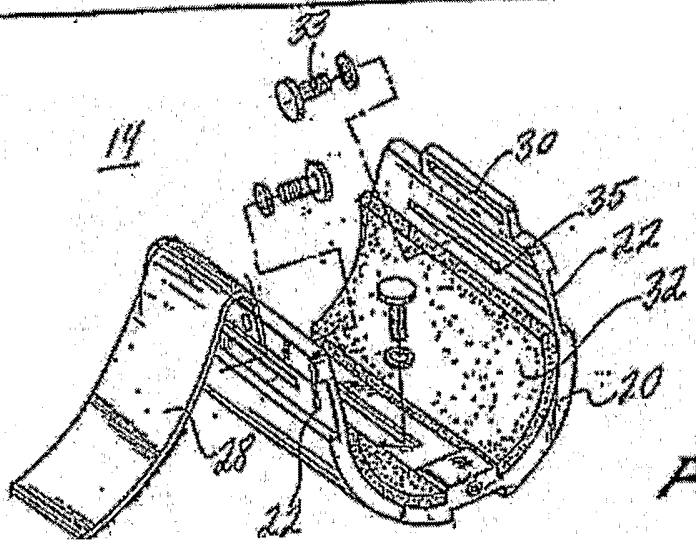
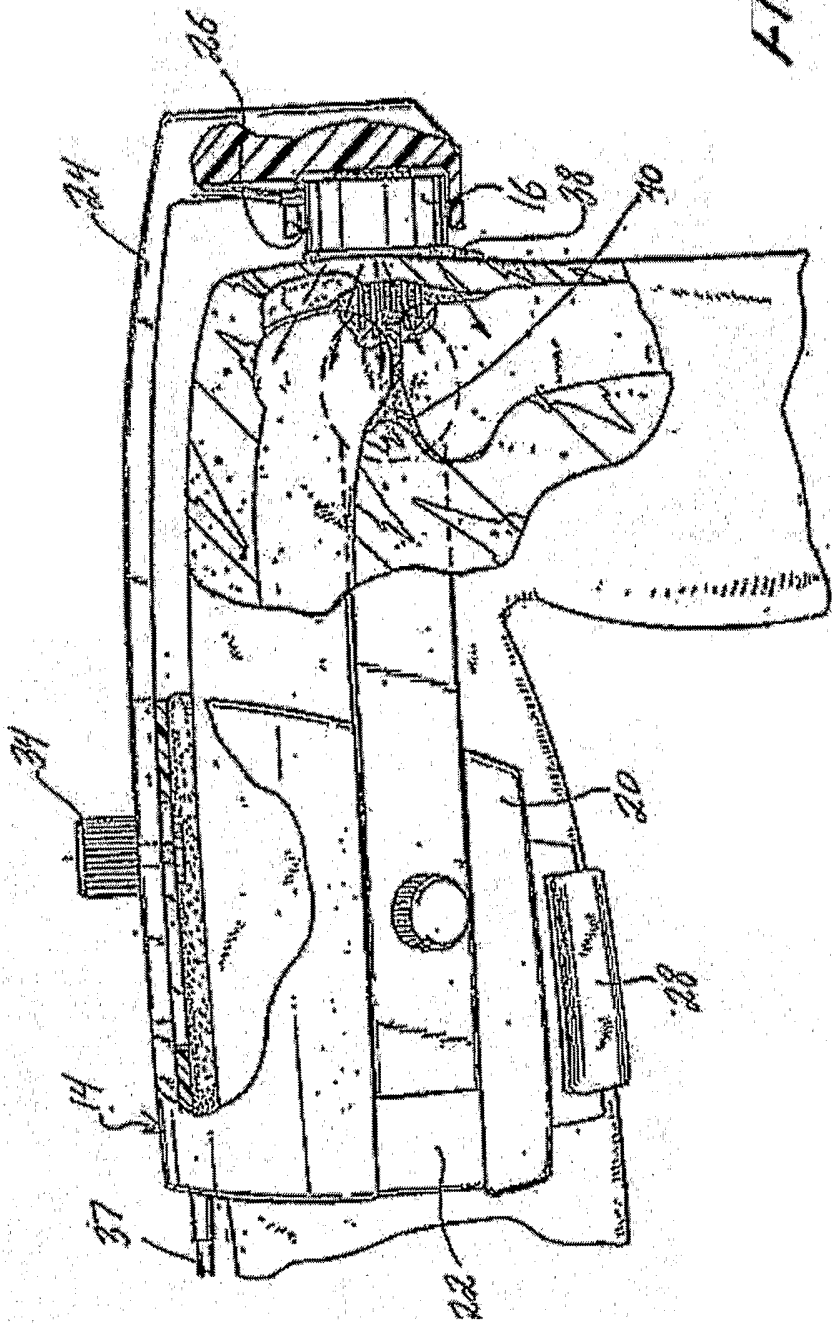

33
14
30
35
22
32
20
28
22

FIG. 2b

FIG. 3



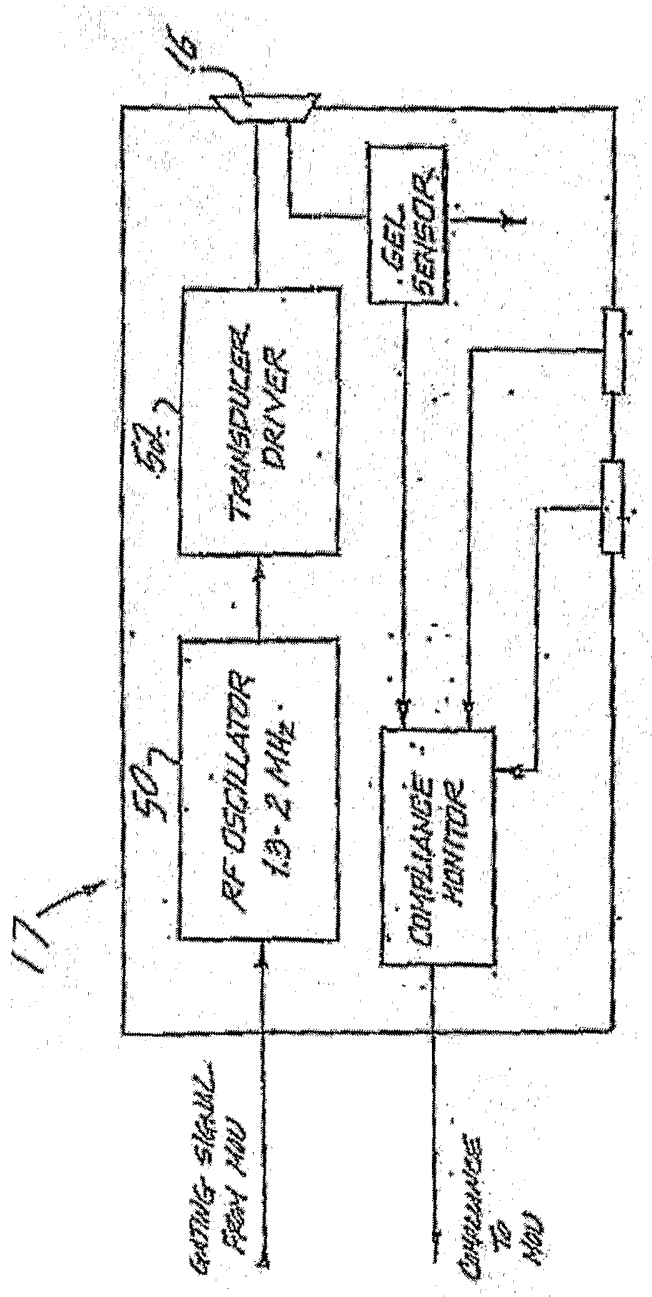

16
GEL SENSOR
TRANSDUCER DRIVER
50
RF OSCILLATOR 1.3-2 MHz
COMPLIANCE MONITOR
17
GATING SIGNAL FROM HMU
COMPLIANCE TO HMU

FIG. 4

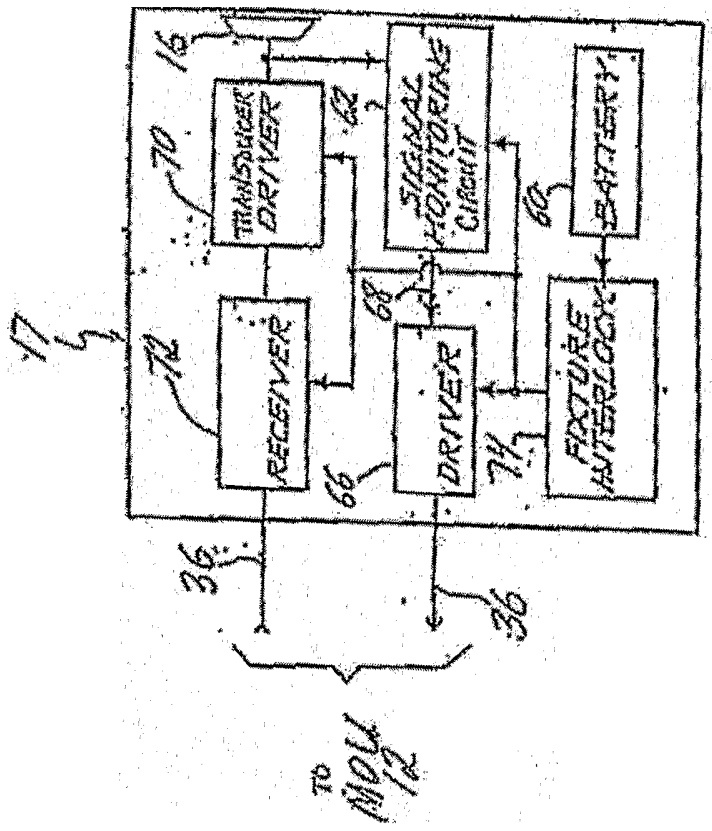

17
16
70
TRANSDUCER DRIVER
22
SIGNAL MONITORING CIRCUIT
60
BATTERY
72
RECEIVER
68
DRIVER
66
74
FIXTURE INTERLOCK
36
36
TO MODULE 12

FIG. 4A

FIG. 5

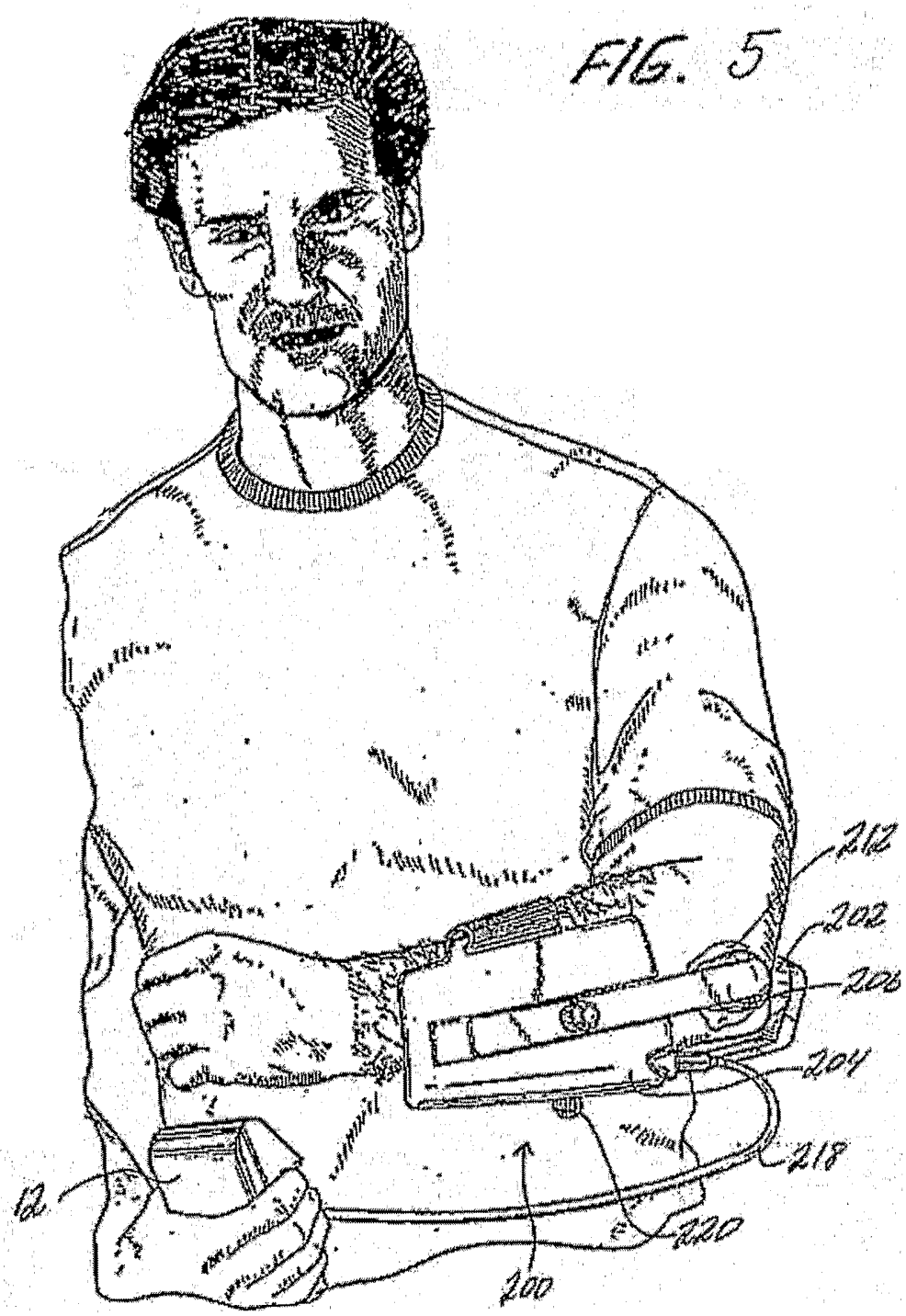


FIG. 6

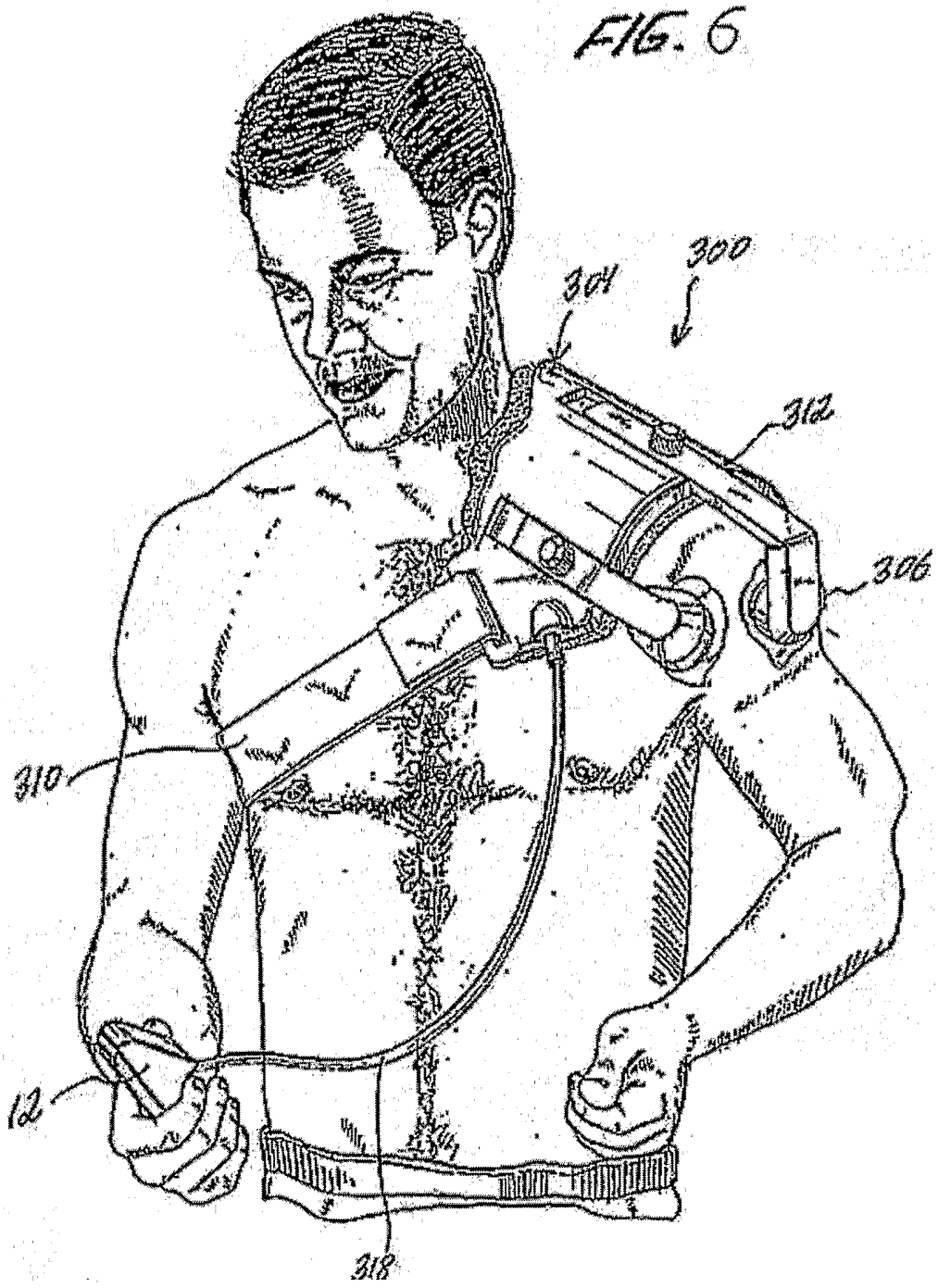
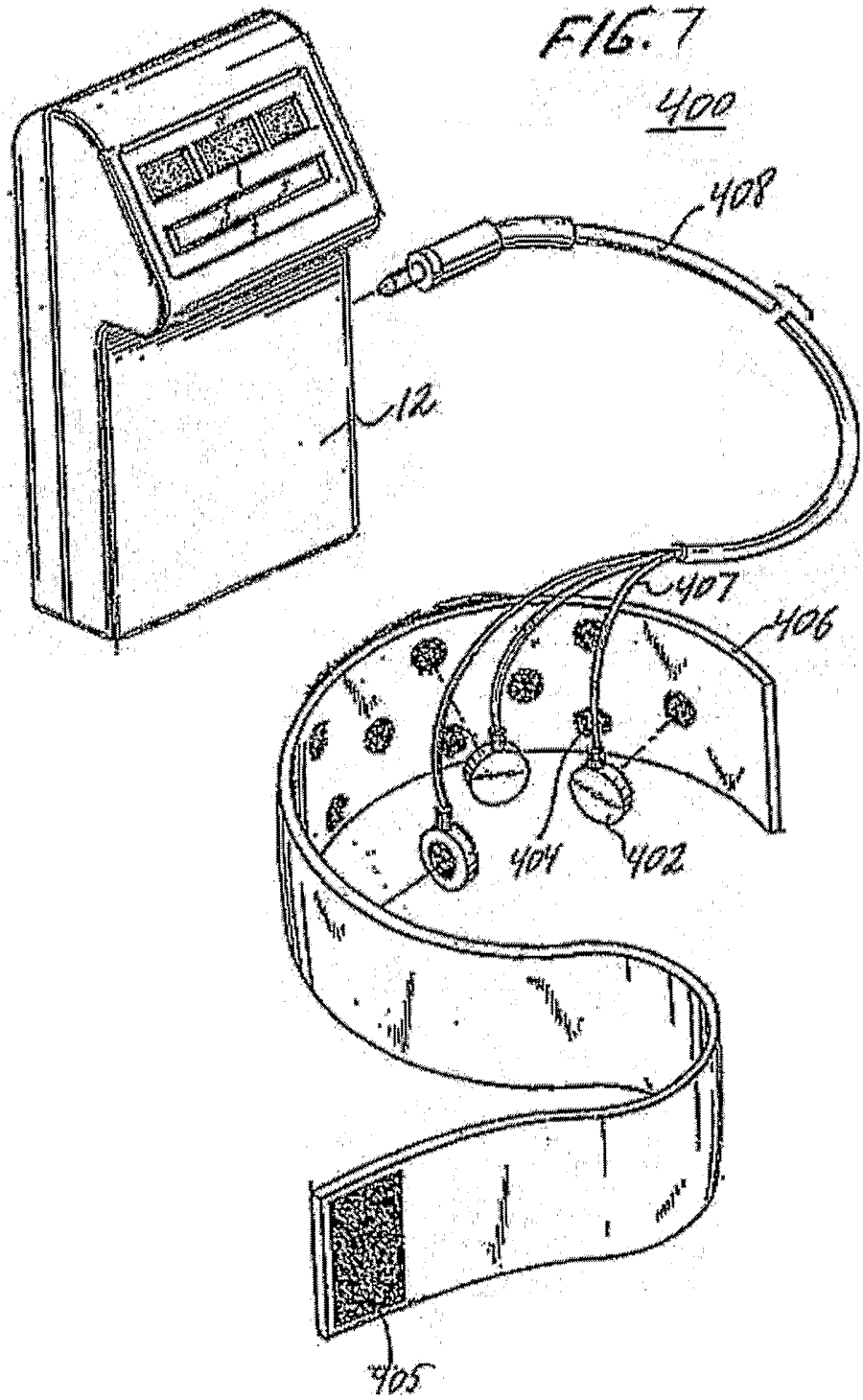


FIG. 7



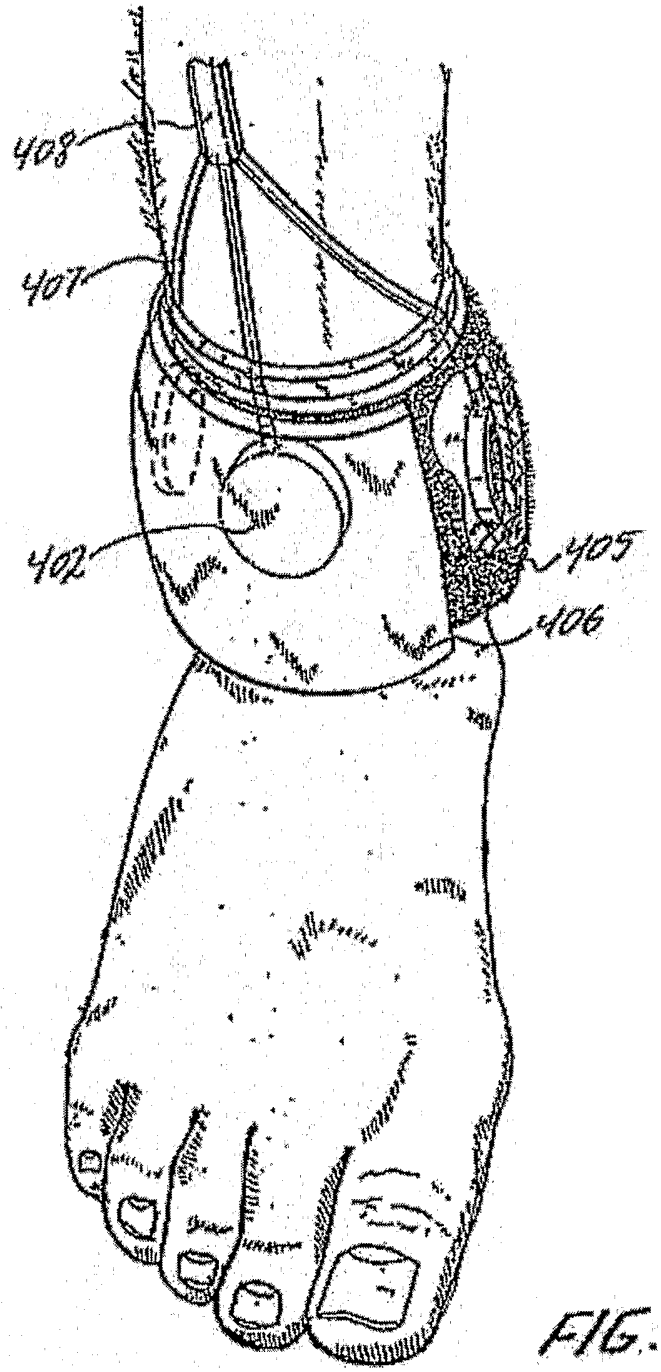


FIG. 8

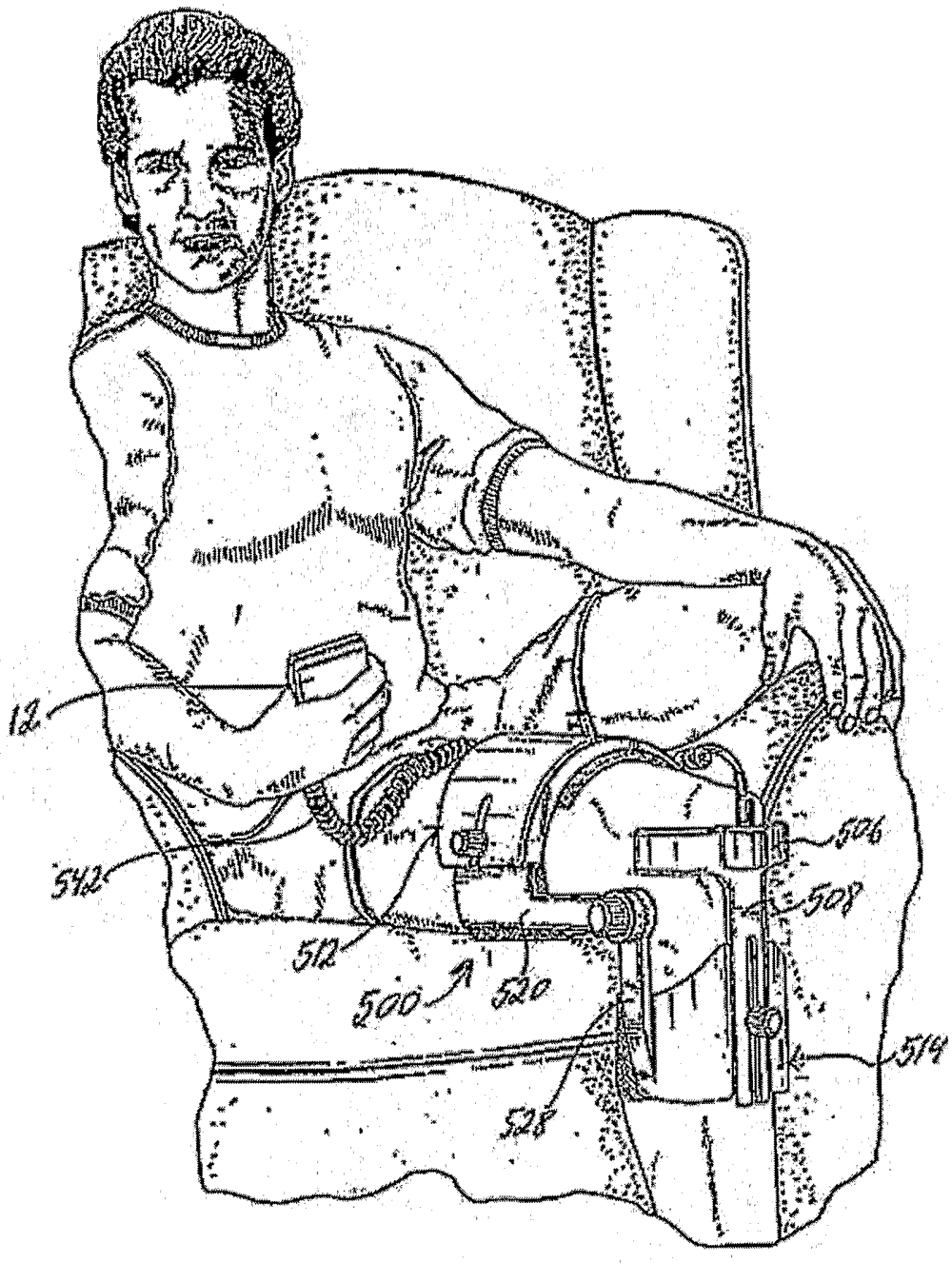


FIG. 9

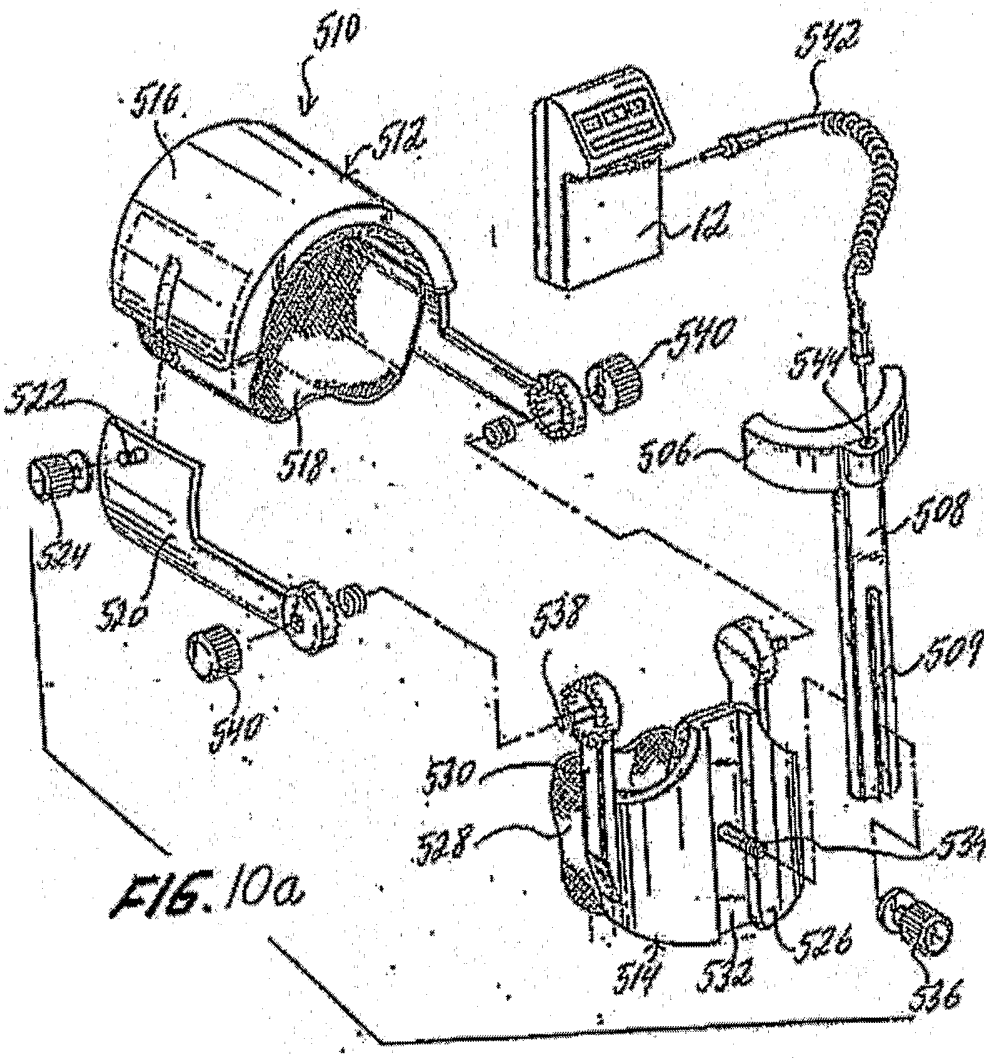


FIG. 10a

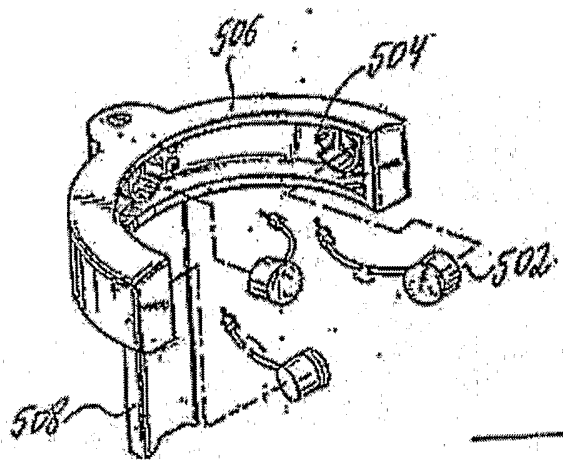
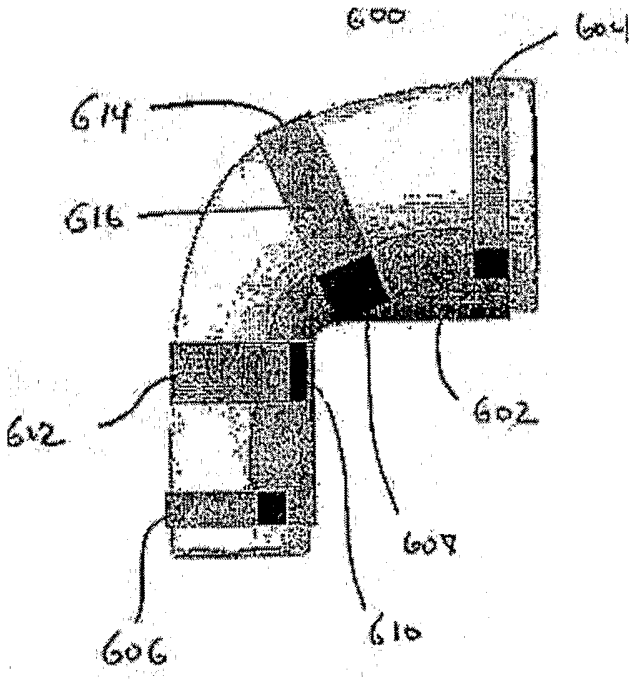
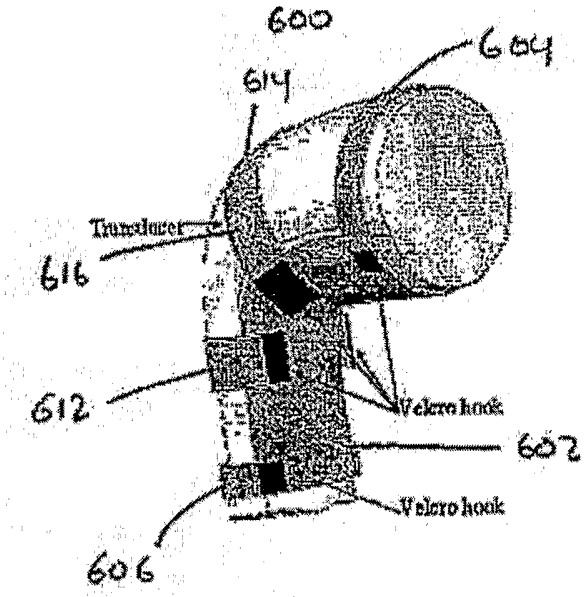


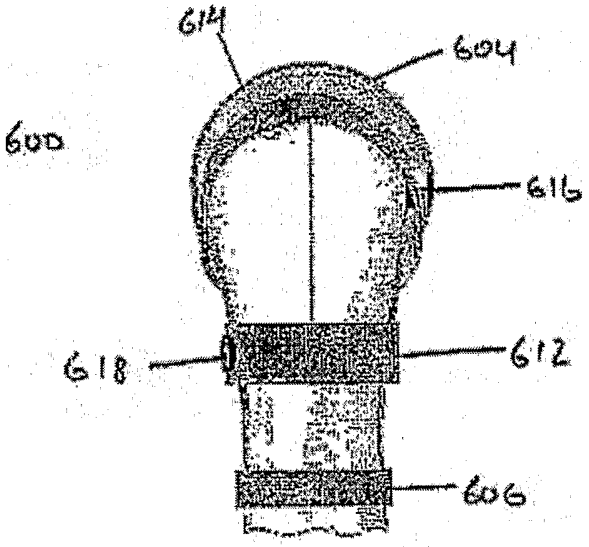
FIG. 10b



11A


600
604
614
Transducer
616
612
Velcro hook
602
Velcro hook
606

11B


614
604
600
616
618
612
606

11C

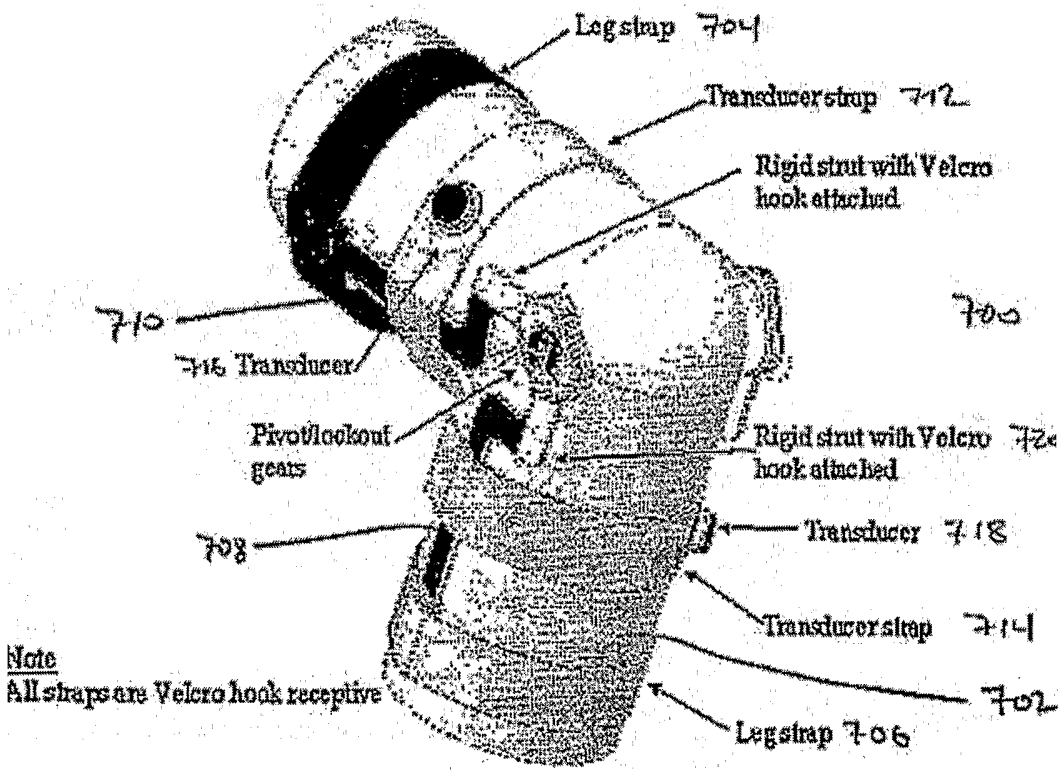

Leg strap 704
Transducer strap 712
Rigid strut with Velcro hook attached
710
700
716 Transducer
Pivot/lockout gears
Rigid strut with Velcro hook attached 724
708
Transducer 718
Transducer strap 714
Note
All straps are Velcro hook receptive
702
Leg strap 706

FIG. 12A

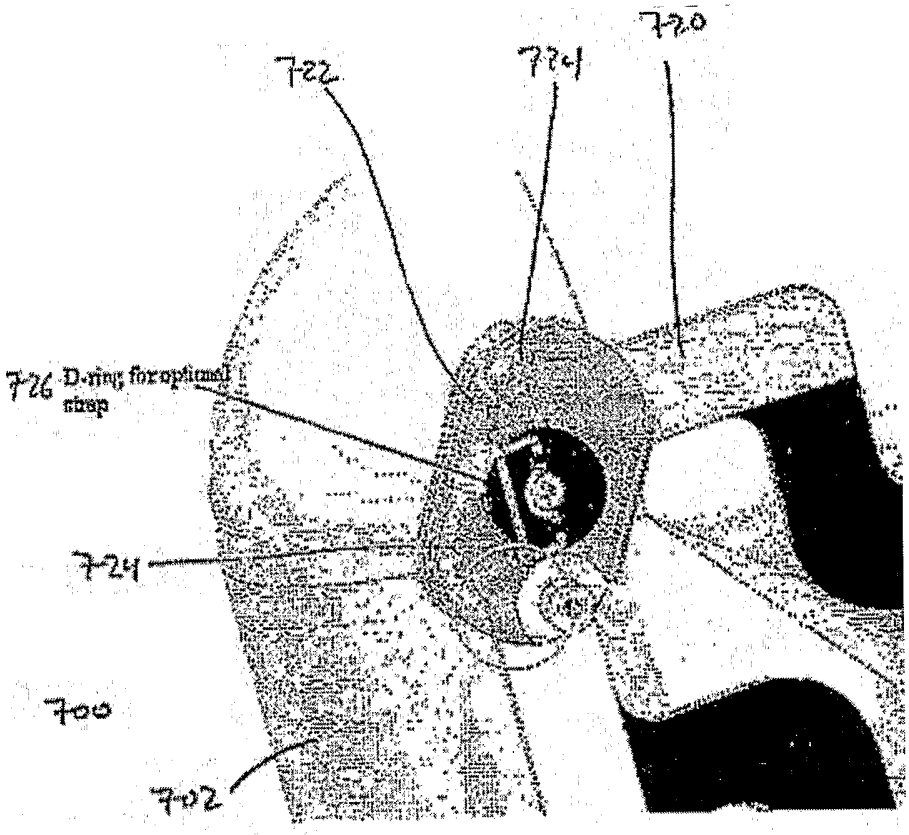


FIG 12C

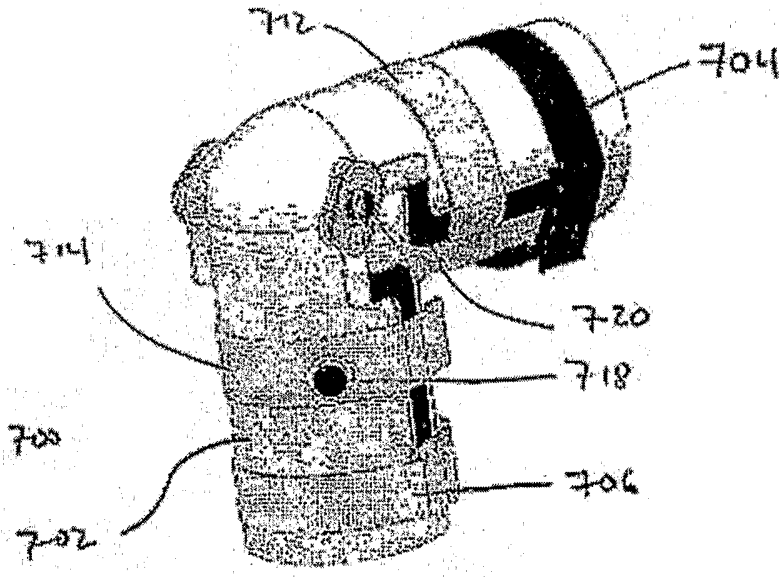


FIG 12B

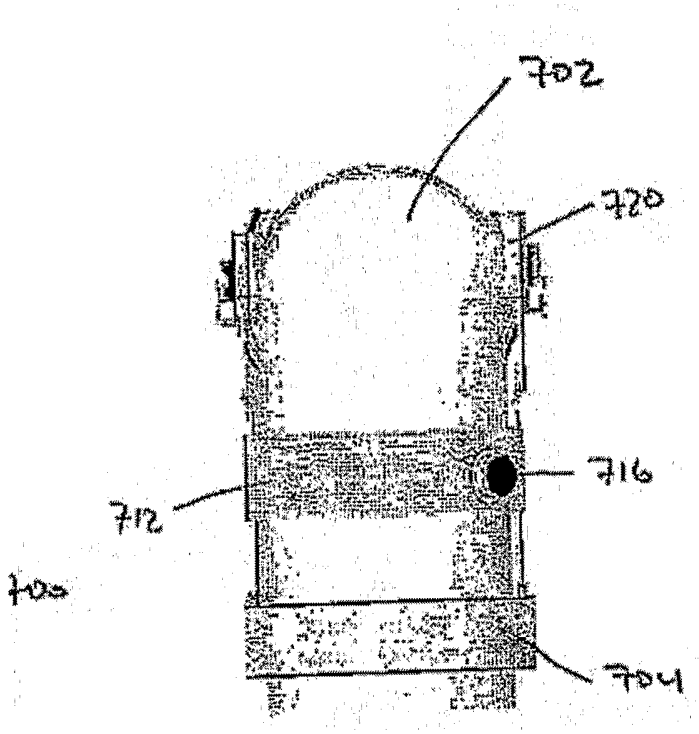


FIG 12 D

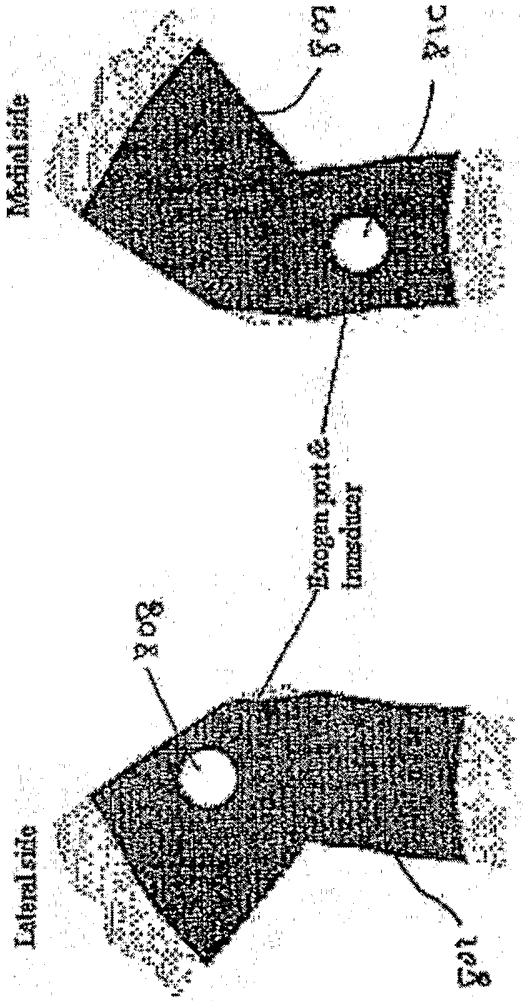


FIG 13B

FIG 13A

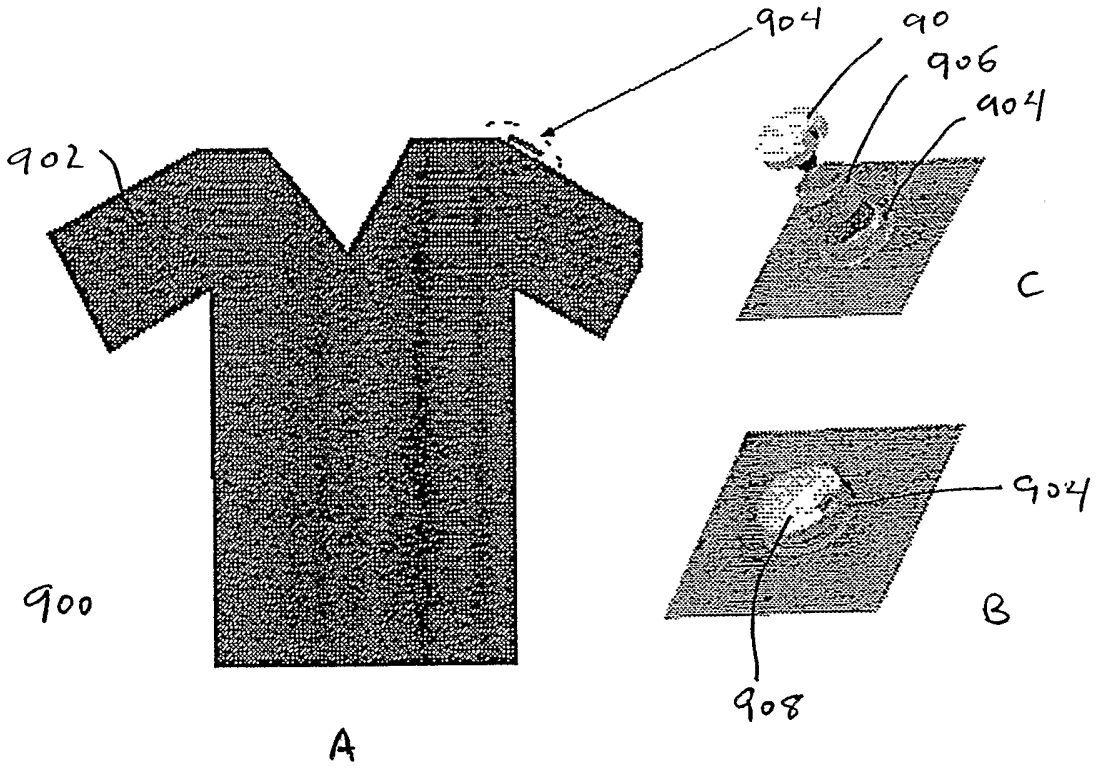


FIG 14

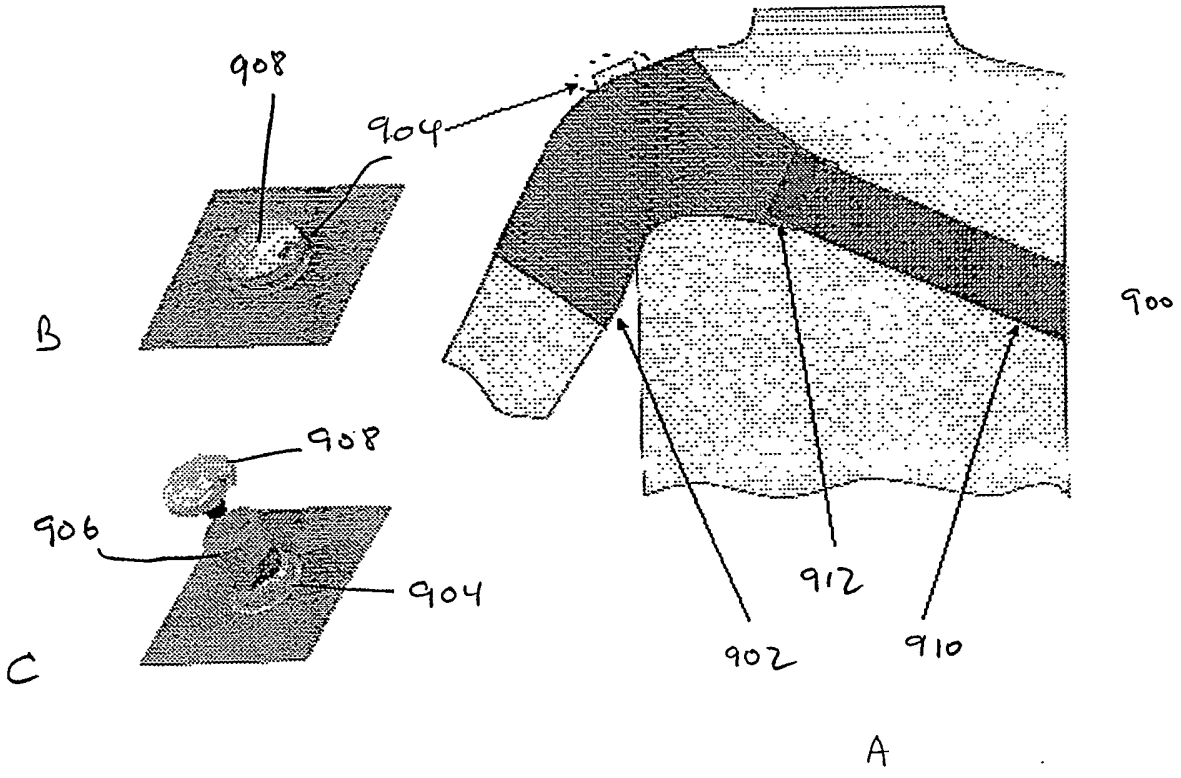


FIG 15

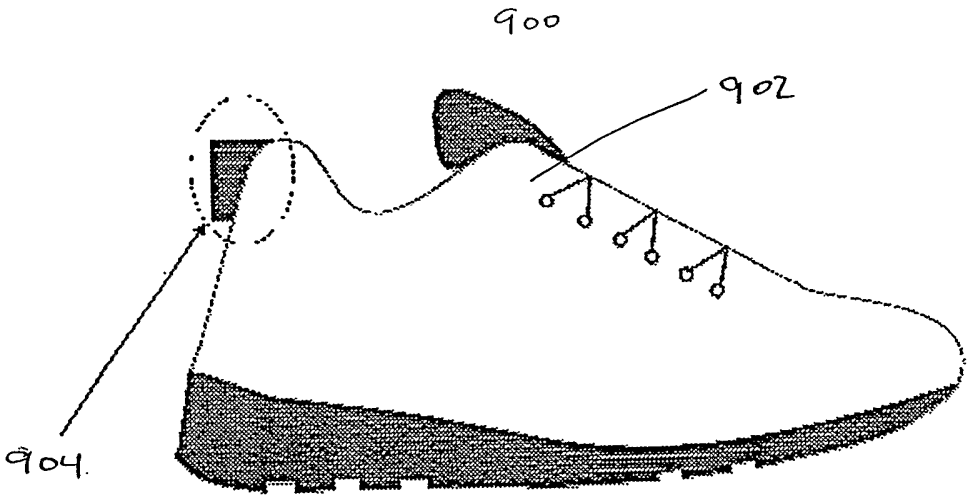


FIG 16

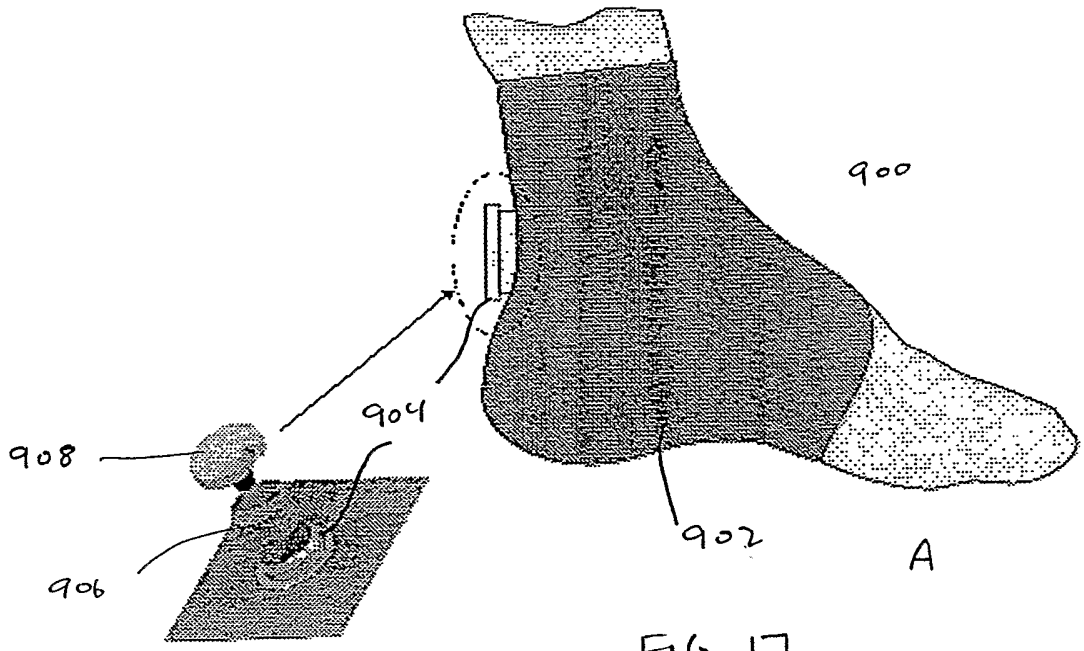


FIG 17

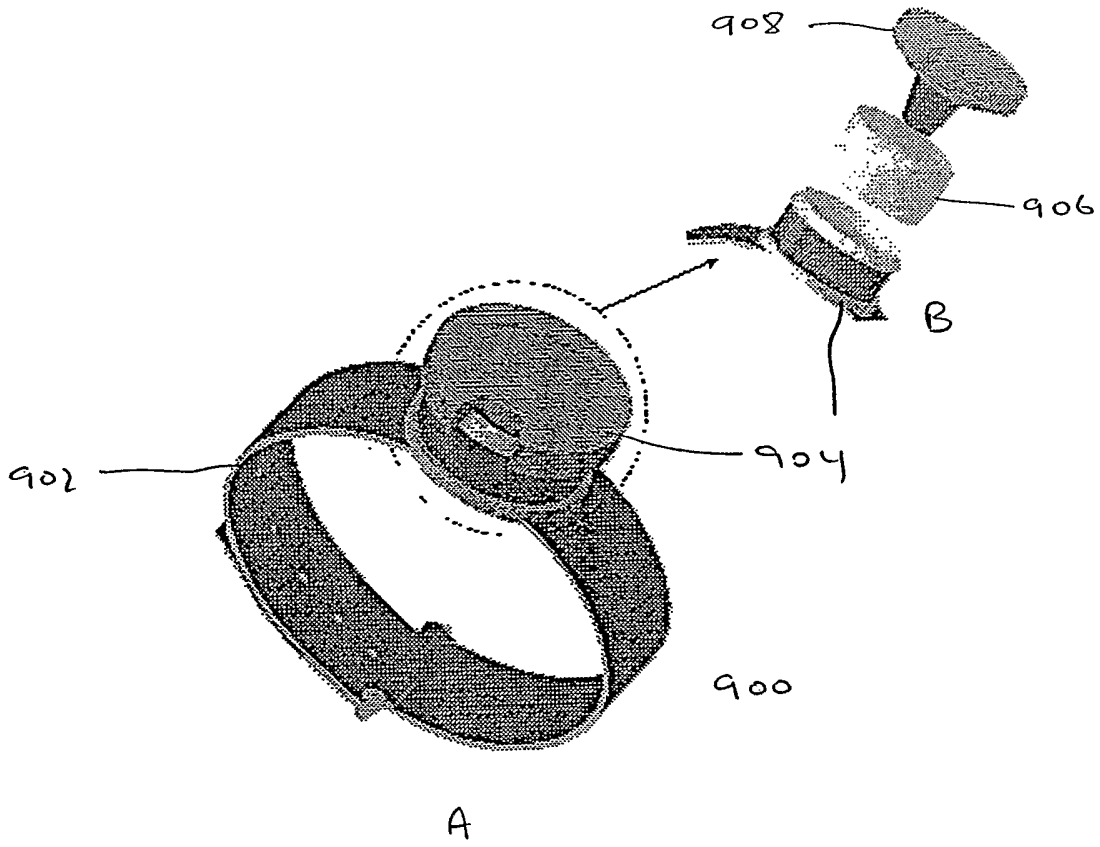


FIG 18

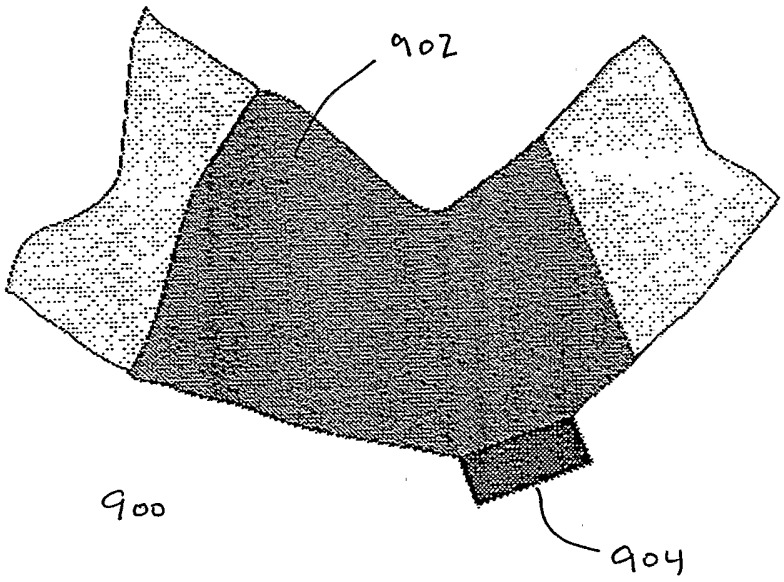


FIG. 19

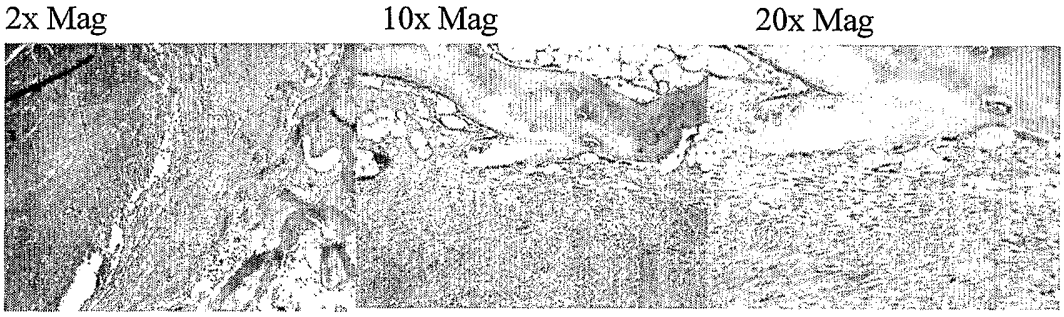


FIG. 21A

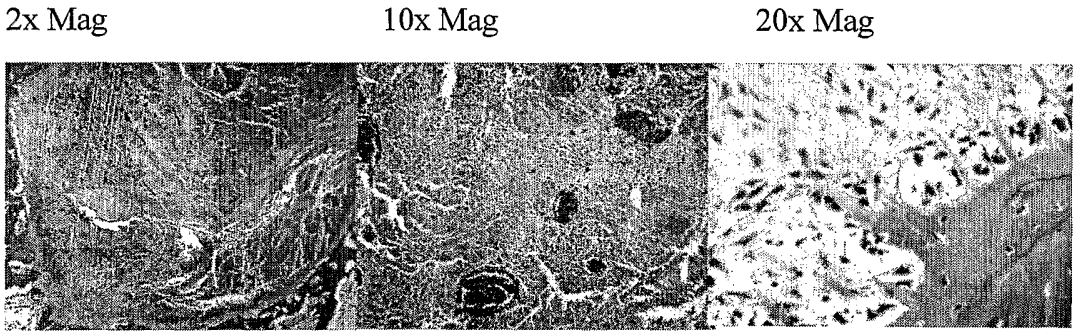


FIG. 21B

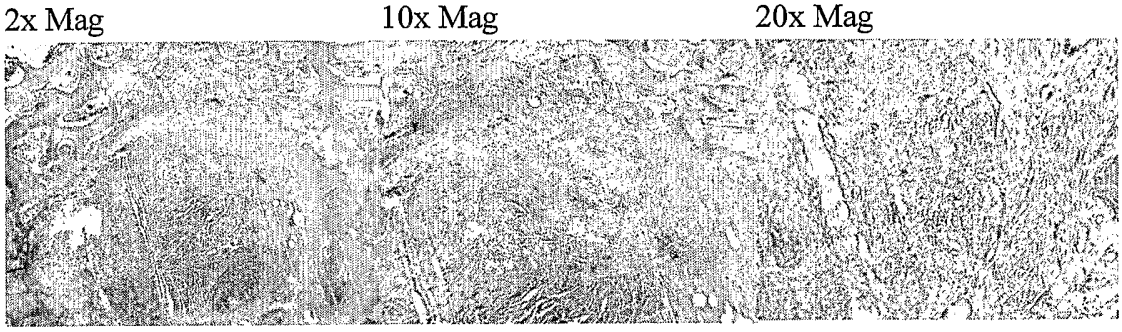


FIG. 20A

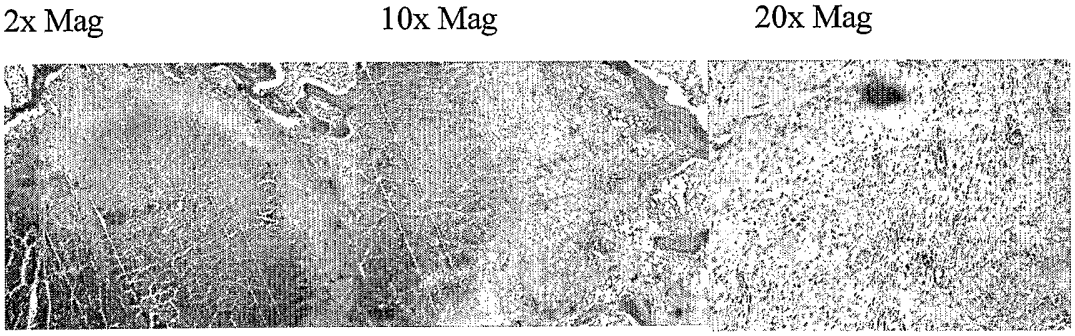
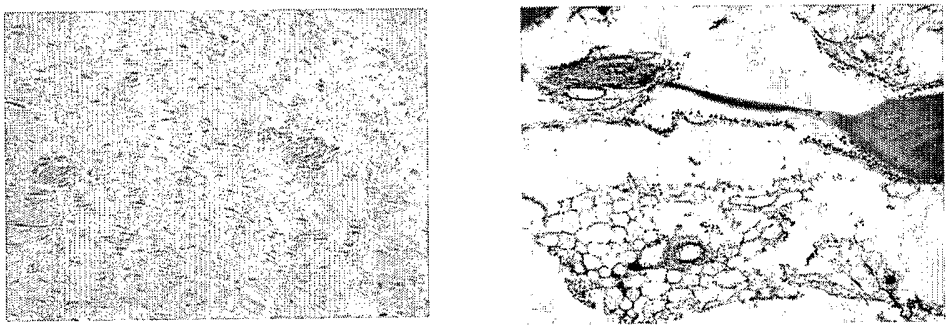
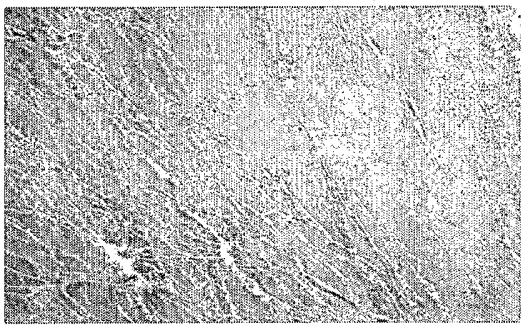


FIG. 20B

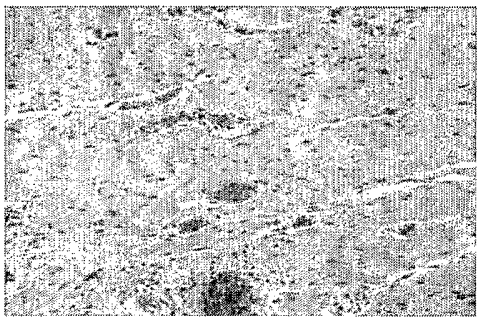


C D

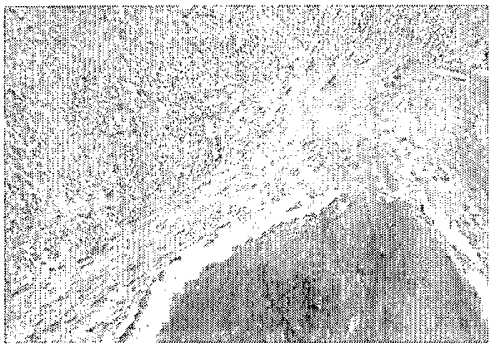
FIG. 21



A



B



C

D

FIG. 22

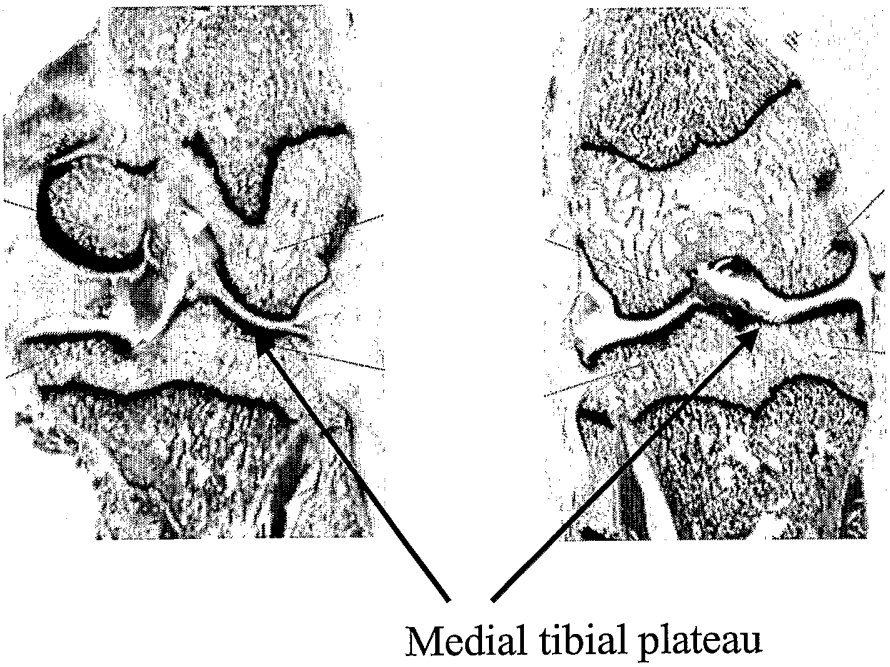


Fig. 23

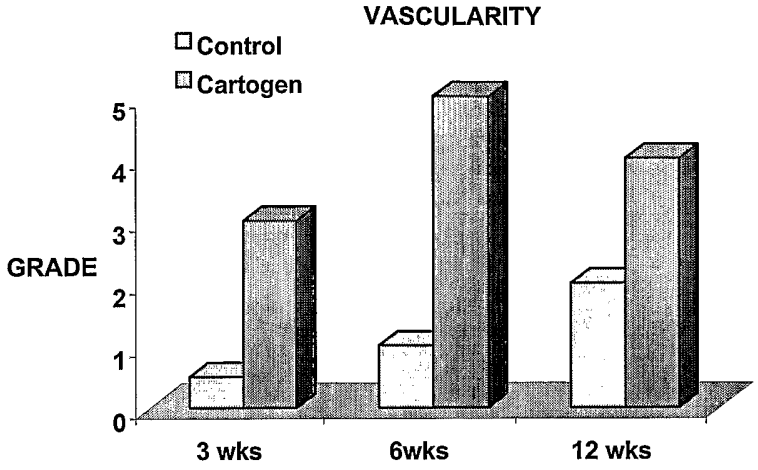


Fig. 24

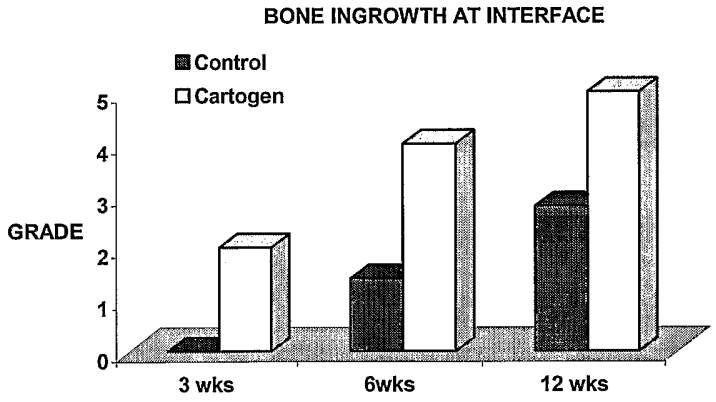


Fig. 25

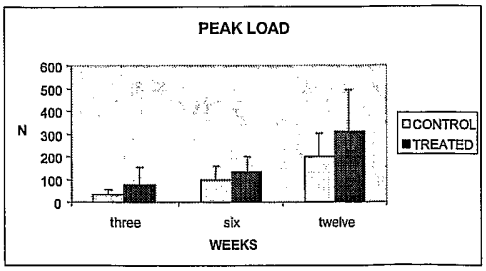


Fig. 26

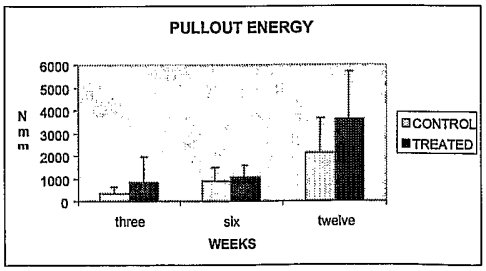


Fig. 27

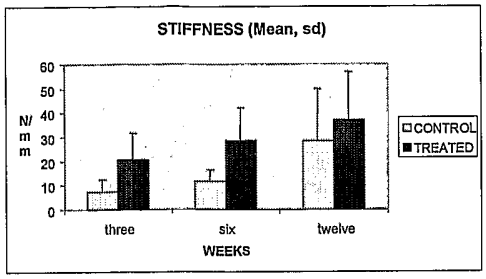


Fig. 28

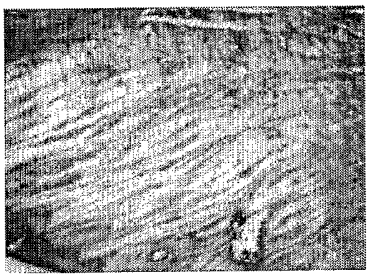


Fig. 29A

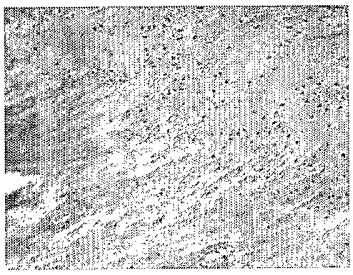


Fig. 29B

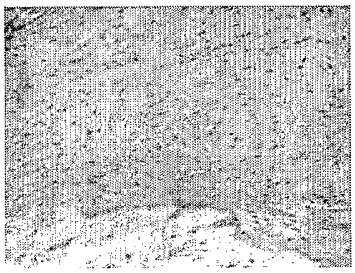


Fig. 29C

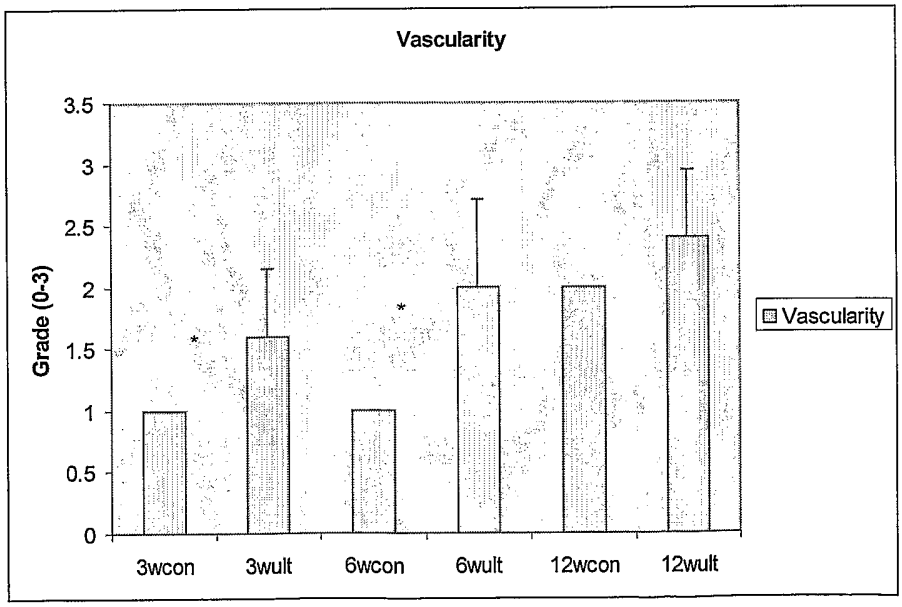


Fig. 30

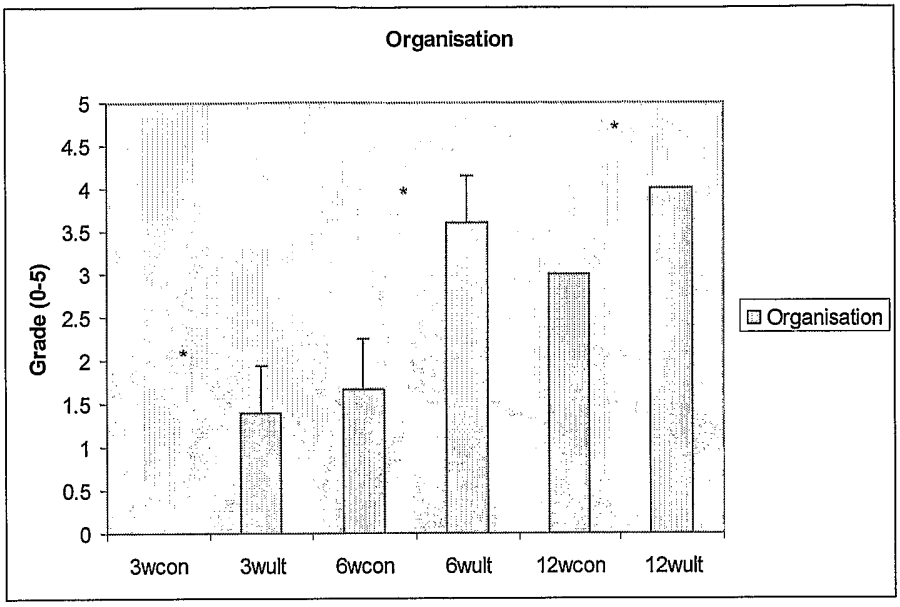


Fig. 31

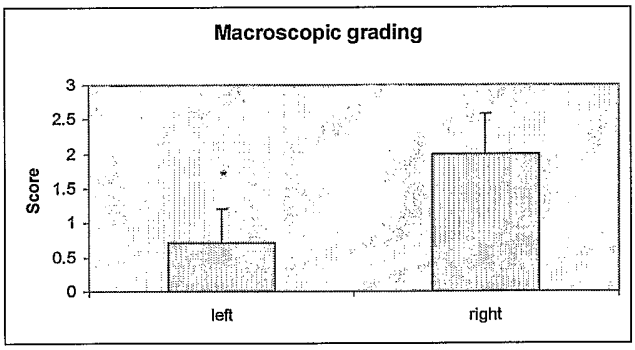


Fig. 32

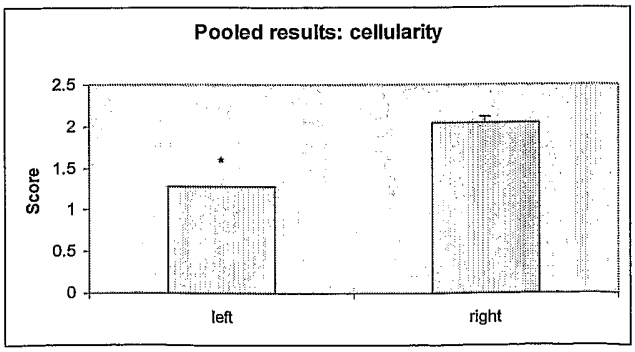


Fig. 33

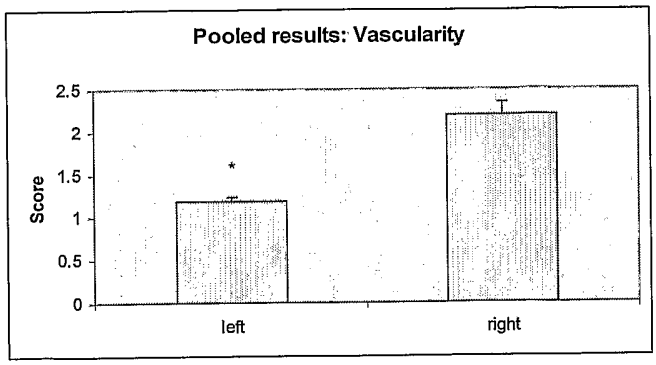


Fig. 34

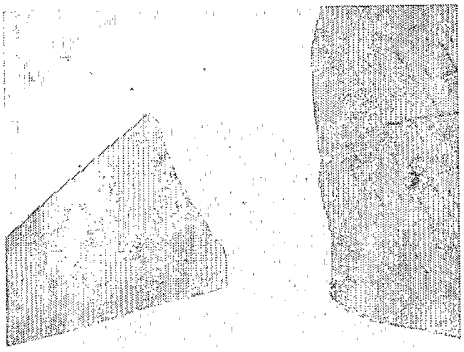


Fig. 35A

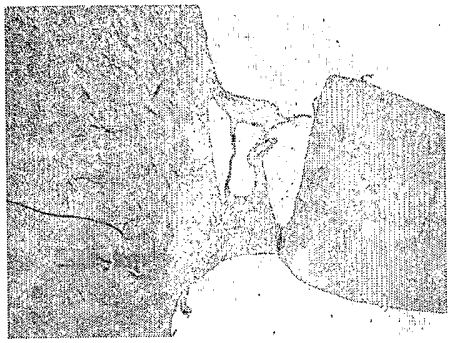


Fig. 35B

INTERNATIONAL SEARCH REPORT

PCT/US 03/12623

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61N7/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 6 355 006 B1 (WINDER ALAN A ET AL) 12 March 2002 (2002-03-12) column 3, line 34 - line 60 column 5, line 26 - line 48 column 7, line 28 -column 8, line 24; claims 1,8; figures 1,7-10	1,4-11 2,3
Y	US 6 258 020 B1 (LOPEZ RICHARD) 10 July 2001 (2001-07-10) column 10, line 26 - line 54; claims 1,6; figures 17,18	2,3
Y	EP 0 695 559 A (RAULI DONATO ;LAZZARI AMBROGIO (IT)) 7 February 1996 (1996-02-07) column 1, line 3 - line 55 column 2, line 36 - line 49; claims 1,3; figure 2	2,3

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 September 2003	02/10/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Rick, K

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 67846 A (EXOGEN INC) 16 November 2000 (2000-11-16) page 12, line 19 -page 14, line 2; claims 1,5-7; figures 11-17	1-6,11
A	US 4 530 360 A (DUARTE LUIZ R) 23 July 1985 (1985-07-23) cited in the application column 1, line 34 -column 2, line 24 column 3, line 4 - line 21 column 4, line 12 - line 22; claim 1 abstract	1-11

INTERNATIONAL SEARCH REPORT

PCT/US 03/12623

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 12-50
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US 03/12623

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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